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Optimal (Control of) Intervention Strategies for Malaria Epidemic in Karonga District, Malawi

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A thesis submitted to the Faculty of Science, University of the Witwatersrand, in fulfillment of the requirements for the degree of Doctor of Philosophy.

December 2, 2014

Declaration

I, **Peter Mpasho Mwamusaku Mwamtobe,** declare that this research work on: "*Optimal (Control of) Intervention Strategies for Malaria Epidemic in Karonga District, Malawi*" is my own original work. It is being submitted for the degree of Doctor of Philosophy at the University of the Witwatersrand, Johannesburg and has not previously been submitted for any degree at this or any other university.

Signature: _____.

Signed in Johannesburg on _____ day of _____ 2014.

Wits ethics clearance number: **H13/03/04.**

Malawi Ministry of Health ethics clearance number: **NHSRC1162.**

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Dedication

To God Almighty

My parents: Gilbert and Gloria Mwamtobe

My relatives, wife and children.

Abstract

Malaria is a public health problem for more than 2 billion people globally. About 219 million cases of malaria occur worldwide and 660,000 people die, most (91%) in the African region despite decades of efforts to control the disease. Although the disease is preventable, it is life-threatening and parasitically transmitted by the bite of the female Anopheles mosquito. A deterministic mathematical model with intervention strategies is developed in order to investigate the effectiveness, optimal control and cost effectiveness of Indoor Residual Spraying (IRS), Insecticide Treated Nets (ITNs) and treatment on the transmission dynamics of malaria in Karonga District, Malawi. The effective reproduction number is analytically computed, and existence and stability conditions of the equilibria are explored. The model does not exhibit backward bifurcation. A structured questionnaire was developed, a one-to-one interview with a randomly sampled set of individuals conducted to assess the knowledge level of inhabitants of Karonga district about the disease in general and their awareness and application of the intervention strategies. Applying Pontryagin's Maximum Principle which uses both the Langragian and Hamiltonian principles with respect to a constant time dependent, we derive the necessary conditions for the optimal control of the disease. An economic evaluation of the strategies is carried out by performing a cost-effectiveness analysis to determine the most cost-effective combination of the three intervention measures. The incremental cost-effectiveness ratio (ICER) is calculated in order to compare the costs and effectiveness of all the possible combinations of the three measures. The results show that the combination of treatment, ITNs and IRS is the most cost-effective combination strategy for malaria control. Numerical simulations indicate that the prevention strategies lead to the reduction of both the mosquito population and infected human individuals. Effective treatment consolidates the prevention strategies. Thus, malaria can be

eradicated by deployment of combined strategies such as vector control via ITNs and IRS complemented with timely treatment of infected people.

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Chapter 1

Introduction

1.1 General introduction

Malaria is an infectious disease which continues to be a major problem in many tropical and sub-tropical countries of Africa, Asia, South and Central America, and the Middle East; around 40% of the world's population live in endemic areas; 90% of deaths occur in sub-Saharan African countries such as Malawi, Zimbabwe, Zambia, mostly in young children [41, 98]. While progress is being made in reducing prevalence in Malawi, malaria is one of the major causes of morbidity and mortality, with approximately 6 million suspected cases treated annually [7, 97]. Despite being prevalent in all parts of Malawi, malaria is more prevalent in lake shore areas like Karonga District, and the lower Shire districts like Chikhwawa. Apart from Malawi being in the tropics, the additional factors that make Malawians vulnerable to malaria are: poverty, inadequate health care infrastructures and low income of the country. Its effects are greatest among children under 5 years of age and pregnant women [82].

In Malawi most hospital admissions and deaths from Malaria are from children under 5 years of age and pregnant women because there immunity is compromised at these levels of life. Inhorn and Brown [43] explained that infectious diseases like malaria, have had a profound effect on human populations, including their evolution and cultural development. Despite significant advances in medical science, infectious diseases continue to impact human population in many parts of the world.

1.1.1 Causes, incidence, and risk factors

Malaria is a life-threatening disease caused by a parasite, *Plasmodium,* which infects red blood cells. It is transmitted to humans through the bites of infected female mosquitoes. The female Anopheles mosquito is infected when it bites someone carrying malaria.

