OPTIMAL CONTROL STRATEGIES FOR MINIMIZING MALARIA TRANSMISSION IN KENYA

BY

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DECLARATION

DECLARATION BY THE CANDIDATE

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DEDICATION

To my family as a whole.

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ABSTRACT

Malaria remains a leading cause of mortality and morbidity among children under five and pregnant women in sub-Saharan Africa. It is however preventable and controllable provided current recommended interventions are properly implemented. Malaria transmission is highly variable across Kenya because of the different transmission intensities. The challenges posed by malaria and the targets for a malaria-free world call for the understanding of malaria dynamics and determining the effective and optimal strategies for preventing and controlling the spread of malaria. Better utilization of malaria intervention strategies will ensure the gain in the value for money by developing a better understanding (and better articulation) of costs and results so that more informed, evidence-based choices are made. The study formulated and analyzed a deterministic model for malaria transmission dynamics with four malaria control strategies used in Kenya namely: Insecticide Treated Nets (ITNs), treatment, Indoor Residual Spraying (IRS) and Intermittent Prevention Treatment for pregnant women (IPTp). The study further formulated an optimal control problem and derived expressions for the optimal control for the malaria model with four control variables, with the aim of minimizing total mosquito population, infected individuals and exposed individuals while keeping the cost low for different transmission settings in Kenya. Cost effective analysis of one or all possible combinations of malaria control strategies for different transmission settings was carried out to assess the extent to which the intervention strategies were beneficial and cost effective. Collected data from both published and hospital records (in Kisumu, Kisii, Chuka and Nyeri representing the four different transmission settings/ epidemiological zones in Kenya) were used to estimate the parameters for the malaria model. Numerical simulations were done in the R Statistical Computing platform. Numerical simulations indicated that malaria control strategies have effect in lowering exposed and infected members of both human and mosquito population. The most sensitive parameters were mosquito death rate and mosquito biting rate. The optimal control strategies for malaria control in both endemic and epidemic-prone areas was the combined use of treatment and IRS; in seasonal areas it was the use of treatment; and in low risk areas was the use of ITNs and treatment. The most cost-effective intervention strategies in endemic areas was the combination of treatment, IRS and IPTp; in epidemic-prone areas it was the use of treatment and IRS; for seasonal areas it was the use of ITNs and treatment, and for the low risk areas it was the use of treatment. In order to minimize malaria transmission in Kenya, the study recommends interventions strategies targeting to reduce mosquito population and mosquito bitting rates. Strategies targeting to reduce mosquito population and mosquito biting rates (vector control) such as ITNs and IRS should be implemented. The study recommends optimal use of treatment and IRS for both endemic and epidemic prone areas, treatment for seasonal areas, and ITNs and treatment for low risk areas. The recommended cost effective strategies for malaria control are use of IRS and IPTp for endemic area, use of treatment and IRS for epidemic-prone areas, use of ITNs and treatment for seasonal and use of treatment for low risk areas. This study provided useful tools that can guide policy makers in designing interventions that suits the groups most at risk for malaria (i.e. under five year-olds and the pregnant women) for different transmission settings, post-2015 malaria eradication strategies and achievement of the UN Sustainable Development Goals.

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ABBREVIATIONS

ACTs	Artemisinin-based Combination Therapies
CDC	Centre for Disease Control
DOMC	Division of Malaria Control
EIR	Entomological Inoculation Rate
GMEP	Global Malaria Eradication Programme
IAR	Infection Averted Ratio
ICER	Incremental Cost-Effectiveness Ratio
IPTp	Intermittent Preventive treatment for pregnant women
IRS	Indoor Residual Spraying
ITNs	Insecticide-Treated bed nets
KEMRI	Kenya Medical Research Institute
LLITNs	Long-Lasting Insecticide Treated Nets
MDG	Millennium Development Goals
MDP	Markov Decision Process
MIS	Malaria Indicator Survey
PfPR	Plasmodium falciparum parasite rate
QALY	Quality Adjusted Life Years
RBM	Roll Back Malaria
RDT	Rapid Diagnostic Tests
SDGs	Sustainable Development Goals
SMC	Seasonal Malaria Chemoprevention
UN	United Nations
WHO	World Health Organization

CHAPTER ONE

INTRODUCTION

1.1 Background Information

Malaria remains the leading cause of mortality and morbidity among the children under five years of age and the pregnant women in Sub-Saharan Africa (WHO Malaria Report, 2014). These groups are at high risk due to weakened and immature immunity respectively. The burden is largely in sub-Saharan Africa where 91% of deaths occurred, with pregnant women and children under five years of age being the most at risk of infection and adverse outcomes (WHO Malaria Report, 2014). Each year, there are an estimated 25 million pregnancies in sub-Saharan Africa at risk of malaria, the consequences of which can be serious for both mother and foetus in terms of morbidity and mortality.

In Kenya most hospital admissions and deaths from malaria are from children under five years of age and pregnant women because there immunity is compromised at these levels of life (DOMC, 2010). Malaria accounts for 30-50% of all outpatient attendance and 20% of all admissions to health facilities (KNBS & ICF Macro, 2010). Most Kenyans are vulnerable to malaria because of poverty, inadequate health care infrastructures and low income of the country. The level of endemicity of malaria in Kenya varies from region to region and there is a big diversity in risk of malaria infection largely driven by climate and temperature which includes the effects of altitude.

Malaria is a disease of the blood that is caused by *Plasmodium parasite* transmitted from person to person by certain types of mosquitoes and bites of the infected mosquito. The four parasite species that cause malaria in humans are *Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae* and *Plasmodium ovale* (WHO Malaria Report, 2014). *Plasmodium falciparum* which causes the severest form of the disease accounts for 98 percent of all malaria infections in Kenya (DOMC, 2010). After infection, the parasites called sporozoites travel through the bloodstream to the liver, where they mature and release another form, the merozoites which then enter the bloodstream and infect red blood cells. Thereafter, the parasites multiply inside the red blood cells, which

then break open within 48 to 72 hours, infecting more red blood cells. The first symptoms usually occur 10 days to 4 weeks after infection, though they can appear as early as 8 days or as long as a year after infection (Okosun & Makinde, 2011). Malaria may also be transmitted from a mother to her unborn infant before or during delivery (congenital malaria).

Symptoms of malaria include fever and flu-like illness, including shaking chills, headache, muscle aches, and tiredness. Nausea, vomiting, and diarrhea may also occur. Malaria may cause anemia and jaundice (yellow coloring of the skin and eyes) because of the loss of red blood cells. If not promptly treated, the infection can become severe and may cause kidney failure, seizures, mental confusion, coma, and death. For most people, symptoms begin 10 days to 4 weeks after infection, although a person may feel ill as early as 7 days or as late as 1 year later (WHO Malaria Report, 2014; DOMC, 2010).

Malaria transmission is highly variable across Kenya because of the different transmission intensities driven by climate and temperature. Kenya has four malaria epidemiological zones (Guerra *et al.,* 2008). The endemic areas of stable malaria have altitudes ranging from 0 to 1300 meters and these are areas around Lake Victoria in western Kenya and in the coastal regions. Rainfall, temperature and humidity are the determinants of the perennial transmission of malaria. The seasonal malaria transmission are in arid and semi-arid areas of northern and south-eastern parts of Kenya which experiences short periods of intense malaria transmission during the rainfall seasons. Temperatures are usually high and water pools created during the rainy season provide the malaria vectors breeding sites. The malaria epidemic prone areas of western highlands of Kenya where malaria transmission in the area is seasonal, with considerable year-to-year variation. The increase in minimum temperatures during the long rains period favours and sustains vector breeding resulting in increased intensity of malaria transmission. Low risk malaria areas covers the central highlands of Kenya including Nairobi. The temperatures are usually too low to allow completion of the sporogonic cycle of the malaria parasite in the vector. In Kenya, high transmission accounts for 36%, Low transmission (40%) and malaria free (24%) (WHO Malaria Report, 2014).

Malaria is an entirely preventable and treatable disease, provided the currently recommended interventions are properly implemented. Controlling malaria transmission involves interrupting the malaria transmission for specific transmission settings since malaria is heterogeneous. With the recent conversion of the Millennium Development Goals (MDGs) to Sustainable Development Goals (SDGs) as part of Global Malaria Action Plan for a malaria-free world by 2030, reducing malaria is critical to achieving the SDGs such as ensuring healthy lives and promote well-being for all at all ages. At the moment several African countries are working towards achieving malaria elimination (WHO Malaria Report, 2014). Kenya is currently implementing the 2009-2017 National Malaria Strategy (DOMC, 2009) as part of the health sector programmes within the framework of the Kenya Vision 2030 long term development blueprints.

Malaria is highly heterogeneous across different settings in Sub-Saharan Africa implying that different intervention strategies will be most effective in different settings (Guerra *et al.,* 2008). Prompt access to effective treatment for malaria is unacceptably low in Kenya due to the socio-economic barriers to accessing health care. The challenges posed by malaria calls for the effective and optimal strategies for preventing and controlling the spread of malaria disease. Hence the need to understand the dynamics of malaria disease transmission.

People living in poor rural areas are confronted with a multitude of barriers when accessing malaria prevention and treatment. Lack of skilled health personnel and equipment add to the general burden of poverty; insufficient knowledge about health care, problems connected to accessing the health facility in time, insufficient initiatives to prevent malaria attacks, and a general lack of attention to the long term debilitating effects of a malaria (DOMC, 2010). These challenges call for urgent need for a better understanding of important parameters in the disease transmission and develop effective and optimal strategies for prevention and control of the spread of malaria disease.

The current reduction in the number of malaria related cases are due to the scale up efforts of the current malaria interventions in Kenya but there are few guidelines about how best to deploy scarce resources for malaria control (DOMC, 2010). Better utilization of the malaria intervention strategies will ensure the gain the value for money. Value for

money is essentially about maximizing the impact of each money spent. The purpose of the value for money drive is to develop a better understanding (and better articulation) of costs and results so that we can make more informed, evidence-based choices. Cost effectiveness analysis is carried out to inform decision makers on how to determine where to allocate resources for malaria interventions (Phillips, 2009). Cost-effectiveness analysis is often used in the field of health services, where it may be inappropriate to monetize health effect. The most commonly used outcome measure is quality-adjusted life years (QALY).

The main malaria prevention strategies in pregnancy include the use of intermittent preventive treatment with anti-malarial medications, as well as the regular and timely use of long-lasting, insecticide-treated nets (LLITNs). Preventive chemotherapies are key elements of the comprehensive package of malaria prevention and control measures recommended by World Health Organization (WHO) (WHO Malaria Report, 2014). WHO recommended preventive therapies include intermittent preventive treatment of pregnant women (IPTp), intermittent preventive treatment of infants (IPTi), and seasonal malaria chemoprevention (SMC). The objective of these interventions is to prevent malarial illness by maintaining therapeutic drug levels in the blood throughout the period of greatest malarial risk.

The current reduction in malaria related case in Kenya is attributed to the scale up effort of the combinations of the several WHO recommended intervention strategies over the past decades to effectively prevent, diagnose, and treat malaria (DOMC, 2010). They include vector control through the use of long-lasting insecticide-treated bed nets (LLITNs), indoor residual spraying (IRS), chemoprevention for most vulnerable such as IPTp, confirmation of malaria diagnostics through rapid diagnostics tests (RDTs) and microscopy for every suspected case and timely treatment with artemisinin-based combination therapies (ACTs) (WHO Malaria Report, 2014).

WHO recommends IPTp-SP for all pregnant women at each schedule of antenatal care (ANC) for high transmission settings of *Plasmodium falciparum.* WHO recommends the use of ITNs as a measure to reduce the mentioned adverse effects during pregnancy. In Kenya, the control strategies being used include ITNs/ LLITNs, IRS, IPTp, ACTs

(Diagnosis and Treatment) their levels of effect shows that there is 44% reduction in childhood mortality (DOMC, 2010). The optimal use of the current malaria intervention strategies will help reduce malaria transmission and fast track the prospects towards malaria elimination and eradication.

Mathematical models have become important tools in analyzing the spread and control of infectious diseases. Mathematical models of epidemiology can be used to understand the dynamics of the spread of malaria in a population (Koella & Anita, 2003; Okosun & Makinde, 2011). The mathematical modeling can help in figuring out decisions that are of significant importance on the outcomes. Mathematical models provide a tool with which to explore the expected impact of different interventions against malaria, both individually and in combination, on a range of program endpoints (Okell *et al.,* 2008; Smith *et al.,* 2009). Ross (1911) developed the first mathematical model for malaria transmission focusing on mosquito control. Since then several models have been developed to extend his work (McDonald, 1956; Anderson & May, 1992; Ngwa & Shu, 2000; Koella & Anita, 2003) with some influencing malaria eradication programmes. No malaria transmission model incorporating interventions strategies for different transmission settings and for the most at risk groups for malaria exist for Kenya.

Although some of these studies considered different interventions for malaria control, the effect of IPTp and other malaria control and prevention strategies have not been studied in an optimal control and cost effectiveness analysis for the most at risk group for malaria. Mathematical models for malaria intervention in Kenya is the OpenMalaria simulation model (Stuckey *et al.,* 2014). Optimal control is a branch of mathematics developed to find optimal ways to control a dynamic system (Pontryagin *et al.,* 1962). Optimal control is a set of ordinary differential equations describing the paths of the control variables that minimize the cost function. A control problem includes a cost functional that is a function of state and cost variables. The optimal control problem is solved using direct or indirect methods. The direct method uses the optimal functional and the state system while the indirect method uses an iterative method with a Runge-Kutta scheme. Rodrigues *et al.,* (2009) explained that the state system with an initial guess is solved forward in time and then the adjoint system with the transversality conditions is solved backward in time. The optimal control efforts are carried out to limit

the spread of the disease. Application of optimal control theory can be an important tool to estimate the efficacy of various policies and control measures and the cost of implementing them. Since the development of the Pontryagin maximum principle by Pontryagin *et al.* (1962), the theory of optimal control has been successfully used in decision making in various applications. Different mathematical models and optimal control approaches have been previously used to study the dynamics of transmission and treatment of infectious diseases such as malaria (Rafikov *et al.,* 2009), Tuberculosis (Moualeu *et al.,* 2015; Silva & Tores, 2012), HIV (Adams, *et al.,* 2004), and Influenza (Tchuenche *et al.,* 2011). The application of optimal control in malaria have only used up to three control measures and the use of four control variable in the optimal control is limited.

Cost effectiveness analysis is carried out to inform decision makers on how to determine where to allocate resources for malaria interventions especially when they are limited (Phillips, 2009). The analysis compares the costs and health effects of an intervention to assess the extent to which it can be regarded as providing value for money and the choice of the technique depends on the nature of the benefits specified. The incremental cost-effectiveness ratio (ICER) has become the common measure for cost effectiveness analysis and is calculated in order to achieve the goal of comparing the costs and the effectiveness of the intervention strategies (Okosun *et al.,* 2013; Ridrogues *et al.,* 2014; White *et al.,* 2011). There is no cost effectiveness analysis done for the optimal malaria control strategies for different malaria transmission settings in Kenya considering the most at risks age groups. No cost effectiveness analysis has been done for the IPTp for the most at risk group of malaria.

The modeling approach presented will explore the potential for current control measures to reduce malaria transmission in different transmission settings to a low level as laid out in the control phase of the global elimination framework (Smith & Hay, 2009) while keeping the cost very low. The result will be illustrated by applying the model to four well characterized transmission sites in Kenya which represent the full range of transmission intensity most commonly observed across Africa.

1.2 Statement of the Problem

Malaria is a leading cause of mortality and morbidity among the children under five and the pregnant women in Kenya. Malaria accounts for accounts for 30-50% of all outpatient attendance and 20% of all admissions to health facilities in Kenya (DOMC, 2010; WHO Malaria Report, 2014). Malaria in Kenya is heterogeneous as a result of the different transmission settings because of the varying intensities. This implies that different transmission settings will require different malaria intervention strategies. Malaria is however preventable and controllable provided currently recommended interventions are properly implemented. There are few guidelines about how best to deploy scarce resources for malaria control and the need for value of money calls for the cost effective analysis of malaria interventions. The optimal use of the current malaria intervention strategies will help reduce malaria transmission, mortality, morbidity, for post 2015 malaria strategies, achievement of Kenyan Vision 2030 and fast-track the prospects towards malaria elimination and eradication (SDGs).

Mathematical models provide a framework for understanding the dynamics of disease transmission and can be used to determine the effectiveness and optimal allocation of different interventions against malaria (McDonald, 1956). Previous studies on mathematical modelling for malaria transmission dynamics in Kenya (Stuckey *et al.*, 2012) did not consider the combined effect of ITNs, IRS, and natural death on reducing the mosquito population, use of IPTp and the most at risk groups. IPTp use has shown to have effect in reducing mortality among the under-five and the pregnant women who are the most at risk group for malaria (Hansen *et al.*, 2012) and it's one of the WHO recommended preventive therapy for pregnant women in sub-Saharan Africa but has not been studied in modelling of malaria transmission dynamics for the most at risk groups for malaria.

Optimal control is a branch of mathematics developed to find optimal ways to control a dynamic system (Pontryagin *et al.*, 1962). The theory of optimal control has previously been successfully applied in decision making. Optimal control in malaria intervention has not been applied to guide the design of malaria interventions strategies for the most at risk groups for malaria and for the different transmission settings in Kenya. There is little

application of four control variables for different transmission settings in optimal control theory in malaria control studies. Most optimal control theory malaria interventions studies have not considered the effect of IPTP and the combined effect of ITNs, IRS, and natural death in reducing the mosquito population.

Cost effective analysis compares the costs and health effects of an intervention to assess the extent to which it can be regarded as providing value for money and can help guide the optimal allocation of malaria intervention resources. The benefits and cost-effectiveness of malaria control strategies for the most at risk groups for malaria (pregnant women and the under five children) are less well documented, especially for different malaria transmission settings in Kenya.

This study therefore investigates the optimal control strategies for minimizing malaria transmission with four control variables for different transmission settings in Kenya. The mathematical model for human-vector interactions with malaria control strategies was used.

1.3 Objective of the Study

1.3.1 General Objective

The general objective of the study was to investigate the optimal control strategies for minimizing malaria transmission in Kenya using mathematical modeling techniques

1.3.2 Specific Objectives

The specific objectives of the proposed study are:

(i) To formulate and analyze a model for malaria transmission dynamics with four malaria intervention strategies in Kenya
(ii) To formulate an optimal control problem and derive expressions for the optimal control for the malaria model with four control variables
(iii) To investigate the impact of the different combinations of malaria control and propose the optimal control strategies for malaria control for different transmission settings.

(iv) To carry out cost effective analysis of one or all possible combinations of malaria control strategies for different transmission settings.

1.4 Scope of the Study

The malaria transmission model with four control strategies based on Susceptible (S) – Exposed (E) – Infectious (I) – Recovered (R) compartmental structure for humans and Susceptible (S) – Exposed (E) – Infectious (I) compartmental structure for mosquitoes was used to illustrate the human-vector interaction and to derive the differential equations for the analysis of the optimal control.

The basic reproduction number (R_0) which is a fundamental parameter governing the spread of the disease was computed using the next generation operator approach. This provides the necessary condition for the disease to be eradicated or minimized. The qualitative analysis of the model was conducted to determine the possibility of existence and stability of endemic and disease-free equilibria. Sensitivity analysis was carried out to compute sensitivity indices of the reproduction number which enables us to single out parameters that have a high impact to the reproduction number R_0 and which are used to enhance the intervention strategies.

Pontryagin's Maximum Principle which uses the Lagrangian and Hamiltonian principles with respect to a time dependent constant was used to derive the necessary conditions for the optimal control of malaria disease in order to determine optimal strategies for controlling the spread of the disease. Data was collected from the literature, Division of Malaria Control (DOMC), Kenya National Bureau of Statistics, Malaria Indicator Survey for Kenya, Demographic Health Survey (DHS) for Kenya, World Malaria Report 2014 by the WHO and hospital records (from Kisumu, Kisii, Chuka (Tharaks-Nithi) and Nyeri counties representing the four different transmission settings/ epidemiological zones in Kenya). All these collected data guided in the calculations/ estimation of parameter for the malaria model while the unknown parameters values were assumed. Incremental Cost Effectiveness Ratio (ICER) was done as part of the cost effective analysis. The computer package (R Statistical Software) was used for the model simulations.

1.5 Significance of the Study

The study will be able to evaluate the current intervention strategies and suggest innovative intervention strategies for different transmission settings with minimum cost. This will also inform the policy makers, the stakeholders for malaria elimination, National Malaria Control Programs and global plan for malaria eradication. Specific generated information will guide on how malaria can be eradicated in Kenya. Knowing costs and outcomes of alternative control strategies is important to decision makers who are often faced with the challenge of resource allocation. This will help in investing resources more strategically and the targeted interventions will reach the most vulnerable people with no barriers to access. It will also provide policy makers with information on where resources should be allocated when these are limited.

The findings of this study will contribute to the knowledge gap and add value to the current literature on malaria transmission dynamics, optimal control and cost effectiveness analysis of malaria intervention strategies. Scholars and academicians wishing to carry out research in the area of disease transmission dynamics, optimal control and cost effectiveness analysis of malaria intervention strategies may use findings of this study for further research.

CHAPTER TWO

LITERATURE REVIEW

2.1 Malaria Mathematical Models

Mathematical models of Mosquito-borne pathogen transmission originated with the work of Ronald Ross (Ross, 1915; McDonald, 1956) and thereafter several models have been developed to provide insights into effective eradication of malaria. Ross (1911) focused on mosquito control and showed that mosquito population should be brought to a certain threshold for malaria disease to be eliminated. MacDonald (1957) analyzed an updated version of Ross model and highlighted that increasing the mortality of adult mosquito will be more significant in the control effort of malaria transmission. The Macdonald model influenced the decision of WHO to launch the Global Malaria Eradication Programme (GMEP) between 1955 -1969 (McDonald, 1956). The lesson learned from the GMEP, 1955 - 1969 was that no single strategy can be sufficient to eradicate malaria in all areas (Najera *et al.,* 2011).

Aron & May (1982) describe the properties of Ross-Mcdonald model, by including the derivation of the reproductive number, R_0. The reproductive number, R_0, is defined as the number of secondary infections that one infectious person would produce in a fully susceptible population through the entire duration of the infectious period. Yang (2000) described a compartmental model where humans follow a Susceptible-Exposed-Infectious-Recovered-Susceptible (SEIRS) pattern for human and mosquitoes follow a Susceptible-Exposed-Infectious (SEI) pattern. He further stated that the disease-free equilibrium is stable for $R_0 < 1$ and unstable when $R_0 > 1$. Li *et al.,* (2002) derived a model where humans move through multiple Susceptible-Exposed-Infectious-Recovered (SEIR) stages, where a history is kept of previous infections. Ngwa & Shu (2000), extended the works of Ross (1915) and McDonald (1957) to come up with the popular generalized SEIR malaria model.

IPTp is one of the WHO recommended prevention therapy for the pregnant women. IPTp has been shown to be effective in reducing maternal and infant mortality that are related to malaria (Le Port *et al.,* 2011; Parise *et al.,* 1998; Shulman *et al.,* 1999, Rogerson *et al.,*

2000). Hansen *et al.,* (2012) showed that IPTp reduced maternal mortality by 3% in low transmission settings of Uganda.

Several modelling techniques have been previously used for to study malaria transmission dynamics with intervention strategies. Oduro *et al.,* (2015) modelled malaria transmission dynamics with interventions using SEIR-SEI but not for different transmission settings and the at risk groups. The study further did not consider the combined effect of ITNs, IRS, and natural death on reducing the mosquito population. Oduro *et al.,* (2012) modelled malaria transmission dynamics but did not consider malaria interventions, different malaria transmission settings, the most at risks groups and the combined effect of ITNs, IRS, and natural death on reducing the mosquito population. Stuckey *et al.,* (2012) showed the malaria simulation model for the western highlands Kenya without considering the most at risks groups, effect of IPTp and the different transmission settings in Kenya. King *et al.,* (2012) developed a SEIR-SEI mathematical model for studying malaria transmission without incorporating the interventions, considering the different transmission settings and the combined effect of ITNs, IRS, and natural death on reducing the mosquito population. Griffin *et al.,* (2010) developed model for malaria transmission dynamics for six different sites in Africa representing the different transmission settings in Africa but did not consider the effect of IPTp and stratifying the population to those at risk group of malaria. Other approaches that have been used to study malaria interventions include Markov Decision Process (Dimitrov *et al.,* 2012) and the openmalaria software program created by Smith *et al.,* (2008). They however did not stratify the population by the most at risk groups for malaria and for different transmission settings.

2.2 Optimal Control

Optimal control is a branch of mathematics developed to find optimal ways to control a dynamic system (Pontryagin *et al.,* 1962). Optimal control is a set of ordinary differential equations describing the paths of the control variables that minimize the cost function. The cost functional equation with weights related to the costs of intervention strategies and implementation is used. Optimal control functions have been used in the study of optimal control in order to determine the best intervention methods for vector borne

disease related to Dengue disease (Rodrigues *et al.,* 2012). The optimal control is qualitatively derived using Pontryagin's Maximum Principle or by solving the Hamilton-Jacobi-Bellman equation. This principle has provided research with suitable conditions for optimization problems with differential equations as constraints. The aim of the optimal control problem is to minimize the number of infected humans while keeping the cost as low as possible. This approach allows studying the most cost-effective intervention design by generating an implementation design that minimizes an objective function. The intensity of interventions can be relaxed along time, which is not the case considered in most models, for which interventions are modeled by constant rates (Gomes *et al.,* 2007).

Optimal control approach has been applied optimal control theory in controlling infectious diseases such as tuberculosis (Moualeu *et al.,* 2015; Silva & Torres, 2012). Adams *et al.,* (2004) used optimal control to examine the role of chemotherapy in controlling the virus reproduction in HIV patients. Xiefei *et al.,* (2007) applied optimal control methods to study the outbreak of SARS using Pontryagin's Maximum Principle and a genetic algorithm. Zaman *et al.,* (2008) used optimal control to determine the optimal vaccination strategy to reduce the susceptible and infective individuals for a general SIR epidemic model. Kbenesh *et al.,* (2009) used optimal control to study a model for vector-borne diseases with treatment and prevention as control measures. To the best of the researcher's knowledge, no such methods have been used in Kenya to determine the optimal combination of malaria intervention strategies for different malaria transmission settings and for the most at risk groups for malaria.

Optimal control theory has also been applied in malaria control to assess the impact of antimalarial control measures by formulating the model as an optimal control problem. The results of optimal control in malaria interventions are mixed and different. Okosun *et al.,* (2013) applied optimal control theory to SEIR/SEI malaria model and considered three malaria preventive measures as control variables (use of treated bednets, spray of insecticides and treatment of infective humans) and further assessed cost effectiveness of the interventions. The findings indicated that the most cost-effective strategy for malaria control was the combination of the spray of insecticides and treatment of infective individuals. He however did not stratify the population into the under-five and the

pregnant women who are at risk population for malaria and did not assess the effect of IPTp and the combination effect of ITN, IRS and natural death on mosquito population for different malaria transmission settings. Mwamtobe *et al.,* (2014) used three control variables (IRS, ITNs and treatment) in a SEIR/SEI malaria model and for only one region in Malawi. The findings indicate that the most cost effective control measure was ITNs and IRS complemented with timely treatment. The study however did not stratify the population into under-five and the pregnant women, the effect of IPTp together with the combined effect of ITN, IRS and natural death on mosquito population was not investigated. Kim *et al.,* (2012) investigated the optimal control strategy for *Plasmodium vivax* malaria transmission in Korea using two control efforts in SEI/SI malaria model type. The findings show that the cost of reducing the reproduction rate of the mosquito population was more than that of prevention measures to minimize mosquito-human contacts. The study did not stratify the population into at risk groups and the effect of IPTp together with the combined effect of ITN, IRS and natural death on mosquito mortality was not investigated. Agusto *et al.,* (2012) used three system control variables (ITN, IRS, treatment) using SEIR/SEI malaria model. The findings indicated that the combination of the three controls had the highest impact on the control of the disease. The effect of the combination of ITN, IRS and natural death on mosquito mortality was however not investigated together and the population was stratified by those at risk age group and pregnant women. Silva & Torres (2013) presented an optimal control approach and used only one control variable (use of ITNs) using SI/SI malaria model. The findings showed the effectiveness of the optimal control interventions. The study did not consider other malaria control variables such as IRS, treatment and IPTp in addition to the combined effect of ITN, IRS and natural death on mosquito mortality and stratifying the population by at most risk group for malaria. Otieno *et al.,* (2014) provided a general explanation of optimal control using four control variables in which additional control variable (IPTp) was introduced into the model. IPTp effect in optimal control theory has not been investigated and this will be done in this study.

2.3 Cost-Effectiveness Analysis

Cost effective analysis compares the costs and health effects of an intervention to assess the extent to which it can be regarded as providing value for money. White *et al.,* (2011)

conducted cost effective analysis for malaria interventions through systematic review but not for different transmission setting and for the at risk groups. Ridrogues *et al.,* (2014) conducted cost effective analysis using ICER but for TB. Okosun *et al.,* (2013) conducted cost effective analysis using ICER for three malaria intervention strategies and not for different transmission settings. He further did not consider the cost effective intervention strategies for the at risk group i.e. the pregnant and the under five children. No cost effective analysis of the optimal control strategies for malaria has been done for the at risk group showing the effect of IPTp and different transmission settings.

The review of the literature shows that IPTp has effect on reducing mortality among the under-five and the pregnant women who are the most at risk group for malaria. Most malaria models for analyzing transmission dynamics for malaria with interventions are the standard SEIR-SEI models. The review also shows that the combined effect of ITNs, IRS, and natural death in reducing mosquito population has not been demonstrated in modelling of malaria transmission dynamics. The effect of IPTp which is WHO recommended preventive therapy for the most at risk group for malaria (pregnant women) has not been studied as part of modeling transmission dynamics of malaria with interventions.

The review of literature shows that very few studies have been applying optimal control theory to malaria transmission models for different transmission settings. Most malaria models for analyzing effect of interventions in optimal control used the standard SEIR-SEI models. The combined effect of ITNs, IRS, and natural death on reducing the mosquito population has not been demonstrated in optimal control theory for malaria control. There is no cost effectiveness analysis that has been done for the optimal malaria control strategies for different malaria transmission settings in Kenya considering the most at risks groups.

The effect of IPTp which is WHO recommended preventive therapy for the most at risk group for malaria (pregnant women) has not been studied in optimal control theory. No model for malaria transmission dynamics incorporating interventions strategies exist for Kenya. No study has been done in Kenya to evaluate the optimal control strategies for malaria interventions for different transmission settings. No model for malaria

transmission dynamics incorporating the IPTp exist for Kenya. No malaria dynamics model with interventions has been stratified by the most at risk groups for malaria (under five and pregnant women). No optimal control model for four control variables incorporating the IPTp malaria intervention studies exits for Kenya. No optimal control model has been stratified by the age group (under five) and specific categories (pregnant women). No cost effective analysis for the optimal malaria control strategies has been done for different transmission settings in Kenya. No cost effectiveness analysis has been done for the WHO recommended malaria control strategies for the most at risk groups for malaria.

This study formulated and analyzed a model for malaria transmission dynamics which incorporated four intervention strategies used in Kenya, formulated an optimal control problem and derived expressions for the optimal control for the malaria model with four control variables and then use optimal control theory to study the impact of one or all possible combinations of four malaria control strategies, and carried out cost effective analysis of one or all possible combinations of the optimal malaria control strategies for different transmission settings.

CHAPTER THREE

METHODOLOGY

3.1 Introduction

This chapter illustrates the approach for formulating and analyzing the malaria control model with intervention strategies. We have a description of the human-vector model, stating the assumptions and definitions of the various parameters of the model. Analysis of the proposed model is done. Parameters for the malaria model are described and sensitivity analysis is also done.

The malaria dynamics model is extended and an optimal control problem is formulated. We formulate an optimal control model for malaria disease in order to determine optimal prevention (ITNs, IRS and IPTp) and treatment strategies with minimal implementation cost. Using Pontryagin maximum principle we derived and analyzed the necessary conditions for the optimal control of malaria with effective use of ITNs, treatment, IRS and IPTp.

After using the optimal control to investigate the optimality of the intervention strategies being practiced at different transmission settings in Kenya, economic evaluation of the strategies is carried out by performing a cost-effectiveness study to determine the most cost-effective as one or combination of the four intervention strategies namely, treatment effort of infected individuals, ITNs, IRS and IPTp

3.2 Formulation of Malaria Model with Intervention Strategies

A deterministic malaria transmission dynamics model with intervention strategies for the most at risk groups for malaria (under five children and the pregnant women) is formulated and analyzed. The population under study is subdivided into compartments according to the individual's disease status. We consider a seven-dimensional model, which consists of population of Susceptible S_h , Exposed humans E_h , Infected humans I_h , Recovered humans R_h , Susceptible mosquitoes S_m , Exposed mosquitoes E_m and Infected mosquitoes I_m. The total population sizes at time t for humans and mosquitoes are denoted by $N_h(t)$ and $N_m(t)$ respectively. We employ the SEIRS type model for

humans to describe a disease with temporary immunity on recovery from infection. Mosquitoes are assumed not to recover from the parasites so the mosquito population can be described by the SEI model. In the model we incorporate four time dependent control measures simultaneously: (i) the use of treated bednets $u_1(t)$, (ii) treatment of infective humans $u_2(t)$, (iii) spray of insecticides $u_3(t)$ and (iv) treatment to protect pregnant women and their new born children: intermittent preventive treatment (IPTp) for pregnant women $u_4(t)$. The SEIRS/ SEI model were chosen in line with what is known in the literature on optimal control in malaria interventions as used by Ngwa & Shu (2000), Mwamtobe *et al.*, (2014), Okosun *et al.*, (2013), and Agusto *et al.*, (2012).

The susceptible pregnant and under five human (S_h) are recruited at the rate, Λ_h. They either die from natural causes (at a rate μ_h) or move to the exposed class (E_h) by acquiring malaria through contact with infectious mosquitoes at a rate $(1-u_1)\frac{\beta\epsilon\phi I_m}{N_h}S_h$ or $(1-u_4)\frac{\beta\epsilon\phi I_m}{N_{hw}}S_h$, where β is the transmission probability per bite, ϵ is the per capita biting rate of mosquitoes, ϕ is the contact rate of vector per human per unit time, $u_1(t) \in [0,1]$ is the preventive measure using ITNs, $u_4(t) \in [0,1]$ is the preventive measure using IPTp, $I_m(t)$ is the infectious mosquitoes at time t, $N_h(t)$ is the total number of individuals (pregnant and under 5) and $N_{hw}(t)$ is the total number of pregnant women. Susceptible class S_h is divided into whole population (under five years and pregnant women) being exposed and the population for the pregnant women being exposed. Exposed individuals move to the infectious class after the development of clinical symptoms at the rate α_h. Infectious individuals are assumed to recover at a rate $b+\tau u_2$, where b is the rate of spontaneous recovery, $u_2(t) \in [0,1]$ is the control on treatment of infected individuals and $\tau \in [0,1]$ is the efficacy of treatment. Infectious individuals who do not recover die at a rate $\delta_h+\mu_h$. Individuals infected with malaria suffer a disease induced death (for pregnant and under 5) at rate of δ_h, and natural death μ_h. Infected individuals then progress to partially immune group where upon recovery the partially immune individual losses immunity at the rate ψ and becomes susceptible again.

Susceptible mosquitoes (S_m) are recruited at the rate Λ_m and acquire malaria infection (following contact with humans infected with malaria) at the rate λ_m. They either die

from natural causes (at a rate μ_m) or move to the exposed class by acquiring malaria through contacts with infected humans at a rate $(1-u_1)\frac{\lambda\epsilon\phi I_h}{N_h}S_m$, where λ is the probability for a vector to get infected after biting an infectious human and $I_h(t)$ are individuals infected by malaria at time t . The mosquito population is reduced, due to the use of insecticides spray, at a rate pu_3, where $u_3(t) \in [0,1]$ represents the control due to IRS and p represents the efficacy of IRS. Mosquito population is also reduced as a result of natural death (μ_m) and at the rate au_1, where $u_1(t)$ represents the control due to ITNs and a is the efficacy due to ITNs. Newly infected mosquitoes are moved into the exposed class (E_m) at a rate α_m and progresses to the class of symptomatic mosquitoes (I_m). $\lambda_m = \frac{\lambda\epsilon\phi I_h}{N_h}$ is the percapita incidence rate among mosquitoes (force of infection for susceptible vectors), and $\lambda_h = \frac{\beta\epsilon\phi I_m}{N_h}$ is the force of infection for susceptible humans (pregnant and under 5), $\lambda_{hw} = \frac{\beta\epsilon\phi I_m}{N_{hw}}$ is the force of infection for susceptible pregnant humans and N_{hw} is the total population for pregnant women. The total population sizes for the human (pregnant and under 5) is $N_h(t) = S_h(t) + E_h(t) + I_h(t) + R_h(t)$ and for vector is $N_m(t) = S_m(t) + E_m(t) + I_m(t)$.

The model state variables are represented and described in Table 3.1. Table 3.2 presents and describes the parameters of the model. Table 3.3 represents and describes the malaria prevention and control strategies practiced in Kenya

Table 3.1: State variables of the malaria model

Symbol	Description
$S_h(t)$	Number of susceptible individuals (pregnant and under 5) at time *t*
$E_h(t)$	Number of exposed individuals (pregnant and under 5) at time *t*
$I_h(t)$	Number of infectious humans (pregnant and under 5) at time t
$R_h(t)$	Number of recovered humans (pregnant and under 5) at time t
$S_m(t)$	Number of susceptible mosquitoes at time t
$E_m(t)$	Number of exposed mosquitoes at time t
$I_m(t)$	Number of infectious mosquitoes at time t
$N_h(t)$	Total number of individuals (pregnant and under 5) at time t
$N_{hw}(t)$	Total number of pregnant women at time t
$N_m(t)$	Total mosquito population at time t

Table 3.2: Prevention and control variables in the model

Symbol	Description
$u_1(t)$	Preventive measure using insecticide treated bed nets (ITNs)
$u_2(t)$	The control effort on treatment of infectious individuals
$u_3(t)$	Preventing measure using indoor residual spraying (IRS)
$u_4(t)$	Preventive measure using intermittent preventive treatment for pregnant women (IPTp)
p	Rate constant due to use of indoor residual spraying
τ	Rate constant due to use of treatment effort
a	Rate constant due to use of insecticide treated bed nets

Table 3.3: Description of parameter variables of the malaria model

Parameter	Description
ϕ	Mosquito contact rate with human
ϵ	Mosquito biting rate
β	Probability of human getting infected
λ	Probability of a mosquito getting infected
μ_h	Per capita natural death rate of humans
μ_m	Per capita natural death rate of mosquitoes
ψ	Per capita rate of loss of immunity by recovered individuals
α_h	Humans progression rate from exposed to infected
α_m	Mosquitoes progression rate from exposed to infected
Λ_h	Recruitment rate of human by birth and by getting pregnant
Λ_m	Recruitment of mosquitoes by birth
δ_h	Per capita disease induced death rate for humans (pregnant and under 5)
b	Proportion of spontaneous individual recovery
λ_h	Force of infection for susceptible humans (pregnant and under 5) to exposed individuals
λ_{hw}	Force of infection for susceptible pregnant humans to exposed individuals
λ_m	Force of infection for susceptible mosquitoes to exposed mosquitoes

Putting the above formulations and assumptions together gives the following vector-host model (Figure 3.1).

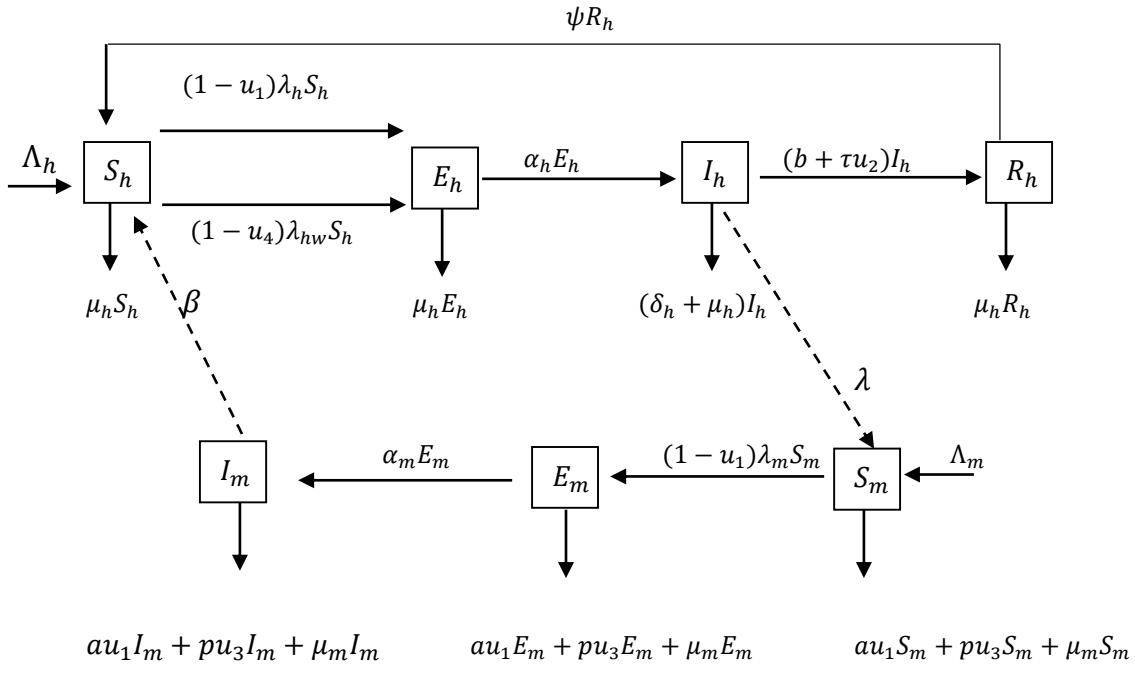


Figure 3.1: Malaria model with interventions

The following systems of non-linear differential equations describing the dynamics of malaria in human and mosquito populations together with interventions

$$\frac{dS_h}{dt} = \Lambda_h + \psi R_h - (1-u_1)\lambda_h S_h - (1-u_4)\lambda_{hw} S_h - \mu_h S_h$$

$$\frac{dE_h}{dt} = (1-u_1)\lambda_h S_h + (1-u_4)\lambda_{hw} S_h - (\alpha_h + \mu_h)E_h$$

$$\frac{dI_h}{dt} = \alpha_h E_h - (\delta_h + \mu_h)I_h - (b+\tau u_2)I_h$$

$$\frac{dR_h}{dt} = (b+\tau u_2)I_h - (\psi + \mu_h)R_h$$

$$\frac{dS_m}{dt} = \Lambda_m - (1-u_1)\lambda_m S_m - (\mu_m + au_1 + pu_3)S_m$$

$$\frac{dE_m}{dt} = (1-u_1)\lambda_m S_m - \alpha_m E_m - (\mu_m + au_1 + pu_3)E_m$$

$$\frac{dI_m}{dt} = \alpha_m E_m - (\mu_m + au_1 + pu_3)I_m.$$

(3.1)

3.3 Analysis of the Malaria Model with Intervention Strategies

We will assume that the control parameters are constant so as to determine the basic reproduction number, steady states and their stability as well as the bifurcation analysis. We describe the basic properties of the formulated malaria model with control strategies through mathematical analysis of the model. The model is analyzed to check if malaria disease can be controlled (eliminated). First, we determine the invariant region to check whether the SEIR-SEI malaria model is in a biologically feasible region for both human and mosquito populations and showing that all solutions of equation (3.1) are positive for all $t \geq 0$ and are attracted in that region. Then existence of disease free equilibrium points, followed by the derivation of the reproduction number. Stability analysis of the disease free equilibrium is done (local and global). Establishing for the existence of the endemic equilibrium points is done together with the local and global stability of the endemic equilibrium point. Lastly, sensitivity analysis of the reproductive number is also done.

3.3.1 Positive Invariant Region

The total population sizes are $N_h = S_h + E_h + I_h + R_h$ and $N_m = S_m + E_m + I_m$ with their differential equations

$$\frac{N_h}{dt} = \frac{S_h}{dt} + \frac{E_h}{dt} + \frac{I_h}{dt} + \frac{R_h}{dt} = \Lambda_h - \delta_h I_h - \mu_h N_h,$$

(3.2)

$$\frac{N_m}{dt} = \frac{S_m}{dt} + \frac{E_m}{dt} + \frac{I_m}{dt} = \Lambda_m - \mu_m N_m - au_1 N_m - pu_3 N_m.$$

(3.3)

The Theorem below shows how the positive invariant region can be obtained

Theorem 3.1: The solutions of the system (3.1) are feasible for all $t > 0$ if they enter the invariant region $D = D_h \times D_m$

Proof:

Let $D_h = (S_h, E_h, I_h, R_h, S_m, E_m, I_m) \in R_+^7$ be any solution of the system (3.1) with non-negative initial conditions.

Assuming the disease does not kill ($\delta_h = 0$) or in the absence of the disease (malaria), that is, $I_h = 0$, equation (3.2) becomes

$$\frac{dN_h}{dt} \leq \Lambda_h - \mu_h N_h$$

$$\frac{dN_h}{dt} + \mu_h N_h \leq \Lambda_h. \tag{3.4}$$

Using the differential equation of the form $y' + p(t)y = q(t)$ we have $p(t) = \mu_h$ and $q(t) = \Lambda_h$. Therefore the integrating factor (IF) for (3.4) is given by

$$IF = e^{\int p(t)dt} = e^{\int \mu_h dt} = e^{\mu_h t}.$$

Multiplying both sides of equation (3.4) by $e^{\mu_h t}$ give

$$e^{\mu_h t}\frac{dN_h}{dt} + \mu_h N_h e^{\mu_h t} \leq e^{\mu_h t}\Lambda_h$$

$$\frac{d}{dt}(N_h e^{\mu_h t}) \leq e^{\mu_h t}\Lambda_h. \tag{3.5}$$

Integrating both sides of equation (3.5) we have

$$N_h e^{\mu_h t} = \frac{\Lambda_h}{\mu_h t} e^{\mu_h t} + c$$

where c is the constant of integration

$$N_h = \frac{\Lambda_h}{\mu_h t} e^{\mu_h t} \times \frac{1}{e^{\mu_h t}} + c e^{\mu_h t}$$

$$N_h = \frac{\Lambda_h}{\mu_h t} + ce^{-\mu_h t}.$$

Using the initial conditions at $t = 0$, $N_h(0)$

$$N_h(0) \leq \frac{\Lambda_h}{\mu_h t} + c \rightarrow N_h(0) - \frac{\Lambda_h}{\mu_h t} \leq c$$

$$N_h \leq \frac{\Lambda_h}{\mu_h} + \left(N_h(0) - \frac{\Lambda_h}{\mu_h}\right) e^{-\mu_h t}.$$

(3.6)

Using the theorem of differential inequality (Birkhoff & Rota, 1982), we obtain

$$0 \leq N_h \leq \frac{\Lambda_h}{\mu_h} \; as \; t \rightarrow \infty.$$

(3.7)

Therefore, as $t \rightarrow \infty$ in (3.6), the human population N_h approaches $K = \frac{\Lambda_h}{\mu_h}$ (that is, $N_h \rightarrow K = \frac{\Lambda_h}{\mu_h}$), the parameter $K = \frac{\Lambda_h}{\mu_h}$ is usually called the carrying capacity (Namawejje, 2011).

Consider the feasible region $D = D_h \cup D_m \subset \mathbb{R}_+^4 \times \mathbb{R}_+^3$

Hence all feasible solutions set of the human population of the model (3.1) enters the region

$$\mathbb{R}_+^4 : S_h + E_h + I_h + R_h$$

$$D_h = \left\{(S_h, E_h, I_h, R_h) \in R_+^4 : S_h > 0, E_h \geq 0, I_h \geq 0, R_h \geq 0, N_h \leq \frac{\Lambda_h}{\mu_h}\right\}.$$

Similarly the feasible solutions set for the model (3.1) is given by

$$\mathbb{R}_+^3 : S_m + E_m + I_m$$

$$D_m = \left\{(S_m, E_m, I_m) \in R_+^3 : S_m > 0, E_m \geq 0, I_m \geq 0, N_m \leq \frac{\Lambda_m}{\mu_m + au_1 + pu_3}\right\}.$$

Therefore, the feasible solutions set for the model (3.1) is given by

$$D = \left\{(S_h, E_h, I_h, R_h, S_m, E_m, I_m) \in R_+^7 : (S_h, S_m) > 0, (E_h, I_h, R_h, E_m, I_m) \geq 0; N_h \leq \frac{\Lambda_h}{\mu_h}; N_m \leq \frac{\Lambda_m}{\mu_m + au_1 + pu_3}\right\}.$$

Therefore, the region D is positively-invariant (i.e. solution remain positive for all times, (t) and the model (3.1) is biologically, epidemiologically meaningful and mathematically well-posed in the domain D. Therefore in this model it is sufficient to consider the dynamics of the flow generated by the model (3.1). In addition, the usual existence, uniqueness and continuation of results holds for the system

3.3.2 The Positivity of State Variables

It is important to prove that all the state variables remain non-negative for all $t \geq 0$ for the system (3.1).

Theorem 3.2: Let the initial data be $\{(S_h(0), S_m(0)) > 0, (E_h(0), I_h(0), R_h(0), E_m(0), I_m(0)) \geq 0\} \in D$. Then the solution set $\{S_h, E_h, I_h, R_h, S_m, E_m, I_m\}(t)$ of the system (1) is positive for all $t > 0$.

Proof:

From the first equation in the model (3.1), we have

$$\frac{dS_h}{dt} = \Lambda_h + \psi R_h - \mu_h S_h - (1-u_1)\lambda_h S_h - (1-u_4)\lambda_{hw} S_h$$
$$\geq -\mu_h S_h - (1-u_1)\lambda_h S_h - (1-u_4)\lambda_{hw} S_h$$

$$\frac{dS_h}{dt} \geq -(\mu_h + (1-u_1)\lambda_h + (1-u_4)\lambda_{hw})S_h.$$

Using separation of variables and integrating both sides gives

$$\frac{1}{S_h} dS_h \geq -\int (\mu_h + (1-u_1)\lambda_h + (1-u_4)\lambda_{hw} S_h) dt$$

$$lnS_h \geq -(\mu_h + (1-u_1)\lambda_h + (1-u_4)\lambda_{hw} S_h)t + c$$

$$S_h(t) = e^{[-(\mu_h + (1-u_1)\lambda_h + (1-u_4)\lambda_{hw} S_h)t + c]}$$

$$S_h(t) = e^{-(\mu_h+(1-u_1)\lambda_h+(1-u_4)\lambda_{hw}S_h)t} \times e^c$$

$$S_h(t) = e^{-(\mu_h+(1-u_1)\lambda_h+(1-u_4)\lambda_{hw}S_h)t} \times K$$

$$S_h(t) = Ke^{-(\mu_h+(1-u_1)\lambda_h+(1-u_4)\lambda_{hw}S_h)t}$$

$$S_h(t) \geq Ke^{-(\mu_h+(1-u_1)\lambda_h+(1-u_4)\lambda_{hw}S_h)t}.$$

Using the initial conditions: $t = 0, S_h(0) \geq K$

$$\Longrightarrow S_h(t) \geq S_h(0)e^{-(\mu_h+(1-u_1)\lambda_h+(1-u_4)\lambda_{hw}S_h)t} \geq 0.$$

Therefore

$$S_h(t) \geq S_h(0)e^{-(\mu_h+(1-u_1)\lambda_h+(1-u_4)\lambda_{hw}S_h)t} \geq 0.$$

From the second equation,

$$\frac{dE_h}{dt} = (1-u_1)\lambda_h S_h + (1-u_4)\lambda_{hw}S_h - \mu_h E_h - \alpha_h E_h$$

$$\frac{dE_h}{dt} = (1-u_1)\lambda_h S_h + (1-u_4)\lambda_{hw}S_h - \mu_h E_h - \alpha_h E_h \geq -(\mu_h + \alpha_h)E_h$$

$$\int \frac{1}{E_h} dE_h \geq \int -(\mu_h + \alpha_h)dt$$

$$\ln(E_h) \geq -(\mu_h + \alpha_h)t + c$$

$$\Longrightarrow E_h(t) = e^{-(\mu_h+\alpha_h)t+c}$$

$$E_h(t) = Ke^{-(\mu_h+\alpha_h)t}$$

where $K = e^c$.

Therefore

$$E_h \geq E_h(0)e^{-(\mu_h+\alpha_h)t} \geq 0.$$

From the third equation we have

$$\frac{dI_h}{dt} = \alpha_h E_h - (\delta_h + \mu_h)I_h - (b + \tau u_2)I_h$$

$$\frac{dI_h}{dt} = \alpha_h E_h - (\delta_h + \mu_h)I_h - (b + \tau u_2)I_h \geq -[(\delta_h + \mu_h)I_h + (b + \tau u_2)]I_h$$

$$\frac{dI_h}{dt} \geq -[(\delta_h + \mu_h)I_h + (b + \tau u_2)]I_h.$$

Using separation of variables and integrating both sides gives

$$\int \frac{1}{I + h} dI_h \geq \int -\big((\delta_h + \mu_h)I_h + (b + \tau u_2)\big)dt$$

$$\ln(I_h) \geq -\big((\delta_h + \mu_h)I_h + (b + \tau u_2)\big)t + c$$

$$\Longrightarrow I_h = e^{-[((\delta_h+\mu_h)I_h+(b+\tau u_2))t+c]}$$

$$I_h \geq Ke^{-[((\delta_h+\mu_h)I_h+(b+\tau u_2))t]}$$

$$I_h \geq I_h(0)e^{-[((\delta_h+\mu_h)I_h+(b+\tau u_2))t]}$$

where $K = I_h(0)$.

$$I_h \geq I_h(0)e^{-[((\delta_h+\mu_h)I_h+(b+\tau u_2))t]} \geq 0.$$

Similarly, it can be shown that $S_m > 0$, $E_m > 0$, and $I_m > 0$ for all $t > 0$.

Now it has been established that our model has both the invariant and positivity of solutions, we can move on to determine the existence of disease free equilibrium point which will assist in calculating the basic reproduction number using the next generation operator approach.

3.3.3 Existence and Stability of Steady-state solutions

In this, we assume that the control parameters are constant and determine the basic reproduction number, the steady state solutions or equilibrium points and their stabilities as well as the bifurcation behavior of the system.

The $E = (S_h^*, E_h^*, I_h^*, R_h^*, S_m^*, E_m^*, I_m^*)$ is the steady-state of the system (3.1) which can be calculated by setting the right hand side of the model (3.1) to zero, giving us the following

$$\Lambda_h + \psi R_h - (1-u_1)\lambda_h S_h - (1-u_4)\lambda_{hw} S_h - \mu_h S_h = 0$$

$$(1-u_1)\lambda_h S_h + (1-u_4)\lambda_{hw} S_h - (\alpha_h + \mu_h)E_h = 0$$

$$\alpha_h E_h - (\delta_h + \mu_h)I_h - (b + \tau u_2)I_h = 0$$

$$(b + \tau u_2)I_h - (\psi + \mu_h)R_h = 0$$

$$\Lambda_m - (1-u_1)\lambda_m S_m - (\mu_m + au_1 + pu_3)S_m = 0$$

$$(1-u_1)\lambda_m S_m - \alpha_m E_m - (\mu_m + au_1 + pu_3)E_m = 0$$

$$\alpha_m E_m - (\mu_m + au_1 + pu_3)I_m = 0.$$

(3.8)

3.3.4 The Existence of the Trivial Equilibrium point

For as long as the human recruitment term Λ_h and the mosquito recruitment term Λ_m are not zero, the population will not be extinct. This implies that there is no trivial equilibrium point, thus $(S_h^*, E_h^*, I_h^*, R_h^*, S_m^*, E_m^*, I_m^*) \neq (0,0,0,0,0,0,0)$.

3.3.5 Disease Free Equilibrium, $\boldsymbol{E_0}$

Disease-free equilibrium points (DFE) are steady state solutions where there is no malaria in the human population or *Plasmodium* parasite in the mosquito population. In absence of the disease, it implies that (E_h, I_h, E_m, I_m) and $R_h = 0$ since there is no disease to recover from. Forces of infections are also equal to zero. We get

$$\Lambda_h - (\mu_h + (1-u_1)\lambda_h + (1-u_4)\lambda_{hw})S_h^* = 0$$

$$\Lambda_m - \big((1-u_1)\lambda_m + (\mu_m + au_1 + pu_3)\big)S_m^* = 0$$

(3.9)

which gives

$$S_h^* = \frac{\Lambda_h}{\mu_h}$$

$$S_m^* = \frac{\Lambda_m}{(\mu_m + au_1 + pu_3)}.$$

The disease-free equilibrium point of the malaria model (3.1) is given by,

$$E_0 = (S_h^*, E_h^*, I_h^*, R_h^*, S_m^*, E_m^*, I_m^*) = \left(\frac{\Lambda_h}{\mu_h}, 0,0,0, \frac{\Lambda_m}{(\mu_m + au_1 + pu_3)}, 0,0\right) \tag{3.10}$$

which represents the state in which there is no infection (in the absence of malaria) in the society.

3.3.6 The Basic Reproduction Number R_0

We use the next generation operator approach as described by Van den Driessche & Watmough (2002) to define the basic reproduction number, R_0 , as the number of secondary infections that one infectious individual would create over the duration of the infectious period, provided that everyone else is susceptible. Reproduction number R_0 is the threshold for many epidemiology models, it determines whether a disease can invade a population or not. When $R_0 < 1$, each infected individual produces on average less than one new infected individual, so we would expect the disease to die out. On the other hand, if $R_0 > 1$ each individual produces more than one new infected individual, so we would expect the disease to spread in the population. This means that the threshold quantity for eradicating the disease is to reduce the value of R_0 to value less than one. The basic reproduction number cannot be determined from the structure of the mathematical model alone, but depends on the definition of infected and uninfected compartments. Let us assume that there are n compartments of which the first m compartments correspond to infected individuals.

Let $\mathcal{F}_i$ be the rate of appearance of new infections in compartment, $V_i = V_i^- - V_i^+$, where V_i^+ is the rate of transfer of individuals into compartment i by all other means and V_i^- is the rate of transfer of individual out of the i^{th} compartment.

Rewriting the system (3.1) starting with the infected compartments for both populations; E_h, I_h, E_m, I_m also from the two populations, then the model system becomes:

$$\frac{dE_h}{dt} = \frac{(1-u_1)\beta\epsilon\phi S_h I_m}{N_h} + \frac{(1-u_4)\beta\epsilon\phi S_h I_m}{N_{hw}} - \mu_h E_h - \alpha_h E_h$$

$$\frac{dI_h}{dt} = \alpha_h E_h - (\delta_h + \mu_h) I_h - (b + \tau u_2) I_h$$

$$\frac{dE_m}{dt} = \frac{(1-u_1)\lambda\epsilon\phi I_h S_m}{N_h} - \alpha_m E_m - (\mu_m + a u_1 + p u_3) E_m$$

$$\frac{dI_m}{dt} = \alpha_m E_m - (\mu_m + a u_1 + p u_3) I_m$$

$$\frac{dS_h}{dt} = \Lambda_h + \psi R_h - \mu_h S_h - \frac{(1-u_1)\beta\epsilon\phi S_h I_m}{N_h} - \frac{(1-u_4)\beta\epsilon\phi S_h I_m}{N_{hw}}$$

$$\frac{dR_h}{dt} = (b + \tau u_2) I_h - \mu_h R_h - \psi R_h$$

$$\frac{dS_m}{dt} = \Lambda_m - \frac{(1-u_1)\lambda\epsilon\phi I_h S_m}{N_h} - (\mu_m + a u_1 + p u_3) S_m. \tag{3.11}$$

From the system (3.11), $\mathcal{F}_i$ and V_i are defined as:

$$\mathcal{F}_i = \begin{bmatrix} \frac{(1-u_1)\beta\epsilon\phi I_m S_h}{N_h} + \frac{(1-u_4)\beta\epsilon\phi S_h I_m}{N_{hw}} \\ 0 \\ \frac{(1-u_1)\lambda\epsilon\phi I_h S_m}{N_h} \\ 0 \end{bmatrix}$$

and

$$V_i = \begin{bmatrix} (\mu_h + \alpha_h) E_h \\ (\delta_h + \mu_h + b + \tau u_2) I_h - \alpha_h E_h \\ (\alpha_m + \mu_m + a u_1 + p u_3) E_m \\ (\mu_m + a u_1 + p u_3) I_m - \alpha_m E_m \end{bmatrix} \tag{3.12}$$

The square matrices $\mathcal{F}$ and V of order $(m \times m)$ is computed by obtaining the Jacobian matrices of $\mathcal{F}_i$ and V_i , where m is the number of infected classes, defined by $\mathcal{F} = \left[\frac{\partial \mathcal{F}_i}{\partial x_j}(x_0)\right]$ and $V = \left[\frac{\partial V_i}{\partial x_i}(x_0)\right]$ with $1 \leq i, j \leq m$, such that F is nonnegative, V is a nonsingular M-matrix and x_0 is the disease-free equilibrium point (DFE).

The partial derivatives of (3.12) with respect to (I_h, I_m) and the Jacobian matrix of $\mathcal{F}_i$

$$F = \begin{bmatrix} 0 & 0 & 0 & \frac{(1-u_1)\beta\epsilon\phi I_m S_h}{N_h} + \frac{(1-u_4)\beta\epsilon\phi S_h I_m}{N_{hw}} \\ 0 & 0 & 0 & 0 \\ 0 & \frac{(1-u_1)\lambda\epsilon\phi I_h S_m}{N_h} & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} \tag{3.13}$$

substituting the equilibrium points $S_h^* = \frac{\Lambda_h}{\mu_h}$, $S_m^* = \frac{\Lambda_m}{(\mu_m + au_1 + pu_3)}$, $N_h = \frac{\Lambda_h}{\mu_h}$ into the Jacobian matrix of $\mathcal{F}_i$ we have

$$F = \begin{bmatrix} 0 & 0 & 0 & (1-u_1)\beta\epsilon\phi + (1-u_4)\beta\epsilon\phi \\ 0 & 0 & 0 & 0 \\ 0 & \frac{(1-u_1)\lambda\epsilon\phi\Lambda_m\mu_h}{(\mu_m + au_1 + pu_3)\Lambda_h} & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}.$$

Similarly, the partial derivatives of (3.13) with respect to (E_h, I_h, E_m, I_m) and the Jacobian matrix of V_i is :

$$V = \begin{bmatrix} (\mu_h + \alpha_h) & 0 & 0 & 0 \\ \alpha_h & (\delta_h + \mu_h + b + \tau u_2) & 0 & 0 \\ 0 & 0 & \alpha_m + \mu_m + au_1 + pu_3 & 0 \\ 0 & 0 & -\alpha_m & \mu_m + au_1 + pu_3 \end{bmatrix}. \tag{3.14}$$

The inverse of V is given as

$$V^{-1} = \begin{bmatrix} \frac{1}{(\mu_h + \alpha_h)} & 0 & 0 & 0 \\ \frac{\alpha_h}{(\mu_h + \alpha_h)(\delta_h + \mu_h + b + \tau u_2)} & \frac{1}{(\delta_h + \mu_h + b + \tau u_2)} & 0 & 0 \\ 0 & 0 & \frac{1}{\alpha_m + \mu_m + au_1 + pu_3} & 0 \\ 0 & 0 & \frac{\alpha_m}{(\alpha_m + \mu_m + au_1 + pu_3)(\mu_m + au_1 + pu_3)} & \frac{1}{\mu_m + au_1 + pu_3} \end{bmatrix}. \tag{3.15}$$

We compute the matrix FV^{-1}

$$\begin{bmatrix} 0 & 0 & 0 & (1-u_1)\beta\epsilon\phi + (1-u_4)\beta\epsilon\phi \\ 0 & 0 & 0 & 0 \\ 0 & \frac{(1-u_1)\lambda\epsilon\phi\Lambda_m\mu_m}{(\mu_m + au_1 + pu_3)\Lambda_h} & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

$$\times \begin{bmatrix} \frac{1}{(\mu_h + \alpha_h)} & 0 & 0 & 0 \\ \frac{\alpha_h}{(\mu_h + \alpha_h)(\delta_h + \mu_h + b + \tau u_2)} & \frac{1}{(\delta_h + \mu_h + b + \tau u_2)} & \frac{1}{\alpha_m + \mu_m + au_1 + pu_3} & 0 \\ 0 & 0 & \frac{\alpha_m}{(\alpha_m + \mu_m + au_1 + pu_3)(\mu_m + au_1 + pu_3)} & 0 \\ 0 & 0 & & \frac{1}{\mu_m + +au_1 + pu_3} \end{bmatrix}$$

$$FV^{-1} = \begin{bmatrix} 0 & 0 \\ 0 & 0 \\ \frac{\alpha_h(1-u_1)\lambda\epsilon\phi\Lambda_m\mu_h}{(\mu_m + au_1 + pu_3)(\mu_h + \alpha_h)(\delta_h + \mu_h + b + \tau u_2)\Lambda_h} & \frac{(1-u_1)\lambda\epsilon\phi\Lambda_m\mu_h}{(\mu_m + au_1 + pu_3)(\delta_h + \mu_h + b + \tau u_2)\Lambda_h} \\ 0 & 0 \end{bmatrix}$$

$$\times \begin{bmatrix} \frac{(1-u_1)\beta\epsilon\phi\alpha_m + (1-u_4)\beta\epsilon\phi\alpha_m}{(\alpha_m + \mu_m + au_1 + pu_3)(\mu_m + au_1 + pu_3)} & \frac{(1-u_1)\beta\epsilon\phi + (1-u_4)\beta\epsilon\phi}{(\mu_m + au_1 + pu_3)} \\ 0 & 0 \\ 0 & 0 \\ 0 & 0 \end{bmatrix}$$

$$FV^{-1} = \begin{bmatrix} 0 & 0 & a & b \\ -\alpha_h & (b + \tau u_2 + \mu_h + \delta_h) & 0 & 0 \\ c & d & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} \tag{3.16}$$

where $a = \frac{(1-u_1)\beta\epsilon\phi\alpha_m + (1-u_4)\beta\epsilon\phi\alpha_m}{(\alpha_m + \mu_m + au_1 + pu_3)(\mu_m + au_1 + pu_3)}$, $b = \frac{(1-u_1)\beta\epsilon\phi + (1-u_4)\beta\epsilon\phi}{(\mu_m + au_1 + pu_3)}$,

$c = \frac{\alpha_h(1-u_1)\lambda\epsilon\phi\Lambda_m\mu_h}{(\mu_m + au_1 + pu_3)(\mu_h + \alpha_h)(\delta_h + \mu_h + b + \tau u_2)\Lambda_h}$, $d = \frac{(1-u_1)\lambda\epsilon\phi\Lambda_m\mu_h}{(\mu_m + au_1 + pu_3)(\delta_h + \mu_h + b + \tau u_2)\Lambda_h}$.

From (3.16), we can now calculate the eigenvalues to determine the basic reproduction number R_0 by taking the spectral radius (dominant eigenvalue) of the matrix FV^{-1}.

The eigenvalues of FV^{-1} are calculated as $J = [FV^{-1} - \lambda I]$, we have

$$J = \begin{bmatrix} 0-\lambda & 0 & a & b \\ 0 & 0-\lambda & 0 & 0 \\ c & d & 0-\lambda & 0 \\ 0 & 0 & 0 & 0-\lambda \end{bmatrix}.$$

Therefore $|J| = |FV^{-1} - \lambda I| = 0$, we have

$$|J| = \begin{vmatrix} 0-\lambda & 0 & a & b \\ 0 & 0-\lambda & 0 & 0 \\ c & d & 0-\lambda & 0 \\ 0 & 0 & 0 & 0-\lambda \end{vmatrix} = \begin{vmatrix} -\lambda & 0 & a & b \\ 0 & -\lambda & 0 & 0 \\ c & d & -\lambda & 0 \\ 0 & 0 & 0 & -\lambda \end{vmatrix} = 0$$

$$= -b\begin{vmatrix} 0 & -\lambda & 0 \\ c & d & -\lambda \\ 0 & 0 & 0 \end{vmatrix} - \lambda\begin{vmatrix} -\lambda & 0 & a \\ 0 & -\lambda & 0 \\ c & d & -\lambda \end{vmatrix} = -b(0) - \lambda(-\lambda^3 + \lambda ac) = 0$$

$$= \lambda^2(\lambda^2 - ac) = 0 \Rightarrow \lambda^2 = 0 \; or \; \lambda^2 - ac = 0$$

$$\Longrightarrow \lambda^2 = ac$$

$$\lambda = \pm\sqrt{ac}.$$

Therefore $\lambda_1 = 0, \lambda_2 = 0, \lambda_3 = \sqrt{ac}$ and $\lambda_4 = -\sqrt{ac}$.

From the four eigenvalues, the dominant eigenvalue of the matrix FV^{-1} is $\lambda = \sqrt{ac}$.

Therefore the basic reproduction number $R_0 = \sqrt{ac}$.

Hence

$$R_0$$

$$= \sqrt{\frac{\alpha_h(1-u_1)\lambda\epsilon\phi\Lambda_m\mu_h}{(\mu_m + au_1 + pu_3)(\mu_h + \alpha_h)(\delta_h + \mu_h + b + \tau u_2)\Lambda_h} \times \frac{(1-u_1)\beta\epsilon\phi\alpha_m + (1-u_4)\beta\epsilon\phi\alpha_m}{(\alpha_m + \mu_m + au_1 + pu_3)(\mu_m + au_1 + pu_3)}}$$

$$R_0 = \sqrt{\frac{\alpha_h(1-u_1)\lambda\epsilon\phi\Lambda_m\mu_h(1-u_1)\beta\epsilon\phi\alpha_m + \alpha_h(1-u_1)\lambda\epsilon\phi\Lambda_m\mu_h(1-u_4)\beta\epsilon\phi\alpha_m}{(\mu_m + au_1 + pu_3)(\mu_h + \alpha_h)(\delta_h + \mu_h + b + \tau u_2)\Lambda_h(\alpha_m + \mu_m + au_1 + pu_3)(\mu_m + au_1 + pu_3)}}$$

(3.17)

where

$\frac{\alpha_h}{\alpha_h + \mu_h}$ means the probability that a human will survive the exposed state to become infectious.

$\frac{\alpha_m}{\alpha_m + \mu_m + au_1 + pu_3}$ is the probability that a mosquito will survive the exposed state to become infectious.

$\frac{\alpha_m \lambda \epsilon \phi (1-u_1)}{(\mu_m + a u_1 + p u_3)(\alpha_m + \mu_m + a u_1 + p u_3)}$ is the number of humans that one mosquito infects during its infectious lifetime, provided all humans are susceptible.

$\frac{\beta \epsilon \phi (1-u_1) + \beta \epsilon \phi (1-u_4)}{(\mu_h + \alpha_h)(\delta_h + \mu_h + b + \tau u_2)}$ is the number of mosquitoes that one human infects during the duration of the infectious period, provided all mosquitoes are susceptible.

The threshold parameter R_0 can be defined as square roots of the product of number of humans one mosquito infects during its infectious lifetime (R_{oh}) and number of mosquitoes one human infects during the duration of the infectious period (R_{om}) provided all humans and mosquitoes are susceptible.

$$R_0 = \sqrt{R_{oh} \times R_{om}}$$

$$R_0 = \sqrt{\frac{(1-u_1)\beta \epsilon \phi \alpha_h \mu_h + (1-u_4)\beta \epsilon \phi \alpha_h \mu_h}{(\mu_h + \alpha_h)(\delta_h + \mu_h + b + \tau u_2)\Lambda_h} \times \frac{\alpha_m (1-u_1)\lambda \epsilon \phi \Lambda_m \mu_h}{(\mu_m + a u_1 + p u_3)^2 (\alpha_m + \mu_m + a u_1 + p u_3)}} \tag{3.18}$$

where

$$R_{oh} = \frac{(1-u_1)\beta \epsilon \phi \alpha_h \mu_h + (1-u_4)\beta \epsilon \phi \alpha_h \mu_h}{(\mu_h + \alpha_h)(\delta_h + \mu_h + b + \tau u_2)\Lambda_h}$$

and

$$R_{om} = \frac{\alpha_m (1-u_1)\lambda \epsilon \phi \Lambda_m \mu_h}{(\mu_m + a u_1 + p u_3)^2 (\alpha_m + \mu_m + a u_1 + p u_3)}$$

where

$\frac{\alpha_h (1-u_1)\lambda \epsilon \phi \Lambda_m \mu_h}{(\delta_h + \mu_h + b + \tau u_2)\Lambda_h}$ is the number of latent infections produced by a typical infectious individual during the mean infectious period.

$\frac{(1-u_1)\beta\epsilon\phi\alpha_m+(1-u_4)\beta\epsilon\phi\alpha_m}{(\mu_m+au_1+pu_3)^2(\alpha_m+\mu_m+au_1+pu_3)}$ is the number of latent infections produced by a typical infectious mosquitoes during the mean infectious period.

The parameter ϵ and ϕ appear in both expressions because the mosquito biting rate (ϵ) and mosquito contact rate with human (ϕ) controls the transmission from humans to mosquitoes and from mosquitoes to humans.

The basic reproduction number can be used to determine the local stability of the disease free equilibrium point.

3.3.7 Local Stability Analysis of Disease Free Equilibrium

The local stability of the DFE, E_0, can be analyzed using the Jacobian matrix of the malaria model (3.1) at the disease free equilibrium point. We state and prove the following theorem (Van den Driessche & Watmough, 2002) to establish the stability of disease free equilibrium point.

Theorem 3.3

The disease free equilibrium point for system (3.1) is locally asymptotically stable if $R_0 < 1$.

Proof:

The Jacobian matrix (J) of the malaria model (3.1) with $S_h = N_h - (E_h + I_h + R_h)$ and $S_m = N_m - (E_m + I_m)$ at the disease-free equilibrium point is given by

$$\begin{bmatrix} 0 & & & & \\ -(\alpha_h+\mu_h) & -(\delta_h+\mu_h+b+\tau u_2) & 0 & 0 & (1-u_1)\beta\epsilon\phi+(1-u_4)\beta\epsilon\phi \\ \alpha_h & (b+\tau u_2) & 0 & 0 & 0 \\ 0 & \frac{(1-u_1)\lambda\epsilon\phi\Lambda_m\mu_h}{(\mu_m+au_1+pu_3)\Lambda_h} & -(\psi+\mu_h) & 0 & 0 \\ 0 & & 0 & -(\alpha_m+\mu_m+au_1+pu_3) & 0 \\ 0 & & 0 & \alpha_m & -(\mu_m+au_1+pu_3) \end{bmatrix}.$$

The eigenvalues of the Jacobian matrix are the solutions of the characteristic equation

$$|J - \lambda I| = 0.$$

That is

$$\begin{bmatrix} -(\alpha_h + \mu_h + \lambda) & 0 & 0 & 0 & (1-u_1)\beta\epsilon\phi + (1-u_4)\beta\epsilon\phi \\ \alpha_h & -(\delta_h + \mu_h + b + \tau u_2 + \lambda) & 0 & 0 & 0 \\ 0 & (b + \tau u_2) & -(\psi + \mu_h + \lambda) & 0 & 0 \\ 0 & \frac{(1-u_1)\lambda\epsilon\phi\Lambda_m\mu_h}{(\mu_m + au_1 + pu_3)\Lambda_h} & 0 & -(\alpha_m + \mu_m + au_1 + pu_3 + \lambda) & 0 \\ 0 & 0 & 0 & \alpha_m & -(\mu_m + au_1 + pu_3 + \lambda) \end{bmatrix}$$

$= 0$

The third column has diagonal entry, therefore one of the eigenvalues of the Jacobian matrix is $-(\psi + \mu_h)$.

The remaining eigenvalues can be obtained as follows:

$$\begin{vmatrix} -(\alpha_h + \mu_h + \lambda) & 0 & 0 & (1-u_1)\beta\epsilon\phi + (1-u_4)\beta\epsilon\phi \\ \alpha_h & -(\delta_h + \mu_h + b + \tau u_2 + \lambda) & 0 & 0 \\ 0 & \frac{(1-u_1)\lambda\epsilon\phi\Lambda_m\mu_h}{(\mu_m + au_1 + pu_3)\Lambda_h} & -(\alpha_m + \mu_m + au_1 + pu_3 + \lambda) & 0 \\ 0 & 0 & \alpha_m & -(\mu_m + au_1 + pu_3 + \lambda) \end{vmatrix}$$

$= 0$

$$(\alpha_h + \mu_h + \lambda)(\delta_h + \mu_h + b + \tau u_2 + \lambda)(\alpha_m + \mu_m + au_1 + pu_3 + \lambda)(\mu_m + au_1 + pu_3 + \lambda) - \frac{(1-u_1)^2\lambda\epsilon^2\phi^2\Lambda_m\mu_h\alpha_m\beta\alpha_h + (1-u_4)(1-u_1)\lambda\epsilon^2\phi^2\Lambda_m\mu_h\alpha_m\beta\alpha_h}{(\mu_m + au_1 + pu_3)\Lambda_m} = 0. \quad (3.19)$$

To simplify the equation, we let $A_1 = (\mu_m + au_1 + pu_3), A_2 = (\alpha_m + \mu_m + au_1 + pu_3), A_3 = (\delta_h + \mu_h + b + \tau u_2), A_4 = (\alpha_h + \mu_h)$ and

$$Q = \frac{(1-u_1)^2\lambda\epsilon^2\phi^2\Lambda_m\mu_h\alpha_m\beta\alpha_h + +(1-u_4)(1-u_1)\lambda\epsilon^2\phi^2\Lambda_m\mu_h\alpha_m\beta\alpha_h}{(\mu_m + au_1 + pu_3)\Lambda_m}$$

This implies that

$$(\lambda + A_1)(\lambda + A_2)(\lambda + A_3)(\lambda + A_4) - Q = 0$$

$$\lambda^4 + B_1\lambda^3 + B_2\lambda^2 + B_3\lambda + B_4 = 0$$

(3.20)

where

$$B_1 = A_4 + A_3 + A_2 + A_1$$

$$B_2 = A_4(A_3 + A_2 + A_1) + A_3(A_2 + A_1) + A_1A_2$$

$$B_3 = A_4A_3A_2 + A_4A_3A_1 + A_4A_2A_1 + A_3A_2A_1$$

$$B_4 = A_4A_3A_2A_1 - Q.$$

(3.21)

The expression of R_0 can be written in terms of A_i

$$R_0^2 = \frac{\alpha_h\alpha_m\Lambda_m\mu_h(1-u_1)^2\phi^2\epsilon^2\beta\lambda + +(1-u_4)\lambda\epsilon^2\phi^2\Lambda_m\mu_h\alpha_m\beta\alpha_h}{\Lambda_hA_4A_3A_2A_1^2}$$

(3.22)

Routh - Hurwitz Criteria is applied to equation (3.20) to determine whether all roots of the polynomial (3.20) have negative real parts (Oduro *et al.*, 2015).

Lemma 3.1 (Routh - Hurwitz Criteria): *The roots of the characteristic equation has a negative real parts if and only if all the principal diagonal minors of the Hurwitz matrix provided* $B_i > 0$

For the characteristic polynomial, when $n = 4$*, the Routh-Hurwitz criteria as described by Flores (2011) are*

$$B_1 > 0, B_2 > 0, B_3 > 0, B_4 > 0$$

$$det(H_1) = B_1 > 0$$

$$det(H_2) = \begin{pmatrix} B_1 & 1 \\ 0 & B_2 \end{pmatrix} = B_1B_2 > 0$$

$$det(H_3) = \begin{pmatrix} B_1 & 1 & 0 \\ B_3 & B_2 & B_1 \\ 0 & 0 & B_3 \end{pmatrix} = B_1B_2B_3 - B_3^2 > 0 \Longrightarrow B_1B_2 - B_3 > 0$$

$$det(H_4) = \begin{pmatrix} B_1 & 1 & 0 & 0 \\ B_3 & B_2 & B_1 & 1 \\ 0 & B_4 & B_3 & B_2 \\ 0 & 0 & 0 & B_4 \end{pmatrix} = B_3(B_2B_1 - B_3) - B_4B_1^2 > 0.$$

We now show that all determinants of Hurwitz matrices are positive, which means that all the Eigen values of the Jacobian (3.20) have negative real parts implying that DFE point is stable

$$\det(H_1) = B_1 = A_4 + A_3 + A_2 + A_1 > 0$$

$$\det(H_2) = B_1B_2$$

$$= 3A_4A_3(A_1 + A_2) + 3A_2A_1(A_4 + A_3) + A_4^2(A_3 + A_2 + A_1) + A_3^2(A_4 + A_2 + A_1) + A_2^2(A_4 + A_3 + A_1) + A_1^2(A_4 + A_3 + A_2) > 0$$

$$\det(H_4) = B_3(B_2B_1 - B_3) - B_4B_1^2$$

$$= B_3C + QB_1^2 - A_4A_3A_2A_1B_1^2 > 0$$

where $C = B_2B_1 - B_3$.

This means that all determinants of the Hurwitz matrices are positive. Hence all the eigenvalues of the Jacobian have negative real part, implying that the DFE point is (at least) locally stable($R_0 < 1$).

Conversely, if $R_0 > 1$ it implies that $B_4 < 0$, and since the remaining coefficients ($B_1, B_2\ and\ B_3$) of the polynomial are positive then all the roots of this polynomial cannot have negative real parts. Hence, the DFE point is unstable ($R_0 > 1$).

3.3.8 Global Stability Analysis of the Disease Free Equilibrium Point

Theorem 3.4. The DFE, E_0, of system of equations (3.1) is globally asymptotically stable if $R_0 < 1$.

Proof:

We consider the following Lyapunov function

$$L = c_1E_h + c_2I_h + c_3E_m + c_4I_m$$

Where $c_1 = \frac{\alpha_h}{(\mu_m+au_1+pu_3)(\alpha_h+\mu_h)(b+\tau u_2+\delta_h+\mu_h)}$, $c_2 = \frac{1}{(\mu_m+au_1+pu_3)(b+\tau u_2+\delta_h+\mu_h)}$,

$c_3 = \frac{1}{(1-u_1)\epsilon\phi\lambda\Lambda_m}$, $c_4 = \frac{\alpha_m+\mu_m+au_1+pu_3}{(1-u_1)\epsilon\phi\lambda\Lambda_m\alpha_m}$.

Computing the derivative of L along the solution of the system of differential equation (3.1)

$$\begin{aligned}\dot{L} = \frac{\alpha_h}{(\mu_m + au_1 + pu_3)(\alpha_h + \mu_h)(b + \tau u_2 + \delta_h + \mu_h)}&[(1-u_1)\lambda_h S_h + (1-u_4)\lambda_{hw}S_h \\ &- (\alpha_h + \mu_h)E_h] \\ &+ \frac{1}{(\mu_m + au_1 + pu_3)(b + \tau u_2 + \delta_h + \mu_h)}[\alpha_h E_h - (\delta_h + \mu_h)I_h - (b + \tau u_2)I_h] \\ &+ \frac{1}{(1-u_1)\epsilon\phi\lambda\Lambda_m}[(1-u_1)\lambda_m S_m - \alpha_m E_m - (\mu_m + au_1 + pu_3)E_m] \\ &+ \frac{\alpha_m + \mu_m + au_1 + pu_3}{(1-u_1)\epsilon\phi\lambda\Lambda_m\alpha_m}[\alpha_m E_m - (\mu_m + au_1 + pu_3)I_m]\end{aligned}$$

$$\begin{aligned}\dot{L} = &\left[\frac{\alpha_h[(1-u_1)\lambda_h S_h + (1-u_4)\lambda_{hw}S_h - (\alpha_h + \mu_h)]}{(\mu_m + au_1 + pu_3)(\alpha_h + \mu_h)(b + \tau u_2 + \delta_h + \mu_h)}\right]E_h \\ &+ \left[\frac{[\alpha_h E_h - (\delta_h + \mu_h)I_h - (b + \tau u_2)]}{(\mu_m + au_1 + pu_3)(b + \tau u_2 + \delta_h + \mu_h)}\right]I_h \\ &+ \left[\frac{[(1-u_1)\lambda_m S_m - \alpha_m E_m - (\mu_m + au_1 + pu_3)]}{(1-u_1)\epsilon\phi\lambda\Lambda_m}\right]E_m \\ &+ \left[\frac{(\alpha_m + \mu_m + au_1 + pu_3)(\mu_m + au_1 + pu_3)}{(1-u_1)\epsilon\phi\lambda\Lambda_m\alpha_m}\right]I_m\end{aligned}$$

$$\begin{aligned}&\dot{L} \\ &= \frac{(\alpha_m + \mu_m + au_1 + pu_3)(\mu_m + au_1 + pu_3 + \delta_h)}{(1-u_1)\epsilon\phi\lambda\Lambda_m\alpha_m} \\ &\times \left[\frac{\alpha_h(1-u_1)\lambda\epsilon\phi\Lambda_m\mu_h(1-u_1)\beta\epsilon\phi\alpha_m + \alpha_h(1-u_1)\lambda\epsilon\phi\Lambda_m\mu_h(1-u_4)\beta\epsilon\phi\alpha_m}{(\mu_m + au_1 + pu_3)(\mu_h + \alpha_h)(\delta_h + \mu_h + b + \tau u_2)\Lambda_h(\alpha_m + \mu_m + au_1 + pu_3)(\mu_m + au_1 + pu_3)}\right. \\ &\left. - 1\right]I_h\end{aligned}$$

$$\dot{L} = \frac{(\alpha_m + \mu_m + au_1 + pu_3)(\mu_m + au_1 + pu_3 + \delta_h)}{(1-u_1)\epsilon\phi\lambda\Lambda_m\alpha_m}[R_0 - 1]I_h \leq 0 \; if \; and \; only \; if \; R_0 \leq 1.$$

Thus we have established that $\dot{L} \leq 0$ if $R_0 < 1$ and the equality $\dot{L} = 0$ hold if and only if $R_0 = 1$ and $E_h = I_h = E_m = I_m = 0$. If $R_0 > 1$ then $\dot{L} > 0$ when $S_h(t)$ and $S_m(t)$ is

sufficiently close to $\frac{\Lambda_h}{\mu_h}$ and $\frac{\Lambda_m}{\mu_m+au_1+pu_3}$ respectively except when $E_h = I_h = E_m = I_m = 0$.

On the boundary when $E_h = I_h = E_m = I_m = 0$; $\dot{N}_h(t) = \Lambda_h - \mu_h N_h$ and $\dot{N}_m(t) = \Lambda_m - (\mu_m + au_1 + pu_3)$ and $N_h(t) \longrightarrow \frac{\Lambda_h}{\mu_h}$, $N_m(t) \longrightarrow \frac{\Lambda_m}{\mu_m+au_1+pu_3}$ as $t \longrightarrow \infty$.

Therefore the largest compact invariant $D = \{(S_h, E_h, I_h, R_h, S_m, E_m, I_m) \in R_+^7 : \dot{L} = 0\}$ when $R_0 < 1$ is the singleton $\{E_0\}$. By LaSalle's invariant principle (LaSalle, 1976), E_0 is globally asymptotically stable.

3.3.9 Existence and Stability Analysis of the Endemic Equilibrium Point, E_1

Endemic equilibrium points are steady state solutions where the disease persists in the population (all the state variables are positive). That is, malaria infection will persists in the population and the endemic equilibrium (E_1) of the model is given by

$$E_1 = (S_h^{**}, E_h^{**}, I_h^{**}, R_h^{**}, S_m^{**}, E_m^{**}, I_m^{**}) \tag{3.23}$$

where $(S_h^{**}, E_h^{**}, I_h^{**}, R_h^{**}, S_m^{**}, E_m^{**}, I_m^{**}) > 0$.

To derive the E_1, we have to solve model (3.1) by equating it to zero

$$\Lambda_h + \psi R_h - \frac{(1-u_1)\beta\epsilon\phi I_m S_h}{N_h} - \frac{(1-u_4)\beta\epsilon\phi I_m S_h}{N_{hw}} - \mu_h S_h = 0$$

$$\frac{(1-u_1)\beta\epsilon\phi I_m S_h}{N_h} + \frac{(1-u_4)\beta\epsilon\phi I_m S_h}{N_{hw}} - (\alpha_h + \mu_h)E_h = 0$$

$$\alpha_h E_h - (\delta_h + \mu_h)I_h - (b + \tau u_2)I_h = 0$$

$$(b + \tau u_2)I_h - (\psi + \mu_h)R_h = 0$$

$$\Lambda_m - \frac{(1-u_1)\lambda\epsilon\phi I_h S_m}{N_h} - (\mu_m + au_1 + pu_3)S_m = 0$$

$$\frac{(1-u_1)\lambda\epsilon\phi I_h S_m}{N_h} - \alpha_m E_m - (\mu_m + au_1 + pu_3)E_m = 0$$

$$\alpha_m E_m - (\mu_m + au_1 + pu_3)I_m = 0.$$

(3.24)

Solving the second equation of (3.1) for E^{**} we have

$$\frac{(1-u_1)\beta\epsilon\phi S_h I_m}{N_h} + \frac{(1-u_4)\beta\epsilon\phi S_h I_m}{N_{hw}} - (\alpha_h + \mu_h)E_h = 0$$

$$E_h^{**} = \frac{(1-u_1)\beta\epsilon\phi I_m^{**} + (1-u_4)\beta\epsilon\phi I_m^{**}}{N_{hw}N_h(\mu_h + \alpha_h)} S_h^{**}.$$

From the sixth equation of the model (3.1) we have

$$\frac{(1-u_1)\lambda\epsilon\phi I_m S_m}{N_h} - \alpha_m E_m - (\mu_m + au_1 + pu_3)E_m = 0$$

$$E_m^{**} = \frac{(1-u_1)\alpha_h\lambda\epsilon\phi I_m^{**}}{N_h(\alpha_m + \mu_m + au_1 + pu_3)} S_m^{**}.$$

(3.25)

From the seventh equation we have

$$\alpha_m E_m - (\mu_m + au_1 + pu_3)I_m = 0$$

$$I_m^{**} = \frac{\alpha_m}{(\mu_m + au_1 + pu_3)} E_m^{**}.$$

(3.26)

Substituting equation (3.25) into equation (3.26) for I_m^{**} gives

$$I_m^{**} = \frac{\alpha_m(1-u_1)\lambda\epsilon\phi I_h^{**} S_m^{**}}{N_h(\mu_m + au_1 + pu_3)(\alpha_m + \mu_m + au_1 + pu_3)}.$$

(3.27)

From the fifth equation of the model (3.1) we have

$$\Lambda_h - \frac{(1-u_1)\lambda\epsilon\phi I_m S_m}{N_h} - (\mu_m + au_1 + pu_3)S_m = 0$$

$$S_m^{**} = \frac{\Lambda_m N_h}{(1-u_1)\lambda\epsilon\phi I_h^{**} + (\mu_m + au_1 + pu_3)N_h}.$$

(3.28)

Substituting (3.28) into equation (3.27) we have

$$I_m^{**} = \frac{\alpha_m \Lambda_m (1-u_1)\lambda\epsilon\phi I_h^{**}}{(\mu_m + au_1 + pu_3)(\alpha_m + \mu_m + au_1 + pu_3)(1-u_1)\lambda\epsilon\phi I_h^{**} + N_h(\mu_m + au_1 + pu_3)(\mu_m + au_1 + pu_3)(\alpha_m + \mu_m + au_1 + pu_3)}$$

$$I_m^{**} = \frac{(1-u_1)(\mu_m + au_1 + pu_3)R_{om} I_h^{**}}{(1-u_1)\lambda\epsilon\phi I_h^{**} + N_h(\mu_m + au_1 + pu_3)}.$$

(3.29)

From the second equation of model (3.1) we have

$$\frac{(1-u_1)\beta\epsilon\phi S_h I_m}{N_h} + \frac{(1-u_4)\beta\epsilon\phi S_h I_m}{N_{hw}} - (\alpha_h + \mu_h)E_h = 0.$$

Substituting equation (3.29) into the second equation we have

$$\frac{(1-u_1)^2(\mu_m + au_1 + pu_3)\beta\epsilon\phi R_{0m} I_h^{**} S_h^{**}}{N_h(1-u_1)\lambda\epsilon\phi I_h^{**} + N_h(\mu_m + au_1 + pu_3)} + \frac{(1-u_4)(1-u_1)(\mu_m + au_1 + pu_3)\beta\epsilon\phi R_{0m} I_h^{**} S_h^{**}}{N_{hw}(\mu_m + au_1 + pu_3) + (1-u_1)\lambda\epsilon\phi I_h^{**}} - (\alpha_h + \mu_h)E_h = 0.$$

(3.30)

From the third equation of model (3.1) we have

$$\alpha_h E_h - (\delta_h + \mu_h)I_h - (b + \tau u_2)I_h = 0$$

$$E_h^{**} = \frac{(\delta_h + \mu_h + b + \tau u_2)I_h^{**}}{\alpha_h}.$$

(3.31)

Substituting equation (3.31) into equation (3.30) we have

$$\frac{(1-u_1)^2(\mu_m+au_1+pu_3)\beta\epsilon\phi R_{0m}I_h^{**}S_h^{**}}{N_h(1-u_1)\lambda\epsilon\phi I_h^{**}+N_h(\mu_m+au_1+pu_3)} + \frac{(1-u_4)(1-u_1)(\mu_m+au_1+pu_3)\beta\epsilon\phi R_{0m}I_h^{**}S_h^{**}}{N_{hw}(\mu_m+au_1+pu_3)+(1-u_1)\lambda\epsilon\phi I_h^{**}} - \frac{(\alpha_h+\mu_h)(\delta_h+\mu_h+b+\tau u_2)I_h^{**}}{\alpha_h}=0$$

$$\begin{aligned} &N_{hw}\alpha_h(1-u_1)^2(\mu_m+au_1+pu_3)\beta\epsilon\phi R_{0m}I_h^{**}S_h^{**} \\ &\quad+N_h\alpha_h(1-u_4)(1-u_1)(\mu_m+au_1+pu_3)\beta\epsilon\phi R_{0m}I_h^{**}S_h^{**} \\ &\quad-N_hN_{hw}(\alpha_h+\mu_h)(\delta_h+\mu_h+b+\tau u_2)I_h^{**}\big((1-u_1)\lambda\epsilon\phi I_h^{**} \\ &\quad+N_h(\mu_m+au_1+pu_3)\big)=0 \end{aligned}$$

$$\begin{aligned} &I_h^{**}\big[N_{hw}\alpha_h(1-u_1)^2(\mu_m+au_1+pu_3)\beta\epsilon\phi R_{0m}S_h^{**} \\ &\quad+N_h\alpha_h(1-u_4)(1-u_1)(\mu_m+au_1+pu_3)\beta\epsilon\phi R_{0m}S_h^{**} \\ &\quad-N_hN_{hw}(\alpha_h+\mu_h)(\delta_h+\mu_h+b+\tau u_2)\big((1-u_1)\lambda\epsilon\phi I_h^{**} \\ &\quad+N_h(\mu_m+au_1+pu_3)\big)\big]=0. \end{aligned} \tag{3.32}$$

Hence $I_h^{**}=0$ or

$$\begin{aligned} &N_{hw}\alpha_h(1-u_1)^2(\mu_m+au_1+pu_3)\beta\epsilon\phi R_{0m}S_h^{**} \\ &\quad+N_h\alpha_h(1-u_4)(1-u_1)(\mu_m+au_1+pu_3)\beta\epsilon\phi R_{0m}S_h^{**} \\ &\quad-N_{hw}N_h(\alpha_h+\mu_h)(\delta_h+\mu_h+b+\tau u_2)\big((1-u_1)\lambda\epsilon\phi I_h^{**} \\ &\quad+N_h(\mu_m+au_1+pu_3)\big)=0. \end{aligned} \tag{3.33}$$

Dividing equation (3.33) by $N_h(\alpha_h+\mu_h)(\delta_h+\mu_h+b+\tau u_2)$ we have

$$\frac{N_{hw}\alpha_h(1-u_1)^2(\mu_m+au_1+pu_3)\beta\epsilon\phi R_{0m}S_h^{**}}{N_h(\alpha_h+\mu_h)(\delta_h+\mu_h+b+\tau u_2)} + \frac{N_h\alpha_h(1-u_4)(1-u_1)(\mu_m+au_1+pu_3)\beta\epsilon\phi R_{0m}S_h^{**}}{N_h(\alpha_h+\mu_h)(\mu_m+au_1+pu_3)} - N_{hw}\big((1-u_1)\lambda\epsilon\phi I_h^{**}+N_h(\mu_m+au_1+pu_3)\big)=0$$

We know that

$$N_h=\frac{\Lambda_h}{\mu_h}.$$

$$\frac{N_{hw}\mu_h\alpha_h(1-u_1)^2(\mu_m+au_1+pu_3)\beta\epsilon\phi R_{0m}S_h^{**}}{\Lambda_h(\alpha_h+\mu_h)(\delta_h+\mu_h+b+\tau u_2)} + \frac{\alpha_h(1-u_4)(1-u_1)(\mu_m+au_1+pu_3)\beta\epsilon\phi R_{0m}S_h^{**}}{(\alpha_h+\mu_h)(\delta_h+\mu_h+b+\tau u_2)} - N_{hw}\big((1-u_1)\lambda\epsilon\phi I_h^{**}+N_h(\mu_m+au_1+pu_3)\big)=0.$$

$$R_{0h}\times R_{0m}(1-u_1)^2(\mu_m+au_1+pu_3)N_{hw}S_h^{**}\mu_h + \frac{\alpha_h(1-u_4)(1-u_1)(\mu_m+au_1+pu_3)\beta\epsilon\phi R_{0m}S_h^{**}\mu_h}{(\alpha_h+\mu_h)(\delta_h+\mu_h+b+\tau u_2)} - N_{hw}\mu_h(1-u_1)\lambda\epsilon\phi I_h^{**}-\Lambda_h N_{hw}(\mu_m+au_1+pu_3)=0.$$

$$R_{0h}\times R_{0m}(1-u_1)^2(\mu_m+au_1+pu_3)N_{hw}S_h^{**}\mu_h + \frac{\alpha_h(1-u_4)(1-u_1)(\mu_m+au_1+pu_3)\beta\epsilon\phi R_{0m}S_h^{**}\mu_h}{(\alpha_h+\mu_h)(\delta_h+\mu_h+b+\tau u_2)} = N_{hw}\mu_h(1-u_1)\lambda\epsilon\phi I_h^{**}+\Lambda_h N_{hw}(\mu_m+au_1+pu_3).$$

Let $R_{0h}\times R_{0m}=R_0^2$ hence we have

$$R_0^2(1-u_1)^2(\mu_m+au_1+pu_3)N_{hw}S_h^{**}\mu_h + \frac{\alpha_h(1-u_4)(1-u_1)(\mu_m+au_1+pu_3)\beta\epsilon\phi R_{0m}S_h^{**}\mu_h}{(\alpha_h+\mu_h)(\delta_h+\mu_h+b+\tau u_2)} = N_{hw}\mu_h(1-u_1)\lambda\epsilon\phi I_h^{**}+\Lambda_h N_{hw}(\mu_m+au_1+pu_3).$$

Which gives

$$S_h^{**}=\frac{N_{hw}\mu_h(1-u_1)\lambda\epsilon\phi I_h^{**}+\Lambda_h N_{hw}(\mu_m+au_1+pu_3)}{\mu_h N_{hw}R_0^2(1-u_1)^2(\mu_m+au_1+pu_3)(\alpha_h+\mu_h)(\delta_h+\mu_h+b+\tau u_2)+\alpha_h(1-u_4)(1-u_1)(\mu_m+au_1+pu_3)\beta\epsilon\phi R_{0m}\mu_h}.$$

(3.34)

From the fourth equation of model (3.1)

$$(b+\tau u_2)I_h-(\psi+\mu_h)R_h=0$$

$$R_h=\frac{(b+\tau u_2)I_h^{**}}{(\psi+\mu_h)}.$$

(3.35)

Using the first equation of model (3.1) we can solve for I_h^{**}

$$\Lambda_h+\psi R_h-\frac{(1-u_1)\beta\epsilon\phi I_m S_h}{N_h}-\frac{(1-u_4)\beta\epsilon\phi I_m S_h}{N_{hw}}-\mu_h S_h=0.$$

(3.36)