The World Health Organisation [126] emphasized that there are four different types of *Plasmodium* parasites: *Plasmodium falciparum* is the only parasite which causes malignant malaria. It causes symptoms straight away which can be mild or severe. Plasmodium falciparum accounts for the majority of malaria cases in southern Africa and may be associated with severe and fatal disease. Secondly, *Plasmodium vivax* causes benign malaria with less severe symptoms. The vector can remain in the liver for up to three years and can lead to a relapse. Thirdly, *Plasmodium malarie* also causes benign malaria and is relatively rare. Lastly, *Plasmodium ovale* also causes benign malaria and can remain in the blood and liver for many years without causing symptoms. *Plasmodium falciparum* is responsible for about three-quarters of reported malaria cases in Karonga District, Malawi. Most of the other cases of malaria are caused by *Plasmodium vivax* with just a few caused by the other two species. However, Medicinenet, [72] reported another relatively new species,

Plasmodium knowlesi which has triggered malaria in Malaysia and areas of South-East Asia. It is also a dangerous species that is typically found only in long-tailed and pigtail macaque monkeys, and like *P. falciparum, P. knowlesi* may be deadly to anyone infected. It is possible to be infected with more than one species of *Plasmodium* parasite at the same time. Each parasite causes a slightly different type of illness. This study focuses on malignant malaria which is fatal in Malawi.

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 [71]. Malaria can also be transmitted from a mother to her unborn baby (congenitally) and by blood transfusions [99]. This is the reason why in Malawi all pregnant women who visit health facilities for their antenatal check-up are given the anti-malaria drug to prevent this transmission. But the transmission of malaria from mother to child is still a challenge in Malawi because most women live in rural areas where most health services are absent. Some pregnant women do not go to health facilities because they believe the anti-malaria drugs will lead to abortion.

1.1.2 Symptoms and complications

The first symptoms of malaria resemble that of flu. The patient may have: a headache, aching muscles, tummy ache, and weakness or lack of energy. A day or so later, the body temperature may rise (up to 40 degrees Celsius) and the patient may have: a fever, shivers, mild chills, severe headache, vomiting, diarrhoea, and loss of

appetite. Since most Malawians live far away from health facilities, they opt to buying drugs over the counter whenever they have symptoms, and sometimes they are not healed but the situation worsens and they may even develop complicated malaria. However, it takes at least six days for symptoms to appear; and the time it takes for symptoms to appear can vary with the type of parasite that the mosquito was carrying and the immunity of an individual [13, 80].

If the person is infected with *Plasmodium falciparum*, malaria can progress to a more severe form called complicated malaria. The following symptoms may appear: low blood sugar levels, severe anaemia, jaundice, fluid on one's lungs (pulmonary oedema), acute respiratory distress syndrome, meningitis, kidney failure, spontaneous bleeding (hemorrhage), state of shock (circulatory collapse), fits (convulsions), paralysis and coma. Severe malaria can affect the patient's brain and central nervous system and can be fatal [13, 126]. Complications are likely to be more severe in pregnant women, children, older people and people who have a weakened immune system, such as persons living with HIV.

1.1.3 Transmission

Malaria transmission rates can differ depending on local factors such as rainfall patterns (mosquitoes breed in wet conditions), the proximity of mosquito breeding sites to people, and types of mosquito species in the area. Some regions have a fairly constant number of cases throughout the year, these countries are termed "malaria endemic", while in other areas, there are "malaria seasons"usually coinciding with the rainy season [125]. In Malawi, the lake shore and the lower Shire areas are most prevalent to malaria because of the large water bodies from Lake Malawi and Shire river, which make these areas swampy in rainy season making them a

favourable breeding environment for mosquitoes. Large and devastating epidemics can occur when the mosquito-borne parasite is introduced into areas where people have had little prior contact with the infecting parasite and have little or no immunity to malaria, or when people with low immunity move into areas where malaria is endemic; these epidemics can be triggered by wet weather conditions and further aggravated by floods or mass population movements driven by conflict [93]. Non-immune pregnant women and travelers from malaria-free regions, with little or no immunity, who travel or move to areas with high disease prevalence are very vulnerable and are at high risk of being infected with malaria [41, 80]. Karonga District bordering with Tanzania and Zambia, it is prone to immigrants who come for business or employment in mines. These immigrants who are exposed to malaria in their countries act as carriers of malaria parasite, thereby increasing the vulnerability of more people in Karonga District, despite the campaign being carried out in the district to reduce the malaria epidemic. The illness can result in high rates of miscarriage and can cause over 10% of maternal deaths (soaring to a 50% death rate in cases of severe disease) annually; semi-immune pregnant women risk severe anemia and impaired fetal growth even if they show no signs of acute disease [126].

1.1.4 Prevention and treatment

The World Health Organisation [125] emphasises that early treatment of malaria shortens its duration, prevents complications and avoids a majority of deaths. Because of its considerable drag on health in low-income countries, malaria disease management is an essential part of global health development. Pan American Health Organisation [93] explained further that treatment aims to cure patients of the disease rather than to diminish the number of parasites carried by an infected

person. The best available treatment, particularly for *Plasmodium falciparum* malaria, is a combination of drugs known as *artemisinin-based combination therapies* (ACTs). However, the growing potential for parasite resistance to these medicines is undermining malaria control efforts. WHO [126] recommends: use of insecticide-treated nets (ITNs) for night-time prevention of mosquito bites; for pregnant women in highly endemic areas, preventive doses of *sulfadoxine-pyrimethamine (IPT/SP)* to periodically clear the placenta of parasites, indoor residual spraying(IRS) to kill mosquitoes that rest on the walls and ceilings of houses.