Substituting equation (3.29), (3.34), and (3.35) into equation (3.36), and solving for I_h^{**} (as an expression of parameters only) through some algebraic manipulation gives

$$\Lambda_h+\psi\frac{(b+\tau u_2)I_h^{**}}{(\psi+\mu_h)}+\left[\frac{(1-u_1)\beta\epsilon\phi}{N_h}\right]\left[\frac{(1-u_1)(\mu_m+au_1+pu_3)R_{0m}I_h^{**}}{(1-u_1)\lambda\epsilon\phi I_h^{**}+N_h(\mu_m+au_1+pu_3)}\right]$$
$$\times\left[\frac{N_{hw}\mu_h(1-u_1)\lambda\epsilon\phi I_h^{**}+\Lambda_h N_{hw}(\mu_m+au_1+pu_3)}{\mu_h N_{hw}R_0^2(1-u_1)^2(\mu_m+au_1+pu_3)(\alpha_h+\mu_h)(\delta_h+\mu_h+b+\tau u_2)+\alpha_h(1-u_4)(1-u_1)(\mu_m+au_1+pu_3)\beta\epsilon\phi R_{0m}\mu_h}\right]$$
$$+\left[\frac{(1-u_4)\beta\epsilon\phi}{N_{hw}}\right]\left[\frac{(1-u_4)(\mu_m+au_1+pu_3)R_{0m}I_h^{**}}{(1-u_4)\lambda\epsilon\phi I_h^{**}+N_{hw}(\mu_m+au_1+pu_3)}\right]$$
$$\times\left[\frac{N_{hw}\mu_h(1-u_1)\lambda\epsilon\phi I_h^{**}+\Lambda_h N_{hw}(\mu_m+au_1+pu_3)}{\mu_h N_{hw}R_0^2(1-u_1)^2(\mu_m+au_1+pu_3)(\alpha_h+\mu_h)(\delta_h+\mu_h+b+\tau u_2)+\alpha_h(1-u_4)(1-u_1)(\mu_m+au_1+pu_3)\beta\epsilon\phi R_{0m}\mu_h}\right]$$
$$-\mu_h\left[\frac{N_{hw}\mu_h(1-u_1)\lambda\epsilon\phi I_h^{**}+\Lambda_h N_{hw}(\mu_m+au_1+pu_3)}{\mu_h N_{hw}R_0^2(1-u_1)^2(\mu_m+au_1+pu_3)(\alpha_h+\mu_h)(\delta_h+\mu_h+b+\tau u_2)+\alpha_h(1-u_4)(1-u_1)(\mu_m+au_1+pu_3)\beta\epsilon\phi R_{0m}\mu_h}\right]$$
$$=0$$

which can be written as

$$(\psi+\mu_h)\Lambda_h[\mu_h N_{hw}R_0^2(1-u_1)^2(\mu_m+au_1+pu_3)(\alpha_h+\mu_h)(\delta_h+\mu_h+b+\tau u_2)$$
$$+\alpha_h(1-u_4)(1-u_1)(\mu_m+au_1+pu_3)\beta\epsilon\phi R_{0m}\mu_h][(1-u_1)\lambda\epsilon\phi I_h^{**}$$
$$+N_h(\mu_m+au_1+pu_3)]N_{hw}N_h+\psi(b$$
$$+\tau u_2)I_h^{**}[\mu_h N_{hw}R_0^2(1-u_1)^2(\mu_m+au_1+pu_3)(\alpha_h+\mu_h)(\delta_h+\mu_h+b$$
$$+\tau u_2)+\alpha_h(1-u_4)(1-u_1)(\mu_m+au_1$$
$$+pu_3)\beta\epsilon\phi R_{0m}\mu_h][(1-u_1)\lambda\epsilon\phi I_h^{**}+N_h(\mu_m+au_1+pu_3)]N_{hw}N_h$$
$$+(\psi+\mu_h)[(1-u_1)\beta\epsilon\phi][(1-u_1)(\mu_m+au_1$$
$$+pu_3)R_{0m}I_h^{**}][N_{hw}\mu_h(1-u_1)\lambda\epsilon\phi I_h^{**}+\Lambda_h N_{hw}(\mu_m+au_1+pu_3)]N_{hw}$$
$$+(\psi+\mu_h)[(1-u_4)\beta\epsilon\phi][(1-u_4)(\mu_m+au_1$$
$$+pu_3)R_{0m}I_h^{**}][N_{hw}\mu_h(1-u_1)\lambda\epsilon\phi I_h^{**}+\Lambda_h N_{hw}(\mu_m+au_1+pu_3)]N_h$$
$$-(\psi+\mu_h)\mu_h[N_{hw}\mu_h(1-u_1)\lambda\epsilon\phi I_h^{**}$$
$$+\Lambda_h N_{hw}(\mu_m+au_1+pu_3)][(1-u_1)\lambda\epsilon\phi I_h^{**}+N_h(\mu_m+au_1$$
$$+pu_3)]N_{hw}N_h=0$$

or

$$A(I_h^{**})^2+BI_h^{**}+C=0. \tag{3.37}$$

where

$$A=(\psi+\mu_h)\Lambda_h[\mu_h N_{hw}R_0^2(1-u_1)^2(\mu_m+au_1+pu_3)(\alpha_h+\mu_h)(\delta_h+\mu_h+b+\tau u_2)$$
$$+\alpha_h(1-u_4)(1-u_1)(\mu_m+au_1+pu_3)\beta\epsilon\phi R_{0m}\mu_h][(1-u_1)\lambda\epsilon\phi I_h^{**}$$
$$+N_h(\mu_m+au_1+pu_3)]N_{hw}N_h+\psi(b$$
$$+\tau u_2)I_h^{**}[\mu_h N_{hw}R_0^2(1-u_1)^2(\mu_m+au_1+pu_3)(\alpha_h+\mu_h)(\delta_h+\mu_h+b$$
$$+\tau u_2)+\alpha_h(1-u_4)(1-u_1)(\mu_m+au_1$$
$$+pu_3)\beta\epsilon\phi R_{0m}\mu_h][(1-u_1)\lambda\epsilon\phi I_h^{**}+N_h(\mu_m+au_1+pu_3)]N_{hw}N_h$$

$$B=(\psi+\mu_h)[(1-u_1)\beta\epsilon\phi][(1-u_1)(\mu_m+au_1$$
$$+pu_3)R_{0m}I_h^{**}][N_{hw}\mu_h(1-u_1)\lambda\epsilon\phi I_h^{**}+\Lambda_h N_{hw}(\mu_m+au_1+pu_3)]N_{hw}$$
$$+(\psi+\mu_h)[(1-u_4)\beta\epsilon\phi][(1-u_4)(\mu_m+au_1$$
$$+pu_3)R_{0m}I_h^{**}][N_{hw}\mu_h(1-u_1)\lambda\epsilon\phi I_h^{**}+\Lambda_h N_{hw}(\mu_m+au_1+pu_3)]N_h$$

$$C = (\psi + \mu_h)\mu_h[N_{hw}\mu_h(1-u_1)\lambda\epsilon\phi I_h^{**} + \Lambda_h N_{hw}(\mu_m + au_1 + pu_3)][(1-u_1)\lambda\epsilon\phi I_h^{**} + N_h(\mu_m + au_1 + pu_3)]N_{hw}N_h$$

We use the quadratic formula to find the roots of equation (3.37)

$$x = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}$$

Which gives

$$I_h^* = \frac{-B \pm \sqrt{B^2 - 4AC}}{2A}$$

$$= \frac{-B + \sqrt{B^2 - 4ac}}{2A} \; or \; \frac{-B - \sqrt{B^2 - 4ac}}{2A}$$

$$= \frac{-B + \sqrt{B^2 - 4ac}}{2A} = \frac{-B - \sqrt{B^2 - 4ac}}{2A} = \Phi$$

Hence substituting Φ as the value of I_h^* in model (3.1) gives,

$$S_h^{**} = \frac{N_{hw}\mu_h(1-u_1)\lambda\epsilon\phi\Phi + \Lambda_h N_{hw}(\mu_m + au_1 + pu_3)}{\mu_h N_{hw}R_0^2(1-u_1)^2(\mu_m + au_1 + pu_3)(\alpha_h + \mu_h)(\delta_h + \mu_h + b + \tau u_2) + \alpha_h(1-u_4)(1-u_1)(\mu_m + au_1 + pu_3)\beta\epsilon\phi R_{0m}\mu_h}$$

$$E_h^{**} = \left[\frac{\big((1-u_1)\beta\epsilon\phi + (1-u_4)\beta\epsilon\phi\big)(1-u_1)(\mu_m + au_1 + pu_3)R_{0m}\Phi}{N_{hw}N_h(\mu_h + \alpha_h)\big((1-u_1)\lambda\epsilon\phi\Phi + N_h(\mu_m + au_1 + pu_3)\big)}\right] \times \left[\frac{N_{hw}\mu_h(1-u_1)\lambda\epsilon\phi\Phi + \Lambda_h N_{hw}(\mu_m + au_1 + pu_3)}{\mu_h N_{hw}R_0^2(1-u_1)^2(\mu_m + au_1 + pu_3)(\alpha_h + \mu_h)(\delta_h + \mu_h + b + \tau u_2) + \alpha_h(1-u_4)(1-u_1)(\mu_m + au_1 + pu_3)\beta\epsilon\phi R_{0m}\mu_h}\right]$$

$$I_h^{**} = \Phi = \left[\frac{\alpha_h\big((1-u_1)\beta\epsilon\phi + (1-u_4)\beta\epsilon\phi\big)(1-u_1)(\mu_m + au_1 + pu_3)R_{0m}\Phi}{(\delta_h + \mu_h + b + \tau u_2)N_{hw}N_h(\mu_h + \alpha_h)\big((1-u_1)\lambda\epsilon\phi\Phi + N_h(\mu_m + au_1 + pu_3)\big)}\right] \times \left[\frac{N_{hw}\mu_h(1-u_1)\lambda\epsilon\phi\Phi + \Lambda_h N_{hw}(\mu_m + au_1 + pu_3)}{\mu_h N_{hw}R_0^2(1-u_1)^2(\mu_m + au_1 + pu_3)(\alpha_h + \mu_h)(\delta_h + \mu_h + b + \tau u_2) + \alpha_h(1-u_4)(1-u_1)(\mu_m + au_1 + pu_3)\beta\epsilon\phi R_{0m}\mu_h}\right] \geq 0$$

$$R_h^{**} = \left[\frac{(b + \tau u_2)\alpha_h\big((1-u_1)\beta\epsilon\phi + (1-u_4)\beta\epsilon\phi\big)(1-u_1)(\mu_m + au_1 + pu_3)R_{0m}\Phi}{(\mu_h + \psi)(\delta_h + \mu_h + b + \tau u_2)N_{hw}N_h(\mu_h + \alpha_h)\big((1-u_1)\lambda\epsilon\phi\Phi + N_h(\mu_m + au_1 + pu_3)\big)}\right] \times \left[\frac{N_{hw}\mu_h(1-u_1)\lambda\epsilon\phi\Phi + \Lambda_h N_{hw}(\mu_m + au_1 + pu_3)}{\mu_h N_{hw}R_0^2(1-u_1)^2(\mu_m + au_1 + pu_3)(\alpha_h + \mu_h)(\delta_h + \mu_h + b + \tau u_2) + \alpha_h(1-u_4)(1-u_1)(\mu_m + au_1 + pu_3)\beta\epsilon\phi R_{0m}\mu_h}\right]$$

$$S_m^{**} = \frac{\Lambda_m N_h}{(1-u_1)\lambda\epsilon\phi\Phi + (\mu_m + au_1 + pu_3)N_h}$$

$$E_m^{**} = \left[\frac{(1-u_1)\alpha_h\lambda\epsilon\phi((1-u_1)(\mu_m + au_1 + pu_3)R_{0m}\Phi)\Lambda_m N_h}{N_h(\alpha_m + \mu_m + au_1 + pu_3)\big((1-u_1)\lambda\epsilon\phi\Phi + N_h(\mu_m + au_1 + pu_3)\big)\big((1-u_1)\lambda\epsilon\phi\Phi + (\mu_m + au_1 + pu_3)N_h\big)}\right]$$

$$I_m^{**} = \frac{(1-u_1)(\mu_m + au_1 + pu_3)R_{0m}\Phi}{(1-u_1)\lambda\epsilon\phi\Phi + N_h(\mu_m + au_1 + pu_3)}$$

From the quadratic equation (3.37) we analyze the possibility of multiple equilibria. It is important to note that the coefficient A is always positive with B and C having different signs. We realize that C is positive if R_0 is less than unity, and B is negative if R_0 is greater than R_c.

It follows that:

(i) There is a unique endemic equilibrium if $B < 0$ and $C = 0$ or $B^2 - 4AC = 0$,

(ii) There is a unique endemic equilibrium if $C < 0$ (i.e. $R_0 > 1$);

(iii) There are two endemic equilibria if $C > 0, B < 0\ and\ B^2 - 4AC > 0$,

(iv) There are no endemic equilibria otherwise.

Note that the hypotheses $C > 0$ is equivalent to $R_o < 1$

Hence the endemic equilibrium points have been determined

The results of this section can be summarized in the following Theorem

Theorem 3.5: If $R_0 < 1$, the E_0 is an equilibrium of the system (3.1) and it is locally asymptotically stable. Furthermore, there exist an endemic equilibrium if conditions (i) are satisfied, or two endemic equilibria if conditions (iii) are satisfied. If $R_0 > 1$, then E_0 is unstable and there exist a unique endemic equilibrium.

The item (iii) indicates the possibility of backward bifurcation in the model (3.1) when $R_0 < 1$. In the next section we will prove the occurrence of multiple equilibria for $R_0 < 1$ comes from the backward bifurcation and this will give information on the local stability of the endemic equilibria. We will also prove that if $R_0 > 1$, then the unique endemic equilibrium is globally asymptotically stable in the interior of D.

3.3.10 Local Stability Analysis of the Endemic Equilibrium

The stability analysis of the endemic equilibrium of the model (3.1) can be analyzed using the *Centre Manifold Theory* (Castilo-Chavez & Song, 2004) where we carry out ***bifurcation analysis of the system (1)*** at $R_0 = 1$. We consider a transmission rate β as bifurcation parameter Ψ so that $R_0 = 1$.

We intend to determine the stability of the endemic equilibrium and to investigate the possibility of the existence of backward bifurcation due to existence of multiple equilibrium and reinfection (The possible presence of two endemic equilibria shown in Remark 1, Case (iii)). Bifurcation makes the control of disease to be difficult.

To apply the theory, we introduce dimensionless state variables into the system (3.1).

The system of equations (3.1) can be written as

$$\frac{dS_h}{dt} = \Lambda_h + \psi R_h - \mu_h S_h - \frac{(1-u_1)\beta\epsilon\phi S_h I_m}{N_h} - \frac{(1-u_4)\beta\epsilon\phi S_h I_m}{N_{hw}}$$

$$\frac{dE_h}{dt} = \frac{(1-u_1)\beta\epsilon\phi S_h I_m}{N_h} + \frac{(1-u_4)\beta\epsilon\phi S_h I_m}{N_{hw}} - \mu_h E_h - \alpha_h E_h$$

$$\frac{dI_h}{dt} = \alpha_h E_h - (\delta_h + \mu_h) I_h - (b + \tau u_2) I_h$$

$$\frac{dR_h}{dt} = (b + \tau u_2) I_h - \mu_h R_h - \psi R_h$$

$$\frac{dS_m}{dt} = \Lambda_m - \frac{(1-u_1)\lambda\epsilon\phi I_h S_m}{N_h} - (\mu_m + a u_1 + p u_3) S_m$$

$$\frac{dE_m}{dt} = \frac{(1-u_1)\lambda\epsilon\phi I_h S_m}{N_h} - \alpha_m E_m - (\mu_m + a u_1 + p u_3) E_m$$

$$\frac{dI_m}{dt} = \alpha_m E_m - (\mu_m + a u_1 + p u_3) I_m. \tag{3.38}$$

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

Therefore system (3.1) is written in vector form as

$$\frac{dX_i}{dt} = H(X_i)$$

Where $X_i = (x_1, x_2, \dots, x_7)^T$ and $H_i = (h_1, h_2, \dots, h_7)^T$ are transposed matrices and $N_h = \frac{\Lambda_h}{\mu_h}$ with $\Psi^* = \beta$

$$\frac{dx_1}{dt} = \Lambda_h + \psi x_4 - \mu_h S_h - \frac{(1-u_1)\Psi^* \phi x_7 x_1 \mu_h}{\Lambda_h} - \frac{(1-u_4)\Psi^* \phi x_7 x_1 \mu_h}{\Lambda_h} = h_1$$

$$\frac{dx_2}{dt} = \frac{(1-u_1)\Psi^* \phi x_7 x_1 \mu_h}{\Lambda_h} + \frac{(1-u_4)\Psi^* \phi x_7 x_1 \mu_h}{\Lambda_h} - (\mu_h + \alpha_h)x_2 = h_2$$

$$\frac{dx_3}{dt} = \alpha_1 x_2 - (\delta_h + \mu_h + b + \tau u_2)x_3 = h_3$$

$$\frac{dx_4}{dt} = (b + \tau u_2)x_3 - (\mu_h + \psi)x_4 = h_4$$

$$\frac{dx_5}{dt} = \Lambda_m - \frac{(1-u_1)\lambda \epsilon \phi x_3 x_5 \mu_h}{\Lambda_h} - (\mu_m + a u_1 + p u_3)x_5 = h_5$$

$$\frac{dx_6}{dt} = \frac{(1-u_1)\lambda \epsilon \phi x_3 x_5 \mu_h}{\Lambda_h} - (\alpha_2 + \mu_m + a u_1 + p u_3)x_6 = h_6$$

$$\frac{dx_7}{dt} = \alpha_2 x_6 - (\mu_m + a u_1 + p u_3)x_7 = h_7 \tag{3.39}$$

The following theorem is used to analyze the dynamics of the model (3.39)

Theorem 3.6

Consider the following general system of ordinary differential equation with a parameter Ψ (Castilo-Chavez & Song, 2004; Gumel & Song, 2008)

$$\frac{dx}{dt} = h(x, \Psi), h: \mathbb{R}^n \times \mathbb{R} \longrightarrow \mathbb{R} \ and \ h\epsilon\mathbb{C}^2(\mathbb{R}^n \times \mathbb{R})$$

Where 0 is an equilibrium point of the system (that is, $h(0, \Psi) \equiv 0$ for all Ψ) and

1. *$A = D_x h(0,0) = \left(\frac{\partial h_i}{\partial x_i}(0,0)\right)$ is the linearization matrix of the system around the equilibrium 0 with Ψ evaluated at 0.*
2. *Zero is a simple eigenvalue of A and other eigenvalues of A have negative real parts.*
3. *Matrix A has a nonnegative right eigenvector w and a left eigenvector v corresponding to the zero eigenvalue.*

Let h_k be the k^{th} component of h and

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

and

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

Then, the local dynamics of the system (1) around the equilibrium point (0,0) is totally determined by the sign of a and b.

i. *$a > 0, b > 0$. When $\Psi < 0$ with $|\Psi| \ll 1,0$ is locally asymptotically stable and there exists a positive unstable equilibrium; when $0 < \Psi \ll 1,0$ is unstable and there exists a negative, locally asymptotically stable equilibrium.*

ii. *$a < 0, b < 0$. When $\Psi < 0$ with $|\Psi| \ll 0,1$ is unstable; when $0 < \Psi \ll 1,0$ is locally asymptotically stable, and there exist a positive unstable equilibrium.*

iii. $a > 0, b < 0$. *When* $\Psi < 0$ *with* $|\Psi| \ll 0{,}1$ *is unstable, and there exist a locally asymptotically stable negative equilibrium; when* $0 < \Psi \ll 1{,}0$ *is stable, and a positive unstable equilibrium appears.*

iv. $a < 0, b > 0$. *When* Ψ *changes from negative to positive, 0 changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable.*

If $a > 0$ *and* $b > 0$, *then a backward bifurcation occurs at* $\Psi = 0$.

Let Ψ^* be the bifurcation parameter, the system (3.39) is linearized at disease free equilibrium point when $\beta = \Psi^*$ with $R_0 = 1$

Thus Ψ^* can be solved from (3.39) when $\beta = \Psi^*$ with $R_0 = 1$. Thus Ψ^* can be solved from (3.17) when

$$R_0 = \sqrt{\frac{\alpha_h\alpha_m\Lambda_m\mu_h(1-u_1)^2\phi^2\epsilon\beta\lambda + \alpha_h\alpha_m\Lambda_m\mu_h(1-u_1)(1-u_4)\phi^2\epsilon^2\beta}{\Lambda_h(pu_3+au_1+\mu_m)^2(\mu_h+\alpha_1)(pu_3+\mu_m+au_1+\alpha_m)(\mu_h+\delta_h+b+\tau u_2)}}$$

$$1^2 = \frac{\alpha_h\alpha_m\Lambda_m\mu_h(1-u_1)^2\phi^2\epsilon\beta\lambda + \alpha_h\alpha_m\Lambda_m\mu_h(1-u_1)(1-u_4)\phi^2\epsilon^2\beta}{\Lambda_h(pu_3+au_1+\mu_m)^2(\mu_h+\alpha_1)(pu_3+\mu_m+au_1+\alpha_m)(\mu_h+\delta_h+b+\tau u_2)}$$

$$\Psi^* = \frac{\Lambda_h(pu_3+au_1+\mu_m)^2(\mu_h+\alpha_h)(pu_3+\mu_m+au_1+\alpha_m)(\mu_h+\delta_h+b+\tau u_2)}{\alpha_h\alpha_m\Lambda_m\mu_h(1-u_1)^2\phi^2\epsilon\lambda + \alpha_h\alpha_m\Lambda_m\mu_h(1-u_1)(1-u_4)\phi^2\epsilon^2}$$

The Jacobian matrix of (3.1) calculated at Ψ^* is given by

$$\begin{pmatrix} 0 & & & & & & \\ 0 & & & & & & \\ -\mu_h & 0 & -\delta_h-\mu_h-b-\tau u_2 & \psi & 0 & 0 & -\Psi^*\epsilon\phi \\ 0 & -\alpha_h-\mu_h & b+\tau u_2 & 0 & 0 & 0 & \Psi^*\epsilon\phi \\ 0 & \alpha_h & \frac{-(1-u_1)\lambda\epsilon\phi\Lambda_m\mu_h}{\Lambda_h(\mu_m+au_1+pu_3)} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -\mu_h-\psi & 0 & 0 & 0 \\ 0 & 0 & \frac{(1-u_1)\lambda\epsilon\phi\Lambda_m\mu_h}{\Lambda_h(\mu_m+au_1+pu_3)} & 0 & -(\mu_m+au_1+pu_3) & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -\alpha_m-\mu_m-au_1-pu_3 & 0 \\ 0 & 0 & 0 & 0 & 0 & -\alpha_m & -\mu_m-au_1-pu_3 \end{pmatrix}. \tag{3.40}$$

A right eigen vector associated with the eigen value zero is $w = (w_1, w_2, \dots, w_7)$.

We get the following system

$$-\mu_h w_1 + \psi w_4 - \Psi^* \phi w_7 = 0$$

$$-(\alpha_h + \mu_h) w_2 + \Psi^* \phi w_7 = 0$$

$$\alpha_h w_2 - (\delta_h + \mu_h + b + \tau u_2) w_3 = 0$$

$$(b + \tau u_2) w_3 - (\mu_h + \psi) w_4 = 0$$

$$\frac{-(1-u_1)\lambda \epsilon \phi \Lambda_m \mu_h w_3}{\Lambda_h(\mu_m + a u_1 + p u_3)} - w_5(\mu_m + a u_1 + p u_3) = 0$$

$$\frac{(1-u_1)\lambda \epsilon \phi \Lambda_m \mu_h w_3}{\Lambda_h(\mu_m + a u_1 + p u_3)} - (\alpha_m + \mu_m + a u_1 + p u_3) w_6 = 0$$

$$-\alpha_m w_6 - w_7(\mu_m + a u_1 + p u_3) = 0.$$

(3.41)

Solving the system (3.41), the Jacobian matrix of (3.1) at Ψ^* has the following right eigenvector

$$w_1 = \frac{\psi w_4 - \Psi^* \epsilon \phi w_7}{\mu_h}$$

$$w_2 = \frac{\Psi^* \epsilon \phi w_7}{\alpha_h + \mu_h}$$

$$w_3 = \frac{\alpha_h w_2}{b + \tau u_2 + \mu_h + \delta_h}$$

$$w_4 = \frac{(b + \tau u_2) w_3}{\mu_h + \psi}$$

$$w_5 = \frac{-(1-u_1)\lambda \epsilon \phi \Lambda_m \mu_h w_3}{\Lambda_h(\mu_m + a u_1 + p u_3)^2}$$

$$w_6 = \frac{(1-u_1)\lambda \epsilon \phi \Lambda_m \mu_h w_3}{\Lambda_h(\mu_m + a u_1 + p u_3)(\alpha_m + \mu_m + a u_1 + p u_3)}$$

$$w_7 = \frac{\alpha_m w_6}{\mu_m + a u_1 + p u_3} > 0.$$

(3.42)

The left eigenvectors satisfying $v.w = 1$ is $v = (v_1, v_2, \dots, v_7)$.

To find these left eigenvector associated with the eigenvalue 0 at Ψ^*, the matrix (3.40) should be transposed to give J_{left}

$$\begin{pmatrix} -\mu_h & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -\alpha_h - \mu_h & \alpha_h & 0 & 0 & 0 & 0 \\ 0 & 0 & -\delta_h - \mu_h - b - \tau u_2 & b + \tau u_2 & \dfrac{-(1-u_1)\lambda\epsilon\phi\Lambda_m\mu_h}{\Lambda_h\mu_m} & \dfrac{-(1-u_1)\lambda\epsilon\phi\Lambda_m\mu_h - (1-u_4)\lambda\epsilon\phi\Lambda_m\mu_h}{\Lambda_h\mu_m} & 0 \\ \psi & 0 & 0 & -\mu_h - \psi & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\mu_m & 0 & \alpha_m \\ 0 & 0 & 0 & 0 & 0 & -\alpha_h - \mu_m & -\mu_m \\ -\Psi^*\phi & \Psi^*\phi & 0 & 0 & 0 & 0 & \end{pmatrix}.$$

(3.43)

We have the following system

$$-\mu_h v_1 = 0$$

$$v_3(-\delta_h - \mu_h - b - \tau u_2) + v_3(b + \tau u_2) - \frac{(1-u_1)\lambda\epsilon\phi\Lambda_m\mu_h v_5}{\Lambda_h(\mu_m + au_1 + pu_3)} + \frac{(1-u_1)\lambda\epsilon\phi\Lambda_m\mu_h v_6}{\Lambda_h(\mu_m + au_1 + pu_3)} = v_3(-\delta_h - \mu_h - b - \tau u_2) + \frac{(1-u_1)\lambda\epsilon\phi\Lambda_m\mu_h v_6}{\Lambda_h(\mu_m + au_1 + pu_3)} = 0$$

$$\psi v_1 - (\mu_h + \psi)v_4 = 0$$

$$-(\mu_m + au_1 + pu_3)v_5 = 0$$

$$-(\alpha_m + \mu_m + au_1 + pu_3)v_6 + \alpha_m v_7 = 0$$

$$-\Psi^*\epsilon\phi v_1 + \Psi^*\epsilon\phi v_2 - (\mu_m + au_1 + pu_3)v_7 = 0.$$

(3.44)

Solving the system, the left eigenvector is given by

$$v_1 = 0$$

$$v_2 = \frac{\alpha_h v_3}{\alpha_h + \mu_h}$$

$$v_3 = \frac{v_6(1-u_1)\lambda\epsilon\phi\Lambda_m\mu_h}{\Lambda_h(\mu_m + au_1 + pu_3)(-\delta_h - u_h - b - \tau u_2)}$$

$$v_4 = 0$$

$$v_5 = 0$$

$$v_6 = \frac{\alpha_m v_7}{-\mu_m - \alpha_m - au_1 - pu_3}$$

$$v_7 = \frac{\Psi^* \epsilon \phi v_2}{\mu_m + au_1 + pu_3}.$$

(3.45)

The sign of a and b is computed as indicated in the theorem

$$w_1 = \frac{\psi w_4 - \Psi^* \epsilon \phi w_7}{\mu_h}$$

$$w_2 = \frac{\Psi^* \epsilon \phi w_7}{\alpha_h + \mu_h}$$

$$w_3 = \frac{\alpha_h w_2}{b + \tau u_2 + \mu_h + \delta_h}$$

$$w_4 = \frac{(b + \tau u_2) w_3}{\mu_h + \psi}$$

$$w_5 = \frac{-(1 - u_1)\lambda \epsilon \phi \Lambda_m \mu_h w_3}{\Lambda_h (\mu_m + au_1 + pu_3)^2}$$

$$w_6 = \frac{(1 - u_1)\lambda \epsilon \phi \Lambda_m \mu_h w_3}{\Lambda_h (\mu_m + au_1 + pu_3)(\alpha_m + \mu_m + au_1 + pu_3)}$$

$$w_7 = \frac{\alpha_m w_6}{\mu_m + au_1 + pu_3}$$

$$v_1 = 0$$

$$v_2 = \frac{\alpha_h v_3}{\alpha_h + \mu_h}$$

$$v_3 = \frac{v_6 (1 - u_1)\lambda \epsilon \phi \Lambda_m \mu_h}{\Lambda_h (\mu_m + au_1 + pu_3)(-\delta_h - u_h - b - \tau u_2)}$$

$$v_4 = 0$$

$$v_5 = 0$$

$$v_6 = \frac{\alpha_m v_7}{-\mu_m - \alpha_m - au_1 - pu_3}$$

$$v_7 = \frac{\Psi^* \epsilon \phi v_2}{\mu_m + au_1 + pu_3}.$$

For the system (3.39), the associated non-zero second order partial derivatives (at DFE) are given by

$$\frac{\partial^2 h_2}{\partial x_2 \partial x_7} = \frac{-(1-u_1)\Psi^* \epsilon \phi \mu_h}{\Lambda_h} - \frac{(1-u_4)\Psi^* \epsilon \phi \mu_h}{\Lambda_h}$$

$$\frac{\partial^2 h_2}{\partial x_3 \partial x_7} = \frac{-(1-u_1)\Psi^* \epsilon \phi \mu_h}{\Lambda_h} - \frac{(1-u_4)\Psi^* \epsilon \phi \mu_h}{\Lambda_h}$$

$$\frac{\partial^2 h_6}{\partial x_6 \partial x_3} = \frac{-(1-u_1)\lambda \epsilon \phi \mu_h}{\Lambda_h}$$

$$\frac{\partial^2 h_6}{\partial x_7 \partial x_3} = \frac{-(1-u_1)\lambda \epsilon \phi \mu_h}{\Lambda_h}.$$

Considering only the non-zero components of left eigen vector, it follows that

$$a = \sum_{k,i,j=2}^{3} v_k w_i w_j \frac{\partial^2 h_k}{\partial x_i \partial x_j}(0,0) + \sum_{k,i,j=6}^{7} v_k w_i w_j \frac{\partial^2 h_k}{\partial x_i \partial x_j}(0,0)$$

$$b = \sum_{k,i=2}^{3} v_k w_i \frac{\partial^2 h_k}{\partial x_i \partial x_j}(0,0) + \sum_{k,i=6}^{7} v_k w_i \frac{\partial^2 h_k}{\partial x_i \partial x_j}(0,0).$$

Since $v_1 = v_4 = v_5 = 0$ for $k = 1,4,5$ then $k = 2,3,6,7$ should be considered. That is, the following functions will be used to compute a and b

$$\begin{aligned} h_2 &= \frac{(1-u_1)\Psi^* \phi x_7}{\Lambda_h}\mu_h(N_h - x_2 - x_3) - (\mu_h + \alpha_h)x_2 \\ &= \frac{(1-u_1)\Psi^* \phi \mu_h x_7 N_h}{\Lambda_h} - \frac{(1-u_1)\Psi^* \phi \mu_h x_7 x_2}{\Lambda_h} - \frac{(1-u_1)\Psi^* \phi \mu_h x_7 x_3}{\Lambda_h} \\ &\quad - (\mu_h + \alpha_h)x_2 \end{aligned}$$

$$h_6 = \frac{(1-u_1)\lambda\epsilon\phi x_3\mu_h(N_m - x_6 - x_7)}{\Lambda_h} - \big((\mu_m + pu_3) + \alpha_m\big)x_6$$
$$= \frac{(1-u_1)\lambda\epsilon\phi\mu_h x_3 N_m}{\Lambda_h} - \frac{(1-u_1)\Psi^*\phi\mu_h x_7 x_2}{\Lambda_h} - \frac{(1-u_1)\lambda\epsilon\phi\mu_h x_6 x_3}{\Lambda_h}$$
$$- \frac{(1-u_1)\lambda\epsilon\phi\mu_h x_7 x_3}{\Lambda_h} - (\alpha_m + \mu_m + au_1 + pu_3)x_6.$$

Computing the sign a and b as indicated in the theorem.

Considering only the non-zero components of left eigen vector, it follows that

$$a = v_2 w_2 w_7 \frac{\partial^2 h_2}{\partial x_2 \partial x_7} + v_2 w_3 w_7 \frac{\partial^2 h_2}{\partial x_3 \partial x_7} + v_6 w_6 w_3 \frac{\partial^2 h_6}{\partial x_6 \partial x_3} + v_6 w_7 w_3 \frac{\partial^2 h_6}{\partial x_7 \partial x_3}$$
$$= v_2 w_2 w_7 \left(\frac{-(1-u_1)\Psi^*\epsilon\phi\mu_h}{\Lambda_h} - \frac{(1-u_4)\Psi^*\epsilon\phi\mu_h}{\Lambda_h}\right)$$
$$+ v_2 w_3 w_7 \left(\frac{-(1-u_1)\Psi^*\epsilon\phi\mu_h}{\Lambda_h} - \frac{(1-u_4)\Psi^*\epsilon\phi\mu_h}{\Lambda_h}\right)$$
$$+ v_6 w_6 w_3 \left(\frac{-(1-u_1)\lambda\epsilon\phi\mu_h}{\Lambda_h}\right) + v_6 w_7 w_3 \left(\frac{-(1-u_1)\lambda\epsilon\phi\mu_h}{\Lambda_h}\right)$$

$$a$$
$$= v_2 w_7 \left[\frac{-(1-u_1)\Psi^*\epsilon\phi\mu_h - (1-u_4)\Psi^*\epsilon\phi\mu_h}{\Lambda_h}\right]\left(\left[\frac{\Psi^*\epsilon w_7}{(\alpha_h + \mu_h)}\right]\right.$$
$$\left. + \left[\frac{\alpha_h w_2}{(b + \tau u_2 + \mu_h + \delta_h)}\right]\right)$$
$$+ v_6 w_3 \left[\frac{-(1-u_1)\lambda\epsilon\phi\mu_h}{\Lambda_h}\right]\left(\left[\frac{(1-u_1)\lambda\epsilon\phi\mu_h\Lambda_m w_3}{\Lambda_h(\mu_m + au_1 + pu_3)(\alpha_m + \mu_m + au_1 + pu_3)}\right]\right.$$
$$\left. + \left[\frac{\alpha_m w_3}{(\mu_m + au_1 + pu_3)}\right]\right).$$

The partial derivatives that are not zero when calculating b are

$$\frac{\partial h_2}{\partial \psi} = \frac{-(1-u_1)\epsilon\phi x_1 x_7}{\Lambda_h} - \frac{(1-u_4)\epsilon\phi x_1 x_7}{\Lambda_h}$$

$$\frac{\partial^2 h_2}{\partial x_7 \partial_\psi} = \frac{-(1-u_1)\epsilon\phi x_1}{\Lambda_h} - \frac{(1-u_4)\epsilon\phi x_1}{\Lambda_h} = \phi.$$

Therefore

$$b = v_2 w_7 \epsilon \phi > 0$$

so that b is always positive.

Therefore the following result is established:

Theorem 3.7

The model (3.1) exhibits backward bifurcation at $R_0 = 1$ whenever $a > 0$ and $b > 0$ and $R_0 < 1$.

Whenever $a < 0$ and $b > 0$ then model (3.1) exhibits a forward bifurcation at $R_0 = 1$.

3.3.11 Global Stability Analysis of the Endemic Equilibrium

Global stability results for the endemic equilibrium can be obtained when it is unique and whenever it exists. We have established in theorem 3.5 that if $R_0 > 1$ implies the existence and uniqueness of the endemic equilibrium.

The global behavior of the endemic equilibrium of the model (3.1) when it exists is explored by proving that such an equilibrium is globally asymptotic stable in the interior of the feasible region D. We will use the geometric approach to global stability as described by Li & Muldowney (1996). The following conditions are required for the global stability of the endemic equilibrium, E_1: (i) the uniqueness of E_1 in the interior of D; (ii) the existence of an absorbing compact set in the interior of D; and (iii) the fulfillment of a Bendixson criterion (i.e. the inequality (2a)).

Theorem 3.8: If $R_0 > 1$, then the unique endemic equilibrium of the malaria model (3.1) is globally asymptotically stable in the interior of D.

Proof.

The general method considered is the one developed by Li & Muldowney (1996). Consider the autonomous dynamical system:

$$\dot{x} = f(x) \tag{1a}$$

where $f: D \to \mathbb{R}^n, D \subset \mathbb{R}^n$ *open set and simply connected and* $f \in CD$. *Let* x^* *be an equilibrium of (1a), i.e.* $f(x^*) = 0$. *We recall that* x^* *is said to be globally stable in* D *if it is locally stable and all trajectories in* D *converge to* x^*

Assume that the following hypotheses hold:

(H_1) *there exists a compact absorbing set* $K \subset D$;

(H_2) *the equation (1a) has a unique equilibrium* x^* *in* D

The basic idea of this method is that if the equilibrium x^* *is (locally) stable, then the global stability is assured provided that* $(H_1) - (H_2)$ *hold and no non-constant periodic solution of (1a) exists.*

Bendixson criterion

Li and Muldowney (1996) showed that if $(H_1) - (H_2)$ *hold and (1a) satisfies a Bendixson criterion that is robust under* C *local* ϵ *−perturbations of* f *at all non-equilibrium non-wandering points for (1a), then* x^* *is globally stable in* D *provided it is stable. Then, a new Bendixson criterion robust under C local* ϵ *−perturbation and based on the use of the Lozinskiĭ measure is introduced.*

A function $g \in C(D \to \mathbb{R}^n)$ *is called* C *local* ϵ *−perturbations of* f *at* $x_0 \in D$ *if there exists an open neighbourhood* U *of* x_0 *in* D *such that the support* $supp(f - g) \subset U$ *and* $|f - g|_C < \epsilon$ *, where* $|f - g|_C = sup\{|f(x) - g(x)| + |f_x(x) - g_x(x)|: x \in D\}$.

A point $x_0 \in D$ *is said to be non-wandering for (1a) if for any neighborhood* U *of* x_0 *in* D *and there exists arbitrary large* t *such that* $U \cap x(t, U) \neq \phi$.

Let $P(x)$ *be a* $\binom{n}{2} \times \binom{n}{2}$ *matrix-valued function that is* C *on* D *and consider*

$$B = P_f P^{-1} + P J^{|2|} P^{-1}$$

where the matrix P_f *is*

$$(p_{ij}(x))_f = \left(\partial p_{ij}(x)/\partial x\right)^T . f(x) = \nabla p_{ij} . f(x).$$

And $J^{|2|}$ *is the second additive compound matrix of the Jacobian matrix,* J*, i.e.* $J(x) = Df(x)$*. Generally speaking, for a* $n \times n$ *matrix* $J = (J_{ij})$*,* $J^{|2|}$ *is a* $\binom{n}{2} \times \binom{n}{2}$ *matrix (for a survey on compound matrices and their relations to differential equations as described by Muldowney (1990) and in the special case* $n = 3$*, one has*

$$J^{|2|} = \begin{bmatrix} J_{11} + J_{22} & J_{23} & -J_{13} \\ J_{23} & J_{11} + J_{33} & J_{12} \\ -J_{31} & J_{21} & J_{22} + J_{33} \end{bmatrix}.$$

Consider Lozinskii measure $\mathcal{L}$ *of* B *with respect to a vector norm* $|.|$ *in* $\mathbb{R}^n$ *,* $N = \frac{n}{2}$ *(Martin Jr, 1974)*

$$\mathcal{L}(B) = \lim_{h \to 0^+} \frac{|1 + hB| - 1}{h}.$$

It is proved in (Li & Muldowney, 1996) that if (H_1) *and* (H_2) *hold, condition*

$$\limsup_{t \to \infty} \sup_{x_0 \in D} \frac{1}{t} \int_0^t \mathcal{L}\left(B\left(x(s, x_0)\right)\right) ds < 0 \qquad (2a)$$

guarantees that there are no orbits giving rise to a simple closed rectifiable curve in D which is invariant for (1a), i.e. periodic orbits, homoclinic orbits, heteroclinic cycles. In particular, condition (2a) is proved to be a robust Bendixson criterion for (1a). Besides, it is remarked that under the assumptions $(H_1) - (H_2)$*, condition (2a) also implies the local stability of* x^**.*

As a consequence, the following theorem holds (Li & Muldowney,1996):

Theorem: *Assume that conditions* $(H_1)-(H_2)$ *hold. Then* x^* *is globally asymptotically stable in* D *provided that a function* $P(x)$ *and a Lozinskiĭ measure* $\mathcal{L}$ *exist such that condition (a2) is satisfied.*

For system (3.1), under the assumption of $R_0 > 1$, satisfies conditions $(H_1)-(H_2)$, the existence of the endemic equilibrium has also been shown and the instability of DFE implies the uniform persistence (Freedman *et al.*, 1994) i.e. there exists a constant $c > 0$ such that any solutions $(S_h(t), I_h(t), I_m(t))$ with $(S_h(0), I_h(0), I_m(0))$ in the interior of D satisfies:

$$min\left\{\lim_{t\to\infty} inf\ S_h(t), \lim_{t\to\infty} inf\ I_h(t), \lim_{t\to\infty} inf\ I_m(t),\ \right\}.$$

The uniform persistence together with boundedness of D, is equivalent to the existence of a compact set in the interior of D which is absorbing for (2) (Hutson & Schmitt, 1992). Thus, (H_1) is verified. Moreover, E_1 is the only equilibrium in the interior of D, so that (H_2) is also verified.

It remains to find conditions for which the Bendixson criterion given by (2a) is verified. To this aim, let us begin by observing that from the Jacobian matrix (3.16) associated with a general solution (S_h, I_h, I_m) of reduced system (3.1), we get the second additive compound matrix $J^{|2|}$:

$$J^{|2|}(S_h, I_h, I_m) = \begin{pmatrix} -a_{11} & a_{12} & (1-u_1)\epsilon\phi\beta S_h + (1-u_4)\epsilon\phi\beta S_h \\ (1-u_1)\epsilon\phi\lambda(N_m - E_m - I_m) & -a_{22} & -\delta_h \\ 0 & (1-u_1)\epsilon\phi\beta I_m + (1-u_4)\epsilon\phi\beta I_m & -a_{33} \end{pmatrix}$$

where

$$a_{11} = \mu_h + \alpha_h + (1-u_1)\epsilon\phi\beta I_m + (1-u_4)\epsilon\phi\beta I_m + \mu_h + \delta_h + b + \tau u_2$$

$$a_{12} = (1-u_1)\epsilon\phi\beta S_h + (1-u_4)\epsilon\beta\phi S_h$$

$$a_{22} = \mu_h + \delta_h + (1-u_1)\epsilon\phi\beta I_m + (1-u_4)\epsilon\phi\beta I_m + (1-u_1)\epsilon\phi\lambda I_h + \mu_m + au_1 + pu_3$$

$$a_{33} = m + \mu_m + au_1 + pu_3 + (1-u_1)\epsilon\phi\lambda I_h + (1-u_1)\epsilon\phi\beta I_m + (1-u_4)\epsilon\phi\beta I_m$$

where $m = (\Lambda_m/\mu_m + au_1 + pu_3)/(\Lambda_h/\mu_h)$.

Choose now matrix $P(x) = P(S_h, I_h, I_m) = diag(1, I_h/I_m, I_h/I_m)$. Then $P_f P^{-1} = diag(0, \dot{I_h}/I_h - \dot{I_m}/I_m, \dot{I_h}/I_h - \dot{I_m}/I_m)$, and the matrix $B = P_f P^{-1} + PJ^{|2|}P^{-1}$ can be written in block form as

$$B = \begin{bmatrix} B_{11} & B_{12} \\ B_{21} & B_{22} \end{bmatrix}$$

Where

$$B_{11} = -(\mu_h + \alpha_h + (1-u_1)\epsilon\phi\beta I_m + (1-u_4)\epsilon\phi\beta I_m + \mu_h + b + \tau u_2 + \delta_h)$$

$$B_{12} = \left[\left((1-u_1)\epsilon\phi\beta S_h + (1-u_4)\epsilon\phi\beta S_h\right).\frac{I_m}{I_h}, (1-u_1)\epsilon\phi\beta S_h.\frac{I_m}{I_h} + (1-u_4)\epsilon\phi\beta S_h.\frac{I_m}{I_h}\right]$$

$$B_{21} = [(1-u_1)\epsilon\lambda\phi I_m(N_m - E_m - I_m)(I_h/I_m)]^T$$

$$B_{22} = \begin{bmatrix} \frac{\dot{I}_h}{I_h} - \frac{\dot{I}_m}{I_m} - a_{22} & 0 \\ (1-u_1)\epsilon\phi\beta I_m - (1-u_4)\epsilon\phi\beta I_m - (1-u_1)\epsilon\phi\lambda I_h & \frac{\dot{I}_h}{I_h} - \frac{\dot{I}_m}{I_m} - a_{33} \end{bmatrix}.$$

The vector norm $|.|$ in $\mathbb{R}^3_+$ is here chosen to be

$$|(x, y, z)| = max\{|x|, |y|, |z|\}.$$

Let $\sigma(.)$ denote the Lozinskii measure with respect to this norm. Using the method of estimating $\sigma(.)$ in (Li & Muldowney, 1996), we have

$$\sigma(B) \leq sup\{g_1, g_2\} = sup\{\sigma_1(B_{11}) + |B_{12}|, \quad \sigma_1(B_{22}) + |B_{21}|\}$$

where

$|B_{12}|$ and $|B_{21}|$ are matrix norms with respect to the L vector norm and σ_1 denotes the Lozinskii measure with respect to $L\,norm$. Since B_{11} is a scalar, its Lozinskii measure with respect to any norm in $\mathbb{R}$ is equal to B_{11}.

Therefore

$$\sigma_1(B_{11}) = -(\mu_h + \alpha_h + (1-u_1)\epsilon\phi\beta I_m + (1-u_4)\epsilon\phi\beta I_m + \mu_h + b + \tau u_2 + \delta_h)$$

$$\begin{aligned}\sigma_1(B_{22}) = max\Big\{&\frac{\dot{I_h}}{I_h} - \frac{\dot{I_m}}{I_m} \\ &- (\mu_h + \alpha_h + (1-u_1)\epsilon\phi\beta I_m + (1-u_4)\epsilon\phi\beta I_m + (1-u_1)\epsilon\phi\lambda I_h + \mu_m \\ &+ au_1 + pu_3), \frac{\dot{I_h}}{I_h} - \frac{\dot{I_m}}{I_m} - (1-u_1)\epsilon\phi\beta I_m - (1-u_4)\epsilon\phi\beta I_m \\ &- (1-u_1)\epsilon\phi\lambda I_h - \mu_h - \delta_h - b - \tau u_2 - \mu_m - au_1 - pu_3\Big\}\end{aligned}$$

$$\begin{aligned}\sigma_1(B_{22}) = &\frac{\dot{I_h}}{I_h} - \frac{\dot{I_m}}{I_m} \\ &- (\mu_h + \alpha_h + (1-u_1)\epsilon\phi\beta I_m + (1-u_4)\epsilon\phi\beta I_m + (1-u_1)\epsilon\phi\lambda I_h + \mu_m \\ &+ au_1 + pu_3)\end{aligned}$$

$$|B_{12}| = \big((1-u_1)\epsilon\phi\beta S_h + (1-u_4)\epsilon\phi\beta S_h\big).\frac{I_m}{I_h}$$

$$|B_{21}| = (1-u_1)\epsilon\phi\lambda(N_m - E_m - I_m).\frac{I_h}{I_m}.$$

Therefore

$$\begin{aligned}g_1 = &-(\mu_h + \alpha_h + (1-u_1)\epsilon\phi\beta I_m + (1-u_4)\epsilon\phi\beta I_m + \mu_h + \delta_h + b + \tau u_2) \\ &+ \big((1-u_1)\epsilon\phi\beta S_h + (1-u_4)\epsilon\phi\beta S_h\big).\frac{I_m}{I_h}\end{aligned} \tag{3.46}$$

$$\begin{aligned}g_2 = (1-u_1)\epsilon\phi\lambda(N_m - E_m - I_m).&\frac{I_h}{I_m} + \frac{\dot{I_h}}{I_h} - \frac{\dot{I_m}}{I_m} \\ &- (\mu_h + \alpha_h + \mu_m + au_1 + pu_3 + (1-u_1)\epsilon\phi\lambda I_h).\end{aligned}$$

(3.47)

We rewrite the last two equations of system (3.1) for $\dot{I_h}$ and $\dot{I_m}$ as

$$\frac{\dot{I_h}}{I_h} = \big((1-u_1)\epsilon\phi\beta S_h + (1-u_4)\epsilon\phi\beta S_h\big).\frac{I_m}{I_h} - (\mu_h + \delta_h + b + \tau u_2)$$

(3.48)

$$\frac{\dot{I_m}}{I_m} = (1-u_1)\epsilon\phi\lambda(N_m - E_m - I_m).\frac{I_h}{I_m} - \mu_m - au_1 - pu_3.$$

(3.49)

Substituting equation (3.48) into (3.46) and (3.49) into (3.47) we have

$$g_1(t) = \frac{\dot{I_h}}{I_h} - (\mu_h + \alpha_h + (1-u_1)\epsilon\phi\beta I_m + (1-u_4)\epsilon\phi\beta I_m)$$

(3.50)

$$g_2(t) = \frac{\dot{I_h}}{I_h} - (\mu_h + \alpha_h + (1-u_1)\epsilon\phi\lambda I_h + (1-u_1)\epsilon\phi\beta I_m + (1-u_4)\epsilon\phi\beta I_m).$$

(3.51)

For the uniform persistence constant > 0 , there exists a time $T_0 > 0$ independent of $x(0) \in K$, the compact absorbing set, such that

$$I_h(t) > \varepsilon$$

$$I_m(t) > \varepsilon$$

for $t > T_0$ we have

$$g_1(t) \leq \frac{\dot{I_h}}{I_h} - (\mu_h + \alpha_h + (1-u_1)\epsilon\phi\beta\varepsilon + (1-u_4)\epsilon\phi\beta\varepsilon)$$

$$g_2(t) \leq \frac{\dot{I_h}}{I_h} - (\mu_h + \alpha_h + (1-u_1)\epsilon\phi\lambda\varepsilon).$$

Relations (3.50) and (3.51) imply

$$\sigma(B) \leq \frac{\dot{I}_h}{I_h} - \mu \; for \; t > T_0$$

where

$$\mu = min\{\mu_h + \alpha_h + (1-u_1)\epsilon\phi\beta\varepsilon + (1-u_4)\epsilon\phi\beta\varepsilon, \mu_h + \alpha_h + (1-u_1)\epsilon\phi\lambda\varepsilon\}.$$

Along each solution $(S_h(t), I_h(t), I_m(t))$ to (1) with $(S_h(0), I_h(0), I_m(0)) \in K$ where K is the compact absorbing set, we have for $t > T_0$,

$$\frac{1}{t}\int_0^t \sigma(B)ds \leq \frac{1}{t}\int_0^{T_0} \sigma(B)ds + \frac{1}{t}\ln\frac{I_h(t)}{I_h(T_0)} - \mu\frac{t-T_0}{t}$$

which implies $\bar{q}_2 < {}^{\mu}/_{2} < 0$. This proves that the unique endemic equilibrium is globally asymptotically stable whenever it exist. Thus completing the proof.

3.3.12 Sensitivity Analysis

Sensitivity analysis of the basic reproductive number is conducted to assess the relative impact of each of parameters to the disease transmission and prevalence by calculating the sensitivity index of the basic reproductive number to the model's parameters. Sensitivity analysis is commonly used to determine the robustness of model predictions to parameter values since there are errors in data collection and the presumed parameter values.

This will enable us to determine which of the controls causes the most reduction in R_0 and determine the control measure that is the most effective in controlling malaria transmission. The normalized forward sensitivity index of the reproduction number with respect to these parameters given in Table 3.1 is computed. The index measures the relative change in a variable with respect to relative changes in parameters. The analysis of these indices will help to determine which parameter is more crucial for disease transmission and prevalence.

Definition

The normalized forward sensitivity index of a variable, h , that depends on a parameter, l , is defined as (Chitnis et al., 2008) : $\xi_l = \frac{l}{h} \times \frac{\partial h}{\partial l}$. This process is carried out for all the parameters in the expression for R_0.

Therefore the sensitivity index of R_0 on parameter α_h is given as

$$\xi_{\alpha_h}^{R_0} = \frac{\alpha_h}{R_0} \times \frac{\partial R_0}{\partial \alpha_h}$$

$$\frac{\alpha_h}{R_0} = \frac{\alpha_h(\mu_h + \alpha_h)^{\frac{1}{2}}}{{\alpha_h}^{\frac{1}{2}}}$$

$$\frac{\partial R_0}{\partial \alpha_h} = \frac{{\alpha_h}^{\frac{1}{-2}}(\mu_h + \alpha_h)^{\frac{1}{2}} \times \frac{1}{2} - {\alpha_h}^{\frac{1}{2}}(\mu_h + \alpha_h)^{\frac{1}{2}} \times \frac{1}{2}}{(\mu_h + \alpha_h)}$$

which gives

$$\xi_{\alpha_h}^{R_0} = \frac{\alpha_h(\mu_h + \alpha_h)^{\frac{1}{2}}}{{\alpha_h}^{\frac{1}{2}}} \times \frac{{\alpha_h}^{\frac{1}{-2}}(\mu_h + \alpha_h)^{\frac{1}{2}} \times \frac{1}{2} - {\alpha_h}^{\frac{1}{2}}(\mu_h + \alpha_h)^{\frac{1}{2}} \times \frac{1}{2}}{(\mu_h + \alpha_h)}.$$

Therefore

$$\xi_{\alpha_h}^{R_0} = \frac{\mu_h}{2(\alpha_h + \mu_h)}.$$

The sensitivity index of the other parameters are given by

$$\xi_{\alpha_m}^{R_0} = \frac{pu_3 + \mu_m + au_1}{2(\alpha_m + pu_3 + au_1 + \mu_m)}$$

$$\xi_{\mu_m}^{R_0} = \frac{-\mu_m(2\alpha_m + 3(\mu_m + au_1 + pu_3))}{2(\alpha_m + \mu_m + au_1 + pu_3)(\mu_m + au_1 + pu_3)}$$

$$\xi_{\delta_h}^{R_0} = \frac{-\delta_h}{2(b + \tau u_2 + \delta_h + \mu_h)}$$

$$\xi_b^{R_0} = \frac{-b}{2(b + \tau u_2 + \delta_h + \mu_h)}$$

$$\xi_{\mu_h}^{R_0} = \frac{-\mu_h^2 + \alpha_h\delta_h + \alpha_h b + \alpha_h\tau u_2}{2(\mu_h + \delta_h + b + \tau u_2)(\mu_h + \alpha_h)}.$$

Sensitivity indices for the control parameters

$$\xi_{u_1}^{R_0} = \frac{-\mu_1}{1 - \mu_1}$$

$$\xi_{u_2}^{R_0} = \frac{-\tau\mu_2}{2(\mu_h + \epsilon + b + \tau\mu_2)}$$

$$\xi_{u_3}^{R_0} = \frac{-p(3pu_3 + 3\mu_m + au_1 + 2\alpha_m)u_3}{2(pu_3 + au_1 + \mu_m)(pu_3 + \mu_m + \alpha_m)}$$

$$\xi_{u_4}^{R_0} = \frac{-u_4}{(1 - u_4)}.$$

The positive sign of the index shows that an increase in the value of the parameter results into an increase in the value of R_0 and decrease in the value of the parameter results into the decrease in the value of R_0. The negative sign of the index shows that an increase in the values of the parameter will result to a decrease in the value of R_0 and a decrease in the value of the parameter will result to increase in the value of R_0 . The magnitudes of the indices are used to compare and determine sensitivity of the parameters of the model.

In the next section, we apply the optimal control method using Pontryagin's Maximum Principle to determine the best strategy for minimizing malaria transmission in the population.

3.4 Analysis of Optimal Control of Malaria Model with Intervention Strategies

We consider the case of time-dependent control variables. The malaria dynamics model is extended and an optimal control problem is formulated. We formulate an optimal control model for malaria disease in order to determine optimal malaria control strategies (ITNs, IRS, IPTp and treatment) with minimal implementation cost.

For the optimal control problem of the given system, we consider the control variables $u(t) = (u_1, u_2, u_3, u_4)\epsilon U$ relative to the state variables $S_h, E_h, I_h, R_h, S_m, E_m, I_m$where control variables are bounded and measured with.

$U = \{(u_1, u_2, u_3, u_4)\epsilon U \; is \; Lebsegue \; measurable \; on \; [0,1], 0 \leq u_i(t) \leq 1, t \in [0, T], i = 1,2,3,4.\}$. We define the objective function as

$$J(u_1, u_2, u_3, u_4) = \int_0^T \left(A_1 N_m + A_2 I_h + A_3 E_h + \frac{1}{2}(B_1 u_1^2 + B_2 u_2^2 + B_3 u_3^2 + B_4 u_4^2)\right) dt$$

subject to

$$\frac{dS_h}{dt} = \Lambda_h + \psi R_h - (1 - u_1)\lambda_h S_h - (1 - u_4)\lambda_{hw} S_h - \mu_h S_h$$

$$\frac{dE_h}{dt} = (1 - u_1)\lambda_h S_h + (1 - u_4)\lambda_{hw} S_h - (\alpha_h + \mu_h)E_h$$

$$\frac{dI_h}{dt} = \alpha_h E_h - (\delta_h + \mu_h)I_h - (b + \tau u_2)I_h$$

$$\frac{dR_h}{dt} = (b + \tau u_2)I_h - (\psi + \mu_h)R_h$$

$$\frac{dS_m}{dt} = \Lambda_m - (1 - u_1)\lambda_m S_m - (\mu_m + a u_1 + p u_3)S_m$$

$$\frac{dE_m}{dt} = (1 - u_1)\lambda_m S_m - \alpha_m E_m - (\mu_m + a u_1 + p u_3)E_m$$

$$\frac{dI_m}{dt} = \alpha_m E_m - (\mu_m + a u_1 + p u_3)I_m$$

$$S_h(0) \geq 0, E_h(0) \geq 0, I_h(0) \geq 0, R_h(0) \geq 0, S_m(0) \geq 0, E_m(0) \geq 0, I_m(0) \geq 0. \tag{3.52}$$

In the objective function T is the final time, quantities A_1, A_2 and A_3 are weights constants of the total mosquito population, infected individuals and exposed individuals respectively, while $B_1, B_2,\ B_3$ and B_4 are weight constants for use with ITNs, treatment effort, IRS and IPTp efforts respectively. The total mosquito population ($N_m = S_m + E_m + I_m$) is part of the objective function because it is affected by the use of IRS and

ITNs. In addition, E_h and I_h are included in the objective function because individuals in these classes are affected by the use of ITNs, IPTps and treatment respectively. A quadratic cost on the controls was chosen in line with what is known in the literature on epidemic optimal controls for malaria (Okosun *et al.,* 2013; Mwamtobe *et al.,* 2014). The cost of implementing personal protection using ITNs is $B_1u_1^2$, treatment of infected individuals is $B_2u_2^2$, spraying of houses with IRS is $B_3u_3^2$ and preventive method of IPTp is $B_4u_4^2$. A linear function has been chosen for the cost incurred by exposed individuals A_3E_h , infected individuals, A_2I_h and the mosquito population, A_1N_m . A quadratic form is used for the cost on the controls $B_1u_1^2, B_2u_2^2, B_3u_3^2$ and $B_4u_4^2$, such that the terms $\frac{1}{2}B_1u_1^2, \frac{1}{2}B_2u_2^2, \frac{1}{2}B_3u_3^2$ and $\frac{1}{2}B_4u_4^2$ describe the cost associated with the ITNs, treatment, mosquito control (IRS) and chemoprevention (IPTp) respectively.

Our aim with the given objective function is to minimize the number of latent humans $E_h(t)$ and infected humans $I_h(t)$ while minimizing the cost of control $u_1(t), u_2(t), u_3(t)$ and $u_4(t)$. We select to model the control efforts via a linear combination of quadratic terms and the constants which represents a measure of the relative cost of the interventions over [0, 1]. We seek an optimal control u_1^*, u_2^*, u_3^* and u_4^* such that

$$J(u_1^*, u_2^*, u_3^*, u_4^*) = \min_{u_1,u_2,u_3,u_4 \epsilon U} J(u_1, u_2, u_3, u_4) \tag{3.53}$$

Where U is the set of measurable functions defined from $[0, T]$ onto $[0,1]$ subject to system (3.1) and appropriate initial conditions.

Pontryagin's Maximum Principle is used to solve this optimal control problem and the derivation of necessary conditions that an optimal control must satisfy (Pontryagin *et al.,* 1962). Pontryagin's Maximum Principle converts the state system (3.1) and objective function (3.52) into a problem of minimizing pointwise the Langragian, L , and Hamiltonian, H , with respect to u_1, u_2, u_3 and u_4 .

3.4.1 Existence of Optimal Control Problem

The existence of an optimal control can be proved by using the theorem given in Fleming and Rishel (1975). It can be clearly seen that the system of Equation (3.1) is bounded from above by a linear system. According to the result in (Fleming & Rishel, 1975), the solution exists if the following hypotheses are met:

(H_1) *: The set of controls and corresponding state variables is nonempty.*

(H_2) *: The control set,* U *, is convex and closed.*

(H_3) *: Right hand side of each equation in (3.1) is continuous, bounded above by a sum of the bounded control and state, and can be written as a linear function of* u *with coefficients depending on time and state.*

(H_4) *: There exist constants* $c_1, c_2 > 0$ *and* $\beta > 1$ *such that the integrand* $L(y, u, t)$ *of the objective functional* J *is convex and satisfies*

$$L(y, u, t) \geq c_1(|u_1|^2 + |u_2|^2 + |u_3|^2 + |u_4|^2)^{\frac{\beta}{2}} - c_2.$$

In order to confirm the above hypotheses, a result given by Lukes (1982) is used to establish the existence of solutions of state system (3.1). Since the coefficients are bounded, (H_1) *is satisfied. The solutions are bounded, hence the control set satisfies* (H_2) *as well. The system is bilinear in* u_1, u_2, u_3, u_4 *hence, the right hand side of (3.1) satisfies the condition* (H_3) *(since the solutions are bounded). Note that the integrand of the objective functional is convex. The last condition is also satisfied.*

The state and the control variables of the system (3.1) are non-negative values and non-empty. The control set U is closed and convex. The integrand of the objective cost function J expressed by (3.52) is a convex function of (u_1, u_2, u_3, u_4) on the control set U . The Lipschitz property of the state system with respect to the state variables is satisfied since the state solutions are bounded. It can easily be shown that there exist positive numbers ξ_1, ξ_2 and a constant $\varepsilon > 1$ such that

$$A_1N_m + A_2I_h + A_3E_h + \frac{1}{2}(B_1u_1^2 + B_2u_2^2 + B_3u_3^2 + B_4u_4^2)$$
$$\geq \xi_1(|u_1|^2 + |u_2|^2 + |u_3|^2 + |u_4|^2)^{\varepsilon/2} - \xi_2$$

where $\xi_1, \xi_2 > 0, A_1, A_2, B_1, B_2, B_3, B_4 > 0$ and $\varepsilon > 1$.

This concludes existence of an optimal control since the state variables are bounded. Hence we have the following Theorem:

Theorem 3.9: Given the objective functional $J(u_1, u_2, u_3, u_4) = \int_0^T \Big(A_1N_m + A_2I_h + A_3E_h + \frac{1}{2}(B_1u_1^2 + B_2u_2^2 + B_3u_3^2 + B_4u_4^2)\Big)\,dt$ where $U = \{(u_1, u_2, u_3, u_4)|0 \leq u_1, u_2, u_3, u_4 \leq 1, 0 \leq u_i(t) \leq 1, t \in [0, T], i = 1,2,3,4.\}$ subject to Equations (3.1) with initial conditions, then there exists an optimal control $u^* = (u_1^*, u_2^*, u_3^*, u_4^*)$ such that $J(u_1^*, u_2^*, u_3^*, u_4^*) = \min_U J(u_1, u_2, u_3, u_4)$.

Lagrangian for a problem discusses how the techniques come and Hamiltonian helps in solving for the adjoint variable. In order to find an optimal solution, first we find the Lagrangian and Hamiltonian for the optimal control problem (3.52). The Lagrangian of the optimal problem is given by

$$L(I_h, E_h, N_m, u_1, u_2, u_3, u_4)$$
$$= A_1N_m + A_2I_h + A_3E_h + \frac{1}{2}(B_1u_1^2 + B_2u_2^2 + B_3u_3^2 + B_4u_4^2).$$

We need to find the minimal value of the Lagrangian. To do this, we define the Hamiltonian H for the control problem which consists of the integrand of the objective function (Lagrangian, L) and the inner product of the right hand sides of the state equations and the co-state variables or adjoint variables $(\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6, \lambda_7)$ as

$$H = L + \lambda_1\frac{dS_h}{dt} + \lambda_2\frac{dE_h}{dt} + \lambda_3\frac{dI_h}{dt} + \lambda_4\frac{dR_h}{dt} + \lambda_5\frac{dS_m}{dt} + \lambda_6\frac{dE_m}{dt} + \lambda_7\frac{dI_m}{dt}.$$

Taking $X = (S_h, E_h, I_h, R_h, S_m, E_m, I_m)$, $U = (u_1, u_2, u_3, u_4)$ and

$\lambda = (\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6, \lambda_7)$ we obtain the Hamiltonian given by

$$\begin{aligned} H(X, U, \lambda) = {} & L(I_h, E_h, N_m, u_1, u_2, u_3, u_4) \\ & + \lambda_1[\Lambda_h + \psi R_h - (1-u_1)\lambda_h S_h - (1-u_4)\lambda_{hw} S_h - \mu_h S_h] \\ & + \lambda_2[(1-u_1)\lambda_h S_h + (1-u_4)\lambda_{hw} S_h - (\alpha_h + \mu_h)E_h] \\ & + \lambda_3[\alpha_h E_h - (\delta_h + \mu_h)I_h - (b + \tau u_2)I_h] \\ & + \lambda_4[(b + \tau u_2)I_h - (\psi + \mu_h)R_h] \\ & + \lambda_5[\Lambda_h - (1-u_1)\lambda_m S_m - (\mu_m + a u_1 + p u_3)S_m] \\ & + \lambda_6[\,(1-u_1)\lambda_m S_m - \alpha_m E_m - (\mu_m + a u_1 + p u_3)E_m] \\ & + \lambda_7[\alpha_m E_m - (\mu_m + a u_1 + p u_3)I_m]. \end{aligned} \tag{3.54}$$

3.4.2 The Optimality System

In order to find the necessary conditions for this optimal control, we apply the Pontryagin's Maximum Principle (Lenhart & Workman, 2007) as follows:

If $u_1^*, u_2^*, u_3^*, u_4^*$ is an optimal solution of an optimal control problem, then there exists a nontrivial vector function $\lambda(t) = (\lambda_1(t), \lambda_2(t), \dots, \lambda_n(t))$ satisfying the following conditions

The state equation is

$$\frac{dx}{dt} = \frac{\partial H(t, u_1^*, u_2^*, u_3^*, u_4^*, \lambda(t))}{\partial \lambda}.$$

The optimality condition

$$0 = \frac{\partial H(t, u_1^*, u_2^*, u_3^*, u_4^*, \lambda(t))}{\partial u}$$

and the adjoint equation

$$\frac{d\lambda}{dt} = \frac{\partial H(t, u_1^*, u_2^*, u_3^*, u_4^*, \lambda(t))}{\partial x}.$$

Now, we apply the necessary conditions to the Hamiltonian.

Theorem 3.10: Given the optimal controls $u_1^*, u_2^*, u_3^*, u_4^*$ and solutions $S_h^*, E_h^*, I_h^*, R_h^*, S_m^*, E_m^*, I_m^*$ of the corresponding state system (3.1), there exist adjoint variables $\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6, \lambda_7$ satisfying

$$-\frac{d\lambda_1}{dt} = \frac{\partial H}{\partial S_h} = (1-u_1)\lambda_h(\lambda_2-\lambda_1) + (1-u_4)\lambda_{hw}(\lambda_2-\lambda_1) - \mu_h\lambda_1$$

$$-\frac{d\lambda_2}{dt} = \frac{\partial H}{\partial E_h} = \alpha_h(\lambda_3-\lambda_2) - \mu_h\lambda_2 + A_3$$

$$-\frac{d\lambda_3}{dt} = \frac{\partial H}{\partial I_h} = (b+\tau u_2)\lambda_4 - (b+\tau u_2+\mu_h+\delta_h)\lambda_3 + A_2 - \left(\frac{(1-u_1)\lambda\epsilon\phi S_m}{N_h}\right)\lambda_5 + \left(\frac{(1-u_1)\lambda\epsilon\phi S_m}{N_h}\right)\lambda_6$$

$$-\frac{d\lambda_4}{dt} = \frac{\partial H}{\partial R_h} = \psi\lambda_1 - (\mu_h+\psi)\lambda_4$$

$$-\frac{d\lambda_5}{dt} = \frac{\partial H}{\partial S_m} = (1-u_1)(\lambda_6-\lambda_5)\lambda_m - (\mu_m+au_1+pu_3)\lambda_5 + A_1$$

$$-\frac{d\lambda_6}{dt} = \frac{\partial H}{\partial E_m} = \alpha_m(\lambda_7-\lambda_6) - (\mu_m+au_1+pu_3)\lambda_6 + A_1$$

$$-\frac{d\lambda_7}{dt} = \frac{\partial H}{\partial I_m} = -(\mu_m+au_1+pu_3)\lambda_7 + A_1 + \left(-\frac{(1-u_1)\beta\epsilon\phi S_h}{N_h} - \frac{(1-u_4)\beta\epsilon\phi S_h}{N_{hw}}\right)\lambda_1 + \left(\frac{(1-u_1)\beta\epsilon\phi S_h}{N_h} + \frac{(1-u_4)\beta\epsilon\phi S_h}{N_{hw}}\right)\lambda_2 \tag{3.55}$$

with transversality conditions

$$\lambda_1(T) = \lambda_2(T) = \lambda_3(T) = \lambda_4(T) = \lambda_5(T) = \lambda_6(T) = \lambda_7(T) = 0. \tag{3.56}$$

Furthermore $u_1^*, u_2^*, u_3^*, u_4^*$ are represented by

$$u_1^* = max\left\{0, min\left(1, \frac{(\lambda_2 - \lambda_1)\lambda_h S_h^* + (\lambda_6 - \lambda_5)\lambda_m S_m^* + aS_m^*\lambda_5 + aE_m^*\lambda_6 + aI_m^*\lambda_7}{B_1}\right)\right\}$$

$$u_2^* = max\left\{0, min\left(1, \frac{\tau(\lambda_3 - \lambda_4)I_h^*}{B_2}\right)\right\}$$

$$u_3^* = max\left\{0, min\left(1, \frac{p(\lambda_5 S_m^* + \lambda_6 E_m^* + \lambda_7 I_m^*)}{B_3}\right)\right\}$$

$$u_4^* = max\left\{0, min\left(1, \frac{(\lambda_2 - \lambda_1)\lambda_{hw} S_h^*}{B_4}\right)\right\}.$$

(3.57)

Proof:

To determine the adjoint equations and the transversality conditions we use the Hamiltonian H . The Hamiltonian function, H, is differentiated with respect to $S_h, E_h, I_h, R_h, S_m, E_m$ and I_m . The adjoint/ costate equation is given by

$$-\frac{d\lambda_1}{dt} = \frac{\partial H}{\partial S_h} = (1 - u_1)\lambda_h(\lambda_2 - \lambda_1) + (1 - u_4)\lambda_{hw}(\lambda_2 - \lambda_1) - \mu_h\lambda_1$$

$$-\frac{d\lambda_2}{dt} = \frac{\partial H}{\partial E_h} = \alpha_h(\lambda_3 - \lambda_2) - \mu_h\lambda_2 + A_3$$

$$-\frac{d\lambda_3}{dt} = \frac{\partial H}{\partial I_h} = (b + \tau u_2)\lambda_4 - (b + \tau u_2 + \mu_h + \delta_h)\lambda_3 + A_2 - \left(\frac{(1 - u_1)\lambda\epsilon\phi S_m}{N_h}\right)\lambda_5 + \left(\frac{(1 - u_1)\lambda\epsilon\phi S_m}{N_h}\right)\lambda_6$$

$$-\frac{d\lambda_4}{dt} = \frac{\partial H}{\partial R_h} = \psi\lambda_1 - (\mu_h + \psi)\lambda_4$$

$$-\frac{d\lambda_5}{dt} = \frac{\partial H}{\partial S_m} = (1 - u_1)(\lambda_6 - \lambda_5)\lambda_m - (\mu_m + au_1 + pu_3)\lambda_5 + A_1$$

$$-\frac{d\lambda_6}{dt} = \frac{\partial H}{\partial E_m} = \alpha_m(\lambda_7 - \lambda_6) - (\mu_m + au_1 + pu_3)\lambda_6 + A_1$$

$$-\frac{d\lambda_7}{dt} = \frac{\partial H}{\partial I_m} = -(\mu_m + au_1 + pu_3)\lambda_7 + A_1 + \left(-\frac{(1-u_1)\beta\epsilon\phi S_h}{N_h} - \frac{(1-u_4)\beta\epsilon\phi S_h}{N_{hw}}\right)\lambda_1 + \left(\frac{(1-u_1)\beta\epsilon\phi S_h}{N_h} + \frac{(1-u_4)\beta\epsilon\phi S_h}{N_{hw}}\right)\lambda_2$$

with transversality conditions

$$\lambda_1(T) = \lambda_2(T) = \lambda_3(T) = \lambda_4(T) = \lambda_5(T) = \lambda_6(T) = \lambda_7(T) = 0.$$

Using the optimality conditions we have and the property of the control space U.

In order to minimize Hamiltonian, H , with respect to the controls at the optimal controls, H , is differentiated with respect to u_1, u_2, u_3 and u_4 on the set U, and the solution for the optimal control point is obtained after equating to zero. This is the optimality condition.

Solving $\frac{\partial H}{\partial u_1} = 0$, $\frac{\partial H}{\partial u_2} = 0$, $\frac{\partial H}{\partial u_3} = 0$, and $\frac{\partial H}{\partial u_4} = 0$, evaluating at the optimal control on the interior of the control set, where $0 < u_i < 1$, for $i = 1,2,3,4$, and letting $S_h = S_h^*, E_h = E_h^*, I_h = I_h^*, R_h = R_h^*, S_m = S_m^*, E_m = E_m^*$, and $I_m = I_m^*$ yields

$$\frac{\partial H}{\partial u_1} = B_1 u_1^* + \lambda_1\lambda_h S_h^* - \lambda_2\lambda_h S_h^* + \lambda_5\lambda_m S_m^* - aS_m^*\lambda_5 - aE_m^*\lambda_6 - aI_m^*\lambda_7 = 0$$

$$\frac{\partial H}{\partial u_2} = B_2 u_2^* - \tau\lambda_3 I_h^* + \tau\lambda_4 I_h^* = 0$$

$$\frac{\partial H}{\partial u_3} = B_3 u_3^* - p\lambda_5 S_m^* - p\lambda_6 E_m^* - p\lambda_7 I_m^* = 0$$

$$\frac{\partial H}{\partial u_4} = B_4 u_4^* + \lambda_{hw}\lambda_2 S_h^* - \lambda_1\lambda_{hw} S_h^* = 0$$

for which

$$u_1^* = \frac{(\lambda_2 - \lambda_1)\lambda_h S_h^* + (\lambda_6 - \lambda_5)\lambda_m S_m^* + aS_m^*\lambda_5 + aE_m^*\lambda_6 + aI_m^*\lambda_7}{B_1}$$

$$u_2^* = \frac{\tau(\lambda_3 - \lambda_4)I_h^*}{B_2}$$

$$u_3^* = \frac{p(\lambda_5 S_m^* + \lambda_6 E_m^* + \lambda_7 I_m^*)}{B_3}$$

$$u_4^* = \frac{(\lambda_2 - \lambda_1)\lambda_{hw} S_h^*}{B_4}.$$

(3.58)

By applying the boundary condition of each control, the solution of Equation (3.58) becomes

$$u_1^* = max\left\{0, min\left(1, \frac{(\lambda_2 - \lambda_1)\lambda_h S_h^* + (\lambda_6 - \lambda_5)\lambda_m S_m^* + aS_m^*\lambda_5 + aE_m^*\lambda_6 + aI_m^*\lambda_7}{B_1}\right)\right\}$$

$$u_2^* = max\left\{0, min\left(1, \frac{\tau(\lambda_3 - \lambda_4)I_h^*}{B_2}\right)\right\}$$

$$u_3^* = max\left\{0, min\left(1, \frac{p(\lambda_5 S_m^* + \lambda_6 E_m^* + \lambda_7 I_m^*)}{B_3}\right)\right\}$$

$$u_4^* = max\left\{0, min\left(1, \frac{(\lambda_2 - \lambda_1)\lambda_{hw} S_h^*}{B_4}\right)\right\}.$$

We achieve the uniqueness of the optimal control for small T due to the prior boundedness of the state and adjoint functions and the resulting Lipschitz structure of the ordinary differential equations. The uniqueness of the optimal control trails from the uniqueness of the optimal system, which consists of state equation (3.1), the adjoint/ costate equation (3.55), and initial conditions at $t = 0$, boundary conditions (3.56) with characterization of the optimal control (3.57).

Hence the state and optimal control can be calculated using the optimality system. Hence using the fact that the second derivatives of the Lagrangian with respect to u_1, u_2, u_3 and u_4, respectively, are positive indicates that the optimal problem is a minimum at controls u_1^*, u_2^*, u_3^* and u_4^* .

The optimality system is solved using the forward-backward fourth order Runge-Kutta scheme in R statistical Computing platform (R Development Core Team, 2011). The optimal strategy is obtained by solving the state and adjoint systems and the transversality conditions. First we start to solve the state (3.1) using the Runge-Kutta fourth order forward in time with a guess for the controls u_1, u_2, u_3 and u_4 over the simulated time. Then, using the current iteration of the state equations with the initial guess for the controls, the adjoint/ costate equations in system (3.55) are solved by a backward method with the transversality conditions (3.56). Then the controls are updated by using a convex combination of the previous controls and the value from the characterizations (3.57). This process is repeated and iterations stopped if the values of the unknowns at the previous iterations are very close to the ones at the present iterations (Lenhart & Workman, 2007).

In the next section we look at cost effective analysis by using optimal control theory by developing the objective function and the corresponding Hamiltonian equation.

3.5 Cost Effectiveness Analysis of Optimal Malaria Control Strategies

After using the optimal control to investigate the optimality of the intervention strategies being practiced at different transmission settings in Kenya, economic evaluation of the strategies is carried out by performing a cost-effectiveness study to determine the most cost-effective as one or combination of the four intervention strategies namely, treatment effort of infected individuals, ITNs, IRS and IPTp. Cost-effectiveness analysis is undertaken in order to assess the extent to which the intervention strategies are beneficial and cost effective. The aim is to maximize the level of benefits (health effects) relative to the level of resources available as shown by Okosun *et al.,* (2013). The appraisal of the difference between the costs and health outcomes of the considered intervention strategies will help to achieve the purpose of this study. The health-care effects of the intervention strategies campaigned in the community are maximized under minimal resources. Since the intervention strategies being practiced in the community are mutually exclusive interventions, it is essential to use incremental cost-effectiveness ratios (ICER). The ICER is calculated in order to achieve the goal of comparing the costs

and the effectiveness of the intervention strategies. We start by performing economic evaluation of the intervention strategies then use the ICER.

3.5.1 Economic Evaluation

The economic evaluation of all four intervention techniques is evaluated in which effectiveness and cost-effectiveness of the interventions are investigated in order to minimize or eradicate malaria disease in the area under study. The following cost objective function is used

$$E_c(u_1, u_2, u_3, u_3) = \min_{(u_1,u_2,u_3,u_4)\in U} \int_0^{T_f} \big[b_1 u_1(t)\big(S_h(t) + S_m(t) + E_m(t) + I_m(t)\big) + b_2 \tau u_2(t) I_h(t) + b_3 p u_3(t)\big(S_m(t) + E_m(t) + I_m(t)\big) + b_4 u_4(t)\big(S_h(t) + E_h(t)\big)\big] e^{-\varphi t} dt \tag{3.59}$$

subject to the system of differential equations (3.1), where b_1 denotes the per capita cost of ITNs (u_1); b_2 denotes the per capita cost of treating an individual with malaria (u_2), b_3 represents the per capita area cost of IRS effort (u_3) and spraying houses and b_4 represents the use of IPTp among the pregnant women (u_4).

The compartments of the model which are highly affected by the use of ITNs, IPTp, and treatment are the susceptible, latent and infected individuals, hence the inclusion of these in the cost function. Part of objective function uses the sprayed houses (IRS) which affects the whole mosquito population. The discount rate of 3-5% has been exponentially considered with a parameter φ. The Lagrangian of the cost objective function is

$$L_b = \big[b_1 u_1(t)\big(S_h(t) + E_h(t) + S_m(t) + E_m(t) + I_m(t)\big) + b_2 \tau u_2(t) I_h(t) + b_3 p u_3(t)\big(S_m(t) + E_m(t) + I_m(t)\big) + b_4 u_4(t)\big(S_h(t) + E_h(t)\big)\big] e^{-\varphi t}$$

Then the Hamiltonian equation with Lagrangian, state variables and adjoint variables is

$$H_b = L_b + \lambda_1^* \frac{dS_h}{dt} + \lambda_2^* \frac{dE_h}{dt} + \lambda_3^* \frac{dI_h}{dt} + \lambda_4^* \frac{dR_h}{dt} + \lambda_5^* \frac{dS_m}{dt} + \lambda_6^* \frac{dE_m}{dt} + \lambda_7^* \frac{dI_m}{dt}$$

The developed corresponding Hamiltonian equation is as follows:

$$
\begin{aligned}
H_b = \big[&b_1u_1(t)\big(S_h(t)+E_h(t)+S_m(t)+E_m(t)+I_m(t)\big)+b_2\tau u_2(t)I_h(t)\\
&+b_3pu_3(t)\big(S_m(t)+E_m(t)+I_m(t)\big)+b_4u_4\big(S_h(t)+E_h(t)\big)\big]e^{-\varphi t}\\
&+\left\{\Lambda_h-\frac{(1-u_1)\beta\epsilon\phi I_m(t)S_h(t)}{N_h(t)}-\frac{(1-u_4)\beta\epsilon\phi I_m(t)S_h(t)}{N_{hw}(t)}-\mu_hS_h(t)\right.\\
&\left.+\psi R_h(t)\right\}\lambda_1^*\\
&+\left\{\frac{(1-u_1)\beta\epsilon\phi I_m(t)S_h(t)}{N_h(t)}+\frac{(1-u_4)\beta\epsilon\phi I_m(t)S_h(t)}{N_{hw}(t)}-\alpha_hE_h(t)\right.\\
&\left.-\mu_hE_h(t)\right\}\lambda_2^*+\{\alpha_hE_h(t)-(b+\tau u_2+\mu_h+\delta_h)I_h(t)\}\lambda_3^*\\
&+\{(b+\tau u_2)I_h(t)-(\mu_h+\psi)R_h(t)\}\lambda_4^*\\
&+\left\{\Lambda_m-\frac{(1-u_1)\lambda\epsilon\phi I_h(t)S_m(t)}{N_h(t)}-(\mu_m+au_1+pu_3)S_m(t)\right\}\lambda_5^*\\
&+\left\{\frac{(1-u_1)\lambda\epsilon\phi I_h(t)S_m(t)}{N_h(t)}-(\alpha_m+\mu_m+au_1+pu_3)E_m(t)\right\}\lambda_6^*\\
&+\{\alpha_mE_m(t)-(\mu_m+au_1+pu_3)I_m(t)\}\lambda_7^*
\end{aligned}
\tag{3.60}
$$

where $\lambda_1^*, \lambda_2^*, \lambda_3^*, \lambda_4^*, \lambda_5^*, \lambda_6^*$ and λ_7^* denote the marginal value linked to their corresponding classes. The λ_i^* where $i = (1,2,\dots,7)$ represent the changes in the objective value of an optimal solution of an optimization problem by relaxing the constraint by one unit (Pontryagin *et al.*, 1964). These can be calculated by using Pontryagin's Maximum Principle as we did previously and give

$$\frac{d\lambda_1^*}{dt}=-\frac{\partial H_b}{\partial S_h},\frac{d\lambda_2^*}{dt}=-\frac{\partial H_b}{\partial E_h},\frac{d\lambda_3^*}{dt}=-\frac{\partial H_b}{\partial I_h},\frac{d\lambda_4^*}{dt}=-\frac{\partial H_b}{\partial R_h}$$

$$\frac{d\lambda_5^*}{dt}=-\frac{\partial H_b}{\partial S_m},\frac{d\lambda_6^*}{dt}=-\frac{\partial H_b}{\partial E_m},\frac{d\lambda_7^*}{dt}=-\frac{\partial H_b}{\partial I_m}$$

Hence using the Hamiltonian equation (3.60) gives

$$\frac{d\lambda_1^*}{dt} = -\frac{\partial H_b}{\partial S_h} = -b_1 u_1 e^{-\varphi t} - b_4 u_4 e^{-\varphi t} + (1-u_1)\lambda_h \lambda_1^* + (1-u_4)\lambda_{hw}\lambda_1^* + \mu_h \lambda_1^* - (1-u_1)\lambda_h \lambda_2^* - (1-u_4)\lambda_{hw}\lambda_2^*.$$

$$\frac{d\lambda_2^*}{dt} = -\frac{\partial H_b}{\partial E_h} = -b_1 u_1 e^{-\varphi t} - b_4 u_4 e^{-\varphi t} + \alpha_h \lambda_2^* + \mu_h \lambda_2^* - \alpha_h \lambda_3^*$$

$$\frac{d\lambda_3^*}{dt} = -\frac{\partial H_b}{\partial I_h} = -b_2 \tau u_2 e^{-\varphi t} + (b + \tau u_2 + \mu_h + \delta_h)\lambda_3^* - (b + \tau u_2)\lambda_4^* + \left(\frac{(1-u_1)\lambda \epsilon \phi S_m}{N_h}\right)\lambda_5 - \left(\frac{(1-u_1)\lambda \epsilon \phi S_m}{N_h}\right)\lambda_6$$

$$\frac{d\lambda_4^*}{dt} = -\frac{\partial H_b}{\partial R_h} = -\psi \lambda_1^* + (\mu_h + \psi)\lambda_4^*$$

$$\frac{d\lambda_5^*}{dt} = -\frac{\partial H_b}{\partial S_m} = -b_1 u_1 e^{-\varphi t} - b_3 p u_3 e^{-\varphi t} + (1-u_1)\lambda_m \lambda_5^* + (\mu_m + a u_1 + p u_3)\lambda_5^* - (1-u_1)\lambda_m \lambda_6^*$$

$$\frac{d\lambda_6^*}{dt} = -\frac{\partial H_b}{\partial E_m} = -b_1 u_1 e^{-\varphi t} - b_3 p u_3 e^{-\varphi t} + (\alpha_m + \mu_m + a u_1 + p u_3)\lambda_6^* + \alpha_m \lambda_6^* - \alpha_m \lambda_7^*$$

$$\frac{d\lambda_7^*}{dt} = -\frac{\partial H_b}{\partial I_m} = -b_1 u_1 e^{-\varphi t} - b_3 p u_3 e^{-\varphi t} + (\mu_m + a u_1 + p u_3)\lambda_7^* + \left(\frac{(1-u_1)\beta \epsilon \phi S_h}{N_h} + \frac{(1-u_4)\beta \epsilon \phi S_h}{N_{hw}}\right)\lambda_1 + \left(-\frac{(1-u_1)\beta \epsilon \phi S_h}{N_h} - \frac{(1-u_4)\beta \epsilon \phi S_h}{N_{hw}}\right)\lambda_2.$$

Each intervention strategy is assessed by developing the Hamiltonian equation thereafter the economic tool will be employed.

3.5.1.1 Economic Evaluation of ITNs

The prevention parameter for the ITNs is denoted by $u_1(t)$. The Hamiltonian equation, H_b , is differentiated with respect to u_1 to obtain

$$\frac{\partial H_b}{\partial u_1} = -b_1 e^{-\varphi t}\big(S_h(t) + E_h(t) + S_m(t) + E_m(t) + I_m(t)\big) + \frac{\beta \epsilon \phi I_m S_h}{N_h}(\lambda_2^* - \lambda_1^*) + (\lambda_6 - \lambda_5)\frac{\lambda \epsilon \phi I_h}{N_h} S_m^* + a(S_m \lambda_5^* + E_m \lambda_6^* + I_m \lambda_7^*)$$

in which $\frac{\beta \epsilon \phi I_m S_h}{N_h}(\lambda_2^* - \lambda_1^*) + (\lambda_6 - \lambda_5)\frac{\lambda \epsilon \phi I_h}{N_h} S_m^* + a(S_m \lambda_5^* + E_m \lambda_6^* + I_m \lambda_7^*)$ is the total marginal benefit due to the use of ITNs while $b_1 e^{-\varphi t}\big(S_h(t) + E_h(t) + S_m(t) + E_m(t) + I_m(t)\big)$ is the marginal cost of acquiring the ITNs. The equivalency of the marginal cost and marginal benefit leads one to achieve the optimal policy.

Hence;

$$u_1(t) = \begin{cases} 0 \quad if \quad b_1 e^{-\varphi t}(S_h + E_h + S_m + E_m + I_m) > \frac{\beta \epsilon \phi I_m S_h}{N_h}(\lambda_2^* - \lambda_1^*) + (\lambda_6 - \lambda_5)\frac{\lambda \epsilon \phi I_h}{N_h} S_m^* + a(S_m \lambda_5^* + E_m \lambda_6^* + I_m \lambda_7^*) \\ (0,1) \quad if \quad b_1 e^{-\varphi t}(S_h + E_h + S_m + E_m + I_m) = \frac{\beta \epsilon \phi I_m S_h}{N_h}(\lambda_2^* - \lambda_1^*) + (\lambda_6 - \lambda_5)\frac{\lambda \epsilon \phi I_h}{N_h} S_m^* + a(S_m \lambda_5^* + E_m \lambda_6^* + I_m \lambda_7^*) \\ 1 \quad if \quad b_1 e^{-\varphi t}(S_h + E_h + S_m + E_m + I_m) < \frac{\beta \epsilon \phi I_m S_h}{N_h}(\lambda_2^* - \lambda_1^*) + (\lambda_6 - \lambda_5)\frac{\lambda \epsilon \phi I_h}{N_h} S_m^* + a(S_m \lambda_5^* + E_m \lambda_6^* + I_m \lambda_7^*) \end{cases}. \tag{3.61}$$

The third equation of (3.61), shows that if this is achieved then the total marginal benefit of using ITNs is more than the total marginal cost; hence the gain of optimal malaria prevention. Then we can conclude that the susceptible and exposed individuals should best (effectively) use this prevention strategy in order to fight the epidemic. On the other hand, few susceptible and exposed individuals will use ITNs if the marginal cost is more than the marginal benefit. The effective use of this strategy will lead to achieve the optimal policy which says that increasing the use of ITNs increases the number of susceptible humans and uninfected mosquitoes.

3.4.1.2 Economic Evaluation of Treatment Effort of Infected Individuals

Here the control parameter for treatment of infectious individuals is given by $u_2(t)$. The Hamiltonian equation, H_b, (3.60) is differentiated with respect to $u_2(t)$, giving;

$$\frac{\partial H_b}{\partial u_1} = -b_2\tau I_h e^{-\varphi t} + \tau I_h(\lambda_4^* - \lambda_3^*)$$

in which $b_2\tau I_h$ is the marginal cost and $\tau I_h(\lambda_4^* - \lambda_3^*)$ is the marginal benefit of treating infectious individuals. Hence,

$$u_2(t) = \begin{cases} 0 \quad if \quad b_2\tau I_h e^{-\varphi t} > \tau I_h(\lambda_4^* - \lambda_3^*) \\ (0,1) \quad if \quad b_2\tau I_h e^{-\varphi t} = \tau I_h(\lambda_4^* - \lambda_3^*) \\ 1 \quad if \quad b_2\tau I_h e^{-\varphi t} < \tau I_h(\lambda_4^* - \lambda_3^*) \end{cases}.$$

(3.62)

The optimal policy is to guarantee that the marginal costs for being treated is equal to the marginal benefit for the individuals being treated. Therefore, from (3.62) all infected individuals must look for full treatment if the marginal benefit, $I_h(\lambda_4^* - \lambda_3^*)$, must be greater than the marginal cost, $b_2\tau I_h e^{-\varphi t}$, for being treated. Otherwise, only few infected individuals will look for treatment.

3.5.1.3 Economic Evaluation of IRS

Insecticide residual spraying (IRS) prevention parameter in the system (3.1) and in the Hamiltonian equation, H_b , (3.60) is $u_3(t)$. Then differentiating H_b with respect to u_3 gives

$$\frac{\partial H_b}{\partial u_3} = b_3 p(S_m + E_m + I_m)e^{-\varphi t} - p(S_m\lambda_5^* + E_m\lambda_6^* + I_m\lambda_7^*)$$

where $b_3 p(S_m + E_m + I_m)$ is the marginal cost for IRS and $p(S_m\lambda_5^* + E_m\lambda_6^* + I_m\lambda_7^*)$ is the marginal benefit for using the sprayed houses. Furthermore, it can be deduced that the optimal policy for a sprayed house is given by

$$u_3(t) = \begin{cases} 0 \quad if \quad b_3 p(S_m + E_m + I_m)e^{-\varphi t} > p(S_m\lambda_5^* + E_m\lambda_6^* + I_m\lambda_7^*) \\ (0,1) \quad if \quad b_3 p(S_m + E_m + I_m)e^{-\varphi t} = p(S_m\lambda_5^* + E_m\lambda_6^* + I_m\lambda_7^*) \\ 1 \quad if \quad b_3 p(S_m + E_m + I_m)e^{-\varphi t} < p(S_m\lambda_5^* + E_m\lambda_6^* + I_m\lambda_7^*) \end{cases}.$$

(3.63)

The spraying of insecticides against mosquitoes is optimal for malaria disease control if the marginal cost $b_3 p(S_m + E_m + I_m)$, is less than the marginal benefit, $p(S_m\lambda_5^* + E_m\lambda_6^* + I_m\lambda_7^*)$).

In addition, we will quantitatively analyze the marginal benefit and marginal costs of the four interventions.

3.5.1.4 Economic Evaluation of IPTp

Intermittent Preventive Treatment (IPTp) prevention parameter in the system (3.1) and in the Hamiltonian equation, H_b, (3.60) is $u_4(t)$. Then differentiating $H_b$with respect to u_4 gives

$$\frac{\partial H_b}{\partial u_4} = -b_4 e^{-\varphi t}(S_h + E_h) + \frac{\beta\epsilon\phi I_m S_h}{N_{hw}}(\lambda_2^* - \lambda_1^*)$$

in which $\frac{\beta\epsilon\phi I_m S_h}{N_{hw}}(\lambda_1^* - \lambda_1^*)$ is the total marginal benefit due to the use of IPTp while $b_4 e^{-\varphi t}(S_h + E_h)$ is the marginal cost of acquiring the IPTp. The equivalency of the marginal cost and marginal benefit leads one to achieve the optimal policy.

Hence;

$$u_4(t) = \begin{cases} 0 \quad if \quad b_4 e^{-\varphi t}(S_h + E_h) > \dfrac{\beta\epsilon\phi I_m S_h}{N_{hw}}(\lambda_2^* - \lambda_1^*) \\ (0,1) \quad if \quad b_4 e^{-\varphi t}(S_h + E_h) = \dfrac{\beta\epsilon\phi I_m S_h}{N_{hw}}(\lambda_2^* - \lambda_1^*) \\ 1 \quad if \quad b_4 e^{-\varphi t}(S_h + E_h) < \dfrac{\beta\epsilon\phi I_m S_h}{N_{hw}}(\lambda_2^* - \lambda_1^*) \end{cases}. \tag{3.64}$$

Numerical simulations are done to show the impact of the shadow prices (marginal value/ cost) and marginal benefits by evaluating the shadow prices at the start of the malaria epidemic and as a function of the numbers of recovered or protected at the time of outbreak (susceptible human beings).

3.5.2 Analysis of Optimal Control

We consider the objective function

$$J(u_1, u_2, u_3, u_4) = \int_0^T (A_1 N_m + A_2 I_h + A_3 E_h + (B_1 u_1^2 + B_2 u_2^2 + B_3 u_3^2 + B_4 u_4^2)) e^{-\varphi t} dt \tag{3.65}$$

subject to

$$\frac{dS_h}{dt} = \Lambda_h + \psi R_h - (1-u_1)\lambda_h S_h - (1-u_4)\lambda_{hw} S_h - \mu_h S_h$$

$$\frac{dE_h}{dt} = (1-u_1)\lambda_h S_h + (1-u_4)\lambda_{hw} S_h - (\alpha_h + \mu_h) E_h$$

$$\frac{dI_h}{dt} = \alpha_h E_h - (\delta_h + \mu_h) I_h - (b + \tau u_2) I_h$$

$$\frac{dR_h}{dt} = (b + \tau u_2) I_h - (\psi + \mu_h) R_h$$

$$\frac{dS_m}{dt} = \Lambda_m - (1-u_1)\lambda_m S_m - (\mu_m + a u_1 + p u_3) S_m$$

$$\frac{dE_m}{dt} = (1-u_1)\lambda_m S_m - \alpha_m E_m - (\mu_m + a u_1 + p u_3) E_m$$

$$\frac{dI_m}{dt} = \alpha_m E_m - (\mu_m + a u_1 + p u_3) I_m$$

$$S_h(0) \geq 0, E_h(0) \geq 0, I_h(0) \geq 0, R_h(0) \geq 0, S_m(0) \geq 0, E_m(0) \geq 0, I_m(0) \geq 0$$

and the total cost at time t is given by

$$C = \int_0^T [b_1 u_1 (S_h + S_m + E_m + I_m) + b_2 u_2 I_h + b_3 u_3 (S_m + E_m + I_m) + b_4 u_4 (S_h + E_h)] dt \tag{3.66}$$

where $A_1, A_2, A_3, B_1, B_2, B_3, B_4$ are desired positive weights on the benefits of preventing infection and exposure plus total mosquito population. Here, we assume that there is no

linear relationship between the coverage of these interventions and their corresponding costs, hence we choose a quadratic cost on the controls in keeping with what is in other literature on cost of control of epidemics (Adams *et al.*, 2004; Okosun *et al.*, 2013; Mwamtobe *et al.*, 2014; Joshi, 2002). Our goal with the given objective function is to minimize the number of infected humans, exposed humans and total mosquito population while minimizing the cost of control $u_1(t), u_2(t), u_3(t)$ and $u_4(t)$. We seek an optimal control u_1^*, u_2^*, u_3^* and u_4^* such that

$$J(u_1^*, u_2^*, u_3^*, u_4^*) = \min_{u_1,u_2,u_3,u_4 \epsilon U} J(u_1, u_2, u_3, u_4) \tag{3.67}$$

where U is the set of measurable functions defined from $[0, T]$ onto $[0,1]$.

The necessary conditions that an optimal control must satisfy come from the Pontryagin's Maximum Principle (Pontryagin *et al.*, 1962). This consists in minimizing, with respect to (u_1, u_2, u_3, u_4).

Forming the Hamiltonian from the objective function (3.65) subject to equations (3.1) and (3.66)

$$\begin{aligned} H = \big(&A_1 N_m + A_2 I_h + A_3 E_h + (B_1 u_1^2 + B_2 u_2^2 + B_3 u_3^2 + B_4 u_4^2)\big) e^{-\varphi t} \\ &+ \{\Lambda_h + \psi R_h - (1-u_1)\lambda_h S_h - (1-u_4)\lambda_{hw} S_h - \mu_h S_h\}\lambda_1 \\ &+ \{(1-u_1)\lambda_h S_h + (1-u_4)\lambda_{hw} S_h - (\alpha_h + \mu_h) E_h\}\lambda_2 \\ &+ \{\alpha_h E_h - (\delta_h + \mu_h) I_h - (b + \tau u_2) I_h\}\lambda_3 \\ &+ \{(b + \tau u_2) I_h - (\psi + \mu_h) R_h\}\lambda_4 \\ &+ \{\Lambda_m - (1-u_1)\lambda_m S_m - (\mu_m + a u_1 + p u_3) S_m\}\lambda_5 \\ &+ \{(1-u_1)\lambda_m S_m - \alpha_m E_m - (\mu_m + a u_1 + p u_3) E_m\}\lambda_6 \\ &+ \{\alpha_m E_m - (\mu_m + a u_1 + p u_3) I_m\}\lambda_7 \\ &+ \{[b_1 u_1 (S_h + S_m + E_m + I_m) + b_2 u_2 I_h + b_3 u_3 (S_m + E_m + I_m) \\ &+ b_4 u_4 (S_h + E_h)]\}\lambda_C \end{aligned} \tag{3.68}$$

where $\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6$ and λ_7 are the adjoint variables or co-state variables given by the following system:

$$\frac{d\lambda_1}{dt} = -\frac{\partial H}{\partial S_h} = (1-u_1)\lambda_h\lambda_1^* + (1-u_4)\lambda_{hw}\lambda_1^* + \mu_h\lambda_1^* - (1-u_1)\lambda_h\lambda_2^* - (1-u_4)\lambda_{hw}\lambda_2^* - \lambda_C(b_1u_1 + b_4u_4)$$

$$\frac{d\lambda_2}{dt} = -\frac{\partial H}{\partial E_h} = -A_3 + \alpha_h\lambda_2^* + \mu_h\lambda_2^* - \alpha_h\lambda_3^* - \lambda_C(b_1u_1 + b_4u_4)$$

$$\frac{d\lambda_3}{dt} = -\frac{\partial H}{\partial I_h} = -A_2 + (b + \tau u_2 + \mu_h + \delta_h)\lambda_3^* - (b + \tau u_2)\lambda_4^* - \lambda_C b_2 u_2 + \left(\frac{(1-u_1)\lambda\epsilon\phi S_m}{N_h}\right)\lambda_5 - \left(\frac{(1-u_1)\lambda\epsilon\phi S_m}{N_h}\right)\lambda_6$$

$$\frac{d\lambda_4}{dt} = -\frac{\partial H}{\partial R_h} = -\psi\lambda_1^* + (\mu_h + \psi)\lambda_4^*$$

$$\frac{d\lambda_5}{dt} = -\frac{\partial H}{\partial S_m} = -A_1 + (1-u_1)\lambda_m\lambda_5^* + (\mu_m + au_1 + pu_3)\lambda_5^* - (1-u_1)\lambda_m\lambda_6^* - \lambda_C(b_1u_1 + b_3u_3)$$

$$\frac{d\lambda_6}{dt} = -\frac{\partial H}{\partial E_m} = -A_1 + \alpha_m\lambda_6^* + (\alpha_m + \mu_m + au_1 + pu_3)\lambda_6^* - \alpha_m\lambda_7^* - \lambda_C(b_1u_1 + b_3u_3)$$

$$\frac{d\lambda_7}{dt} = -\frac{\partial H}{\partial I_m} = -A_1 + (\mu_m + au_1 + pu_3)\lambda_7^* - \lambda_C(b_1u_1 + b_3u_3) + \left(\frac{(1-u_1)\beta\epsilon\phi S_h}{N_h} + \frac{(1-u_4)\beta\epsilon\phi S_h}{N_{hw}}\right)\lambda_1 + \left(-\frac{(1-u_1)\beta\epsilon\phi S_h}{N_h} - \frac{(1-u_4)\beta\epsilon\phi S_h}{N_{hw}}\right)\lambda_2$$

$$\frac{d\lambda_C}{dt} = 0$$

(3.69)

By applying Pontryagin's Maximum Principle (Pontryagin *et al.*, 1962) and the existence result for the optimal control from Fleming & Rishel (1975), we obtain

Proposition 1: The optimal control $(u_1^*, u_2^*, u_3^*, u_4^*)$ that minimizes $J(u_1, u_2, u_3, u_4)$ over U is given by

$$u_1^* = max\left\{0, min\left(1, \frac{(\lambda_2 - \lambda_1)\lambda_h S_h^* + (\lambda_6 - \lambda_5)\lambda_m S_m^* + aS_m^*\lambda_5 + aE_m^*\lambda_6 + aI_m^*\lambda_7 + \lambda_C b_1(S_h^* + S_m^*)}{2B_1 e^{-\varphi t}}\right)\right\}$$

$$u_2^* = max\left\{0, min\left(1, \frac{(\tau(\lambda_3 - \lambda_4)I_h^* + \lambda_C b_2 I_h^*)e^{\varphi t}}{B_2}\right)\right\}$$

$$u_3^* = max\left\{0, min\left(1, \frac{\big(p(\lambda_5 S_m^* + \lambda_6 E_m^* + \lambda_7 I_m^*) + \lambda_C b_3(S_m^* + E_m^* + I_m^*)\big)e^{\varphi t}}{B_3}\right)\right\}$$

$$u_4^* = max\left\{0, min\left(1, \frac{(\lambda_2 - \lambda_1)\lambda_{hw} S_h^* + \lambda_C b_4(S_h^* + E_h^*)}{2B_4 e^{-\varphi t}}\right)\right\}$$

(3.70)

where $\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6$ and λ_7 are the adjoint variables or co-state variables satisfying (3.69) and the following transversality conditions:

$$\lambda_1(T) = \lambda_2(T) = \lambda_3(T) = \lambda_4(T) = \lambda_5(T) = \lambda_6(T) = \lambda_7(T) = \lambda_C(T) = 0.$$

(3.71)

Proof: From Fleming and Rishel (1975), the existence of an optimal control is a consequence of the convexity of the integrand of J with respect to u_1, u_2, u_3, u_4, a priori boundedness of the state variables, and the Lipschitz property of the state system with respect to the state variables. The differential equations governing the adjoint variables are obtained by differentiation of the Hamiltonian function, evaluated at the optimal control. Then the adjoint system can be written as,

$$0 = \frac{\partial H}{\partial u_1} = -u_1^c 2B_1 e^{-\varphi t} + (\lambda_2 - \lambda_1)\lambda_h S_h^* + (\lambda_6 - \lambda_5)\lambda_m S_m^* + aS_m^*\lambda_5 + aE_m^*\lambda_6 + aI_m^*\lambda_7 + \lambda_C b_1(S_h^* + S_m^*)$$

$$0 = \frac{\partial H}{\partial u_2} = u_2^c 2B_2 - (\tau(\lambda_3 - \lambda_4)I_h^* + \lambda_C b_2 I_h^*)e^{\varphi t}$$

$$0 = \frac{\partial H}{\partial u_3} = u_3^c 2B_3 - \big(p(\lambda_5 S_m^* + \lambda_6 E_m^* + \lambda_7 I_m^*) + \lambda_C b_3(S_m^* + E_m^* + I_m^*)\big)e^{\varphi t}$$

$$0 = \frac{\partial H}{\partial u_4} = -u_4^c 2B_4 e^{-\varphi t} - (\lambda_2 - \lambda_1)\lambda_{hw} S_h^* + \lambda_C b_4 (S_h^* + E_h^*)$$

Due to the a priori boundedness of the solutions of both the state and adjoint equations and the resulting Lipschitz structure of these equations, we obtain the uniqueness of the optimality system ((3.69) – (3.71)) for small T.