Beyond the human toll, malaria wreaks significant economic havoc in high-rate areas, decreasing Gross Domestic Product (GDP) by as much as 1.3% in countries with high levels of transmission. Over the long-term, these aggregated annual losses have resulted in substantial differences in GDP between countries with and without malaria (particularly in Africa) [93]. Malaria's health costs include both personal and public expenditures on prevention and treatment. In some heavy-burden countries, the disease accounts for: up to 40% of public health expenditures, 30% to 50% of inpatient hospital admissions, up to 60% of outpatient health clinic visits. Malaria disproportionately affects poor people who cannot afford treatment or have limited access to health care, and traps families and communities in a down spiral of poverty [126].

1.2 Problem statement

Malaria is by far the world's most threatening tropical parasitic disease. The disease is endemic in Malawi especially along the lake-shore areas such as Karonga District, and claims many lives. Mathematical models of the dynamics of this disease with special emphasis on Malawi are uncommon. The optimal combination of an

intervention strategy scheme for patients remains the subject of intense debate [56]. Also, no previous mathematical study (in Malawi) has been conducted using optimal control theory to obtain the conditions under which it is optimal to eradicate the disease and examine the impact of combined prevention interventions such as ITNs, IRS and treatment on the disease transmission. Therefore, this study intends to investigate optimal intervention strategies for control of malaria epidemic in Karonga District, Malawi.

1.3 Research objectives

1.3.1 General objective

The main purpose of this study is first to understand the dynamics of malaria infection and transmission through a suitable mathematical model. Secondly, to investigate different intervention strategies and propose an optimal control strategy for the malaria epidemic in the Karonga District of Malawi.

1.3.2 Specific objectives

The objectives of this study are to:

1. develop and mathematically analyze a deterministic model which incorporates the basic epidemiological features of the dynamics of malaria.
2. investigate the transmission dynamics of malaria disease.
3. assess the impact of the intervention strategies of malaria in terms of the basic reproduction number, $\mathcal{R}_0$, (i,e., the number of secondary infections generated by single infected individuals in a totally naive/susceptible population).

4. perform sensitivity and uncertainty analyses wherever data or model parameters values are taken from different sources (mainly theoretical work), since results may be very sensitive to the parameter values.

5. carry out a cost-effectiveness analysis of the control strategies.

1.4 Research hypothesis

(a). Mathematically, models with intervention strategies formulated and analyzed have a locally asymptotically stable disease-free equilibrium when their reproductive threshold is less than unity (that is $\mathcal{R}_0 < 1$). But the disease may not die out owing to the phenomenon of backward bifurcation, a situation in which both a (locally) stable disease-free and a stable endemic equilibrium co-exist when the model reproduction number is less than unity.

(b). The malaria models with intervention strategies exhibit the phenomenon of backward bifurcation (co-existence of a stable disease-free equilibrium with a stable endemic equilibrium), an epidemiological situation where although necessary, having the basic reproduction number less than unity is not sufficient for disease elimination [117].

(c). Assuming that parameters are fixed, the threshold $\mathcal{R}_0$ is influenced by intervention parameter values. The disease can be eliminated from the community when $\mathcal{R}_0 < 1$. The intervention strategies are not enough to maintain $\mathcal{R}_0$ below unity: An application close to 100% is needed.

(d). The multi-strategies are cost-effective if the number of deaths averted is high and the cost associated with providing the services is minimal.

1.5 Methodology

The compartmental model will be formulated as a deterministic system of ordinary differential equations, and dynamical systems techniques will be employed to analyse this model.

Key parameters that drive the disease transmission dynamics and effects any of the control measures will be investigated. Thereafter, the qualitative analysis of the model will be carried out in order to determine the possibility of existence and stability of endemic and disease-free equilibria. A variety of methods including Lyapunov function techniques will be used to determine the global stability of the model.

The basic reproduction number ($\mathcal{R}_0$) which is a fundamental parameter governing the spread of the disease will be computed. The next generation operator approach will be used to calculate the reproduction number ($\mathcal{R}_0$) which provides the necessary condition for the disease to be eradicated or minimized.

The qualitative optimal control analysis will be carried out to determine the necessary conditions for optimal control of the disease using Pontryagin's Maximum Principal in order to determine optimal strategies for controlling the spread of the disease.