The restriction on the length of time interval $[0, T]$ is common in control problems (Okosun *et al.,* 2013; Felippe de Souza *et al.,* 2000; Joshi, 2002), it guarantees the uniqueness of the optimality system.

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

$$u_1^* = \begin{cases} 0 \; if \; u_1^c \leq 0 \\ u_1^c \; if 0 < u_1^c < 1 \\ 1 \; if \; u_1^c \geq 0 \end{cases}, u_2^* = \begin{cases} 0 \; if \; u_2^c \leq 0 \\ u_2^c \; if 0 < u_2^c < 1 \\ 1 \; if \; u_2^c \geq 0 \end{cases}, u_3^* = \begin{cases} 0 \; if \; u_3^c \leq 0 \\ u_1^c \; if 0 < u_3^c < 1 \\ 1 \; if \; u_3^c \geq 0 \end{cases},$$

$$u_4^* = \begin{cases} 0 \; if \; u_4^c \leq 0 \\ u_1^c \; if 0 < u_4^c < 1 \\ 1 \; if \; u_4^c \geq 0 \end{cases}.$$

The optimal control is obtained by solving the optimality system ((3.69) – (3.71)). An iterative scheme is used for solving the optimality system. We start by solving the state equations with a guess for the controls over the simulated time using fourth order Runge–Kutta scheme. Because of the transversality conditions (3.70), the adjoint equations are solved by the backward fourth order Runge–Kutta scheme using the current iterations solutions of the state equation. Then the controls are updated by using a convex combination of the previous controls and the value from the characterizations (3.70). This process is repeated and iterations stopped if the values of the unknowns at the previous iterations are very close to the ones at the present iterations (Lenhart & Workman, 2007). Parameter values from Table 4.1 are used for the numerical simulation.

3.5.3 Cost–Effectiveness Analysis

The intervention strategies in practice are mutually exclusive interventions, therefore it is essential to use incremental cost-effectiveness ratios. Mutually exclusive interventions occur where the implementation of one intervention results in changes to the cost and effects of the other. The incremental cost-effectiveness ratio (ICER) is calculated in order to achieve the goal of comparing the costs and the effectiveness of the intervention strategies.

The ICER is mostly defined as the additional cost per additional health outcome (effect). It provides a means of comparing interventions across various disease status and interventions strategies being implemented in the community or in the nation.

The different intervention measures are compared to determine which provides a most cost-effective control to malaria disease. ICER required the ranking of the alternative intervention strategies according to their effectiveness on the basis of securing maximum effect rather than considering cost.

Then one intervention strategy was compared with the next less effective alternative intervention strategy when relating two or more competing intervention strategies.

We use a more classical approach to analyze the cost-effectiveness of the 15 alternative strategies by using the ICER in Okosun *et al.,* (2013). ICER is applied to achieve the goal of comparing the costs and the health outcomes of two alternative intervention strategies that compete for the same resources. It is generally described as the additional cost per additional health outcomes. The ICER numerator includes the differences in the intervention strategy costs, averted disease costs, costs of prevented cases and averted productivity losses if applicable. The ICER denominator is the differences in health effects (e.g. total number of infections averted, number of susceptibility cases prevented). ICER is given by

$$ICER\ for\ Q = \frac{Cost\ of\ Intervention\ Q - Cost\ of\ Intervention\ P}{Effect\ of\ Intervention\ Q - Effect\ of\ Intervention\ P}$$

where P and Q are the two intervention strategies being compared in this case, and the effect or benefits in health status are measured in terms of quality-adjusted life years

(QALYs) gained or lost. Alternatives that are more expensive and less ineffective are then excluded. This is done after simulating the optimal control model and then ranking strategies in order of increasing effectiveness measured as the total infections averted.

CHAPTER FOUR

RESULTS AND DISCUSSION

4.1 Numerical Results for Malaria Model with Intervention Strategies

In this section the model is solved using Runge-Kutta fourth order scheme in R Statistical computing platform (R Development Core Team, 2011). The aim is to verify some of the analytical results on the stability of system (3.1).

4.1.1 Summary of Data

Data was collected from the literature, Division of Malaria Control (DOMC), Kenya National Bureau of Statistics, Malaria Indicator Survey for Kenya, Demographic Health Survey (DHS) for Kenya, WHO websites and hospital records (from Kisumu, Kisii, Chuka (Tharaka-Nithi) and Nyeri counties representing the four different transmission settings/ epidemiological zones in Kenya). All these collected data guided in the calculations/ estimation of parameter for the malaria model (3.1) while some values were assumed.

4.1.2 Parameter Values for Malaria Transmission Model

The parameters in the model (3.1) were estimated using clinical malaria data and demographics statistics of Kenya. Those that were not available were obtained from literature published by researchers in malaria endemic countries which have similar environmental conditions compare to Kenya. The total population for pregnant women in Kisumu in 2015 is 266343, Kisii is 324658, Chuka (Tharaka Nithi) is 94857 and Nyeri is 200216 (based on census 2009 estimates) (KNBS, 2010). The total number of children under five in Kisumu is 173826, Kisii is 210,435, Chuka is 52975 and Nyeri is 90487 (based on census 2009 estimates). The population growth rate per year is 2.1% for Kisumu, 2.1% for Kisii, 2.0% for Tharaka Nithi and 1.3% for Nyeri. The population of pregnant women was estimated as the population for the fertility/ reproductive age (15-49 years). Furthermore, Life expectancy at birth in 2014 is 51years for Kisumu, 59 years for Kisii, 64 years for Tharaka Nithi and 60 years for Nyeri (KNBS Estimates based on 2009 Census). We estimate that it will take 7 days for human to recover from malaria infection

through chemotherapy and the incubation period of malaria in humans is from 10 to 14 days as per the National Guidelines for Diagnosis, Treatment and Prevention of Malaria in Kenya (DOMC, 2010). Disease induced deaths/ mortality was calculated based on information from hospital records and KDHS. Finally, the probability of transmission of malaria infection from infectious humans to susceptible mosquitoes is estimated to be 0.42 and we also assume that person who has completely recovered from malaria will lose his/her malaria acquired immunity after 3 months based on information received from medical malaria researchers in Kenya.

Gimnig et al., (2003) provided quarterly data for the average number of Anopheles *gambiae* and Anopheles *funestus* mosquitoes in a region of Western Kenya (Asembo). From this data, Chitnis (2005) used an estimate of 2 Anopheles gambiae and 0.8 Anopheles funestus mosquitoes per house for his PhD thesis in high malaria transmission areas; therefore we can also conservatively estimate that we have 10 female Anopheles mosquitoes in each house in Kenya and hence the number of the female Anopheles mosquito population for each region is approximated by multiplying the population by 10. We use an estimate of 0.40 bites on humans per mosquito per day in Kenya. The estimation of biting includes both, the dependence on the mosquito's gonotrophic cycle (the number of days a mosquito requires to produce eggs before it searches for a blood meal again), and the dependence on the mosquito's anthropophilic rate (the mosquito's preference for human blood as opposed to other mammalian blood). The probability of transmission of infection from an infectious mosquito to a susceptible human is estimated to be 0.0655. Latent period in mosquitoes is estimated to be 11 days for malaria endemic areas (Chitnis, 2005) and finally, the life expectancy of an adult anopheles mosquito is assumed to be 25 days considering mortality of mosquitoes due to indoor residual spraying, mosquito coils and insecticide-treated bed nets.

The rate of human infection and rate of mosquito being infected by feeding on blood meal and the disease induced death were varied to represent the different transmission settings/ epidemiological zones in Kenya.

Table 4.1 provides a summary of the estimated values of all parameters.

Table 4.1: Parameter values for the full malaria model

Parameter	Estimated Value				Source
	Endemic	Epidemic	Seasonal	Low risk	
μ_h	0.00005447	0.00004644	0.00004281	0.00004566	KNBS (2010)
μ_m	0.04				Estimated
α_h	0.07143				Estimated
α_m	0.0909				Chitnis (2005)
λ	0.42				Estimated
β	0.0655				Estimated
ϵ	0.2				Kbenesh *et al.*, (2009)
ψ	0.01095				Estimated
Λ_h	0.00000575	0.00000575	0.00000548	0.00000438	KNBS (2015)
Λ_m	0.071				Niger & Gumel (2008)
b	0.005				Chiyaka *et al.*, (2008)
τ	0.5				Assumed
δ_h	0.05				KNBS & ICF Macro (2010)
p	0.25				Assumed
a	0.25				Assumed
ϕ	0.502				Kbenesh *et al.*, (2009)
λ_h	0.00000149	0.00000123	0.00000445	0.00000226	Estimated
λ_{hw}	0.00000247	0.00000203	0.00000693	0.00000328	Estimated
λ_m	0.00000048	0.00000394	0.00000143	0.00000073	Estimated
N_h	440169	535093	147832	290703	KNBS (2010)
N_{hw}	266343	324658	94857	200216	KNBS (2010)
N_m	4401690	5350930	1478320	2907030	Estimated

In addition the effect of the different intervention strategies are estimated as: $u_1 = 0.0904,\ u_2 = 0.165,\ u_3 = 0.076,\ u_4 = 0.035$. The initial state variables are constant across all the epidemiological zones and are chosen as $S_h(0) = 700$, $E_h(0) = 250$, $I_h(0) = 0$, $R_h(0) = 00$, $S_m(0) = 5000$, $E_m(0) = 500$, and $I_m(0) = 100$.

4.1.3 Sensitivity Indices of R_0

Numerical simulations are carried out to for the different parameters impacting on the reproduction number. The resulting sensitivity indices of R_0 to the different parameters in the model is presented in the Table 3.5.

The most sensitive parameter to R_0 across all the epidemiological zones is the mosquito's natural death rate, μ_m , $\left(\xi_{\mu_m}^{R_0} = -1.07211\right)$ followed by the mosquito biting rate, ϵ , $\left(\xi_{\epsilon}^{R_0} = 1\right)$ and the mosquito contact rate with humans, ϕ,

Its evident that an increase (or decrease) in mosquito biting rate, ϵ , by 10% increases or decreases R_0 by 10%. On the other hand an increase (or decrease) in mosquito death rate μ_m by 10% decreases (or increases) R_0 by 10%. It's suggested that strategies that can be applied in controlling and eradicating malaria are to target mosquito biting rate, mosquito contact rate with humans and mosquito death rates.

Further, this is followed by the transmission probability per bite from infectious human to susceptible mosquito, λ , the transmission probability of infection to humans per bite, β , and the recruitment rate of mosquitoes, Λ_m. Other key parameters include the recruitment rate of individuals, Λ_h. With $\xi_{\alpha_h}^{R_0} = 0.00038817$, the progression rate of individuals from the exposed to infectious malaria state, α_h , is the least sensitive.

Table 4.2: Sensitivity indices (SI) of R_0 to parameters for the malaria model

Parameter	Sensitivity Indices			
	Endemic	Seasonal	Epidemic	Low risk
μ_h	-0.0402531	-0.0402531	-0.0402531	-0.0402531
μ_m	-1.07211	-1.07211	-1.07211	-1.07211
α_h	0.00038817	0.00038817	0.00038817	0.00038817
α_m	0.22445	0.22445	0.22445	0.22445
λ	0.5	0.5	0.5	0.5
β	0.5	0.5	0.5	0.5
ϵ	1	1	1	1
Λ_h	-0.4980	-0.4980	-0.4980	-0.4980
Λ_m	0.5	0.5	0.5	0.5
b	-0.01818	-0.02048	-0.01639	-0.02563
τ	-0.322497	-0.322497	-0.322497	-0.322497
δ_h	-0.13695	-0.10336	-011321	-0.03508
ϕ	1	1	1	1

Sensitivity analysis showed that the most sensitive parameters were mosquito biting rate (ϵ) and mosquito death rate (μ_m) (Mwamtobe *et al.,* 2014; Agusto *et al.,* 2012; Oduro *et al.,* 2015). This shows that reducing mosquito deaths and biting rates plays an important role in reducing malaria transmission in Kenya. This can be achieved through use of IRS and ITNs which are regarded as vector control measures (Mwamtobe *et al.,* 2014; Agusto *et al.,* 2012; Oduro *et al.,* 2015). These findings agree with Oduro *et al.,* (2015) who also stated that combinations of control strategies would result in reducing infected mosquito and human population. This may be attributed to the fact that malaria is spared by a bite of an infected mosquito and hence reducing infected mosquito will have impact on the spread of the disease.

Therefore, interventions strategies which targets to reduce mosquito population should be implemented. This will help to reduce the mosquito biting rates and transmission from infectious mosquitoes and humans.

4.1.4 Numerical Simulations

Numerical simulation using the fourth order Range-Kutta method in R Statistical Computing platform is use to solve the malaria model (3.1) using the initial state variables and the parameter values from table (4.1). This will help study the numerically the behavior of the system (3.1). The malaria model 3.1 was simulated when there was no any intervention strategies and when there were the intervention strategies. The simulation was generated in a hundred and forty days' time to show the effect of these intervention strategies on the infected humans and mosquito populations.

4.1.4.1 Dynamics of Human Population of Malaria Model without Intervention Strategies

The simulation of the malaria model with intervention strategies was simulated to find out the dynamics of the disease in the population when there were no intervention strategies.

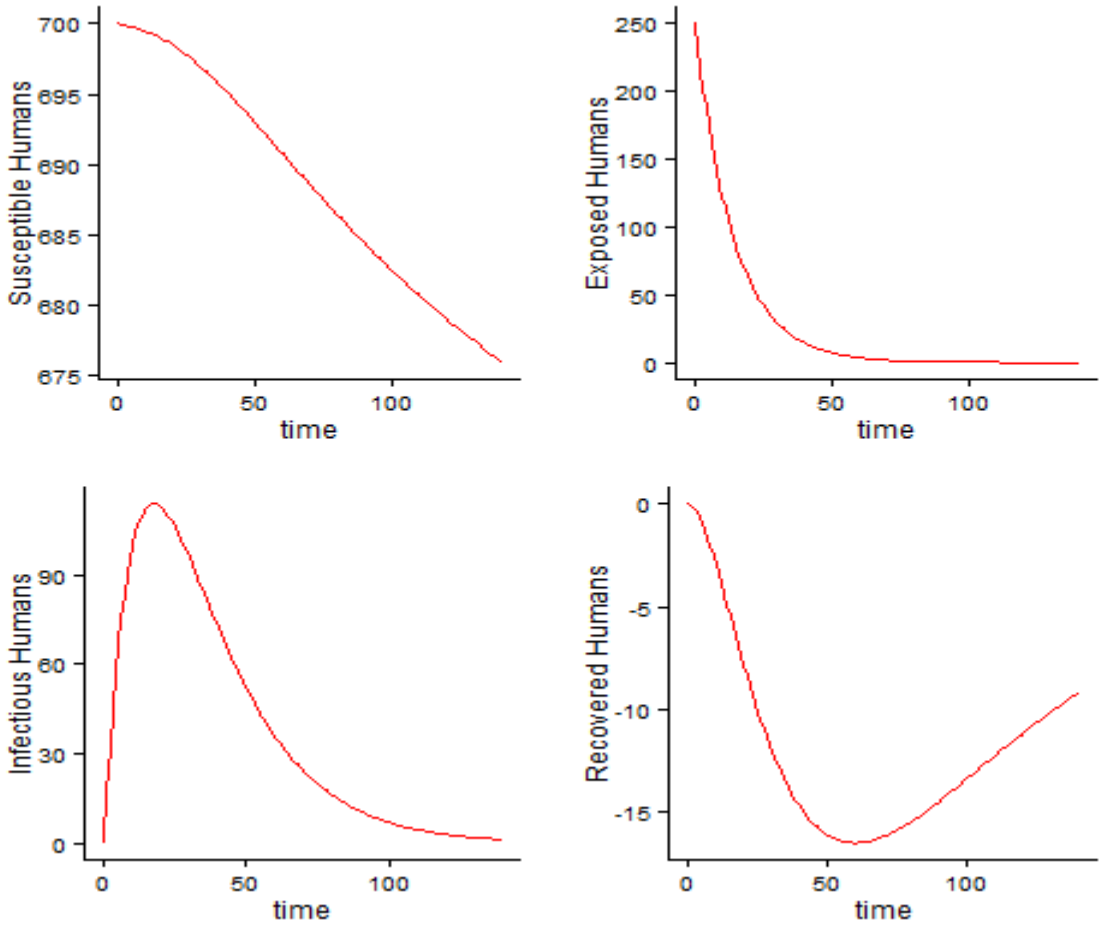


Figure 4.1: Simulations showing the dynamics of human population of malaria model without intervention strategies across all transmission settings

In the absence of the interventions strategies, the susceptible population decreases (Figure 4.1). This explains that the susceptible population will continue being exposed to the disease and as such exposed population will increase. The infected population increases due to the increase in the exposure to the disease. This supports the theorem that disease is endemic when $R_0 > 1$. The recovered population decreases as a result of the presence of the disease in the society in which no intervention strategies are being practiced.

The existence of multiple endemic equilibria emphasizes the fact that $R_0 < 1$ is not sufficient to eradicate disease from the population and the need to lower R_0 much below one to make the disease free equilibrium to be stable globally. R_0 must further reduced below new R_0^* in order to avoid endemic states and guarantee the eradication. These

findings agree with Chitnis *et al.,* (2006) and Wan & Cui (2009) who showed the possibility of backward bifurcation. Malaria transmission therefore can be reduced by deployment of different combinations of malaria control strategies (Mwamtobe *et al.,* 2014; Agusto *et al.,* 2012; Oduro *et al.,* 2015).

4.1.4.2 Dynamics of Human Population with Intervention Strategies

We simulated malaria model with intervention strategies to find the dynamics of human and mosquito populations as shown in Figure 4.2 and Figure 4.3 below. It is observed that the control strategy leads to decrease in the number of infected human (I_h). The uncontrollable case leads to a decrease in the number of infected mosquitoes (I_m), while the control strategy lead to decrease in the infected number.

The number of S_h increases as the exposed and infected human population decreases due to positive effect of the intervention strategies being implemented (Figure 4.2).

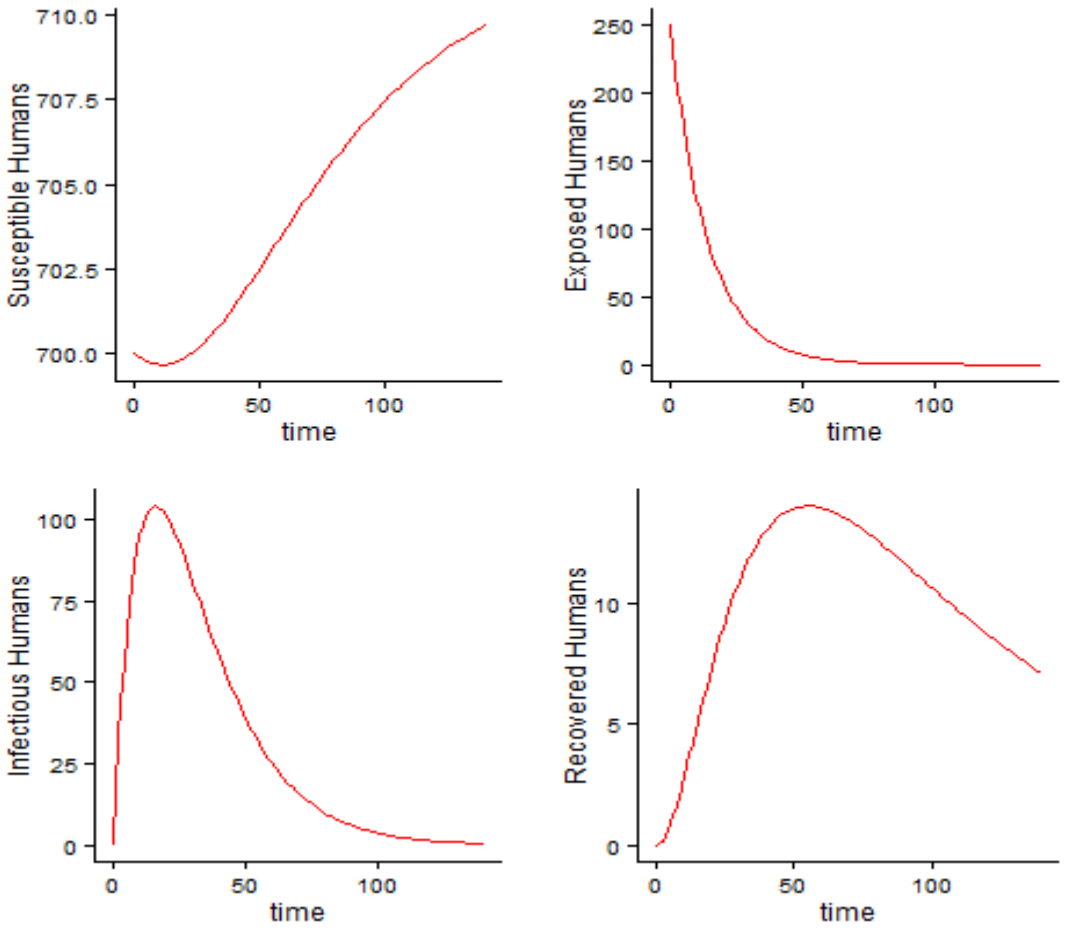


Figure 4.2: Simulations showing the dynamics of human population with intervention strategies across all transmission settings

4.1.4.3 Dynamics of Mosquito Population

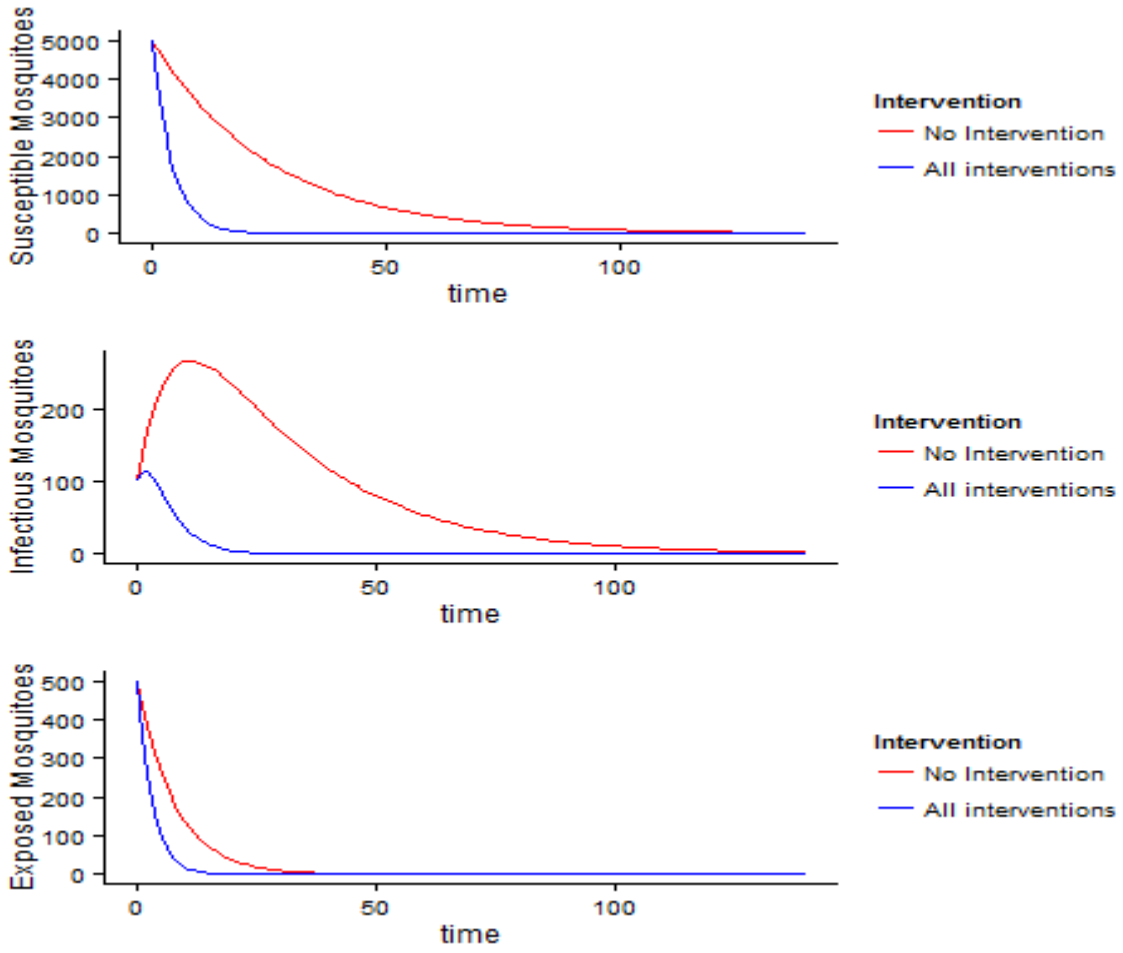


Figure 4.3: Simulations showing the effect of intervention strategies on mosquito population across all transmission settings

Figure 4.3 shows that S_m , E_m and I_m increases with time when there are no intervention strategies but reduces when there are intervention strategies. This confirms the role of intervention strategies in reducing mosquito population.

The effect on the number of infected humans, mosquito population and exposed humans were compared in situations where there were no intervention/ control variable versus when there were the intervention variables. Numerical simulations were used to confirm the analytic results and to explore the behavior of the formulated model. The findings

from our study showed that when there were no intervention strategies the numbers of exposed and infected humans and mosquitoes increases while when there were interventions then the number in the classes increase. This is comparable to the findings from Griffin *et al.,* (2010) who found that for the use of LLINs, IRS coupled with mass screening and treatment would result in the reduction of parasitic prevalence to below 1%. The results confirm the roles that the control strategies have in lowering the exposed and infected classes of mosquito and human populations. This is because malaria control strategies have effect on minimizing transmission of malaria.

Our study was slightly different from other modeling approach for malaria transmission with intervention strategies (Okosun *et al.,* 2013; Mwamtobe *et al.,* 2014) in that we considered the most at risk group (the pregnant and the under five children) and can be applied to different transmission settings for malaria. We also considered the use of IPTp as an intervention strategy for the pregnant women which is recommended by WHO (WHO, 2014). This study provided a useful tool for assessing the effectiveness and the potential impact of the intervention strategies in minimizing malaria transmission.

Since this is the first ever modeling and simulation of four malaria intervention strategies in free R statistical computing platform, more future testing and refinement of the model together with simulation with data form other representative settings should be done to improve the results and the model. This modeling approach can be extended to optimal control theory and cost effectiveness analysis to assess the cost aspect and health benefits of the interventions strategies being practiced in Kenya.

Mathematical models provide a framework for understanding disease dynamics which forms the basis of designing and analyzing the potential impact of intervention strategies. This modeling approach can guide the post-2015 malaria eradication strategies and the achievement of the Sustainable Development Goals.

4.2 Numerical Results on Optimal Control Analysis

In this section we discuss the method and present the results obtained from solving the optimality system numerically using the parameter values in Table 4.1. The initial state

variables for the different epidemiological zones fixed with values $S_h(0) = 700$, $E_h(0) = 250$, $I_h(0) = 0$, $R_h(0) = 0$, $S_m(0) = 5000$, $E_m(0) = 500$, and $I_m(0) = 100$. The following weight factors were also fixed for the different epidemiological scenarios as $B_1 = 20$, $B_2 = 65$, $B_3 = 10$, $B_4 = 10$, $A_3 = 100$, $A_2 = 92$, and $A_1 = 20$. These factors were used for our model numerical simulation purposes on which there is no significant meaning attached. We balance the host populations and control functions in the cost function 3.52 by choosing weight constant values because the magnitudes of the host populations and control functions are on different scales. It is assumed that the weight factor of $A_1 < A_2 < A_3$. We assign the weight factor u_1 when using ITNs greater than the weight factors for treatment u_2 , IRS u_3 and IPTp u_4.

The effect of the several optimal control strategies on the spread of malaria is investigated numerically. We compare the numerical results from the simulation using one control and various combinations of two, three and four control strategies. This was done by comparing when there were no any intervention strategies and when there were the intervention strategies. There are 15 different control strategies for each of the four different epidemiological zones in Kenya that are explored. We use the case of endemic zone with the case of one control variable, two control variables, three control variables and all the four control variables are in use for the illustration purpose.

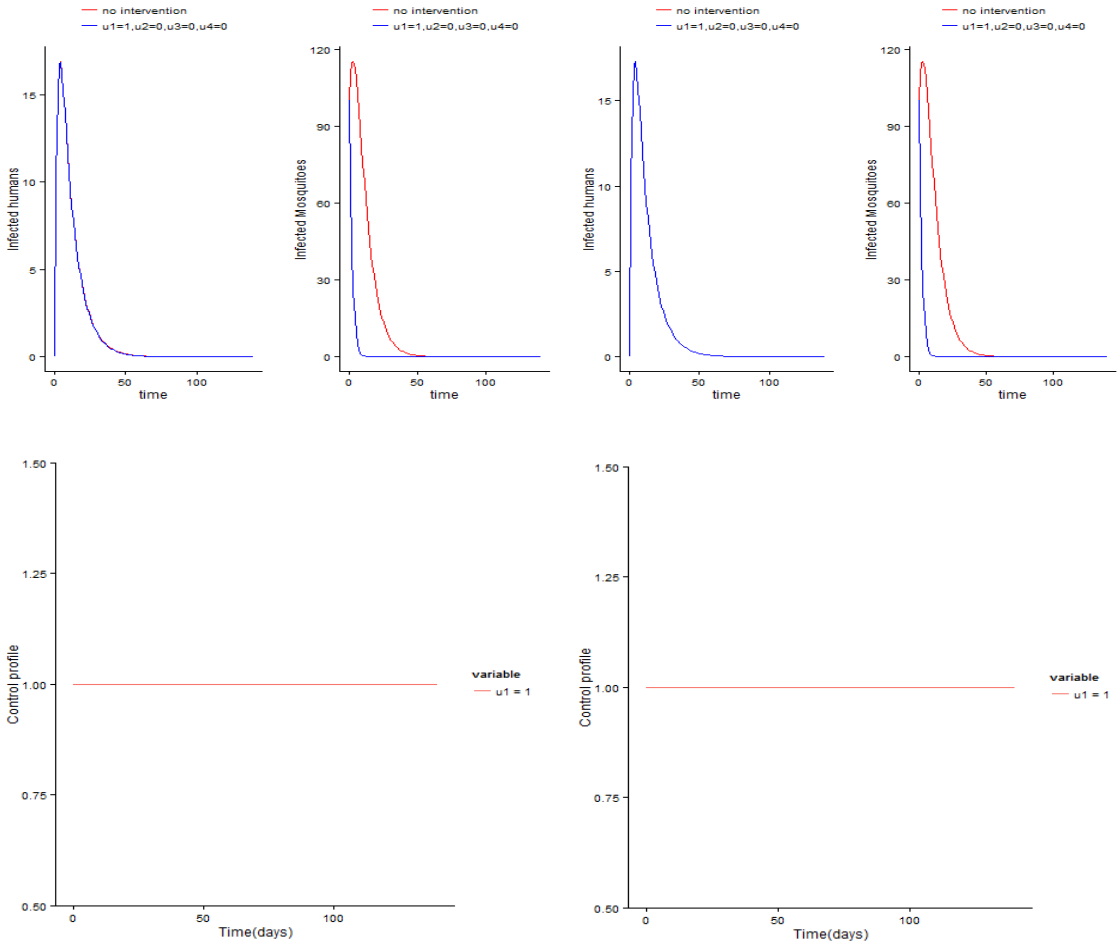
Results of only one intervention strategies for the 4 epidemiological zones for the different combinations of the control strategies are shown in Figure 4.4 – Figure 4.18. Part (a) represents the endemic situation, part (b) represent the epidemic situation, part (c) represent the seasonal situation and part (d) represent the low risk situation. In each of the cases, the results in Figure 4.1 – 4.15 shows a significant difference in I_h and I_m with the control strategy compared to I_h and I_m without the control strategy. It is observed that the control strategy leads to decrease in the number of infected human (I_h). The uncontrollable case leads to a decrease in the number of infected mosquitoes (I_m), while the control strategy lead to decrease in the infected number. The control profiles shows the upper bound time for each strategy for each settings before dropping to the lower bound.

The control profile shows the upper bound time for each strategy for each of the transmission setting before dropping to the lower bound. The time at which its dropping shows the time at which the intervention effect is being felt in reducing the number of infectious humans and mosquito population.

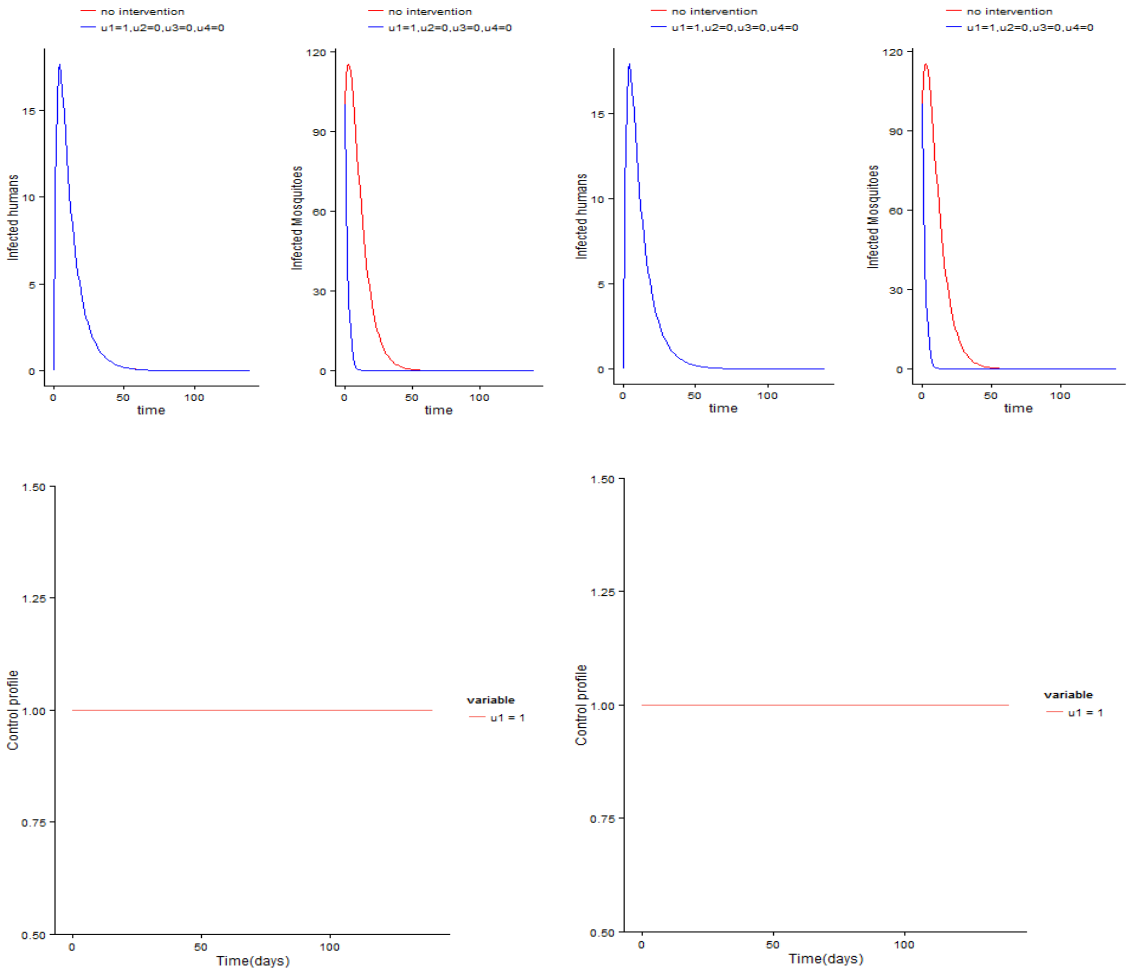
Results of only one intervention strategies for the 4 epidemiological zones

a. <u>Optimal protection using ITN</u>

Only the control (u_1) on ITNs is used to optimize the objective function J, while the control on treatment (u_2), the control on IRS (u_3) and control on IPTp (u_4) are set to zero.



(a) (b)

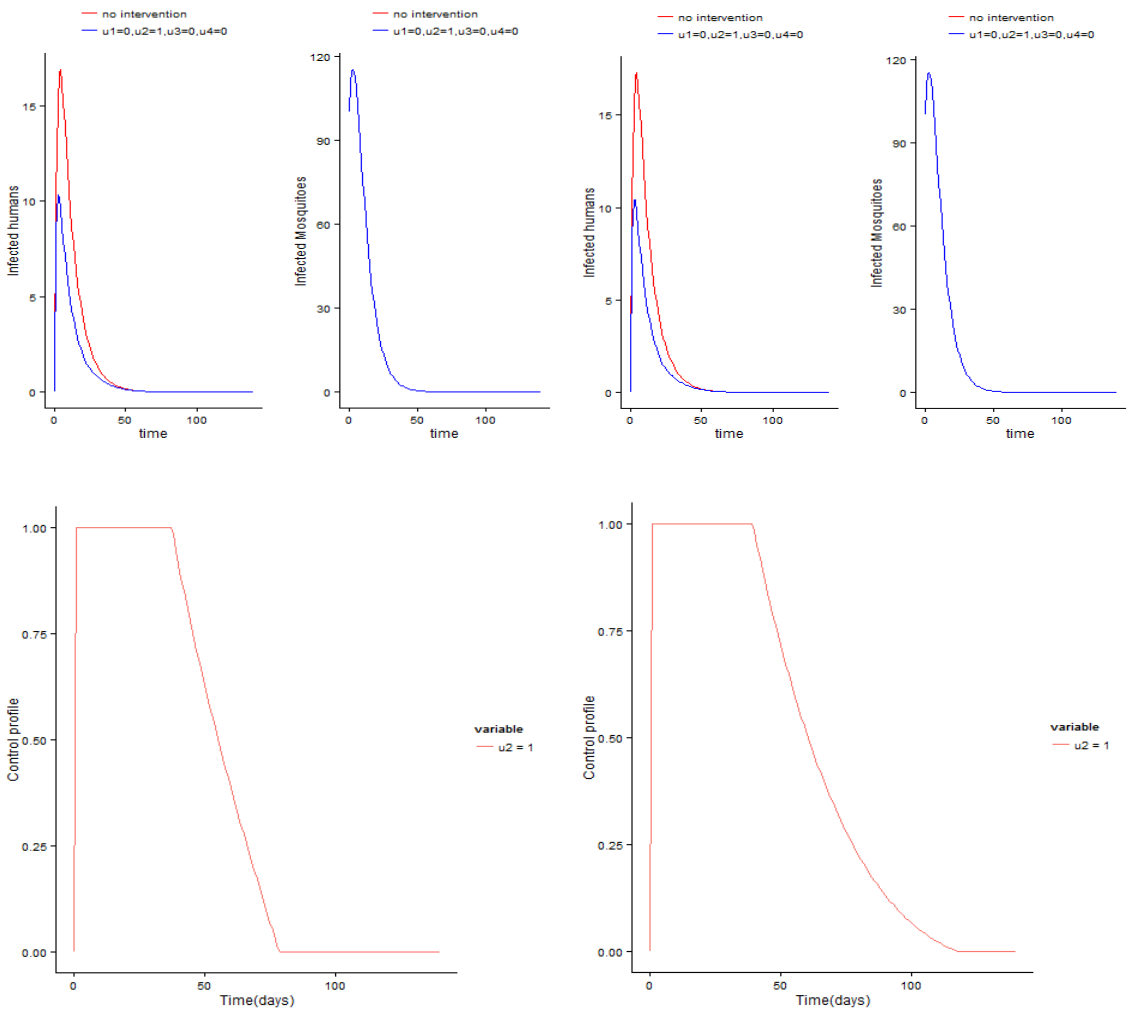


(c) (d)

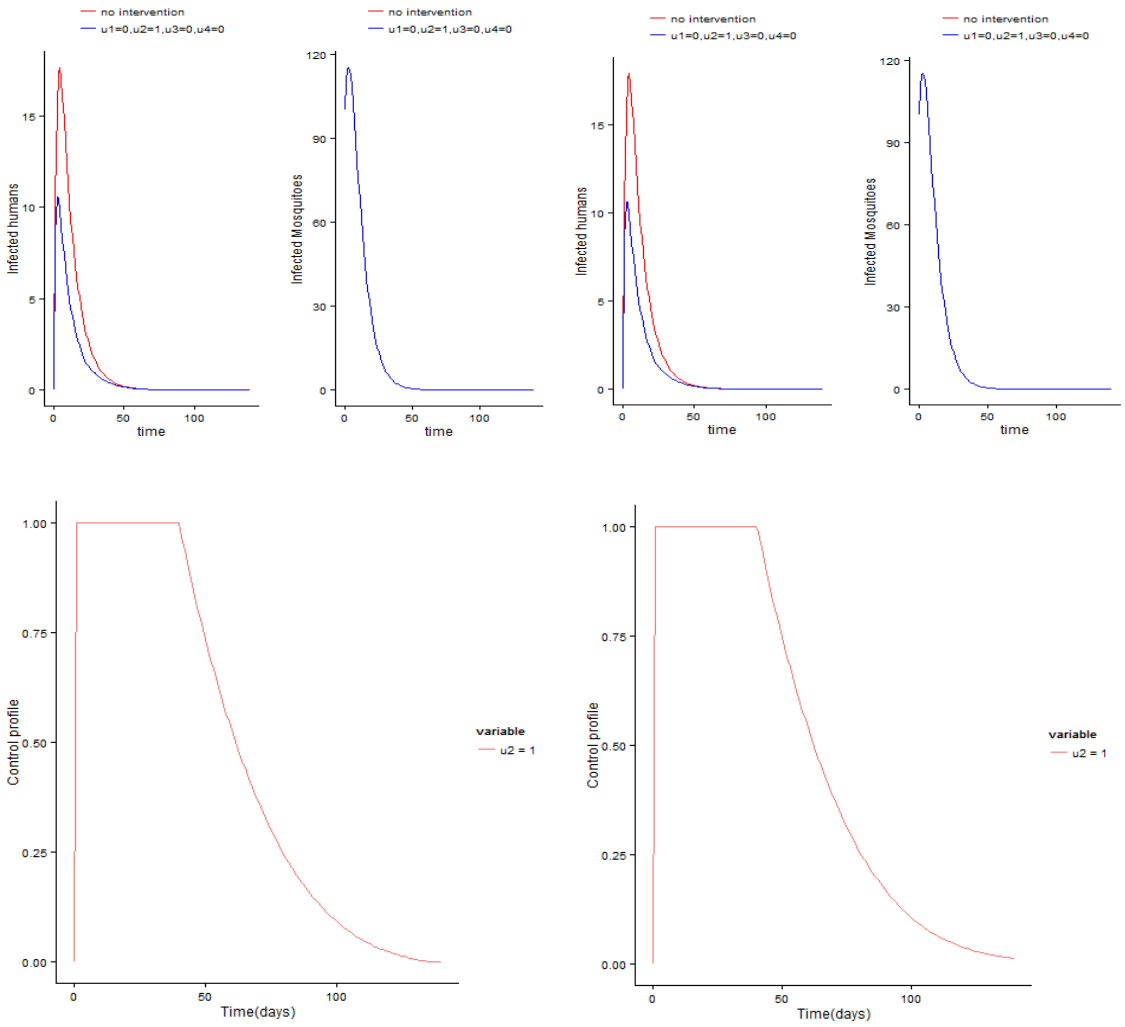
Figure 4.4: Simulations of the model showing the effect of ITNs only on the spread of malaria for the different transmission settings

b. <u>Optimal treatment</u>

Only the control (u_2) on treatment is used to optimize the objective function J, while the control on ITNs (u_1), the control on IRS (u_3) and control on IPTp (u_4) are set to zero.


no intervention
u1=0,u2=1,u3=0,u4=0
Infected humans
Infected Mosquitoes
time
Control profile
Time(days)
variable
u2 = 1

(a) (b)

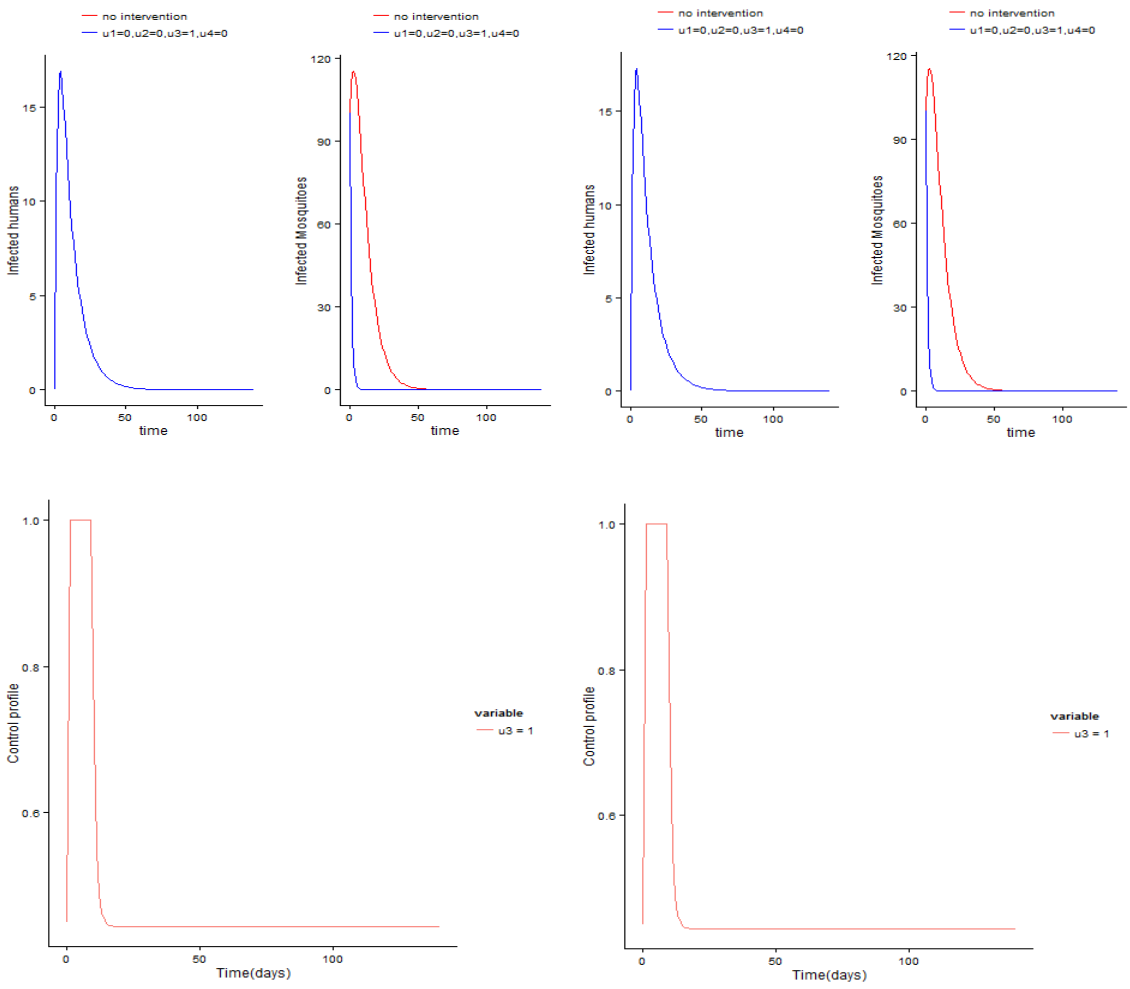


(c) (d)

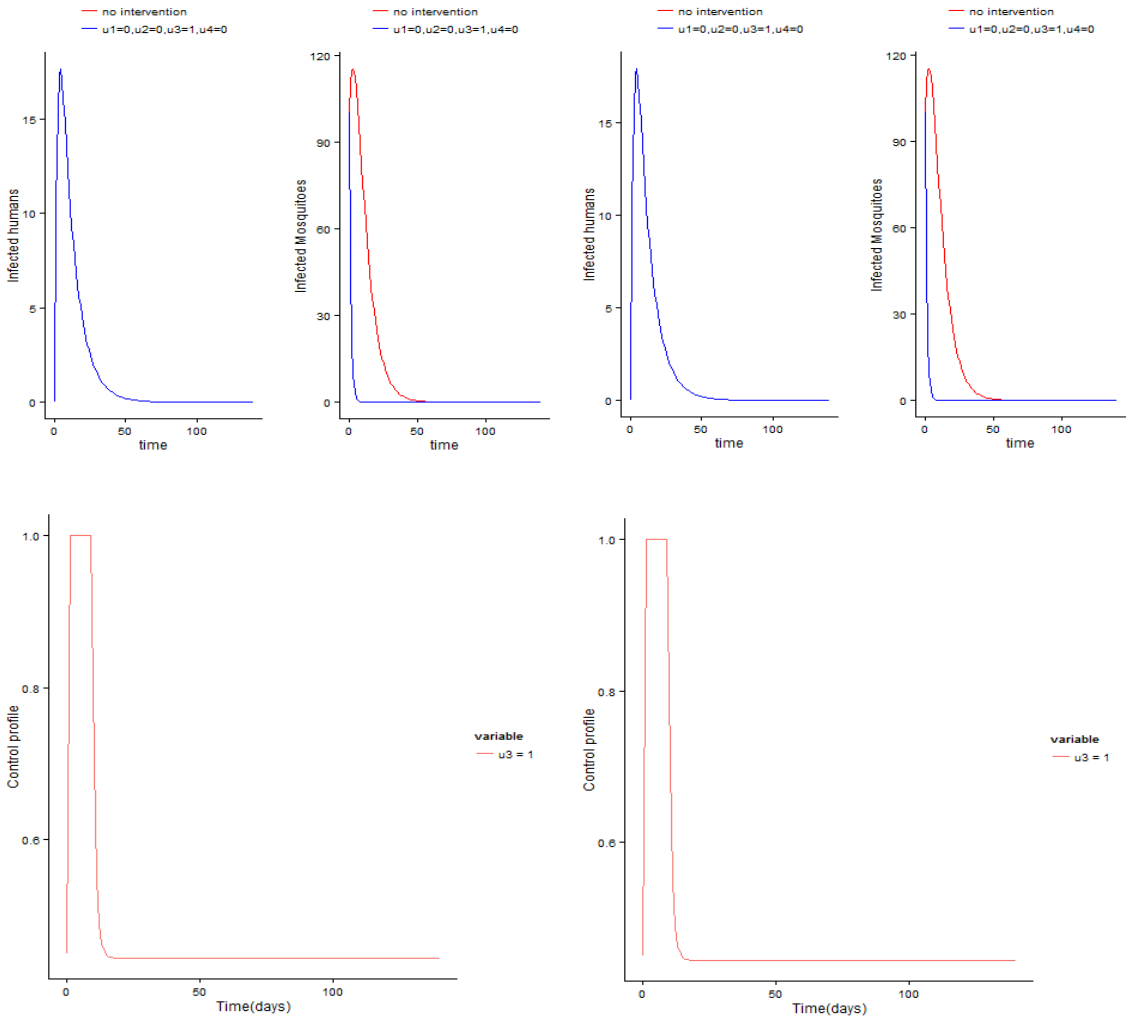
Figure 4.5: Simulations of the model showing the effect of treatment only on the spread of malaria for the different transmission settings

c. <u>Optimal IRS</u>

Only the control (u_3) on IRS is used to optimize the objective function J, while the control on treatment (u_2), the control on ITNs (u_1) and control on IPTp (u_4) are set to zero.


no intervention
u1=0,u2=0,u3=1,u4=0
Infected humans
Infected Mosquitoes
time
Control profile
Time(days)
variable
u3 = 1

(a) (b)

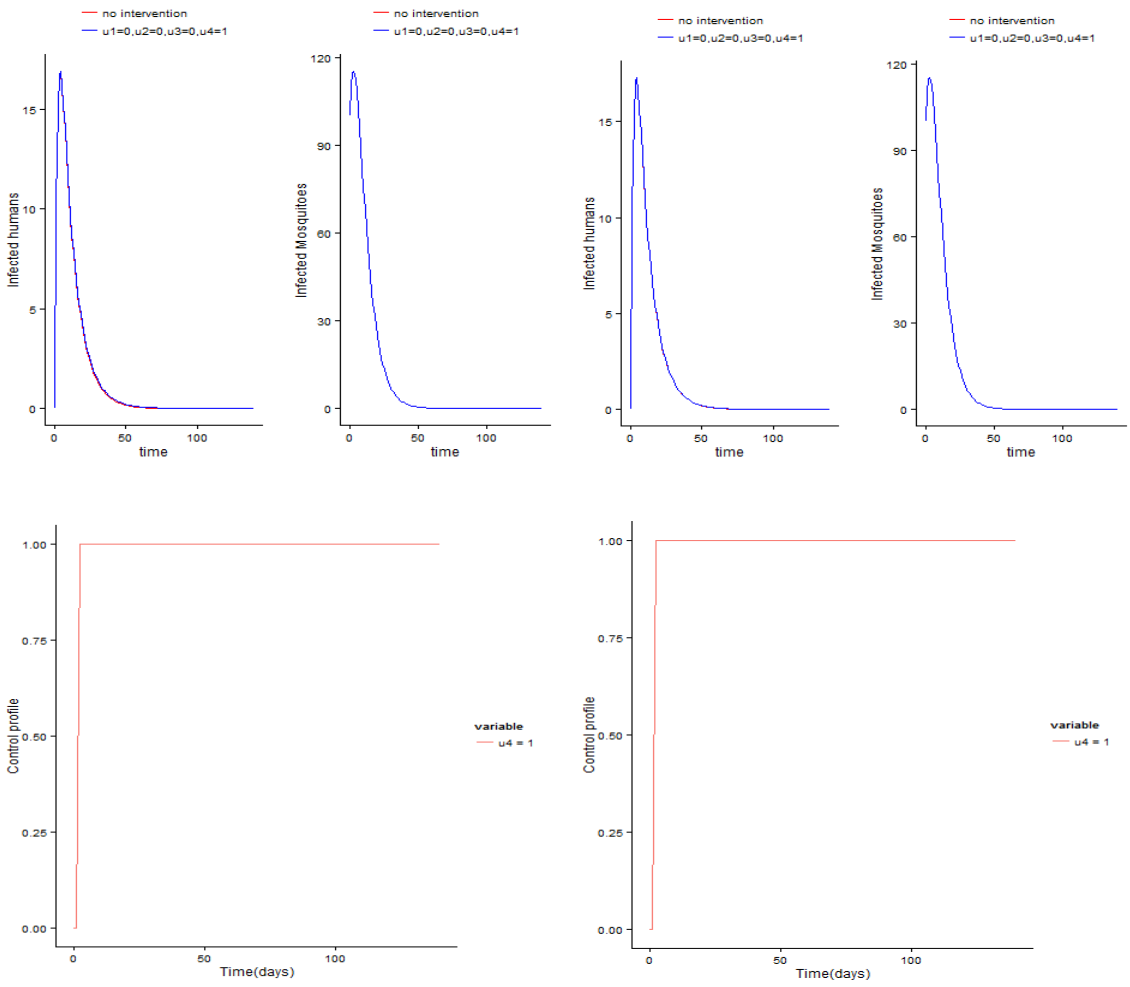


(c) (d)

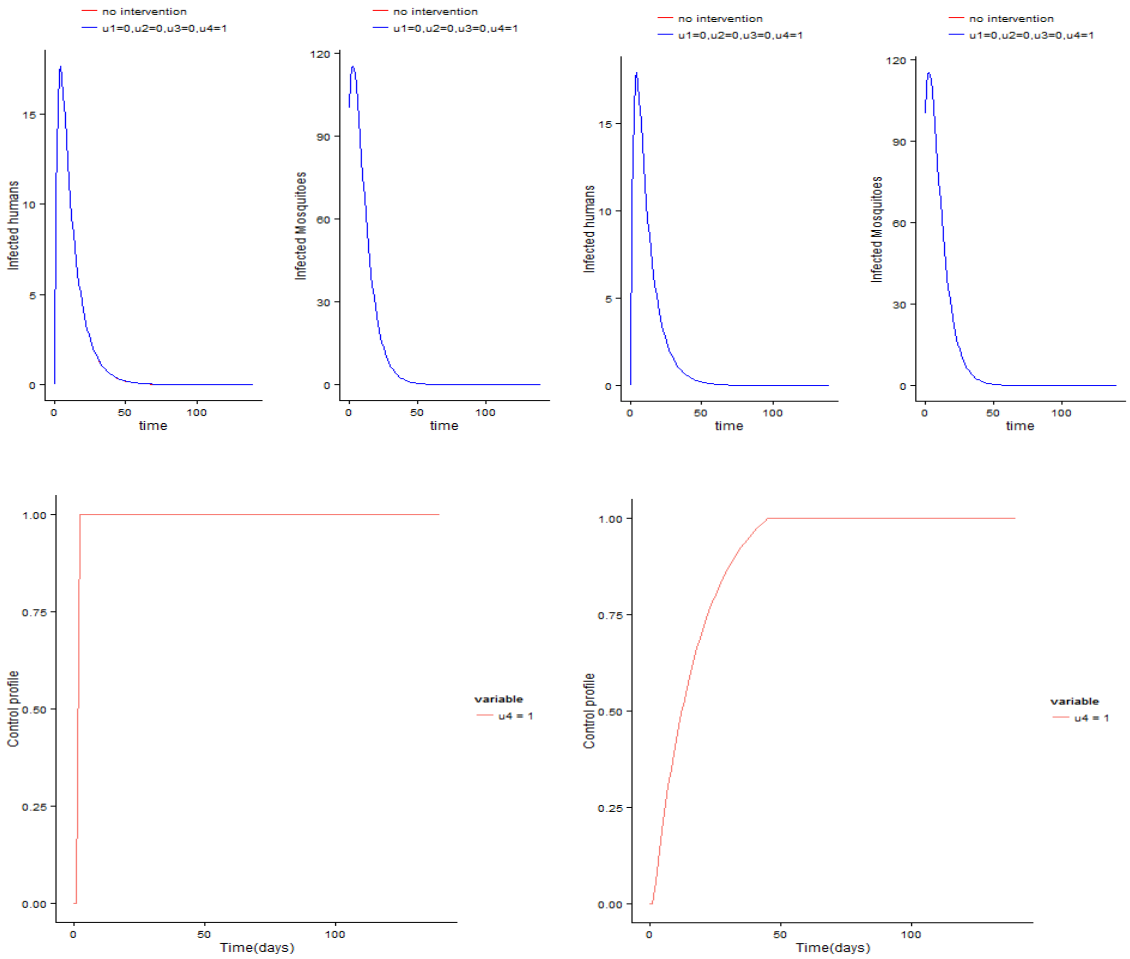
Figure 4.6: Simulations of the model showing the effect of IRS only on the spread of malaria for the different transmission settings

d. Optimal IPTp

Only the control (u_4) on IPTp is used to optimize the objective function J, while the control on treatment (u_2), the control on IRS (u_3) and control on ITNs (u_1) are set to zero.


no intervention
u1=0,u2=0,u3=0,u4=1
Infected humans
Infected Mosquitoes
time
Control profile
Time(days)
variable
u4 = 1

(a) (b)



(c) (d)

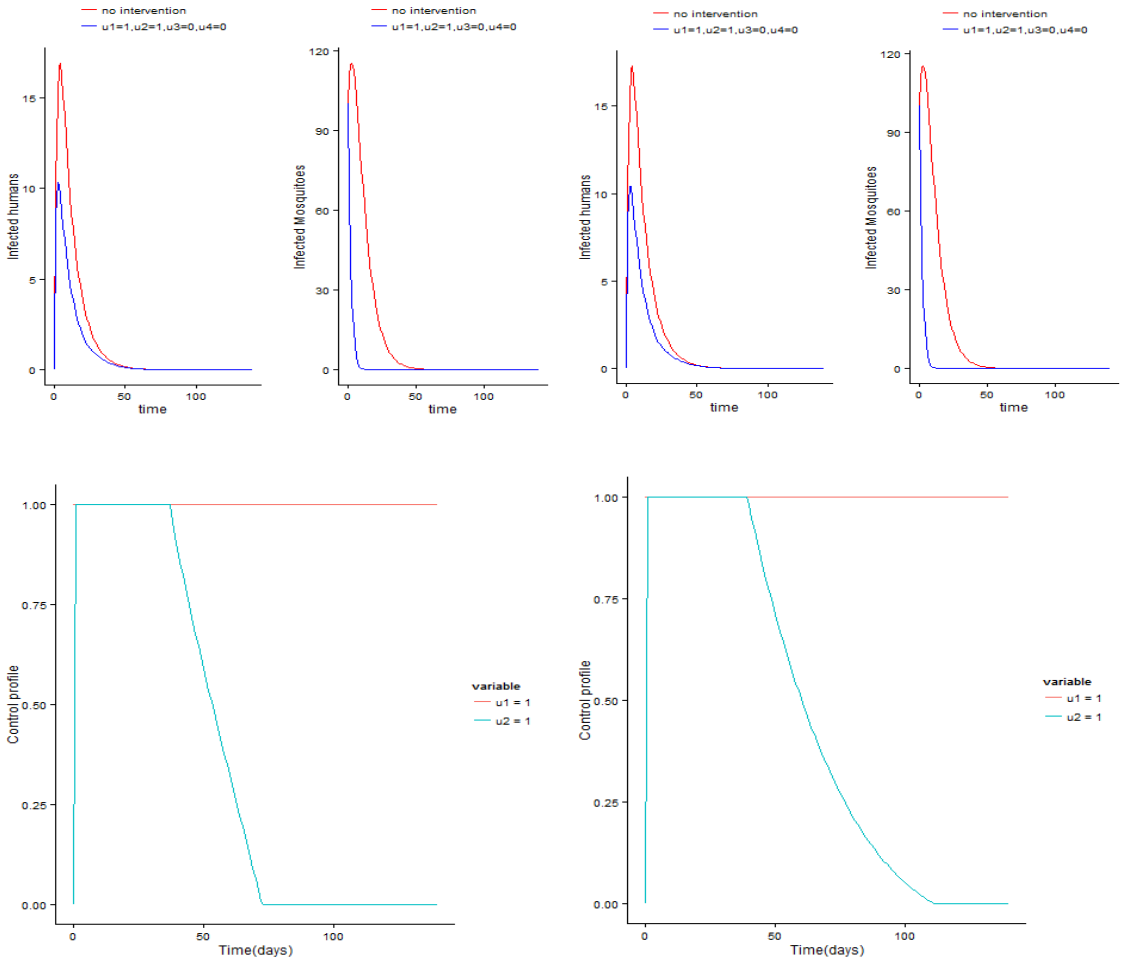
Figure 4.7: Simulations of the model showing the effect of IPTp only on the spread of malaria for the different transmission settings

Results of combining 2 intervention strategies for the 4 epidemiological zones

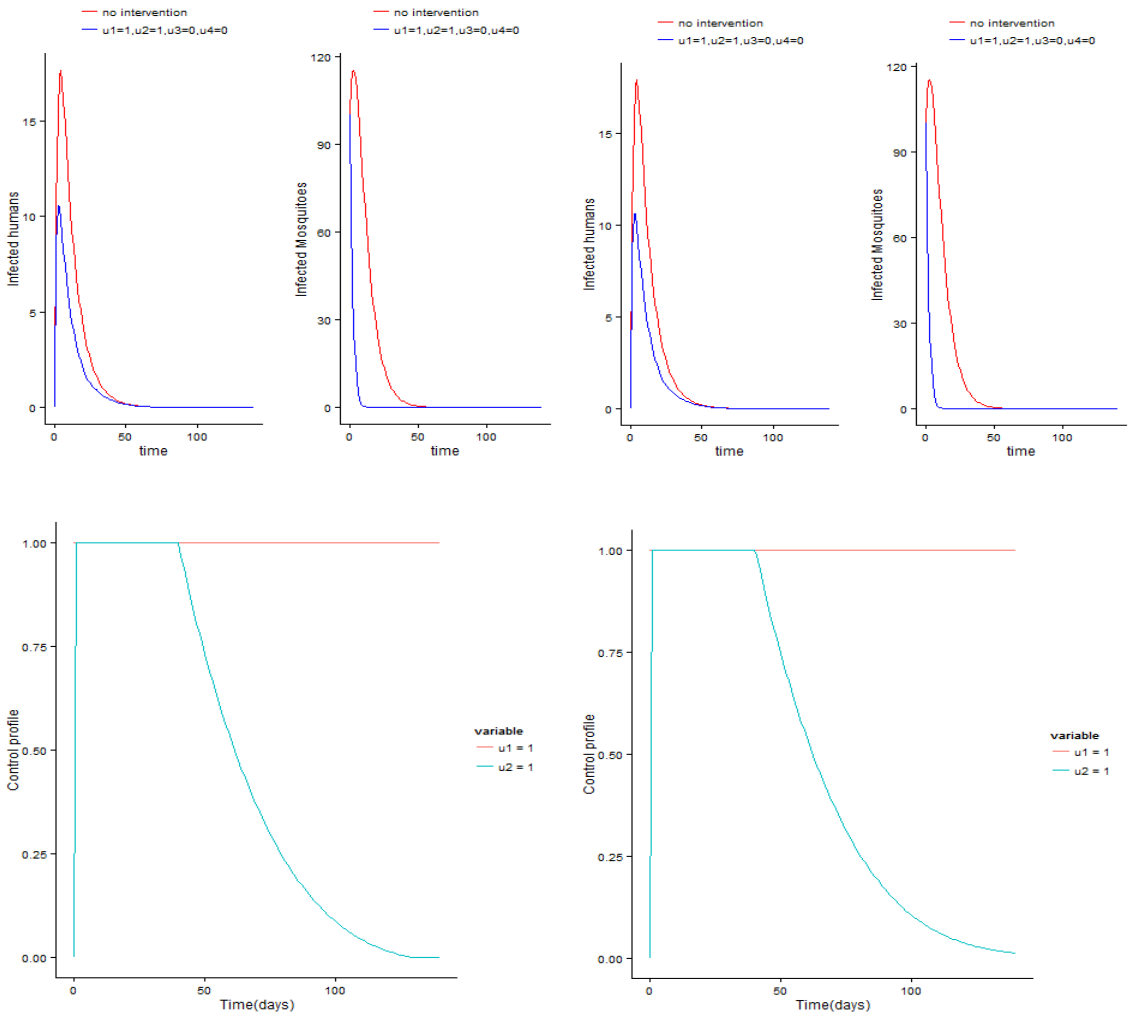
a. <u>Optimal ITNs and treatment</u>

With this strategy, the control on ITNs (u_1) and the treatment (u_2) are used to optimize the objective function J while setting the control on IRS (u_3) and control on IPTp (u_4) to zero. The control u_1 is at the upper bound all the time, while control on treatment u_2 starts and remain at upper bound for 48 days before dropping gradually to the lower bound. The results shows that with ITNs coverage of 100% for 140 days (all the time)

and treatment coverage of 100% for 48 days, the disease incidence will be greatly reduced.



(a) (b)

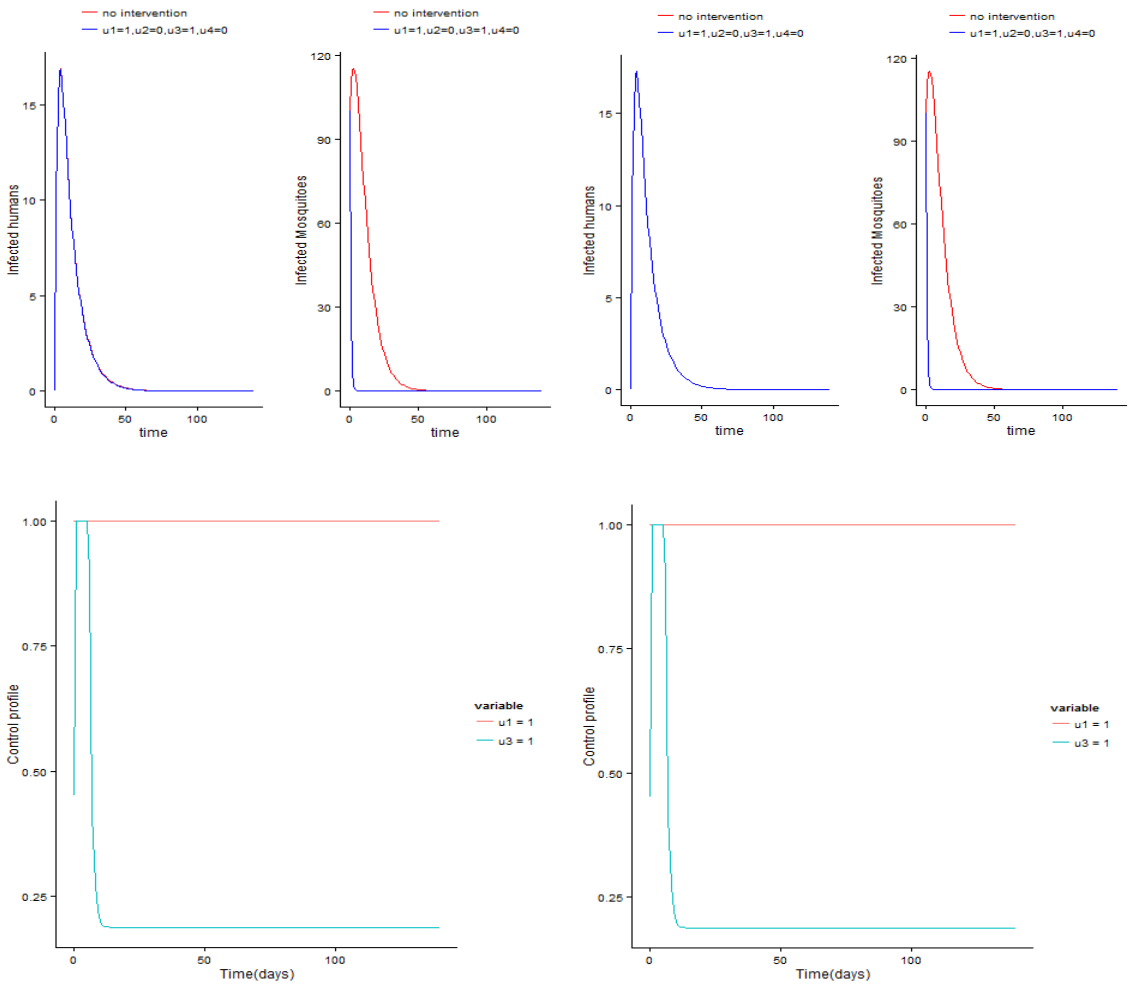


(c) (d)

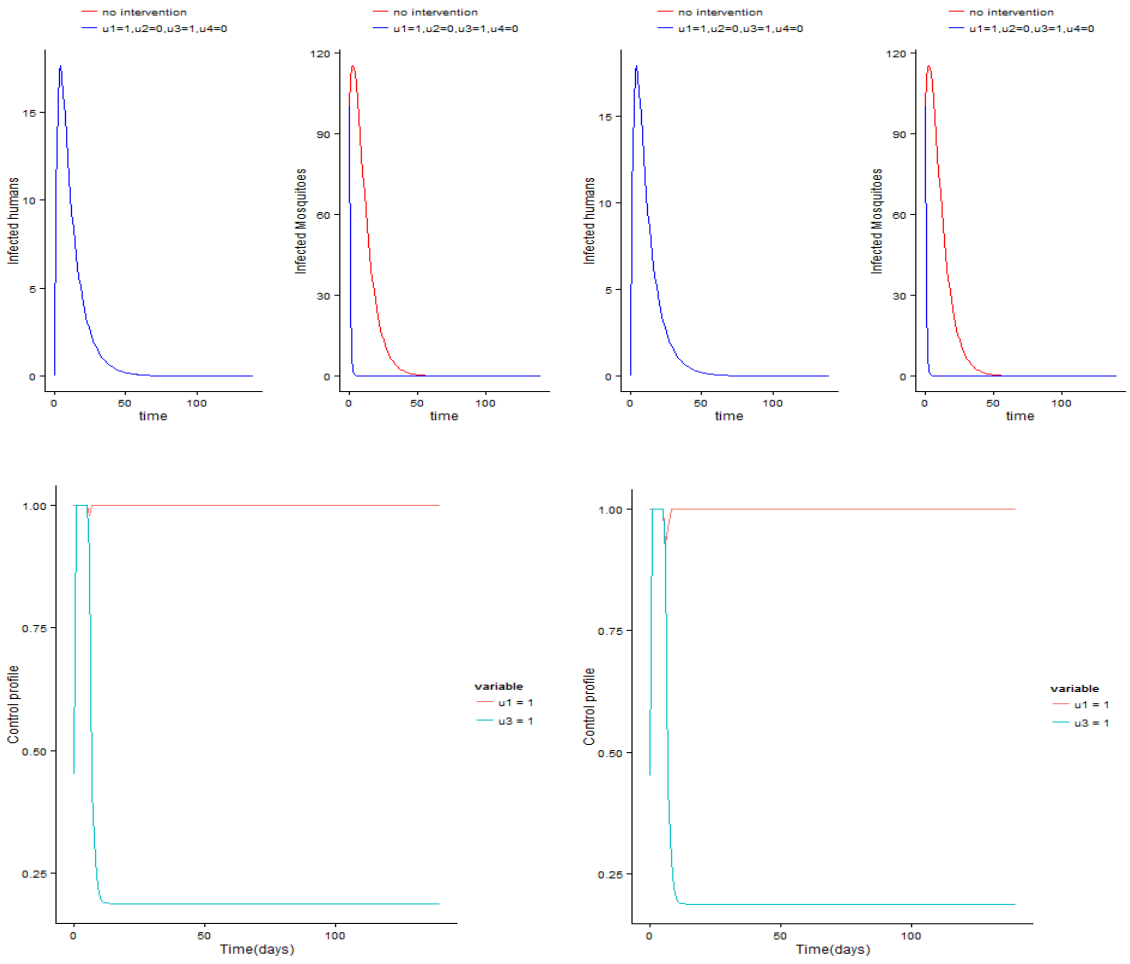
Figure 4.8: Simulations of the model showing the effect of ITNs and treatment on the spread of malaria for the different transmission settings

b. Optimal ITN and IRS

With this strategy, the control on ITNs (u_1) and the IRS (u_3) are used to optimize the objective function J while setting the control on treatment (u_2) and control on IPTp (u_4) to zero.


no intervention
u1=1,u2=0,u3=1,u4=0
Infected humans
Infected Mosquitoes
time
Control profile
Time(days)
variable
u1 = 1
u3 = 1

(a) (b)

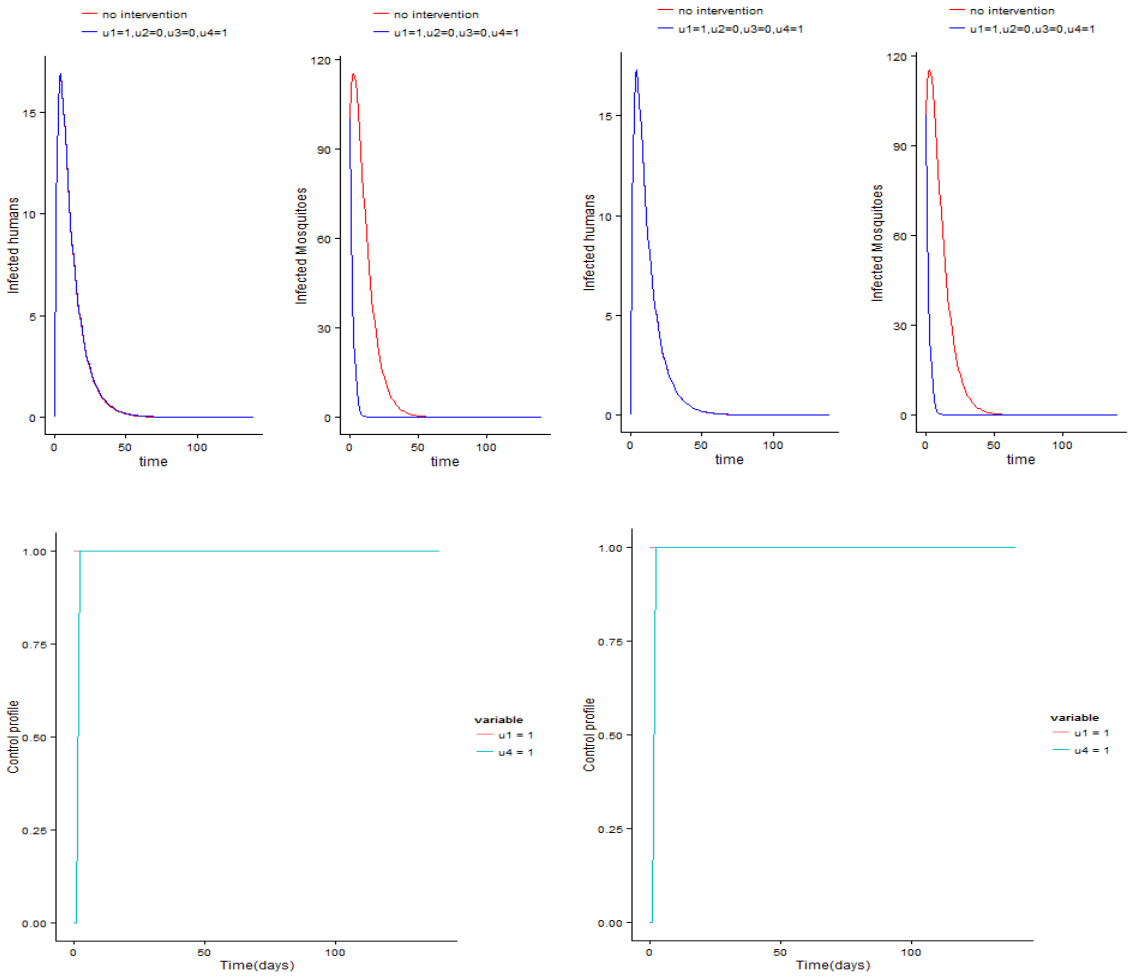


(c) (d)

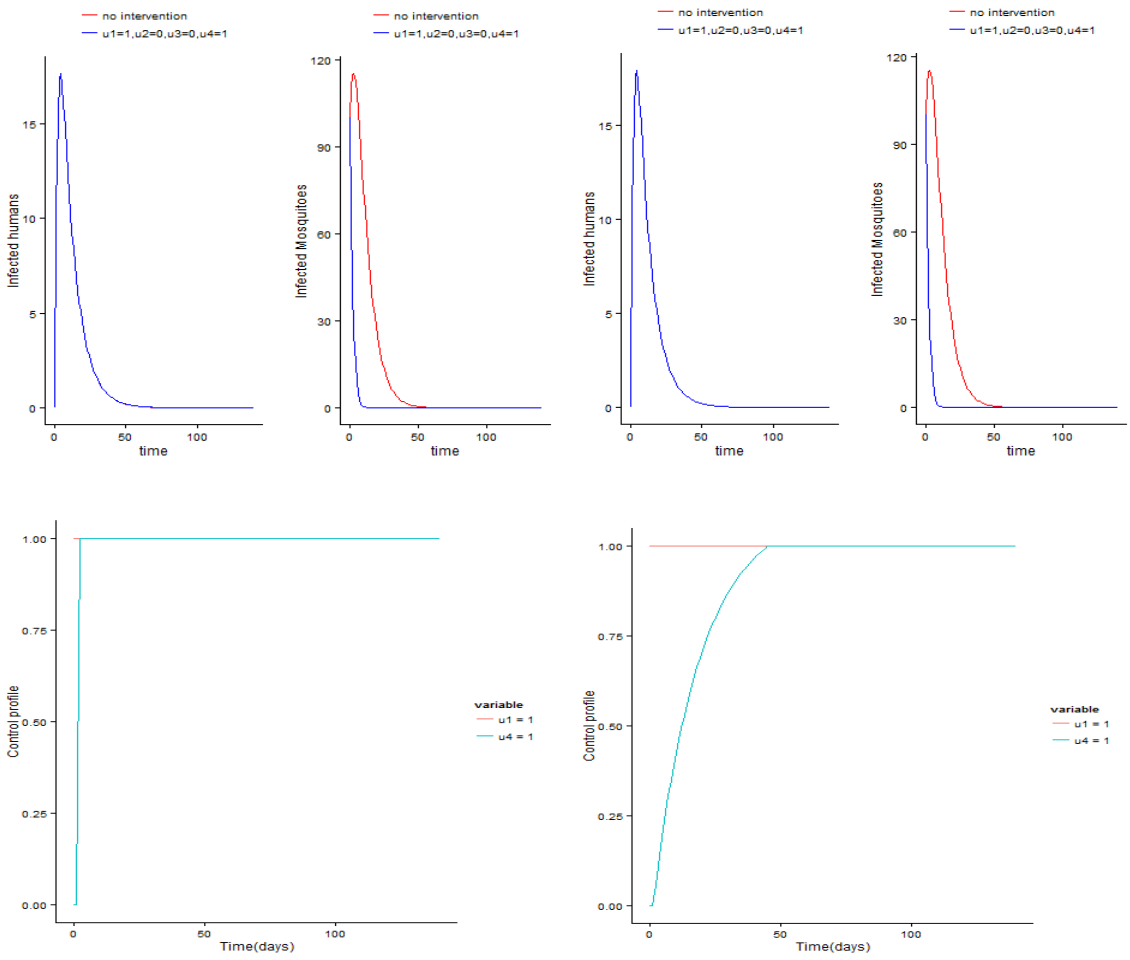
Figure 4.9: Simulations of the model showing the effect of ITNs and IRS on the spread of malaria for the different transmission settings

c. Optimal ITN and IPTp

With this strategy, the control on ITNs (u_1) and IPTp (u_4) are used to optimize the objective function J while setting the control on treatment (u_2) and control on IRS (u_3) to zero.


no intervention
u1=1,u2=0,u3=0,u4=1
Infected humans
Infected Mosquitoes
time
Control profile
Time(days)
variable
u1 = 1
u4 = 1

(a) (b)

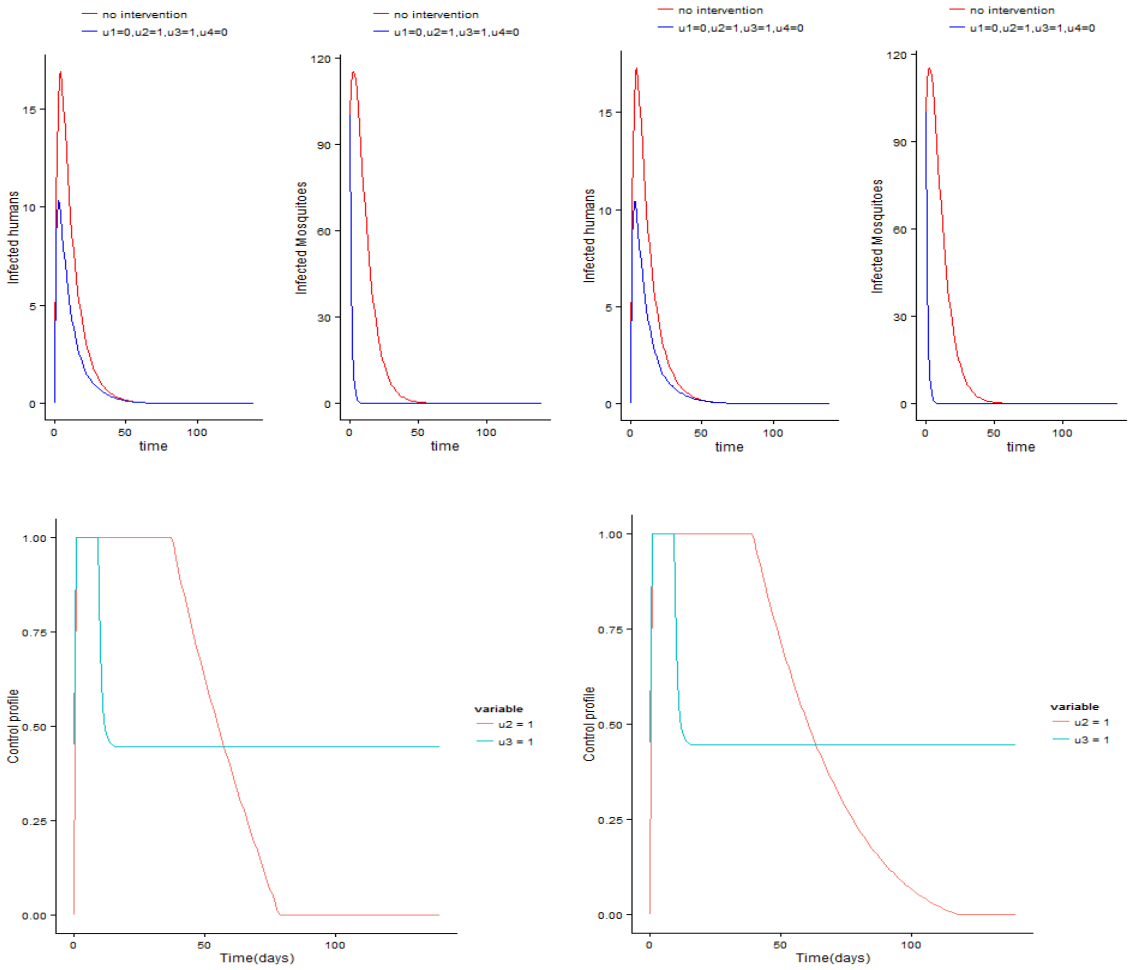


(c) (d)

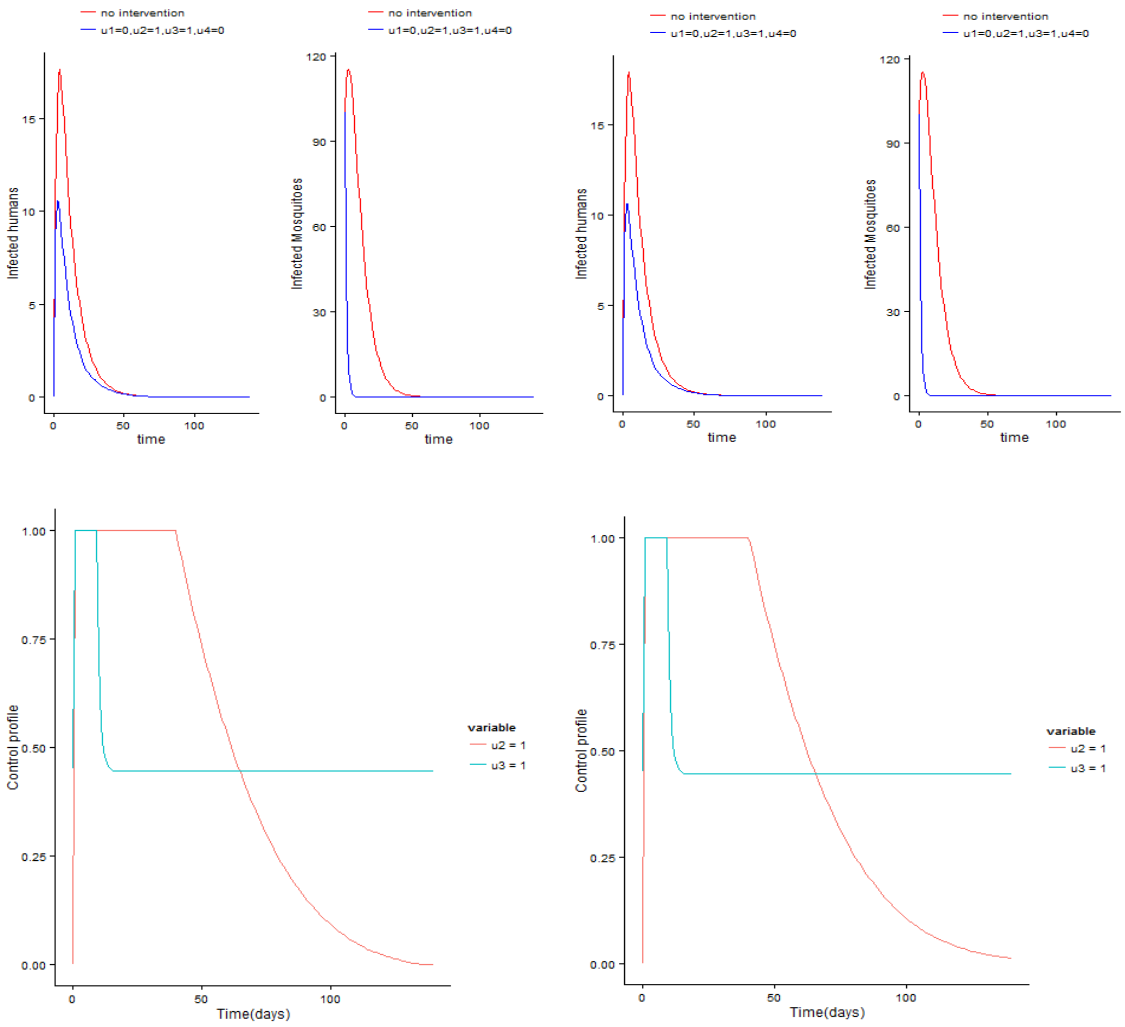
Figure 4.10: Simulations of the model showing the effect of ITNs and IPTp on the spread of malaria for the different transmission settings

d. Optimal Treatment and IRS

With this strategy, the control on treatment (u_2) and the IRS (u_3) are used to optimize the objective function J while setting the control on ITNs (u_1) and control on IPTp (u_4) to zero.


no intervention
u1=0,u2=1,u3=1,u4=0
Infected humans
Infected Mosquitoes
time
Control profile
Time(days)
variable
u2 = 1
u3 = 1

(a) (b)

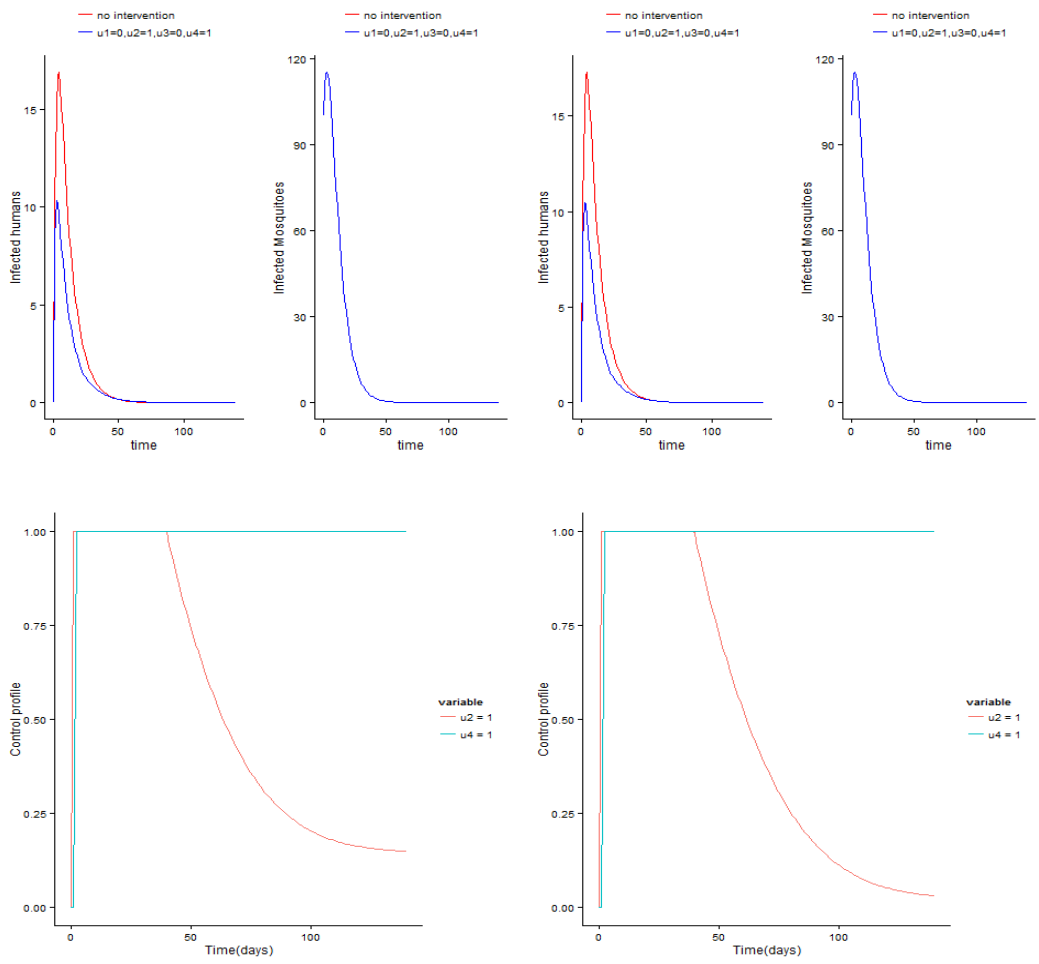


(c) (d)

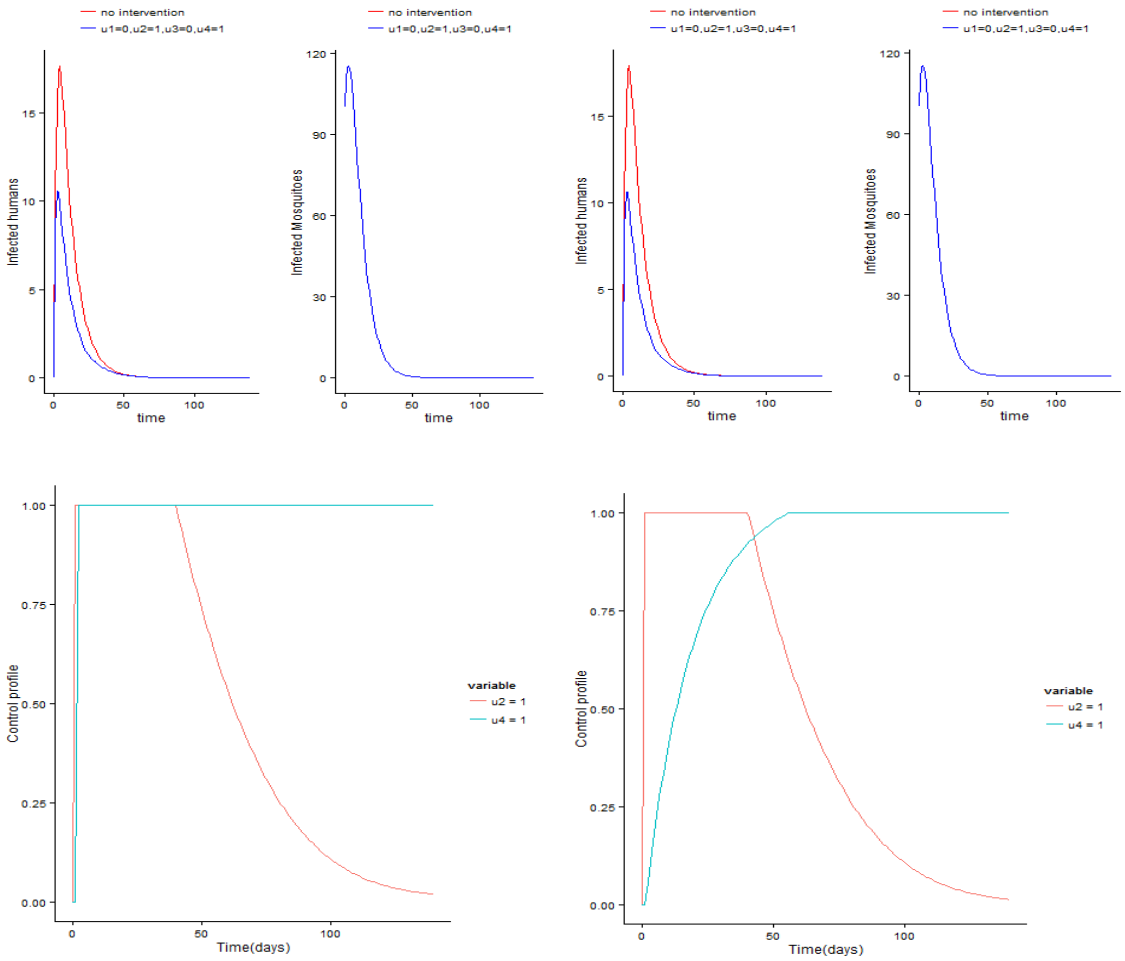
Figure 4.11: Simulations of the model showing the effect of treatment and IRS on the spread of malaria for the different transmission settings

e. Optimal Treatment and IPTp

With this strategy, the control on treatment (u_2) and the IPTp (u_4) are used to optimize the objective function J while setting the control on IRS (u_3) and control on ITNs (u_1) to zero.


no intervention
u1=0,u2=1,u3=0,u4=1
Infected humans
Infected Mosquitoes
time
Control profile
Time(days)
variable
u2 = 1
u4 = 1

(a) (b)

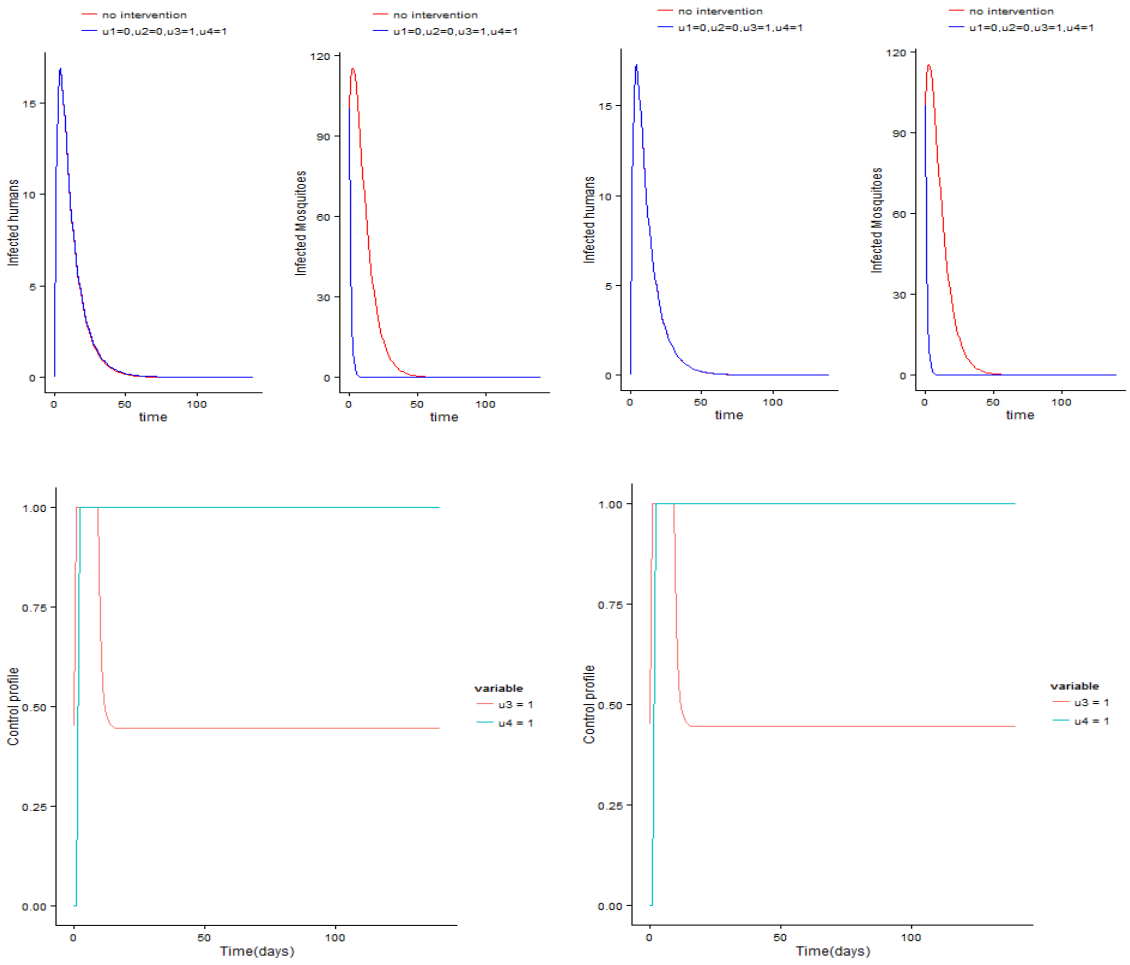


(c) (d)