Estimated and heuristic data will be used for numerical analysis of the model.

In analyzing the model, sub-models will be considered namely: malaria only, malaria and treatment of infected individuals, malaria and individuals using insecticide

treated bed nets, malaria and individuals using insecticide house sprayed. The real data on death rate, cost per person per intervention, number of infected individuals during the use of Sulfadoxine-Pyrimethamine (SP) and Artemisinin-based Combination Therapies (ACTs) obtained from Ministry of Health in Lilongwe, Malawi, will be used for the model simulation. Other data will be collected from the field based on: the number of people using insecticide treated bed nets, the number of people staying in the insecticide treated houses, and prevalence rates data before and after provision of preventive interventions.

The computer packages (MatLab, Mathematica and Maple) will be used for the model simulations. A cost-effectiveness analysis of the different strategies individually and combined using economic concepts will be carried out.

Finally, local sensitivity analysis will be carried out to compute sensitivity indices of the reproduction number which enables us to single out parameters that have a high impact to the effective reproduction number $\mathcal{R}_e$ and which are used to enhance the intervention strategies.

Chapter 2

Literature review

Infectious diseases have had a profound effect on human populations, including their evolution and cultural development. Despite significant advances in medical science, infectious diseases like malaria continue to impact human populations in many parts of the world [93]. In Africa, national governments such as that of Malawi and international organizations are focusing on rapidly scaling up malaria control interventions to at least 60% in vulnerable populations. Countries that have successfully eliminated malaria have shown considerable economic growth when compared to other countries that have not done so. Poor households living in malaria regions struggle to meet the financial cost of treating repeated bouts of illness. Direct and indirect costs of seeking appropriate health care result in households seeking treatment nearer their home [77]. This occurs in Malawi, where despite the free provision of healthcare through the formal health system, these services are under-utilized and home treatment is common using left over drugs or those obtained from vendors. Consequences of private purchasing of drugs include inappropriate drug selection and dosing, potentially leading to death and disability and the emergence and increase of drug resistance.

2.1 Social economic consequences of malaria epidemic

Malaria affects the health and the wealth of nations and individuals alike. In Africa today, malaria is understood to be both a disease of the poor and a cause of poverty. Malaria has significant measurable direct and indirect costs, and has been shown to be a major constraint to economic development [110]. This means the gap in prosperity between countries with malaria and countries without malaria becomes wider every year as it has been shown that where malaria has been eliminated, economic growth has increased substantially [30, 106]. For instance in Malawi, a lot of money is spent on purchasing malaria drugs, test kits, insecticide spraying chemicals and ITNs. This money could be used for other development purposes if malaria was eradicated. Hence the need of determining cost effective interventions.

Mathanga et al., [68] analyzed the present inequalities in access to malaria interventions in Malawi. Equity in access to malaria control measures was assessed using the Malawi Demographic Health Survey (DHS) 2000 and the 2004 national survey on malaria control. Utilization of malaria control methods was compared across the wealth quintiles, to determine whether the poor were being reached with malaria control measures. The researchers concluded that the present distributions strategies for ITNs were not addressing the needs of the vulnerable groups, especially the poor. No income related inequalities were associated with prompt treatment, ITNs and intermittent preventive treatment (IPT) use and the potential health and economic benefits of scaling up depends on equitable access to malaria control measures by the poor.

Prompt access to effective treatment for malaria is unacceptably low in Malawi and

less than 20% of children under the age of five years with fever receive appropriate anti-malaria treatment within 24 hours of fever onset [17]. Chibwana et al., [17] assessed socio-cultural factors associated with delayed treatment of children with fever in Mwanza district, Malawi via a qualitative study using focus group discussions and key informant interviews. Despite sufficient knowledge of malaria, prompt treatment and health-seeking behavior were poor, with the majority of children first being managed at home with treatment regimens other than effective anti-malarial drugs. Traditional beliefs about causes of fever, unavailability of anti-malarial drugs within the community, barriers to accessing the formal health care system, and trust in traditional medicine were all associated with delays in seeking appropriate treatment for fever. For example in Mwanza District, some people believe that fever is an indication that the mother of a child has a problem with her reproductive tract, or maybe she had extra marital affairs. They would then go to the traditional healer for medication for the mother and not the child. The study demonstrated that in order to facilitate prompt and appropriate health-seeking behavior, behavioral change messages must address the prevailing local beliefs about causes of fever and the socio-economic barriers to accessing health care. Hence the need to perform a cost-effective analysis of the malaria interventions.

Larson et al., [54] noted that in Malawi, health ministries and providers are rapidly scaling up insecticide-treated nets (ITNs) distribution to control malaria, yet possession and proper use typically remain below targeted levels. In some areas there are situations whereby instead of using the nets properly, the nets are being used for fishing, and in some cases the nets are washed but not retreated thereby reducing their effectiveness. Health facilities are currently the principal points of ITNs distribution, making it important to understand how access to these ITN sources affects ownership, possession and use. The study revealed that health

providers should look towards community-based distribution services that take ITNs directly to community members to scale up ITN possession more effectively and regular use aimed at protecting children from malaria.

Global malaria programmes and rehabilitation programmes are organized as vertical and separate programmes, and as such they focus on prevention, cure and control, and disability respectively [15]. Despite a local-based health services system, 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 [15, 42]. The importance of building malaria programmes, research and statistics that take into consideration the consequences of permanent impairment after a malaria attack, as well as the context of poverty in which they often occur can be carried out through qualitative and quantitative approaches in local communities.

2.2 Mosquito-human contacts and drug resistance

In Malawi, the main malaria vector Anopheles culicifacies breeds primarily in river bed pools during dry periods, but also in other breeding sites such as seepage areas next to irrigation tanks, hoof prints, and abandoned pits [126]. Briet et al., [12] explained that the extreme south west of Sri Lanka has always been virtually free of malaria. It is attributed to the wet climate in which rivers flow year round without pooling, and this brings to our attention that some areas will affect our assumptions of the model because the continuous flow of rivers reduces the

availability of mosquitoes hence reducing the rate of mosquito human contacts.

Mosquitoes acquire infection from humans after a blood meal [74, 91]. Although malaria is a life-threatening disease, it is preventable and curable when the infected individuals seek treatment early. However, malaria still persists as a major public health problem and the disease burden may rise again. This is due to the costs of interventions, availability of treatment and its adverse effects and also to the increasing rate of parasite drug-resistance and mosquito insecticide resistance. Prompt treatment of uncomplicated malaria with effective antimalarial drugs is a cornerstone of malaria control efforts, provided individuals benefit by curing the infection and preventing disease progression by reducing the infectious reservoir and thus averting the emergence and spread disease resistance [58, 125]. The emergence of resistance to former first-line antimalarial drugs such as chloroquine (CQ) has been an unmitigated disaster. In recent years, artemisinin-based combination therapy (ACT) class drugs have become standard and the drugs are recommended as an essential tool for helping to eradicate malaria [52]. However ability of these drugs to reduce morbidity and mortality and to slow down transmission requires effective maintenance. Malawi replaced first-line medication, sulfadoxine-pyrimethamine, a single-dose regimen, for treating uncomplicated malaria, with artemether-lumefantrine (AL), an artemisinin-based combination therapy that requires a 6-dose, 3-day course. Because of concerns about the complex dosing schedule, Mace et. al., [58] assessed patient adherence to treatment with AL for uncomplicated malaria in rural Malawi. They found that adherence to AL treatment for uncomplicated malaria was moderate, and children, who are most likely to die of malaria, were less adherent than adults. Efforts to improve adherence should be focused on this vulnerable group.

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. Tchuenche et al., [117] developed a model which incorporated both sensitive and resistant strains of the parasites. The analytical results revealed that the model exhibits the phenomenon of backward bifurcation (co-existence of a stable disease-free and endemic equilibira). This occurred despite varying treatment level in high transmission area with different levels of resistance. This agrees with the findings of Chiyaka et al., [20], that an increase in the period within which partial immunity is lost increases the spread of the disease. However these studies did not consider cost-benefit analysis and optimal treatment rate which will be addressed in this study.

White [123] explained the phases of eradication of an infectious disease as defined by Molyneux et al., [75] as follows:

- Elimination of disease: Reduction to zero of the incidence of a specified disease in a defined geographical area as a result of deliberate efforts. Continued intervention measures are required.

- Control: Reduction of disease incidence, prevalence, morbidity or mortality to a locally acceptable level as a result of deliberate efforts. Continued intervention measures are required to maintain the reduction.

- Elimination of infection: Reduction to zero of the incidence of infection caused by a specific agent in a defined geographical area as a result of deliberate efforts. Continued measures to prevent re-establishment of transmission are required.

- Eradication: Permanent reduction to zero of the worldwide incidence of

infection caused by a specific agent as a result of deliberate efforts. Intervention measures are no longer needed.

- Extinction: The specific infectious agent no longer exists in nature or the laboratory.