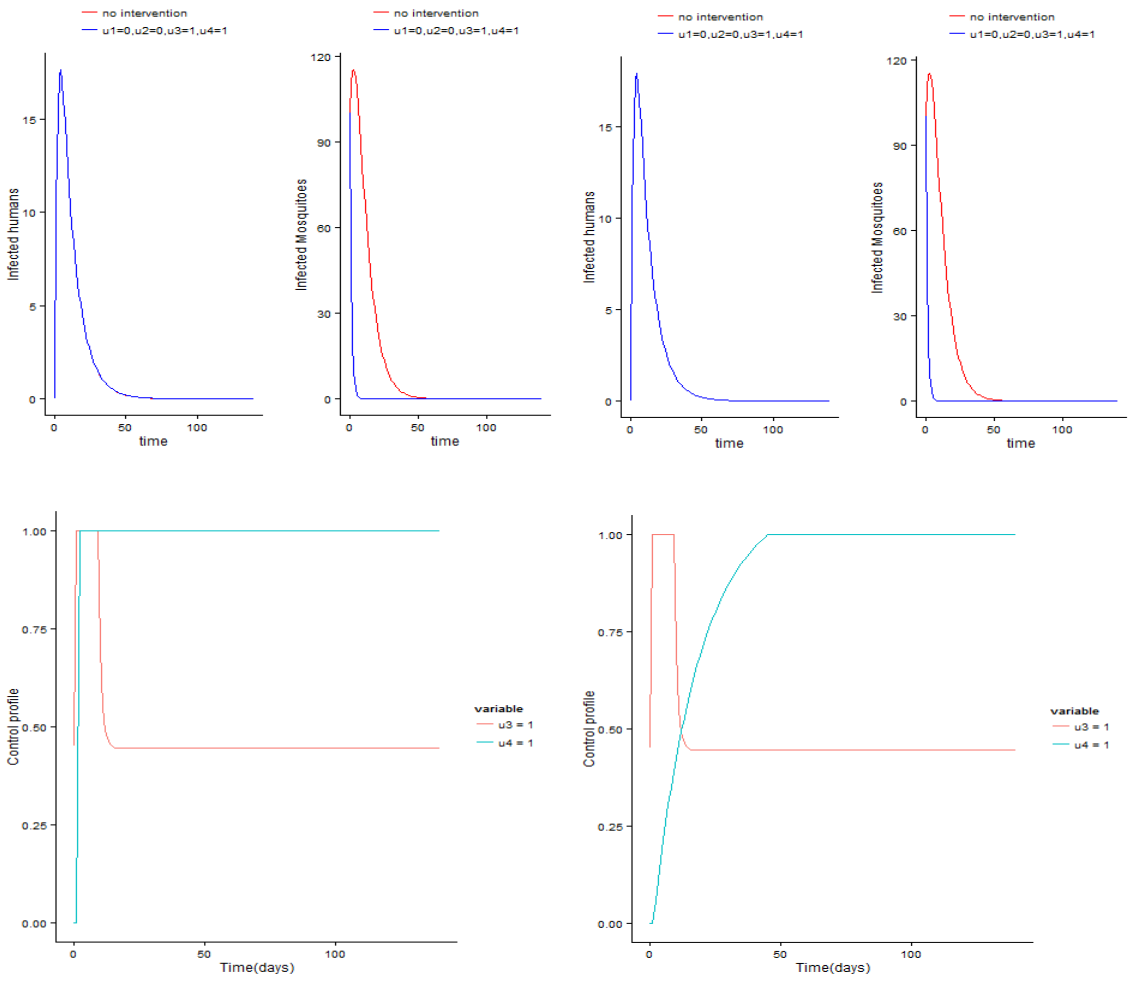
Figure 4.12: Simulations of the model showing the effect of treatment and IPTp on the spread of malaria for the different transmission settings

f. Optimal IRS and IPTp

With this strategy, the control on IRS (u_3) and the IPTp (u_4) are used to optimize the objective function J while setting the control on treatment (u_2) and control on ITNs (u_1) to zero.


no intervention
u1=0,u2=0,u3=1,u4=1
Infected humans
Infected Mosquitoes
time
Control profile
Time(days)
variable
u3 = 1
u4 = 1

(a) (b)



(c) (d)

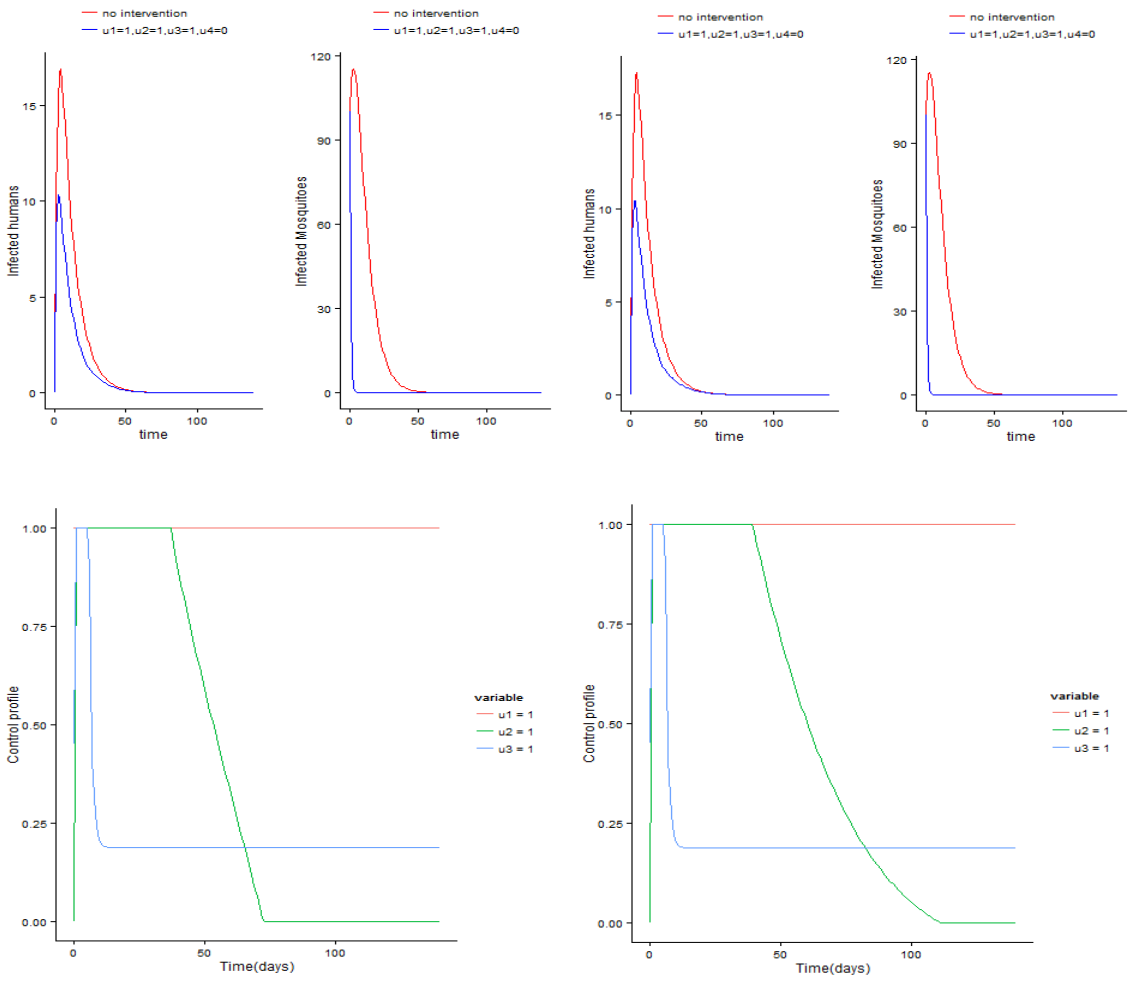
Figure 4.13: Simulations of the model showing the effect of IRS and IPTp on the spread of malaria for the different transmission settings

Results of combining three intervention strategies for the 4 epidemiological zones

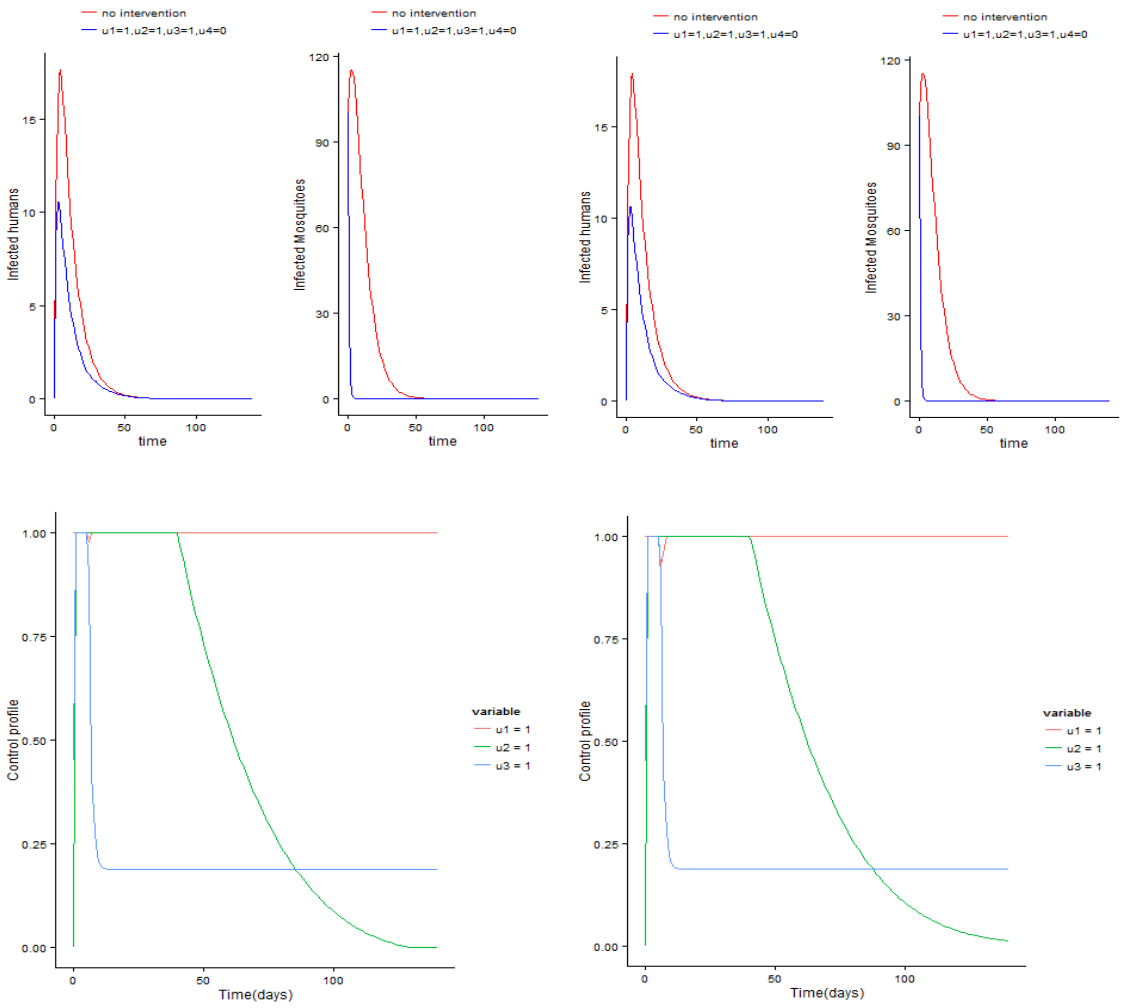
a. <u>Optimal ITN, treatment and IRS</u>

Figure 4.11 shows the simulation of the model whereby ITN control (u_1), treatment control (u_2), and IRS control (u_3) are used to optimize the objective function J, while IPTp control (u_4) is set to zero. The control profile suggest that the control on ITN (u_1) to be at the upper bound until the final time (140 days) while the control on treatment (u_2) to be at the upper bound for 10 days. The optimal IRS is at the upper bound until 48

days before dropping gradually to the lower bound. Therefore an effective IRS use and treatment will be beneficial to the community for the control of malaria disease.



(a) (b)

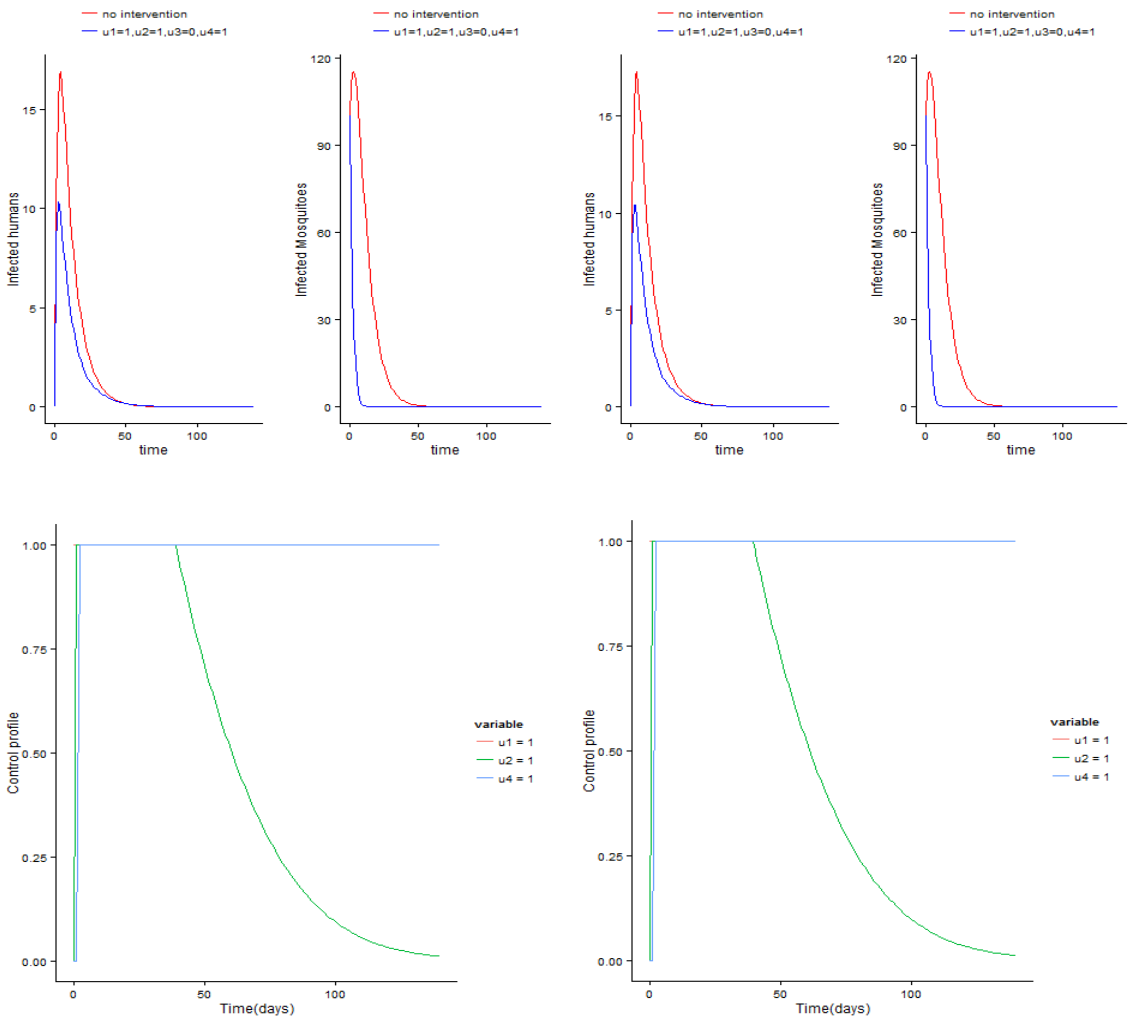


(c) (d)

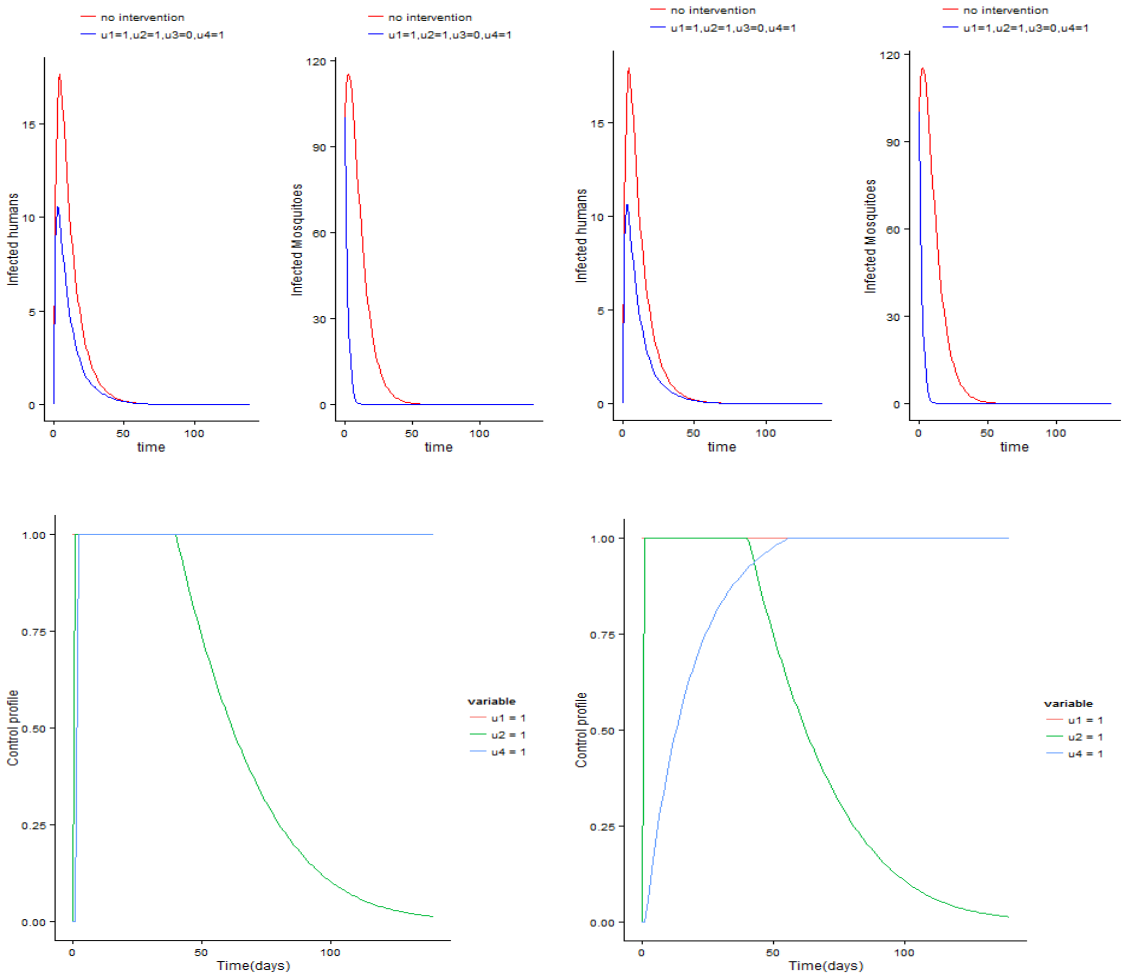
Figure 4.14: Simulations of the model showing the effect of ITNs, treatment and IRS on the spread of malaria for the different transmission settings

b. <u>Optimal ITN, treatment and IPTp</u>

In this case ITNs control (u_1), treatment control (u_2), and IPTp control (u_4) are used to optimize the objective function J, while IRS control (u_3) is set to zero.


no intervention
u1=1,u2=1,u3=0,u4=1
Infected humans
Infected Mosquitoes
time
Control profile
Time(days)
variable
u1 = 1
u2 = 1
u4 = 1

(a) (b)

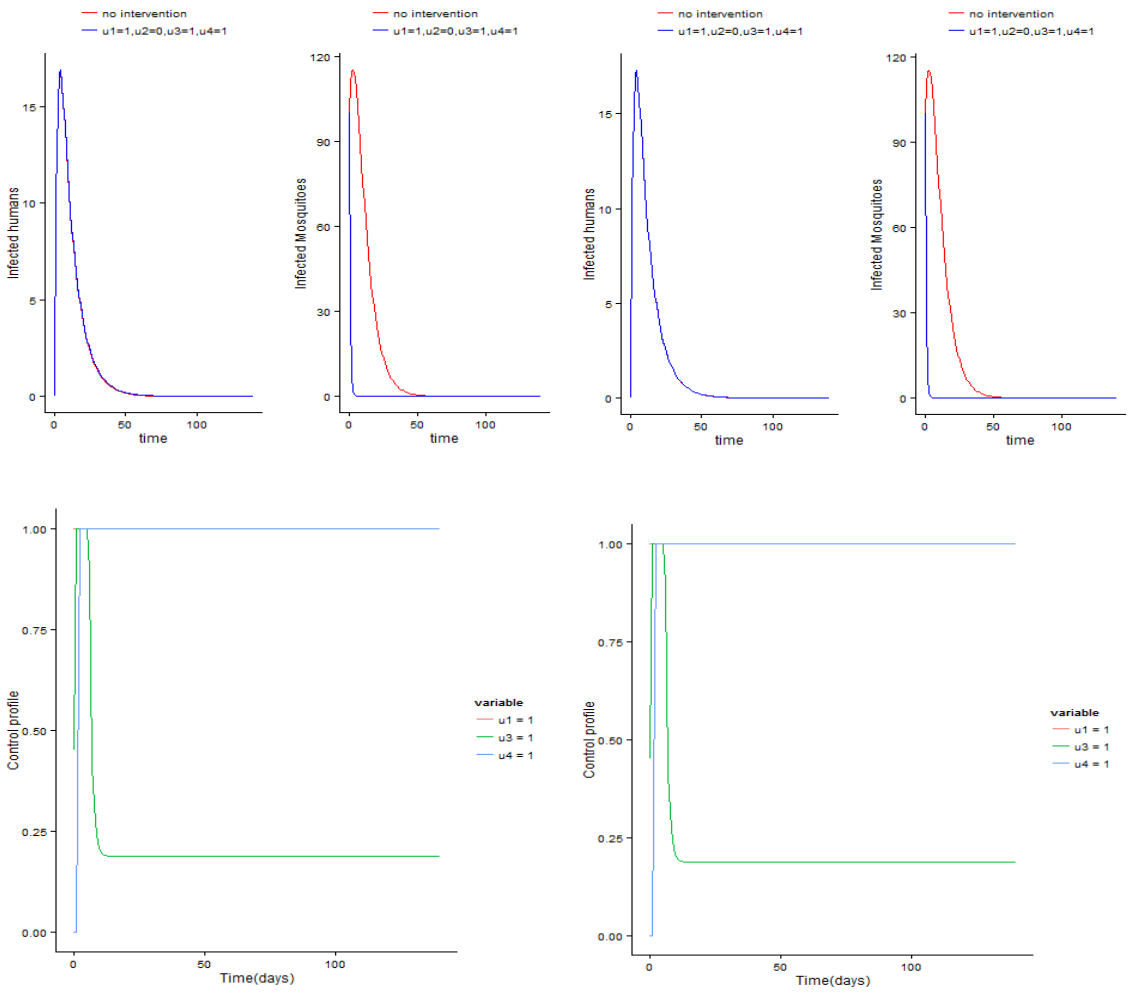


(c) (d)

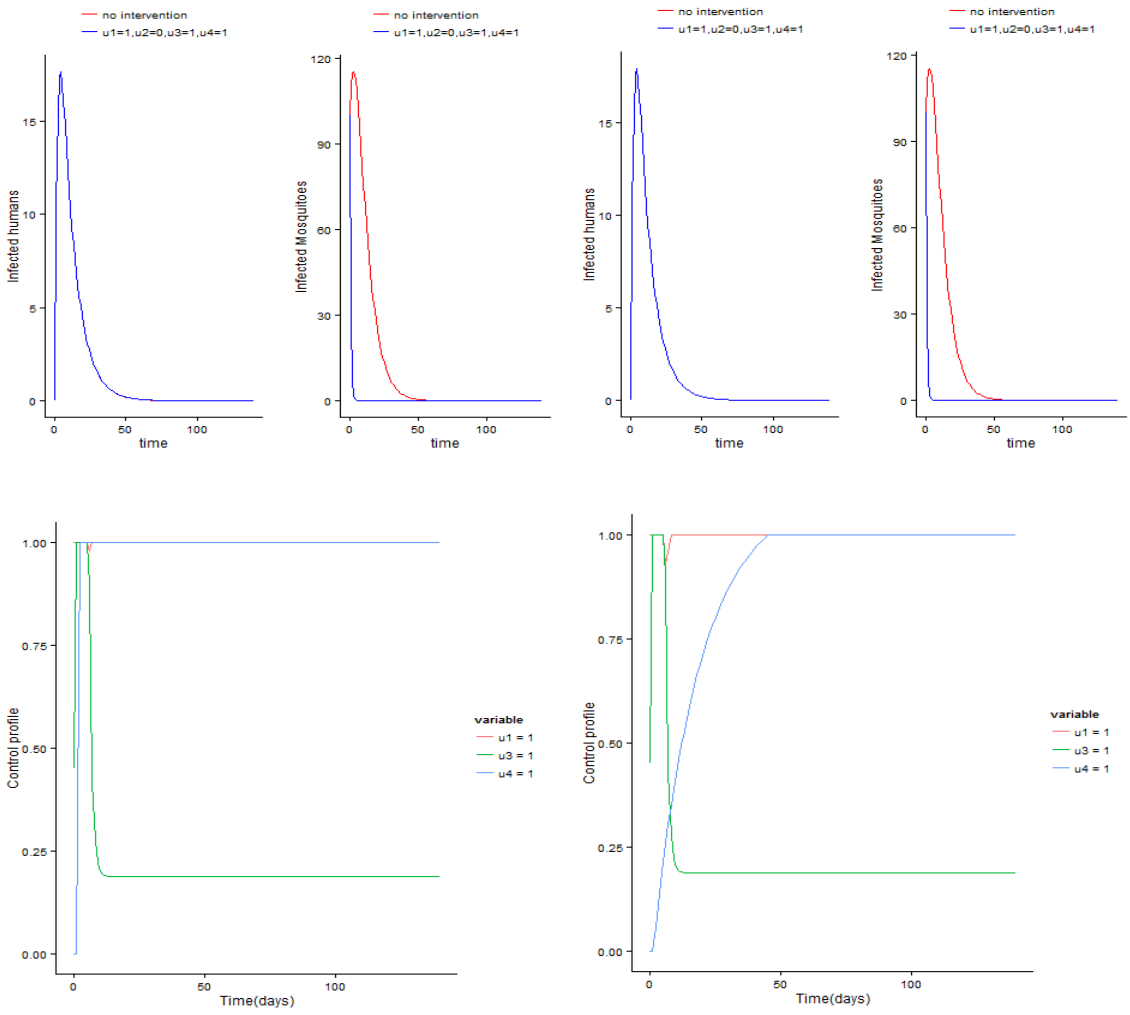
Figure 4.15: Simulations of the model showing the effect of ITNs, treatment and IPTp on the spread of malaria for the different transmission settings

c. <u>Optimal ITN, IRS and IPTp</u>

In this case ITNs control (u_1), IRS control (u_3), and IPTp control (u_4) are used to optimize the objective function J, while treatment control (u_2) is set to zero.


no intervention
u1=1,u2=0,u3=1,u4=1
Infected humans
Infected Mosquitoes
time
Control profile
Time(days)
variable
u1 = 1
u3 = 1
u4 = 1

(a) (b)

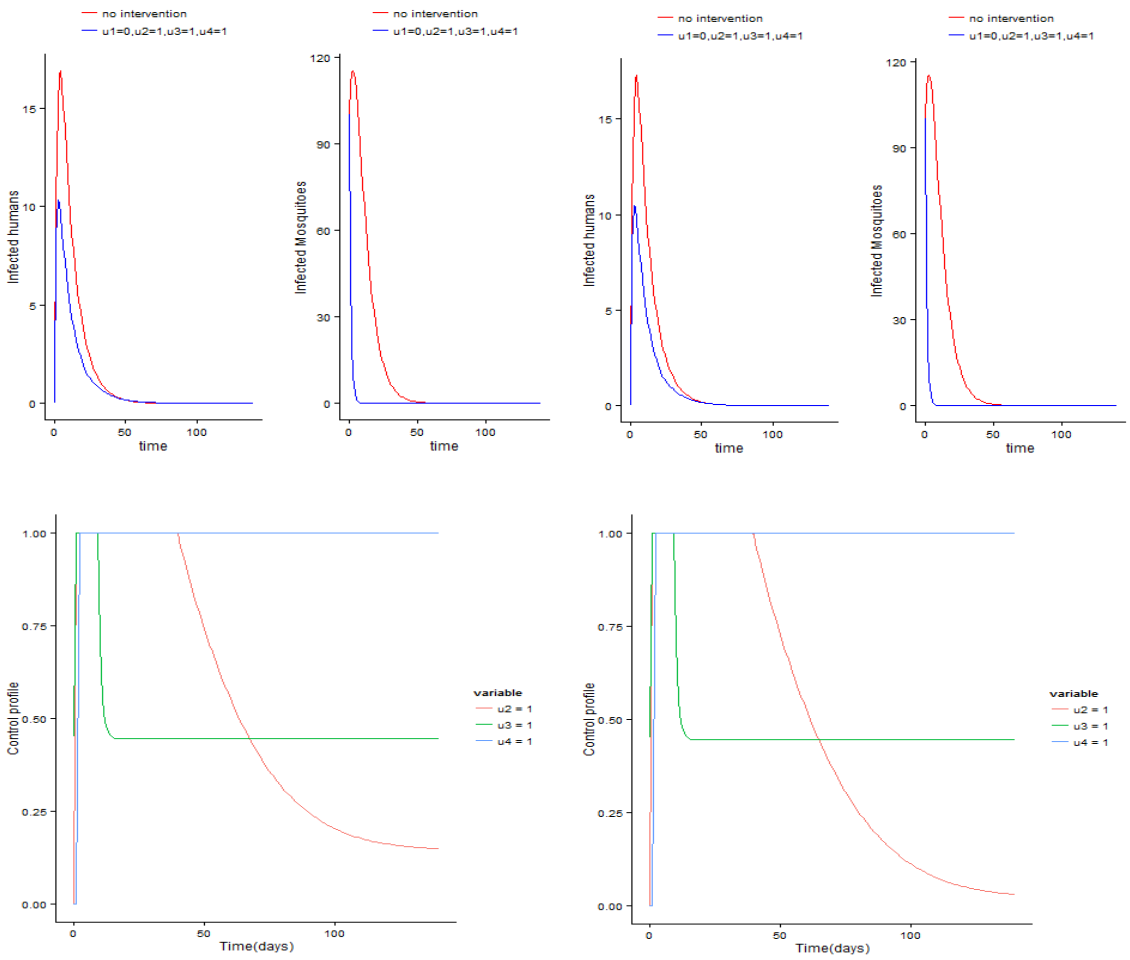


(c) (d)

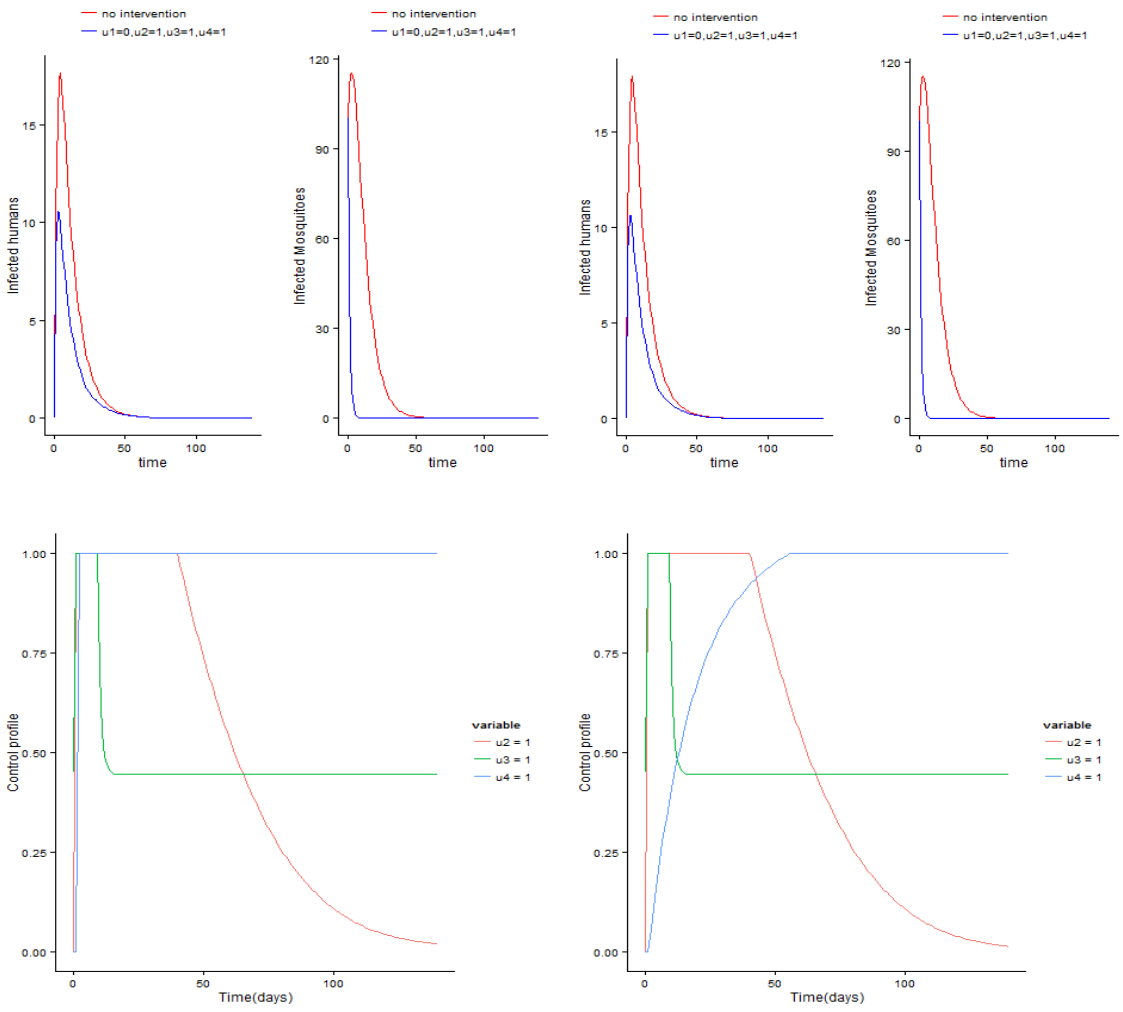
Figure 4.16: Simulations of the model showing the effect of ITNs, IRS and IPTp on the spread of malaria for the different transmission settings

d. Optimal Treatment, IRS and IPTp

In this case ITNs control (u_1), IRS control (u_3), and IPTp control (u_4) are used to optimize the objective function J, while treatment control (u_2) is set to zero.


no intervention
u1=0,u2=1,u3=1,u4=1
Infected humans
Infected Mosquitoes
time
Control profile
Time(days)
variable
u2 = 1
u3 = 1
u4 = 1

(a) (b)



(c) (d)

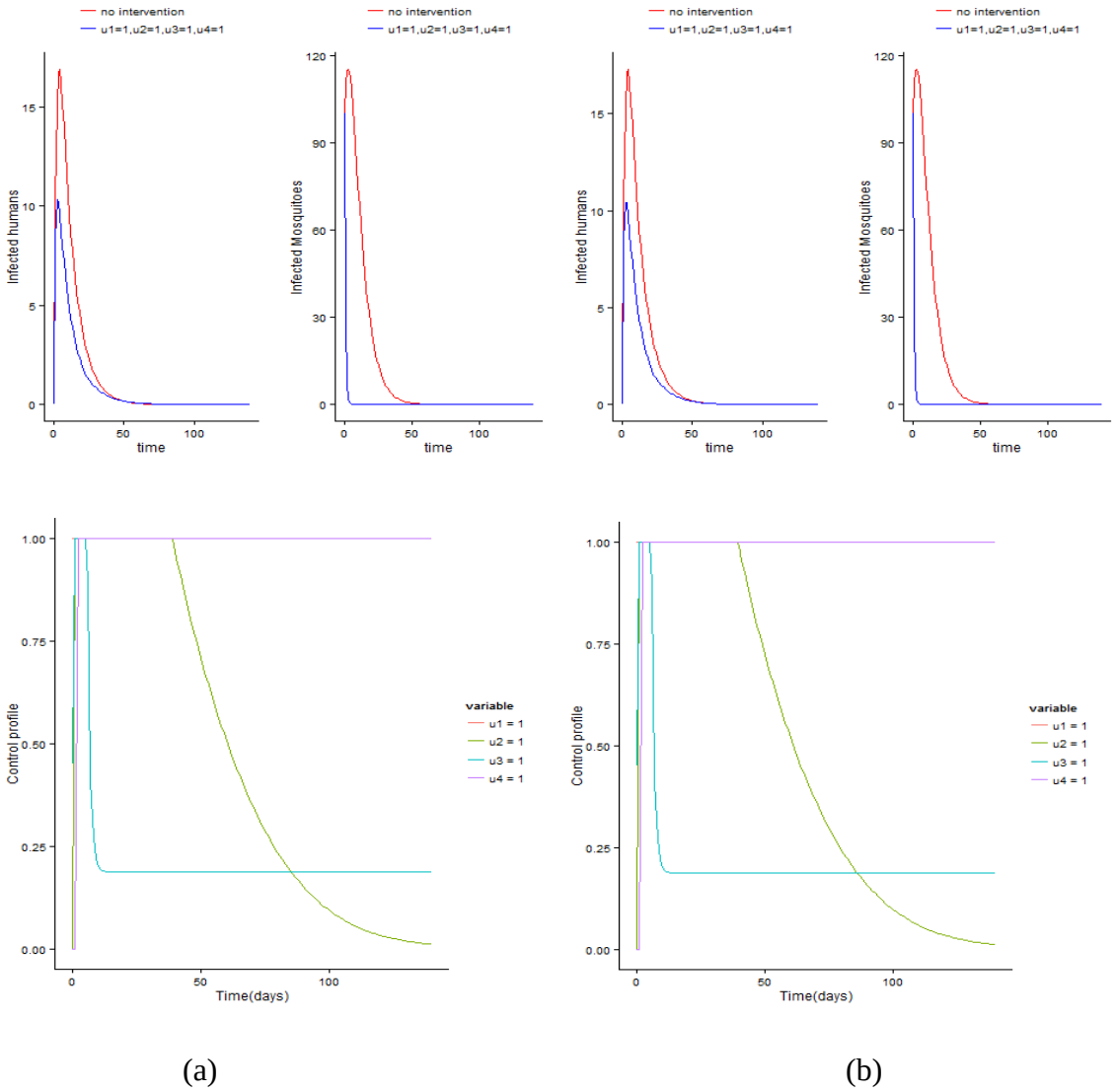
Figure 4.17: Simulations of the model showing the effect of treatment, IRS and IPTp on the spread of malaria for the different transmission settings

Results of combining the four intervention strategies for the 4 epidemiological zones

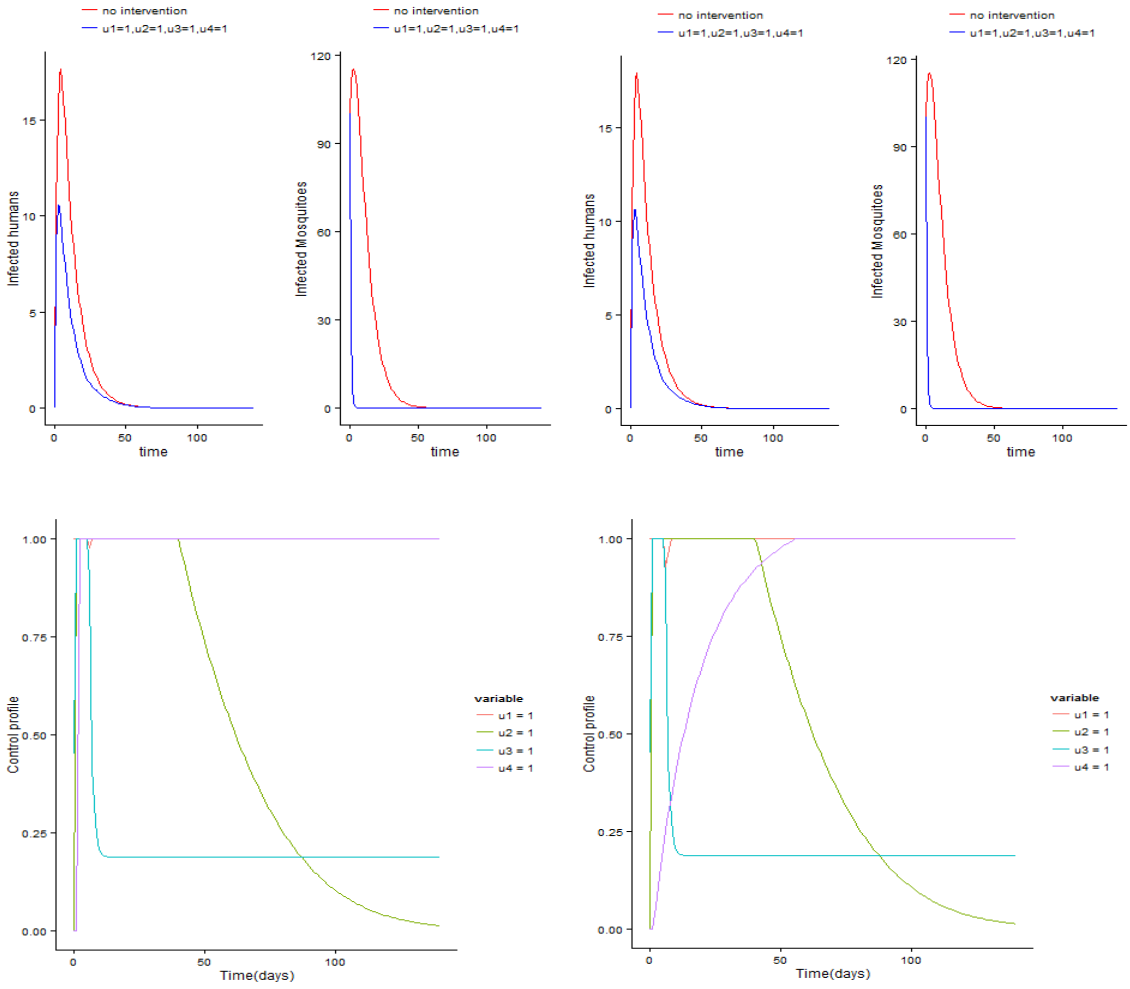
a. <u>Optimal ITN, treatment, IRS and IPTp</u>

In this case all the control function ITNs control (u_1), treatment control (u_2), IRS control (u_3) and IPTp control (u_4) are used to optimize the objective function J. The control profile suggest that the control on ITN (u_1) and on IPTp (u_4) to be at the upper bound until the final time (140 days) while the control on IRS (u_3) to be at the upper bound for

10 days. The optimal treatment is at the upper bound until 48 days before dropping gradually to the lower bound. Therefore an effective IRS use and treatment will be beneficial to the community for the control of malaria disease (Figure 4.18).



(a) (b)



(c) (d)

Figure 4.18: Simulations of the model showing the effect of ITNs, treatment, IRS and IPTp on the spread of malaria for the different transmission settings

Based on the findings for the highest number of infections being inverted at a lower cost, it is evident that the combined use of treatment and IRS reduces the infected human and mosquito population faster at a lower cost for the endemic settings (105 infections at $368.258). For the epidemic prone settings the use of treatment and IRS (111.03 infections at $388.6051) has more impact in reducing the infected human and mosquito population. For seasonal areas much impact will be felt when treatment are used

(115.6983 infections at $231.3967). For the low risk areas, the use ITNs and treatment (119.0659 infections at 595.32) will be sufficient to reduce infected human and mosquito population. This is deduced from the intervention which takes shorter time to start reducing the number of infected mosquitoes and humans. It takes much effort/ scale up to reduce more infections in the endemic areas compared to the low risk areas.

In the optimal control problem considered, we use one control at a time and the combination of two controls at a time or three at a time or all four while setting the other(s) to zero to investigate and compare the effects of the control strategies on malaria eradication. This was different from what was investigated by Mwamtobe *et al.,* (2014), Okosun *et al.,* (2013), Kim *et al.,* (2012) where only three, three and two malaria control measures respectively were used. Numerical results indicate that the optimal control strategies for malaria control in endemic areas that an effective IRS use and treatment will be beneficial to the community for the control of malaria disease (infected human and mosquito population) faster at a lower cost for the endemic settings. This is slightly different from the findings of Agusto *et al.,* (2012) who found that the combination of the personal protection, treatment and insecticides spray had the highest impact on the control of the disease. This could be in endemic settings both preventive and treatment measures work better which implies that the effect of protection using IRS is better. Griffin *et al.,* (2010) found that use of treatment, LLITNs and IRS with high levels coverage would result in reducing malaria transmission for high settings though the study did not consider the cost aspect.

The findings shows that for the epidemic prone areas, the optimal control strategy for reducing the infected human and mosquito population was the use of treatment and IRS. This is slightly different from Agusto *et al.,* (2012) findings on resource limited settings in which the study recommended the use of personal protection and insecticides. This was further different from the findings of Mwamtobe *et al.,* (2014) who noted that the prevention strategies (use of ITNs and IRS) lead to the reduction of both the mosquito population and infected human individuals. This is because in epidemic areas emphasis is usually more placed on preventive strategies.

The results shows that for seasonal areas much impact will be felt when treatment are used which is different from Mwamtobe *et al.,* (2014) who recommended IRS and ITNS. This also comparable to Kim *et al.,* (2012) findings that mosquito-reduction strategies is more effective than personal protection. This is because in seasonal areas malaria transmission is usually not so high and hence if the mosquito reduction strategies can be implemented then malaria transmission can be reduced. Griffin *et al.,* (2010) found that for the high seasonal transmission settings the use of LLITNs, IRS and treatment would help reduce the transmission of malaria.

The results shows that for the low risk areas, just the use ITNs and treatment will be sufficient to reduce infected human and mosquito population. This is comparable to Silva & Torres (2013) who found the optimal use of ITNS would prevent malaria transmission same to Kim *et al.,* (2012). The findings are comparable to by Griffin *et al.,* (2010). In low transmission areas prevention strategies seems to be better because the population is not infected.

These findings supports the WHO concerns on the capability of only one intervention strategy in reducing malaria transmission. The findings are however applicable to the designing of intervention strategies for malaria especially when costs aspects are of concern. This modeling approach also addresses effectiveness of the recommended intervention for at risk group of malaria (pregnant women) by the WHO. The modeling approach has also been implemented in the R statistical computing platform which is free statistical software.

Optimal control approach can help provide Information on the optimal malaria intervention strategies that can be tailored to specific transmission patterns of malaria when costs of interventions are also considered. This will provide basis for informed decision making about malaria control, guide the post-2015 malaria eradication strategies and the achievement of the Sustainable Development Goals and hence the path towards malaria elimination.

4.3 Numerical Results on Cost Effectiveness Analysis

The data collected on the parameters of the model representing different epidemiological zones (transmission settings) in Kenya are summarized in Table 4.1. The rate of human infection and rate of mosquito being infected by feeding on blood meal and the disease induced death were varied to represent the different transmission settings/ epidemiological zones in Kenya. In addition the effect of the different intervention strategies are estimated as: $u_1 = 0.0904$, $u_2 = 0.165$, $u_3 = 0.076$, $u_4 = 0.035$ and the cost of intervention are for: $u_1 = \$2.5 - 5$, $u_2 = \$2.5$, $u_3 = \$1.5$, $u_4 = \$2.5$. The initial state variables are constant across all the epidemiological zones and are chosen as $S_h(0) = 700$, $E_h(0) = 250$, $I_h(0) = 0$, $R_h(0) = 0$, $S_m(0) = 5000$, $E_m(0) = 500$, and $I_m(0) = 100$. The values of $N_h = 800$ and $N_{hw} = 240$. The discount $\varphi = {}^{3}/_{365} - {}^{5}/_{365}\,\%$.

4.3.1 Numerical Simulations of the Economic Evaluations of the Malaria Model

Numerical simulations showing the impact of the shadow prices (marginal value/ cost) and marginal benefits by evaluating the shadow prices at the start of the malaria epidemic and as a function of the numbers of recovered or protected at the time of outbreak (susceptible human beings).

The marginal cost and effect of the intervention strategies for the four different malaria transmission settings are simulated and the results are shown in Figure 4.19.

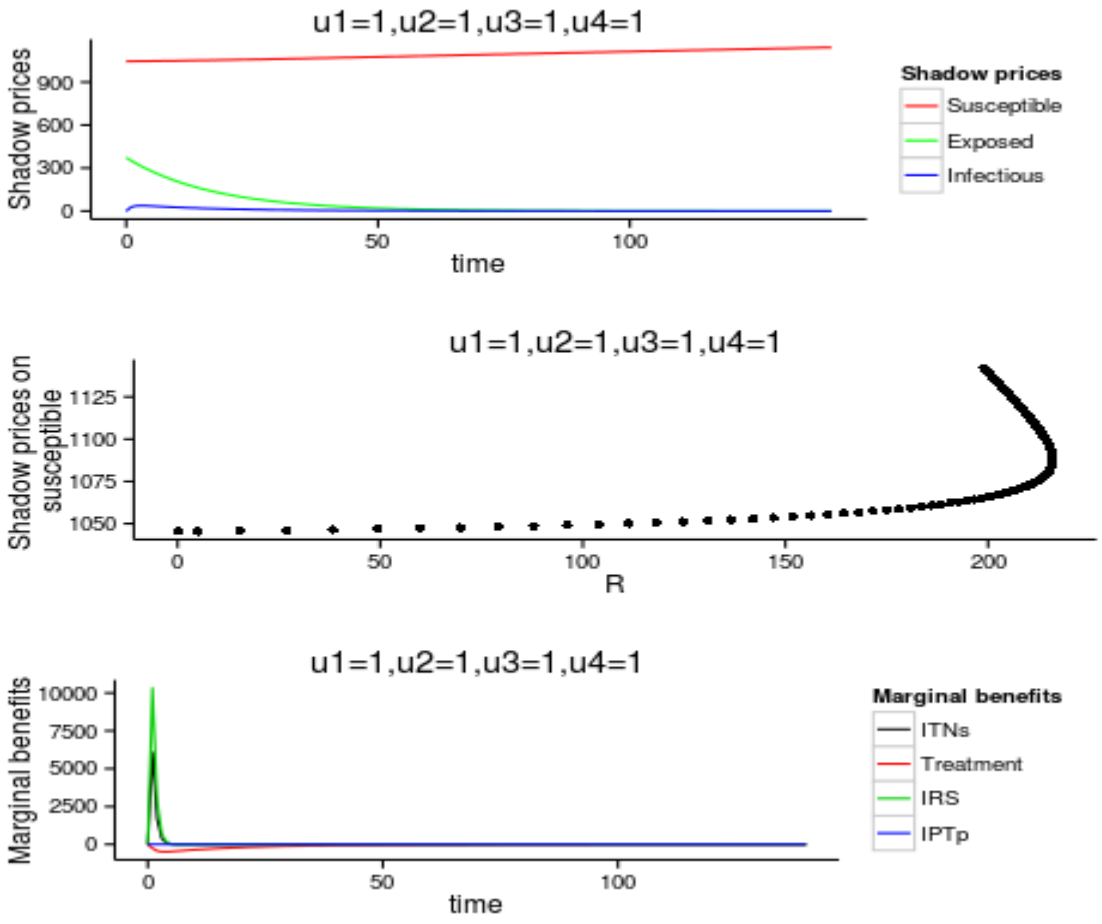


Figure 4.19: Numerical simulations of the economic evaluations of the malaria model across all transmission settings

Across all the transmission settings, it's observed that the marginal value (shadow price) of I_h is much less damaging than the marginal values of E_h and S_h (Figure 4.19). The shadow price on the susceptible humans are increasing overtime while the shadow prices of exposed starts dropping at t=5 days and shadow prices on infected starts dropping at t= 3 days. It's also observed that across all the settings, the shadow price on S_h starts at higher positive values, increases and stabilizes at higher prices closer to the total susceptible population. As more individuals recover from the disease the cost of the disease is still higher. It's further observed that across all the transmission settings, the marginal benefit of use of treatment is much smaller than the marginal benefit of IPTp,

ITNs and IRS in that order. Smaller amounts of treatment are needed compared to IPTp, ITNs and IRS in that order to be able to eliminate the disease.

4.3.2 Numerical Simulation of the Optimal Malaria Control Strategies and Cost-Effectiveness Analysis

Numerical simulations are further done to show the infections averted and the cost associated with the infections averted by the intervention strategies for the four different transmission settings. Rankings of the number infections averted (effectiveness) is then done so that ICER can be applied.

For the different transmission settings we compute the optimal solution for the 15 strategies and their associated effectiveness $\bar{E}$ (infections averted) which is the difference between the numbers of infections when there is no intervention and when there are interventions. The strategies were classified as follows: ITN only (Strategy A), treatment only (Strategy B), IRS only (Strategy C), IPTp only (Strategy D), treatment and ITNs (Strategy E), ITNs and IRS (Strategy F), ITNs and IPTp (Strategy G), treatment and IRS (Strategy H), treatment and IPTp (Strategy I), IPTp and IRS (Strategy J), ITNs, treatment and IRS (Strategy K), ITNs, treatment and IPTp (Strategy L), ITNs, IRS and IPTp (Strategy M), IRS, treatment and IPTp (Strategy N), ITNs, treatment, IRS and IPTp (Strategy O). Based on the model simulation results, the strategies practiced in Kenya for different epidemiological settings were ranked in the order of increasing effectiveness.