A simple mathematical structure is used to consider "control and elimination of infection" phases. The potential of combining multiple strategies that were applied singly in Karonga District, Malawi, would not necessarily result in elimination, but applied in combination have the potential to achieve this aim within the timelines predicted by other complex modeling exercises. Non-treatment control measures such as deployment of an effective vaccine or insecticide-treated bed nets (ITNs) could prevent the spread of drug resistance as suggested in Mackinnon [60] and White [123] in a similar way to drug combination therapy, but at the population rather than individual level as with multiple first-line therapies. In many scenarios even a failure to eliminate the disease would result in a lower cumulative morbidity and mortality than if the attempt were never made. The key exception to this result is the scenario where drug resistance is spreading; and then if the same drugs are used in an elimination strategy, an acceleration of the spread of resistance is predicted, in some cases resulting in higher morbidity following failed elimination attempts.

The ownership and use of insecticide treated mosquito nets is the primary prevention strategy for reducing malaria transmission in Malawi. The long lasting insecticide nets (LLITNs) policy includes free distribution of LLITNs for children born in health facilities and for pregnant women at their first visit to an antenatal care (ANC) clinic. In addition, the LLITN distribution policy also includes giving a free LLITN to children attending their first clinic visit under the Expanded Program on

Immunization (EPI) if an LLITN was not received at birth. In the past five years, over six million ITNs have been distributed countrywide in Malawi [82, 83]. Despite this intervention, malaria remains a challenge in Malawi because the LLITNs or ITNs are given when a woman visits a health facility for antenatal purposes, and since most women live in rural areas, they do not go to hospitals but to traditional birth attendants.

Eradication of any disease is an ambitious aim that to date has only been achieved for smallpox [123]. There are only a few WHO sanctioned disease targets for eradication or elimination and malaria is not listed among them. Therefore, considering the potential outcomes of failure to eliminate this disease is an important task for mathematical modeling. Okosun and Makinde [88] derived and analyzed a deterministic model for the transmission of malaria disease that included classes of individuals with drug resistance and treatment measures in order to study the impact of the drug resistance in transmission. Numerical results for effective control of individuals with drug resistance showed positive impact in reducing the spread of the disease. Most studies are focusing on the disease resistance due to host population. Not much research has been done on insecticide-resistant mosquitoes. This can strongly challenge the fight against mosquito-borne disease. Blayneh and Mohammed-Awel [10] formulated a system of nonlinear difference equations for malaria transmission cycle with the aim of researching insecticide-resistant mosquitoes and malaria control. They showed that the mosquito-human transmission cycle of malaria and its prevalence could be impacted by mutation rate, the personal protection of hosts and the density of mosquitoes. In addition, their results highlighted that given a large mosquitoes population, the presence of even a small number of resistant mosquitoes to an insecticide could cause the insecticide to be ineffective for malaria control.

The World Health Organization [125] recommends artemisinin-based combination therapy (ACT) as the first-line treatment for all falciparum malaria in endemic areas. ACT is available in various formulations, which are generally administered over a period of days. Pongtavornpinyo et. al., [96] applied a comprehensive mathematical model to describe malaria transmission and the spread of drug resistance during the study of spread of anti-malarial drug resistance with applications for ACT drug policies.

There is an increase in Plasmodium falciparum resistance to cheap first line antimalarial drugs and this has increased in malaria-associated morbidity and mortality in sub-Saharan Africa including Malawi. Research has established that malaria is resistant to chloroquine (CQ) and sulphadoxine-pyrimethamine (SP) [84]. Malpractice in drug usage such as over-prescription of anti-malarials (confusion with other febrile diseases) and the uncontrolled selling of poor quality drugs contribute to the increase in drug resistant parasites. The widespread and increasing occurrence of Plasmodium falciparum resistant against affordable anti-malarial drugs (CQ and SP) is more and more hampering the fight against malaria. CQ and SP are still the most widely used drugs for treatment of malaria in Malawi because of low cost and availability even though WHO recommends use of combination therapies, preferably artemisinin-based combination therapies (ACTs). The advantage of using ACT is that it uses a combination of anti-malaria drugs, one of which is artemisinin derivative.

Antimalarial drug resistance has emerged as one of the greatest challenges facing malaria control today; it is a factor in the economic constraints of malaria elimination, and has been implicated in enhanced mortality from malaria [117, 119].

In the absence of any scientific breakthrough for the complete control or eradication of malaria, antimalarial drugs will continue to be needed. It is therefore imperative to understand how drug resistance develops and spreads. Plasmodium falciparum has developed resistance to nearly all available antimalarial drugs. Resistance to infection occurs when there is a low level of continued infection by the parasite, which may also be due to drug failure, a process not directly related to the parasite, but solely dependent on the host organism and the properties (pharmacodynamics) of the drug [117, 124]. Drug resistance necessitates the use of drugs that are more expensive and may have dangerous side effects and creates such an impediment to the successful eradication of malaria as a child is known to die from malaria every 12 or so seconds. In order to combat the continuous pattern of drug resistance developing sequentially to antimalarials used as monotherapy (single drug therapy), combination chemotherapy, preferably including an artemisinin derivative, is recommended [40]. Additional benefits of artemisinin-based combination therapy (ACT) include improved treatment outcomes and decrease in malaria transmission, resulting in greater cost-effectiveness. Partial immunity may be acquired after long-term, repeated exposure to P. facilparum infection, as occurs in residents of perennial high transmission areas, such as in parts of Mozambique, Malawi, Tanzania and some other sub-Saharan African countries.

2.3 Transmission of parasite and global warming

Interventions to prevent or reduce the transmission of malaria are currently being used, with some degree of success, in some parts of the world. Some of the methods include; house spraying with residual insecticides and most recently the use of insecticide treated bed-nets. The methods operate by reducing the contacts rates (hence exposure to infection) between the mosquitoes and humans. Other measures

that employ the use of antimalarial drugs as a control measure may not be very effective when compared with control measures that directly affect the dynamics of transmission of a parasite (that is based on the human mosquito interaction). This is because in endemic areas drug coverage can only be effective if permanent prophylaxis is employed across an entire endemic human population. In most developed countries, where malaria has been eradicated but the mosquito vector is still present, changes in world climate through global warming indicate that these malaria free zones risk being re-colonized by malaria [67, 80]. Given these challenges be it in endemic areas or otherwise, predictive mathematical modeling and computer simulations remain our greatest hope.

Yang, [130] developed a mathematical model for malaria transmission relating global warming and local socio-economic conditions in which sensitivity analysis was applied. The effects of global warming and local socio-economic conditions were assessed analyzing the equilibrium points calculated at different but fixed values of the parameters of the model. By performing sensitivity analysis on equilibrium points which represent the level of malaria infection in a community, different possible scenarios were obtained when the parameters were changed. Then depending on malaria risk, the efforts to control its transmission can be guided by a subset of parameters used in the mathematical model. Regarding malaria transmission, it was observed that the effects of global warming posed a major challenge in the following year, and the effects of variation in local socio-economic conditions were much stronger than the effects of the increasing global temperature.

Malaria is predominantly present in the tropical countries. Even though the disease has been investigated for hundreds of years, it still remains a major public health problem in 109 countries declared as endemic to the disease in 2008 [65]. There

were 243 million malaria cases reported, and nearly a million deaths-primarily of children under 5 years of age [65, 126]. With no effective vaccine in sight and many of the older anti-malarial drugs losing effectiveness due to the parasite evolving drug resistance, prevention (using bed nets) is still the only advice given to affected persons. Malaria has also gained prominence in recent times since climate change or global warming is predicted to have unexpected effects on its incidence [65]. Both increase and fluctuation in temperature affects the vector and parasite life cycle. This can cause reduced prevalence of the disease in some areas, while it may increase it in the others. Global warming which include the increasing extreme weather conditions has brought many climatic changes that influence diseases like malaria which is so sensitive to climate. Malawi has been experiencing increase in temperatures, changes in rainfall patterns thus providing good environment for mosquitoes to increase their reproduction and shorten incubation period. Karonga District which is the study area is one of the districts with high temperatures. Thus climate change can affect the malaria prevalence pattern by moving away from lower latitudes to regions where populations have not developed immunity to the disease.

Chaves et al., [16] suggested that the intervention using ITNs represents an excellent example of implementing an infectious disease control programme. The results emphasize the need to implement infectious disease control programmes focusing on the most vulnerable populations which is the basis of this study. Over the past decade malaria intervention coverage has been scaled up across Africa. Eisele et. al., [27] and Griffin et. al., [31] developed an individual-based simulation model for Plasmodium falciparum transmission in an African context incorporating the three major vector species (Anopheles gambiae s.s., Anopheles arabiensis, and Anopheles funestus) with parameters obtained by fitting parasite prevalence data from 34 transmission settings across Africa. The researchers incorporated the effect

of the switch to artemisinin-combination therapy (ACT) and increasing coverage of long-lasting insecticide treated nets (LLITNs). The impact of transmission of continued roll-out of LLITNs, additional rounds of indoor residual spraying (IRS), mass screening and treatment (MSAT), and a future RTS, S/AS01 vaccine in six representative settings with varying transmission intensity, vector-species combinations, and patterns of seasonality were explored. The researchers concluded that interventions using current tools can result in major reductions in P. falciparum malaria transmission and the associated disease burden in Africa. Malawi which is also malaria endemic is also trying to apply the same ways of reducing malaria cases, whereby they are encouraging prevention through the use of LLITNs or ITNs and IRS. Hence the need for optimal control analysis of the intervention strategies.