The infections averted and cost of the intervention used is used to determine the cost-effectiveness of different combinations of the four intervention strategies. We determined the total cost of the combined intervention strategies and the infections averted for different transmission settings. Interventions that didn't have any effectiveness were dropped. The ICER for every two competing strategies for each epidemiological scenario is calculated and this shows the cost effectiveness for each strategy. The cost-effectiveness calculations are further verified using the computation of incremental cost-effectiveness ratios in table form for each epidemiological zone in order to have a complete overview of the outcome.

4.3.2.1 Simulation Results on Effectiveness for the Endemic Region

The Table 4.3 below summarizes the ranking of simulation results on the effectiveness (infections averted) and the total costs by the different strategies for endemic scenario in Kenya.

Table 4.3: Intervention strategies and its corresponding infections averted plus cost for Endemic region

Strategies	Infections averted	Cost
C	0.0000121135	0.00001817024
A	1.687	5.0613
F	1.6871	7.59196
G	3.68444	20.2644
M	3.6876	4.337343
D	5.35895	13.339738
J	5.368965	21.47586
I	101.7332	57.7995
N	101.7393	610.4358
L	102.8135	771.1012
O	102.818	925.3622
B	105.2167	210.4334
H	105.2167	368.2585
E	106.301	531.5846
K	106.3167	691.0584

The ICER for every two competing strategies was calculated and the results are presented in table 4.4.

Table 4.4: Incremental cost-effectiveness ratios of all combined strategies for Endemic region

Strategy	Strategy effects [E]	Cost ($) [C]	Incremental cost $[\Delta C]$	Incremental effect $[\Delta E]$	ICER $[\Delta C]/[\Delta E]$
C	0.0000121135	0.00001817024	0.00001817024	0.0000121135	1.499999
A	1.687	5.0613	5.06128183	1.686987887	3.000189
F	1.6871	7.59196	2.53066	0.000099999	25306.6
G	3.68444	20.2644	12.67244	1.99734	6.344658
M	3.6876	4.337343	-15.927057	0.00316	-5040.21
D	5.35895	13.339738	9.002395	1.67135	5.386301
J	5.368965	21.47586	8.136122	0.010015	812.3936
I	101.7332	57.7995	36.32364	96.364235	0.376941
N	101.7393	610.4358	552.6363	0.0061	90596.11
L	102.8135	771.1012	160.6654	1.0742	149.5675
O	102.818	925.3622	154.261	0.0045	34280.22
B	105.2167	210.4334	-714.9288	2.3987	-298.048
H	105.2167	368.2585	157.8251	0	Inf
E	106.301	531.5846	163.3261	1.0843	150.6281
K	106.3167	691.0584	159.4738	0.0157	10157.57

Alternatives that are more expensive and less ineffective are excluded (A, F, D, J, N, O and H). These are the strategies that have higher ICER when compared. Having excluded strategy A, F, D, J, N, O and H, ICERs are recalculated for the remaining strategies (C, G, M, I, L, B, E and K) and are shown in Table 4.5.

Table 4.5: Exclusion of more costly and less effective intervention strategies for Endemic region

Strategy	Strategy effects [E]	Cost ($) [C]	Incremental cost $[\Delta C]$	Incremental effect $[\Delta E]$	ICER $[\Delta C] /[\Delta E]$
C	0.0000121135	0.00001817024	0.00001817024	0.0000121135	1.499999
G	3.68444	20.2644	20.26438183	3.684427887	5.500008
M	3.6876	4.337343	-15.927057	0.00316	-5040.21
I	101.7332	57.7995	53.462157	98.0456	0.545278
L	102.8135	771.1012	713.3017	1.0803	660.2811
B	105.2167	210.4334	-560.6678	2.4032	-233.301
E	106.301	531.5846	321.1512	1.0843	296.183
K	106.3167	691.0584	322.7999	1.1	293.4545

The dominated strategies (G, I, L and K) are then excluded and the ICERs are recalculated again (Table 4.6). These are the strategies that have higher ICER when compared

Table 4.6: Exclusion of dominated alternative intervention strategies for Endemic region

Strategy	Strategy effects [E]	Cost ($) [C]	Incremental cost $[\Delta C]$	Incremental effect $[\Delta E]$	ICER $[\Delta C] /[\Delta E]$
C	0.0000121135	0.00001817024	0.00001817024	0.0000121135	1.499999
M	3.6876	4.337343	4.33732483	3.687587887	1.176196
B	105.2167	210.4334	206.096057	101.5291	2.029921
E	106.301	531.5846	321.1512	1.0843	296.183

In Table 4.6 the most cost effective quadrant will be strategy M and strategy B and in deciding between them the size of the available budget must be brought to bear. Strategy M is the combination of ITNs, IRS and IPTp while strategy B is the use of treatment only.

4.3.2.2 Simulation Results on Effectiveness for the Epidemic prone Region

The Table 4.7 below summarizes the simulation results on the effectiveness (infections averted) and the total costs by the different strategies for endemic scenario in Kenya.

Table 4.7: Intervention strategies and its corresponding infections averted plus cost for Epidemic prone region

Strategies	Infections averted	Cost
C	0.0000136	0.0000204639
F	0.173697	0.78166366
M	0.3772208	2.640546
G	0.3773461	2.0754
D	0.5507769	1.376942
J	0.5509108	2.203643
B	11.0302	222.0604
A	17.369998	5210994
N	110.6783	664.07
I	110.6784	498.053
O	110.7885	997.0963
L	110.7889	830.917
H	111.03	388.6051
K	111.1405	722.4134
E	111.1409	555.7043

The ICER for every two competing strategies was calculated and the results are presented in table 4.8.

Table 4.8: Incremental cost-effectiveness ratios of all combined strategies for Epidemic region

Strategy	Strategy effects [E]	Cost ($) [C]	Incremental cost $[\Delta C]$	Incremental effect $[\Delta E]$	ICER $[\Delta C]/[\Delta E]$
C	0.0000136	0.0000204639	0.0000204639	0.0000136	1.504699
F	0.173697	0.78166366	0.781643196	0.1736834	4.500391
M	0.3772208	2.640546	1.85888234	0.2035238	9.133489
G	0.3773461	2.0754	-0.565146	0.0001253	-4510.34
D	0.5507769	1.376942	-0.698458	0.1734308	-4.0273
J	0.5509108	2.203643	0.826701	0.0001339	6174.018
B	11.0302	222.0604	219.856757	10.4792892	20.98012
A	17.369998	52.10994	-169.95046	6.339798	-26.8069
N	110.6783	664.07	611.96006	93.308302	6.558474
I	110.6784	498.053	-166.017	0.0001	-1660170
O	110.7885	997.0963	499.0433	0.1101	4532.637
L	110.7889	830.917	-166.1793	0.0004	-415448
H	111.03	388.6051	-442.3119	0.2411	-1834.56
K	111.1405	722.4134	333.8083	0.1105	3020.89
E	111.1409	555.7043	-166.7091	0.0004	-416773

Alternatives that are more expensive and less ineffective are excluded. Having excluded strategy F, M, J, B, N, O and K, ICERs are recalculated for the remaining strategies (C, G, D, A, I, L, H and E) and are shown in Table 4.9.

Table 4.9: Exclusion of more costly and less effective intervention strategies for Epidemic region

Strategy	Strategy effects [E]	Cost ($) [C]	Incremental cost [ΔC]	Incremental effect [ΔE]	ICER $[\Delta C]/[\Delta E]$
C	0.0000136	0.0000204639	0.0000204639	0.0000136	1.504699
G	0.3773461	2.0754	2.075379536	0.3773325	5.500135
D	0.5507769	1.376942	-0.698458	0.1734308	-4.0273
A	17.369998	52.10994	50.732998	16.8192211	3.01637
I	110.6784	498.053	445.94306	93.308402	4.779238
L	110.7889	830.917	332.864	0.1105	3012.344
H	111.03	388.6051	-442.3119	0.2411	-1834.56
E	111.1409	555.7043	167.0992	0.1109	1506.756

The dominated strategies (G, A, L and E) are then excluded and the ICERs are recalculated again (Table 4.10).

Table 4.10: Exclusion of dominated alternative intervention strategies for Epidemic region

Strategy	Strategy effects [E]	Cost ($) [C]	Incremental cost $[\Delta C]$	Incremental effect $[\Delta E]$	ICER $[\Delta C]/[\Delta E]$
C	0.0000136	0.0000204639	0.0000204639	0.0000136	1.504699
D	0.5507769	1.376942	1.376921536	0.5507633	2.500024
I	110.6784	498.053	496.676058	110.1276231	4.510004
H	111.03	388.6051	-109.4479	0.3516	-311.285

In Table 4.10 the most cost effective quadrant will be strategy C and strategy H and in deciding between them the size of the available budget must be brought to consideration. Strategy H is the combination of treatment and IRS while strategy C is the use of IRS only.

4.3.2.3 Simulation Results on Effectiveness for the Seasonal Region

The Table 4.11 below summarizes the simulation results on the effectiveness (infections averted) and the total costs by the different strategies for endemic scenario in Kenya.

Table 4.11: Intervention strategies and its corresponding infections averted plus cost for Seasonal region

Strategies	Infections averted	Cost
C	0.00003463761	0.00005195642
F	0.0640685	0.2883082
A	0.06416182	0.1924855
G	0.1331041	0.7324025
M	0.1332328	0.9326293
D	0.1972578	0.493144
J	0.1973375	0.7893501
I	115.5753	520.0888
N	115.5754	693.4524
L	115.6155	867.1166
O	115.6157	1040.541
B	115.6983	231.3967
H	115.6985	404.9447
E	115.7387	578.6933
K	115.7387	752.3019

The ICER for every two competing strategies was calculated and the results are presented in table 4.12.

Table 4.12: Incremental cost-effectiveness ratios of all combined strategies for Seasonal region

Strategy	Strategy effects [E]	Cost ($) [C]	Incremental cost $[\Delta C]$	Incremental effect $[\Delta E]$	ICER $[\Delta C]/[\Delta E]$
C	0.00003463761	0.00005195642	0.00005195642	0.00003463761	1.5
F	0.0640685	0.2883082	0.288256244	0.064033862	4.501622
A	0.06416182	0.1924855	-0.0958227	9.332E-05	-1026.82
G	0.1331041	0.7324025	0.539917	0.06894228	7.831435
M	0.1332328	0.9326293	0.2002268	0.0001287	1555.764
D	0.1972578	0.493144	-0.4394853	0.064025	-6.86428
J	0.1973375	0.7893501	0.2962061	7.97E-05	3716.513
I	115.5753	520.0888	519.2994499	115.3779625	4.500855
N	115.5754	693.4524	173.3636	0.0001	1733636
L	115.6155	867.1166	173.6642	0.0401	4330.778
O	115.6157	1040.541	173.4244	0.0002	867122
B	115.6983	231.3967	-809.1443	0.0826	-9795.94
H	115.6985	404.9447	173.548	0.0002	867740
E	115.7387	578.6933	173.7486	0.0402	4322.104
K	115.7387	752.3019	173.6086	0	Inf

Alternatives that are more expensive and less ineffective are excluded. Having excluded strategy F, G, M, J, N, O, H and K, the ICERs are recalculated for the remaining strategies (C, A, D, I, L, B and E) and are shown in Table 4.13.

Table 4.13: Exclusion of more costly and less effective intervention strategies for Seasonal region

Strategy	Strategy effects [E]	Cost ($) [C]	Incremental cost $[\Delta C]$	Incremental effect $[\Delta E]$	ICER $[\Delta C] /[\Delta E]$
C	0.00003463761	0.00005195642	0.00005195642	0.00003463761	1.5
A	0.06416182	0.1924855	0.192433544	0.064127182	3.000811
D	0.1972578	0.493144	0.3006585	0.13309598	2.25896
I	115.5753	520.0888	519.595656	115.3780422	4.503419
L	115.6155	867.1166	347.0278	0.0402	8632.532
B	115.6983	231.3967	-635.7199	0.0828	-7677.78
E	115.7387	578.6933	347.2966	0.0404	8596.45

The dominated strategies (A, I, and L) are then excluded and the ICERs are recalculated again (Table 4.14).

Table 4.14: Exclusion of dominated alternative intervention strategies for Seasonal region

Strategy	Strategy effects [E]	Cost ($) [C]	Incremental cost $[\Delta C]$	Incremental effect $[\Delta E]$	ICER $[\Delta C]/[\Delta E]$
C	0.00003463761	0.00005195642	0.00005195642	0.00003463761	1.5
D	0.1972578	0.493144	0.493092044	0.197223162	2.500173
B	115.6983	231.3967	230.903556	115.5010422	1.999147
E	115.7387	578.6933	347.2966	0.0404	8596.45

In Table 4.14 the most cost effective quadrant will be strategy C and strategy B and in deciding between them the size of the available budget must be brought to consideration. Strategy B is the use of treatment only while strategy C is the use of IRS only.

4.3.2.4 Simulation Results on Effectiveness for the Low risk Region

The Table 4.15 below summarizes the simulation results on the effectiveness (infections averted) and the total costs by the different strategies for low risk region in Kenya.

Table 4.15: Intervention strategies and its corresponding infections averted plus cost for low risk region

Strategies	Infections averted	Cost
C	0.0000485669	0.00007285036
M	0.00104092	0.007286437
G	0.001050199	0.005776093
D	0.001090816	0.00272704
J	0.001139414	0.004557057
F	0.002131766	0.009592945
A	0.002141062	0.06423186
I	119.0639	535.7877
N	119.0641	714.3848
B	119.0646	238.1291
H	119.0647	416.7266
L	119.0653	892.9895
O	119.0656	1071.59
E	119.0659	595.3293
K	119.0662	773.9302

The ICER for every two competing strategies was calculated and the results are presented in table 4.16.

Table 4.16: Incremental cost-effectiveness ratios of all combined strategies for Low risk region

Strategy	Strategy effects [E]	Cost ($) [C]	Incremental cost $[\Delta C]$	Incremental effect $[\Delta E]$	ICER $[\Delta C]/[\Delta E]$
C	0.0000485669	0.00007285036	0.00007285036	0.0000485669	1.5
M	0.00104092	0.007286437	0.007213587	0.000992353	7.269173
G	0.001050199	0.005776093	-0.001510344	0.000009295978	-162.77
D	0.001090816	0.00272704	-0.003049053	4. 0.000040617	-75.0684
J	0.001139414	0.004557057	0.001830017	0.000048598	37.65622
F	0.002131766	0.009592945	0.005035888	0.000992352	5.074699
A	0.002141062	0.06423186	0.054638915	0.000009296	5877.68
I	119.0639	535.7877	535.7234681	119.0617589	4.499543
N	119.0641	714.3848	178.5971	0.0002	892985.5
B	119.0646	238.1291	-476.2557	0.0005	-952511
H	119.0647	416.7266	178.5975	0.0001	1785975
L	119.0653	892.9895	476.2629	0.0006	793771.5
O	119.0656	1071.59	178.6005	0.0003	595335
E	119.0659	595.3293	-476.2607	0.0003	-1587536
K	119.0662	773.9302	178.6009	0.0003	595336.3

Alternatives that are more expensive and less ineffective are excluded. Having excluded strategy M, D, J, A, N, H and O, then the ICERs are recalculated for the remaining strategies (C, G, F, I, B, L, E and K) and are shown in Table 4.17.

Table 4.17: Exclusion of more costly and less effective intervention strategies for Low risk region

Strategy	Strategy effects [E]	Cost ($) [C]	Incremental cost [ΔC]	Incremental effect [ΔE]	ICER $[\Delta C]/[\Delta E]$
C	0.0000485669	0.00007285036	0.00007285036	0.0000485669	1.5
G	0.001050199	0.005776093	0.005703243	0.001001632	5.69395
F	0.002131766	0.009592945	0.003816852	0.001081567	3.529002
I	119.0639	535.7877	535.7781071	119.0617682	4.500001
B	119.0646	238.1291	-297.6586	0.0007	-425227
L	119.0653	892.9895	654.8604	0.0007	935514.9
E	119.0659	595.3293	-297.6602	0.0006	-496100
K	119.0662	773.9302	178.6009	0.0003	595336.3

The dominated strategies (G, I, L, K) are then excluded and the ICERs are recalculated again (Table 4.18).

Table 4.18: Exclusion of dominated alternative intervention strategies for Low risk region

Strategy	Strategy effects [E]	Cost ($) [C]	Incremental cost $[\Delta C]$	Incremental effect $[\Delta E]$	ICER $[\Delta C]/[\Delta E]$
C	0.0000485669	0.00007285036	0.00007285036	0.0000485669	1.5
F	0.002131766	0.009592945	0.009520095	0.002083199	4.56994
B	119.0646	238.1291	238.1195071	119.0624682	1.999954
E	119.0659	595.3293	357.2002	0.0013	274769.4

In Table 4.18 the most cost effective quadrant will be strategy C and strategy B and in deciding between them the size of the available budget must be brought to consideration. Strategy B is the use of treatment only while strategy C is the use of IRS only.

The cost-effectiveness analysis of one or all possible combinations of malaria control strategies for the optimal control problem has been done for the different transmission settings using ICER based on the findings of the simulation optimal control model. The findings indicated that the most cost effective intervention strategies in endemic areas and the endemic region is the combination of ITNs, IRS, and IPTp was the most cost-effective of all the combined strategies developed in this study for malaria disease control and prevention. This finding is different from the findings of Okosun *et al.,* (2013), who found that the combination of the spray of insecticides and treatment of infective individuals were the cost effective strategies. This may be due to the fact that in our study we considered the at most risk groups while in the Okusun *et al.,* (2013) they considered whole population. The findings shows that preventive measures tends to have a greater health benefit in a cost effective or economical manner in minimizing malaria transmission for the most at risk groups. Stuckey *et al.,* (2014) showed that increasing coverage of vector control interventions (preventive strategies) had a larger simulated impact compared to adding treatment measures.

Our results show that for the epidemic prone areas the cost effective strategy was the combination of the treatment and IRS which agrees with Okosun *et al.,* (2013). This is because the combination of the preventive and treatment actions tend to be more effective in the reduction of parasitic prevalence to below 1% (Griffin *et al.,* 2010). This is due to the fact that infected mosquito population is reduced by IRS and the infected human population is reduced via the treatment.

For seasonal areas, the findings of this study showed that the combination ITNs and treatment would be the most cost effective intervention strategy to reduce malaria transmission among the under-five and the pregnant women. This is slightly different with the findings of Griffin et al (2010) who found that for the high seasonal transmission settings the use of LLITNs, IRS and treatment would help reduce the transmission of malaria.

The results showed that for the low risk areas is the use of treatment only. These findings were different from Hansen *et al.,* (2012) who found that the most cost effective strategy was the use of ITNs alone in Uganda low transmission settings.

The result confirms the role which the four intervention strategies are playing in order to eradicate or minimize the spreading of the malaria disease among the at risk groups. The policy implications of these findings are that different transmission settings require different interventions that are health beneficial and cost effective. The results can guide decision makers in making more informed and evidence-based choices on the health resources being allocated. These findings may help inform the development of guidelines for prevention of malaria among the under-five and the pregnant women in different transmission settings in Kenya as well as in other African countries.

Mathematical models can help in getting Information on the optimal malaria intervention strategies tailored to specific transmission patterns of malaria. This will provide basis for informed decision making about malaria control that are beneficial and cost effective and hence the path towards malaria elimination.

CHAPTER FIVE

CONCLUSION AND RECOMMENDATIONS

5.1 Conclusion

In this study, a malaria transmission dynamics model (using a deterministic system of nonlinear ordinary differential equations) incorporating intervention strategies being practiced in Kenya was formulated and analyzed. The aim was to investigate the effect of these control strategies in minimizing malaria transmission in Kenya among the most at risk group of malaria (children under-five years of age and the pregnant women) for different transmission settings in Kenya which represents the different transmission settings across Africa. Interventions considered were those recommended by WHO for the most at risk group for malaria i.e. the use of insecticide treated bednets (ITNs), treatment, Indoor Residual Spray (IRS) and Intermittent Preventive Treatment for Pregnant women (IPTp).

We assumed that the control parameters are constant so as to determine the basic reproduction number, steady states and their stability as well as the bifurcation analysis. From the analysis of the malaria model with intervention strategies, there exists a domain where the model is epidemiologically and mathematically well-posed and that if $R_0 < 1$, the disease cannot survive in the Kenya (different epidemiological zones). The disease free equilibrium is globally asymptotically stable if $R_0 < 1$. The model may exhibit a backward bifurcation (a situation where disease free and endemic equilibrium coexist) at $R_0 = 1$ implying the existence of multiple endemic equilibria for $R_0 < 1$. However, If $R_0 \geq 1$, the model admits a unique endemic equilibrium which is globally asymptotically stable in the interior of the feasible region D . The most sensitive parameters were mosquito biting rate (ϵ) and mosquito death rate (μ_m). Control measures have effect in lowering exposed and infected members of both human and mosquito population. When there are no intervention strategies put in place the number of exposed and infected classes for humans and mosquitoes increases and decreases when there are interventions.

The study formulated and performed optimal control analysis for malaria model with intervention strategies from which we considered the time dependent controls. Using

Pontryagin maximum principle we derived and analyzed the necessary conditions for the optimal control of malaria with effective use of ITNs, treatment, IRS and IPTp. Using the optimal control approach, we can conclude that, according to our model, the optimal control strategies for malaria control in endemic areas that an effective IRS use and treatment will be beneficial to the community for the control of malaria disease (infected human and mosquito population) faster at a lower cost for the endemic settings. For the epidemic prone areas, the optimal control strategy for reducing the infected human and mosquito population was the use of treatment and IRS. For seasonal areas much impact will be felt when treatment and for the low risk areas, just the use ITNs and treatment will be sufficient to reduce infected human and mosquito population.

In assessing the cost effectiveness of the optimal control strategies for malaria, we can conclude that for the endemic regions the combination of ITNs, IRS, and IPTp is the most cost-effective of all the combined strategies developed in this study for malaria disease control and prevention; for the epidemic prone areas is the combination of the treatment, and IRS; for seasonal areas is the combination ITNs plus treatment; and for the low risk areas is the use of treatment only.

Mathematical models can help provide basis for informed decision making about malaria control that are beneficial and cost effective and hence the path towards malaria elimination. Control programs that follow these strategies can effectively reduce the spread of malaria disease in different malaria transmission settings in Kenya.

5.2 Recommendations

Policy makers have to be informed about the research results. The following recommendations should be considered

1. Combination of malaria control strategies plays a bigger role in reducing malaria transmission, the study recommends scale up of intervention strategies being used in Kenya around those who are at most risk of malaria/ exposed to malaria in different transmission settings.

2. Strategies targeting to reduce mosquito population and mosquito biting rates (vector control) such as ITNs and IRS should be implemented since they are proving to be effective in reducing transmission of malaria in Kenya. There will be need for the National Control Programme to create awareness on mosquito reduction strategies.
3. The recommended optimal control strategies are the combined use of treatment and IRS for endemic areas; use of treatment and IRS for endemic regions; use of treatment for seasonal areas; and use of ITNs and treatment for low risk areas. These are the strategies that will minimize malaria transmission at minimum cost
4. The recommended cost effective strategies are the combination of ITNs, IRS and IPTp for endemic areas; use of treatment and IRS for epidemic prone areas; use of ITNs and treatment for seasonal areas; and use of treatment only for low risk areas. These are the strategies which produces health improvements in the most cost effective way for different epidemiological zones.

5.3 Future Work

The proposed model has some limitations. We did not consider immigrants into the susceptible population. Hence the inclusion of immigrants in the model would supplement on the information that would be used on which intervention strategy to prioritize to specific groups.

Other preventive measures that may help to eliminate the existence of mosquitoes such as eradicating breeding grounds for mosquitoes also need to be considered.

Since this is the first ever modeling, simulation, optimal control and cost effectiveness analysis of malaria intervention strategies in free R statistical computing platform, future testing and refinement of the model together with simulation with data from amore designed study from other representative settings should be done to improve the results.

Future studies may explore the use of stochastic models to understand the malaria dynamics which was not covered by our study. Bayesian approaches may also be explored to cater for the uncertainties of the parameters.

The model can be extended to include other environmental effect impacting on the spread of malaria such as climatic change, temperature, rainfall and humidity. These factors may affect some parameters that have been included in the malaria model such as birth rate of mosquito population among others.

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APPENDICES

APPENDIX I: R CODES

```
#ODE solution in R
library(ggplot2)
library(gridExtra)
library(deSolve)

#Model
Lorenz<-function(t, state, parameters) {
  with(as.list(c(state, parameters)),{
    # rate of change
    dS<- v+w*R-(1-u1)*x*S-(1-u4)*q*S-z*S
    dE<- (1-u1)*x*S-(1-u4)*q*S-(n+z)*E
    dI<- n*E-(g+z)*I-(b+f*u2)*I
    dR<- (b+f*u2)*I-(w+z)*R
    dX<- m-(1-u1)*d*X-(e+a*u1+p*u3)*X
    dY<- (1-u1)*d*X-k*Y-(e+a*u1+p*u3)*Y
    dZ<- k*Y-(e+a*u1+p*u3)*Z
    # return the rate of change
    list(c(dS, dE, dI, dR, dX, dY, dZ))
  }) # end with(as.list...
}


#Parameters
parameters    <-    c(v=0.2326,    w=0.0014,    x=0.0001045,
q=0.0003485,  z=0.0000457,  n=0.058,  g=0.05,  b=0.5,  f=0.5,
m=0.071, d=0.00001130, e=0.1429,k=0.0556, a=0.5, p=0.85)

#Initial conditions
state <- c(S=700, E=250, I=0, R=0, X=5000, Y=500, Z=100)

#Interventions
interventions <- c(u1=0.0904 ,u2=0.165, u3=0.076, u4=0.035)

Us<-expand.grid(u1=0:1,u2=0:1,u3=0:1,u4=0:1)

#Time specification
times <-seq(0,140,by=1)
length(times)


#Model Intergration
########################
```

```
Us<-
expand.grid(u1=c(0,0.1),u2=c(0,0.3),u3=c(0,0.7),u4=c(0,0.51
))


outlist<-list()
for(i in 1:nrow(Us)){
  outlist[[i]]<-as.data.frame(ode(y=state,times=times,
method="ode45", func=Lorenz,parms=c(parameters,Us[i,])))
}

for(i in 2:nrow(Us)){
  dat1<-outlist[[1]][,c("time","I","Z")]
  dat2<-outlist[[i]][,c("time","I","Z")]
  dat1$int<-1
  dat2$int<-2
  dat<-rbind(dat1,dat2)
  UU<-Us[i,]
  dat$int<-factor(dat$int,labels=c("no
intervention",paste(paste0("u",1:4),"=",(Us[i,]>0)*1,sep=""
,collapse = ",")))
  plot1<-
ggplot(dat,aes(x=time,y=I,colour=int))+geom_line()+theme_cl
assic()+theme(legend.position="top",legend.direction
     ="vertical")+

scale_color_manual("",values=c("red","blue"))+labs(y="Infec
ted humans")
  plot2<-
ggplot(dat,aes(x=time,y=Z,colour=int))+geom_line()+theme_cl
assic()+theme(legend.position="top",legend.direction
     ="vertical")+

scale_color_manual("",values=c("red","blue"))+labs(y="Infec
ted Mosquitoes")

png(file=paste0(paste(c("u1","u2","u3","u4"),"=",UU,sep="",
collapse = ","),".png"))
  grid.arrange(plot1,plot2,nrow=1)
  dev.off()
}
# dev.off()

infectionlist<-matrix(NA,nrow=nrow(Us),ncol=2)
for(i in 1:nrow(Us)){
```

```
  infectionlist[i,]<-
c(all=sum(outlist[[i]][,"I"]),diff=sum(outlist[[1]][,"I"])-
sum(outlist[[i]][,"I"]))
}
infectiondata<-as.data.frame(infectionlist)
names(infectiondata)<-c("Incidence","Difference")

labs<-NULL
for(i in 1:nrow(Us)){

  labs[i]<-
paste(paste0("u",1:4),"=",(Us[i,]>0)*1,sep="",collapse     =
",")
}

infectiondata$comb<-labs


###Optimal control
#####################################################
rm(list=ls())
library(ggplot2)
library(gridExtra)
library(deSolve)
library(reshape2)
#The Lorenz function
Lorenz2<-function(t, state, parameters) {
  with(as.list(c(state, parameters)),{
    # rate of change
    #Optimal control equation
    u1<-(max(0,min(1,(((L2-L1)*x*S+(L6-
L5)*d*X+a*X*L5+a*Y*L6+a*Z+L7)/b1))))*u1_
    u2<-(max(0,min(1,((f*(L3-L4)*I)/b2))))*u2_
    u3<-(max(0,min(1,((p*X*L5+Y*L6+Z*L7)/b3))))*u3_
    u4<-(max(0,min(1,((L2-L1)*q*S/b))))*u4_

    dL1<-(-(1-u1)*x*L1-(1-u4)*q*L1-z*L1+(1-u1)*x*L2+(1-
u4)*q*L2)*(1)
    dL2<-(a3-(n+z)*L2+L3*n)
    dL3<-(a2-(g+z)*L3-(b+f*u2)*L3+L4*(b+f*u2))
    dL4<-(w*L1-(w+z)*L4)
    dL5<-(-(1-u1)*d*L5-(e+a*u1+p*u3)*L5+(1-u1)*d*L6+a1)
    dL6<-(-(k)*L6-(e+a*u1+p*u3)*L6+k*L7+a1)
    dL7<-(-(e+a*u1+p*u3)*L7+a1)

    dS<- v+w*R-(1-u1)*x*S-(1-u4)*q*S-z*S
    dE<- (1-u1)*x*S-(1-u4)*q*S-(n+z)*E
```

```
    dI<- n*E-(g+z)*I-(b+f*u2)*I
    dR<- (b+f*u2)*I-(w+z)*R
    dX<- m-(1-u1)*d*X-(e+a*u1+p*u3)*X
    dY<- (1-u1)*d*X-k*Y-(e+a*u1+p*u3)*Y
    dZ<- k*Y-(e+a*u1+p*u3)*Z
    # return the rate of change
    list(c(dS,      dE,      dI,      dR,      dX,      dY,
dZ,dL1,dL2,dL3,dL4,dL5,dL6,dL7))
  }) # end with(as.list...
}



#Parameters
parameters    <-    c(v=0.2326,    w=0.0014,    x=0.0001045,
q=0.0003485, z=0.0000457, n=0.058,
                g=0.05,      b=0.5,      f=0.5,      m=0.071,
d=0.00001130, e=0.1429,k=0.0556, a=0.5,a1=20, p=0.85,
                c=0.6,j=0.35,l=0.09,lw=0.015,a3=100,
                a2=92,b1=20,b2=65,b3=10,b4=10,i=0.833
                )

#Initial conditions
state  <-  c(S=700,  E=250,  I=00,  R=00,  X=5000,  Y=500,
Z=100,L1=100,L2=0.02,L3=0.025,L4=000,L5=0000,L6=000,L7=0.04
5)

#Time specification

times <-seq(0,140,by=1)
length(times)

#Model Intergration
Us<-expand.grid(u1_=0:1,u2_=0:1,u3_=0:1,u4_=0:1)

outlist<-list()
for(i in 1:nrow(Us)){
  outlist[[i]]<-as.data.frame(ode(y=state,times=times,
method="ode45", func=Lorenz2,parms=c(parameters,Us[i,])))
}

str(outlist)

maxm<-NULL
cost<-NULL
comb<-NULL
costs<-c(3.0,2.0,1.5,2.5)
```

```
for(i in 1:nrow(Us)){
  maxm[i]<-
match(max(outlist[[i]][,"I"]),outlist[[i]][,"I"])
  comb[i]<-
paste(paste0("u",1:4),"=",(Us[i,]>0)*1,sep="",collapse     =
",")
  cost[i]<-sum((Us[i,]>0)*costs)

}
maxm_dat<-data.frame(comb,maxm)


for(i in 2:nrow(Us)){
  dat1<-outlist[[1]][,c("time","I","Z")]
  dat2<-outlist[[i]][,c("time","I","Z")]

  dat1$int<-1
  dat2$int<-2
  dat<-rbind(dat1,dat2)
  UU<-Us[i,]
  dat$int<-factor(dat$int,labels=c("no
intervention",paste(paste0("u",1:4),"=",(Us[i,]>0)*1,sep=""
,collapse = ",")))
  plot1<-
ggplot(dat,aes(x=time,y=I,colour=int))+geom_line()+theme_cl
assic()+theme(legend.position="top",legend.direction
     ="vertical")+

scale_color_manual("",values=c("red","blue"))+labs(y="Infec
ted humans")
  plot2<-
ggplot(dat,aes(x=time,y=Z,colour=int))+geom_line()+theme_cl
assic()+theme(legend.position="top",legend.direction
     ="vertical")+

scale_color_manual("",values=c("red","blue"))+labs(y="Infec
ted Mosquitoes")

png(file=paste0(paste(c("u1","u2","u3","u4"),"=",UU,sep="",
collapse = ","),".png"))
  grid.arrange(plot1,plot2,nrow=1)
  dev.off()
}


infectionlist<-matrix(NA,nrow=nrow(Us),ncol=2)
for(i in 1:nrow(Us)){
```

```
  infectionlist[i,]<-
c(all=sum(outlist[[i]][,"I"]),diff=sum(outlist[[1]][,"I"])-
sum(outlist[[i]][,"I"]))
}
infectiondata<-as.data.frame(infectionlist)
names(infectiondata)<-c("Incidence","Difference")

labs<-NULL
for(i in 1:nrow(Us)){

  labs[i]<-
paste(paste0("u",1:4),"=",(Us[i,]>0)*1,sep="",collapse     =
",")
}

infectiondata$comb<-labs
infectiondata$cost<-cost
infectiondata$cost_diff<-
with(infectiondata,cost*Difference)

infectiondata<-dplyr::arrange(infectiondata,Difference)
infectiondata$icer<-NA
infectiondata$diff_cost<-NA
infectiondata$diff_effect<-NA
for(i in 2:nrow(Us)){
  infectiondata$diff_cost[i]<-
with(infectiondata,(cost_diff[i]-cost_diff[i-1]))
  infectiondata$diff_effect[i]<-
with(infectiondata,(Difference[i]-Difference[i-1]))
  infectiondata$icer[i]<-with(infectiondata,(cost_diff[i]-
cost_diff[i-1])/(Difference[i]-Difference[i-1]))
}

tab<-
infectiondata[,c("comb","cost_diff","Difference","diff_cost
","diff_effect","icer")]
tab<-tab[tab$icer<0,]

tab$icer<-NA
tab$diff_cost<-NA
tab$diff_effect<-NA
for(i in 2:nrow(tab)){
  tab$diff_cost[i]<-with(tab,(cost_diff[i]-cost_diff[i-1]))
  tab$diff_effect[i]<-with(tab,(Difference[i]-Difference[i-
1]))
  tab$icer[i]<-with(tab,(cost_diff[i]-cost_diff[i-
1])/(Difference[i]-Difference[i-1]))
```

```
}

tab<-tab[tab$icer<0,]

tab$icer<-NA
tab$diff_cost<-NA
tab$diff_effect<-NA
for(i in 2:nrow(tab)){
  tab$diff_cost[i]<-with(tab,(cost_diff[i]-cost_diff[i-1]))
  tab$diff_effect[i]<-with(tab,(Difference[i]-Difference[i-
1]))
  tab$icer[i]<-with(tab,(cost_diff[i]-cost_diff[i-
1])/(Difference[i]-Difference[i-1]))
}


##############################################
u1<-(max(0,min(1,(((L2-L1)*x*S+(L6-
L5)*d*X+a*X*L5+a*Y*L6+a*Z+L7)/b1))))*u1_
u2<-(max(0,min(1,((f*(L3-L4)*I)/b2))))*u2_
u3<-(max(0,min(1,((p*X*L5+Y*L6+Z*L7)/b3))))*u3_
u4<-(max(0,min(1,((L2-L1)*q*S/b))))*u4_

outlist2<-outlist
for(i in 1:length(outlist2)){
  # outlist2[[i]]["u1"]<-NA
  if(Us[i,"u1_"])                        outlist2[[i]]["u1"]<-
with(c(as.list(outlist2[[i]]),as.list(parameters)),pmax(0,p
min(1,(((L2-L1)*x*S+(L6-
L5)*d*X+a*X*L5+a*Y*L6+a*Z+L7)/b1))))
  if(Us[i,"u2_"])                        outlist2[[i]]["u2"]<-
with(c(as.list(outlist2[[i]]),as.list(parameters)),pmax(0,p
min(1,((f*(L3-L4)*I)/b2))))*Us[i,"u2_"]
  if(Us[i,"u3_"])                        outlist2[[i]]["u3"]<-
with(c(as.list(outlist2[[i]]),as.list(parameters)),pmax(0,p
min(1,((p*X*L5+Y*L6+Z*L7)/b3))))

  if(Us[i,"u4_"])                        outlist2[[i]]["u4"]<-
with(c(as.list(outlist2[[i]]),as.list(parameters)),pmax(0,p
min(1,((L2-L1)*q*S/b))))

}

#pdf(file="us.pdf")
for(i in 2:length(outlist2)){
  cols<-names(outlist2[[i]])
  cols2<-cols[!grepl("u",cols)]
```

```
  dat_temp<-melt(outlist2[[i]],id=cols2)
  dat_temp$variable<-paste0(dat_temp$variable," = 1")
  dat_temp$variable<-as.factor(dat_temp$variable)
  plot<-
ggplot(dat_temp,aes(x=time,y=value,colour=variable))+geom_l
ine()
  plot<-plot+labs(x="Time(days)",y="Control
profile")+theme_classic()
  # plot<-plot+scale_colour_manual("",values=1:sum(Us[i,]))
  print(plot)
  png(file=paste0("figure ",i,".png"))
  print(plot)
  dev.off()
}

#dev.off()


####Cost effectiveness analysis
########cost effectiveness analysis
rm(list=ls())
library(ggplot2)
library(gridExtra)
library(deSolve)
library(reshape2)

#Costate function
Lorenz2<-function(t, state, parameters) {
  with(as.list(c(state, parameters)),{
    # rate of change
    #Optimal control equation
    u1<-(max(0,min(1,(((L2-L1)*x*S+(L6-
L5)*d*X+a*X*L5+a*Y*L6+a*Z+L7)/b1))))*u1_
    u2<-(max(0,min(1,((f*(L3-L4)*I)/b2))))*u2_
    u3<-(max(0,min(1,((p*X*L5+Y*L6+Z*L7)/b3))))*u3_
    u4<-(max(0,min(1,((L2-L1)*q*S/b))))*u4_

    dL1<-(-b1*u1*exp(-phi)-b4*u1*exp(-phi)-(1-u1)*x*L1-(1-
u4)*q*L1-z*L1+(1-u1)*x*L2+(1-u4)*q*L2)*(1)
    dL2<-(-b1*u1*exp(-phi)-b4*u1*exp(-phi)+a3-
(n+z)*L2+L3*n)
    dL3<-(-b2*u2*f*exp(-phi)+a2-(g+z)*L3-
(b+f*u2)*L3+L4*(b+f*u2))
    dL4<-(w*L1-(w+z)*L4)
    dL5<-(-b1*u1*exp(-phi)-b3*p*u3*exp(-phi)-(1-u1)*d*L5-
(e+a*u1+p*u3)*L5+(1-u1)*d*L6+a1)
```

```
    dL6<-(-b1*u1*exp(-phi)-b3*p*u3*exp(-phi)-(k)*L6-
(e+a*u1+p*u3)*L6+k*L7+a1)
    dL7<-(-b1*u1*exp(-phi)-b3*p*u3*exp(-phi)-
(e+a*u1+p*u3)*L7+a1)


    dS<- v+w*R-(1-u1)*x*S-(1-u4)*q*S-z*S
    dE<- (1-u1)*x*S-(1-u4)*q*S-(n+z)*E
    dI<- n*E-(g+z)*I-(b+f*u2)*I
    dR<- (b+f*u2)*I-(w+z)*R
    dX<- m-(1-u1)*d*X-(e+a*u1+p*u3)*X
    dY<- (1-u1)*d*X-k*Y-(e+a*u1+p*u3)*Y
    dZ<- k*Y-(e+a*u1+p*u3)*Z


    # return the rate of change
    list(c(dS,      dE,      dI,      dR,      dX,      dY,
dZ,dL1,dL2,dL3,dL4,dL5,dL6,dL7))
  }) # end with(as.list...
}

#Parameters
parameters    <-    c(v=0.2326,    w=0.0014,    x=0.0001045,
q=0.0003485, z=0.0000457, n=0.058,
                g=0.05,     b=0.5,      f=0.5,      m=0.071,
d=0.00001130, e=0.1429,k=0.0556, a=0.5,a1=20, p=0.85,
                c=0.6,j=0.35,l=0.09,lw=0.015,a3=100,phi=3,
                a2=92,b1=20,b2=65,b3=10,b4=10,i=0.833
)

#Initial conditions
state  <-  c(S=700,  E=250,  I=00,  R=00,  X=5000,  Y=500,
Z=100,L1=100,L2=0.02,L3=0.025,L4=000,L5=0000,L6=000,L7=0.04
5)

#Time specification
#0.01 daily intervals. R's function seq() creates the time
sequence.

times <-seq(0,140,by=1)
length(times)


#Model Intergration
Us<-expand.grid(u1_=0:1,u2_=0:1,u3_=0:1,u4_=0:1)
```

```
outlist<-list()
for(i in 1:nrow(Us)){
  outlist[[i]]<-as.data.frame(ode(y=state,times=times,
method="ode45", func=Lorenz2,parms=c(parameters,Us[i,])))
}

maxm<-NULL
cost<-NULL
comb<-NULL
costs<-c(3.0,2.0,1.5,2.5)
for(i in 1:nrow(Us)){
  maxm[i]<-
match(max(outlist[[i]][,"I"]),outlist[[i]][,"I"])
  comb[i]<-
paste(paste0("u",1:4),"=",(Us[i,]>0)*1,sep="",collapse     =
",")
  cost[i]<-sum((Us[i,]>0)*costs)

}

maxm_dat<-data.frame(comb,maxm)

for(i in 2:nrow(Us)){
  dat1<-outlist[[1]][,c("time","I","Z")]
  dat2<-outlist[[i]][,c("time","I","Z")]

  dat1$int<-1
  dat2$int<-2
  dat<-rbind(dat1,dat2)
  UU<-Us[i,]
  dat$int<-factor(dat$int,labels=c("no
intervention",paste(paste0("u",1:4),"=",(Us[i,]>0)*1,sep=""
,collapse = ",")))
  plot1<-
ggplot(dat,aes(x=time,y=I,colour=int))+geom_line()+theme_cl
assic()+theme(legend.position="top",legend.direction
="vertical")+

scale_color_manual("",values=c("red","blue"))+labs(y="Infec
ted humans")
  plot2<-
ggplot(dat,aes(x=time,y=Z,colour=int))+geom_line()+theme_cl
assic()+theme(legend.position="top",legend.direction
     ="vertical")+

scale_color_manual("",values=c("red","blue"))+labs(y="Infec
ted Mosquitoes")
```

```
png(file=paste0(paste(c("u1","u2","u3","u4"),"=",UU,sep="",
collapse = ","),".png"))
  grid.arrange(plot1,plot2,nrow=1)
  dev.off()
}
# dev.off()

infectionlist<-matrix(NA,nrow=nrow(Us),ncol=2)
for(i in 1:nrow(Us)){
  infectionlist[i,]<-
c(all=sum(outlist[[i]][,"I"]),diff=sum(outlist[[1]][,"I"])-
sum(outlist[[i]][,"I"]))
}
infectiondata<-as.data.frame(infectionlist)
names(infectiondata)<-c("Incidence","Difference")

labs<-NULL
for(i in 1:nrow(Us)){

  labs[i]<-
paste(paste0("u",1:4),"=",(Us[i,]>0)*1,sep="",collapse     =
",")
}

infectiondata$comb<-labs
infectiondata$cost<-cost
infectiondata$cost_diff<-
with(infectiondata,cost*Difference)

infectiondata<-dplyr::arrange(infectiondata,Difference)
infectiondata$icer<-NA
infectiondata$diff_cost<-NA
infectiondata$diff_effect<-NA
for(i in 2:nrow(Us)){
  infectiondata$diff_cost[i]<-
with(infectiondata,(cost_diff[i]-cost_diff[i-1]))
  infectiondata$diff_effect[i]<-
with(infectiondata,(Difference[i]-Difference[i-1]))
  infectiondata$icer[i]<-with(infectiondata,(cost_diff[i]-
cost_diff[i-1])/(Difference[i]-Difference[i-1]))
}

tab<-
infectiondata[,c("comb","cost_diff","Difference","diff_cost
","diff_effect","icer")]
tab<-tab[tab$icer<0,]
```

```
tab$icer<-NA
tab$diff_cost<-NA
tab$diff_effect<-NA
for(i in 2:nrow(tab)){
  tab$diff_cost[i]<-with(tab,(cost_diff[i]-cost_diff[i-1]))
  tab$diff_effect[i]<-with(tab,(Difference[i]-Difference[i-
1]))
  tab$icer[i]<-with(tab,(cost_diff[i]-cost_diff[i-
1])/(Difference[i]-Difference[i-1]))
}

tab<-tab[tab$icer<0,]

tab$icer<-NA
tab$diff_cost<-NA
tab$diff_effect<-NA
for(i in 2:nrow(tab)){
  tab$diff_cost[i]<-with(tab,(cost_diff[i]-cost_diff[i-1]))
  tab$diff_effect[i]<-with(tab,(Difference[i]-Difference[i-
1]))
  tab$icer[i]<-with(tab,(cost_diff[i]-cost_diff[i-
1])/(Difference[i]-Difference[i-1]))
}



###control profile
u1<-(max(0,min(1,(((L2-L1)*x*S+(L6-
L5)*d*X+a*X*L5+a*Y*L6+a*Z+L7)/b1))))*u1_
u2<-(max(0,min(1,((f*(L3-L4)*I)/b2))))*u2_
u3<-(max(0,min(1,((p*X*L5+Y*L6+Z*L7)/b3))))*u3_
u4<-(max(0,min(1,((L2-L1)*q*S/b))))*u4_

outlist2<-outlist
for(i in 1:length(outlist2)){
  # outlist2[[i]]["u1"]<-NA
  if(Us[i,"u1_"])                        outlist2[[i]]["u1"]<-
with(c(as.list(outlist2[[i]]),as.list(parameters)),pmax(0,p
min(1,(((L2-L1)*x*S+(L6-
L5)*d*X+a*X*L5+a*Y*L6+a*Z+L7)/b1))))
  if(Us[i,"u2_"])                        outlist2[[i]]["u2"]<-
with(c(as.list(outlist2[[i]]),as.list(parameters)),pmax(0,p
min(1,((f*(L3-L4)*I)/b2))))*Us[i,"u2_"]
  if(Us[i,"u3_"])                        outlist2[[i]]["u3"]<-
with(c(as.list(outlist2[[i]]),as.list(parameters)),pmax(0,p
min(1,((p*X*L5+Y*L6+Z*L7)/b3))))
```

```
  if(Us[i,"u4_"])                        outlist2[[i]]["u4"]<-
with(c(as.list(outlist2[[i]]),as.list(parameters)),pmax(0,p
min(1,((L2-L1)*q*S/b))))

}


for(i in 2:length(outlist2)){
  cols<-names(outlist2[[i]])
  cols2<-cols[!grepl("u",cols)]
  dat_temp<-melt(outlist2[[i]],id=cols2)
  dat_temp$variable<-paste0(dat_temp$variable," = 1")
  dat_temp$variable<-as.factor(dat_temp$variable)
  plot<-
ggplot(dat_temp,aes(x=time,y=value,colour=variable))+geom_l
ine()
  plot<-plot+labs(x="Time(days)",y="Control
profile")+theme_classic()
  # plot<-plot+scale_colour_manual("",values=1:sum(Us[i,]))
  print(plot)
  png(file=paste0("figure ",i,".png"))
  print(plot)
  dev.off()
}


###shadow prices
outlist3<-outlist
for(i in 1:length(outlist3)){
  outlist3[[i]]["sps"]<-
with(c(as.list(outlist3[[i]]),as.list(parameters)),b1*S*(ex
p(-phi))+b4*S*(exp(-phi)))
  outlist3[[i]]["spe"]<-
with(c(as.list(outlist3[[i]]),as.list(parameters)),b1*E*(ex
p(-phi))+b4*E*(exp(-phi)))
  outlist3[[i]]["spi"]<-
with(c(as.list(outlist3[[i]]),as.list(parameters)),b2*I*(ex
p(-phi)))
}

#plot shadow prices against time in one plot
pdf(file="shadow prices.pdf")
for(i in 1:length(outlist3)){
  data<-outlist3[[i]]
  data<-melt(data[,c("time","sps","spe","spi")],id="time")
```

```
  plot<-
ggplot(data,aes(x=time,y=value,colour=variable))+geom_line(
)
  plot<-
plot+labs(title=paste(paste0("u",1:4),"=",(Us[i,]>0)*1,sep=
"",collapse = ","))
  print(plot)
}

dev.off()
#plot shadow prices on Sh against Rh in one plot

pdf(file="shadow prices against Rh.pdf")
for(i in 1:length(outlist3)){
  data<-outlist3[[i]]
  #                                                    data<-
melt(data[,c("time","sps","spe","spi")],id="time")
  plot<-ggplot(data,aes(x=R,y=sps))+geom_point()
  plot<-
plot+labs(title=paste(paste0("u",1:4),"=",(Us[i,]>0)*1,sep=
"",collapse = ","))
  print(plot)

}

dev.off()

###marginal benefit
mbu1<-x*(L1-L2)+(L6-L5)*d*X+a*(X*L5+Y*L6+Z*L7)
mbu2<-f*I*(L4-L3)
mbu3<-p*(X*L5+Y*L6+Z*L7)
mbu4<-q*(L2-L1)

outlist4<-outlist
for(i in 1:length(outlist4)){
  outlist4[[i]]["mbu1"]<-
with(c(as.list(outlist4[[i]]),as.list(parameters)),x*(L1-
L2)+(L6-L5)*d*X+a*(X*L5+Y*L6+Z*L7))
  outlist4[[i]]["mbu2"]<-
with(c(as.list(outlist4[[i]]),as.list(parameters)),f*I*(L4-
L3))
  outlist4[[i]]["mbu3"]<-
with(c(as.list(outlist4[[i]]),as.list(parameters)),p*(X*L5+
Y*L6+Z*L7))
  outlist4[[i]]["mbu4"]<-
with(c(as.list(outlist4[[i]]),as.list(parameters)),q*(L2-
L1))
```

```
}

#plot marginal benefits of (itn, treatment, irs, iptp)
against time in one plot

pdf(file="marginal benefits.pdf")
for(i in 1:length(outlist3)){
  data<-outlist4[[i]]
  data<-
melt(data[,c("time","mbu1","mbu2","mbu3","mbu4")],id="time"
)
  plot<-
ggplot(data,aes(x=time,y=value,colour=variable))+geom_line(
)
  plot<-
plot+labs(title=paste(paste0("u",1:4),"=",(Us[i,]>0)*1,sep=
"",collapse = ","))
  print(plot)
}

dev.off()
```

APPENDIX II: LIST OF PUBLICATIONS

1. Otieno G, Koske JK, Mutiso JM. Cost Effectiveness Analysis of Optimal Malaria Control Strategies in Kenya. *Mathematics* 2016, **4**(1), 14 ; doi:10.3390/math4010014

2. Otieno G, Koske JK, Mutiso JM. Analysis and Optimal Control Strategies for the Spread of Malaria in Kenya *(In Press - Discrete Dynamics in Nature and Society)*

APPENDIX III: MANUSCRIPT SUBMITTED FOR PUBLICATION

1. Otieno G, Koske JK, Mutiso JM. A Model for Malaria Transmission Dynamics with Interventions Strategies in Kenya (Submitted)