Whilst the pattern of reducing the disease in some parts of sub-Saharan Africa countries is encouraging, there remain many countries within Africa that continue to have a high burden of disease and hence malaria remains a leading cause of mortality in children under five years of age [27, 127]. Malawi is one of the countries where malaria remains a great concern. The control of the disease, and ultimately elimination of the parasite in this continent, remain a major public health goal. However, Africa poses the biggest challenge to a global eradication initiative, given the heterogeneous yet ubiquitous nature of Plasmodium falciparum transmission across much of the continent. Levels of transmission in Africa range from absent or low in many urban areas, through epidemic outbreaks in the highlands, to highly seasonal or perennial transmission in rural areas [27, 34, 38]. This variable transmission pattern is complicated by local variation in the major Anopheles vector populations that sustain transmission (principally Anopheles gambiae s.l. and Anopheles funestus, although approximately 70 relevent species have been identified worldwide [39]). Of the 47 countries within sub-Saharan Africa, the majority are

currently classified by WHO/Roll-Back Malaria as being the control stage and thus burden of disease via a reduction in transmission [107]. On the northern countries of the continent, transmission is already low, with Egypt and Algeria in the elimination phase and Morocco and Mauritius having interrupted local transmission. Similarly, in the southernmost countries, a sustained move towards local control and potential elimination in border areas has been agreed upon via cooperation with neighboring countries [27, 63]. On the island of Zanzibar, a highly successful control program has reduced transmission to very low levels [31]. However, a recent assessment of the feasibility of moving to elimination concluded that whilst it is technically feasible to reduce local transmission to zero in this setting, the resources, both financial and operational, required to sustain elimination in the face of repeated reintroduction from mainland Africa make this a difficult prospect.

Compared to the past campaigns in the 1950s, additional tools are now available which, combined with sustained policy commitment, may make local elimination achievable in some settings and can aid control of the disease by dramatically reducing malaria prevalence in countries with high rates of ongoing transmission [27, 31]. These include new LLITNs which have increased elimination effects on the vectors compared to traditional nets and are more durable, and ACTs, which, through their gametocytocidal effect, can impact transmission from humans to vectors [85, 86]. In addition, a pre-erythrocytic malaria vaccine, RTS,S/AS01 vaccine, has shown promising results in Phase II trials [4, 5, 109] and could not contribute to the elimination programs. National control agencies have varying levels of resources but can rarely implement all major control interventions at a given time. Understanding how to choose policy that is appropriate to the local setting is therefore key to effective control. Whilst the efficacies of most interventions have been individually evaluated in the field, the impact of different combinations of these

is not clear. Field trials will be important to inform control policies but will be able to test only a few of the combinations of interventions in a limited number of settings.

Households in malaria endemic countries experience considerable costs in accessing formal health facilities because of childhood malaria. The Ministry of Health in Malawi has defined certain villages as hard-to-reach on the basis of either their distance from health facilities or inaccessibility [28]. This definition gives a limitation already in as far as the reduction of malaria is concerned because it means part of the population does not access the interventions. Some of these villages have been assigned a community health worker responsible for referring febrile children to a health facility. Health facility utilization and household costs of attending a health facility were compared between individuals living near the district hospital and those in hard-to-reach villages. Researchers conducted two cross-sectional household surveys in the Chikhwawa district of Malawi: one during each of the wet and dry seasons. Half of the participating villages were located near the hospital while others were in areas defined as hard-to-reach. Data were collected on attendance to formal health facilities and economic costs incurred due to recent childhood febrile illness. Those living in hard-to-reach areas were less likely to attend a health facility for a childhood febrile event and experience greater associated household costs [28]. Health services in Malawi are provided by three bodies, namely Ministry of Health, Christian Health Association of Malawi (CHAM) and private sector. On CHAM and the private sector, people have to pay for services. Some Malawians who are poor may not be able to pay for the malaria intervention services if the only health facilities close to them are CHAM and private hospitals. Geographic and financial barriers are potential barriers to accessing public health facilities (interventions).

2.4 Cost-utility analysis

The burden of malaria is a key challenge to both human and economic development in malaria endemic countries. Morel et al., [76] used a cost-utility analysis to examine the costs and the effects of scaling-up seven interventions strategies against malaria and their promising combinations. The results showed that high coverage with artimisinin based combination treatments were found to be cost effective for control of malaria in most countries in sub-Saharan Africa. Since researchers have pointed out that, on cost-effective grounds, in most areas in sub-Saharan Africa, greater coverage with highly effective combination treatment should be the cornerstone of malaria control, this study will also determine cost-effectiveness of the selected malaria control interventions using primary data obtained from Malawi. Insecticide-treated nets (ITNs) are a proven intervention to reduce the burden of malaria, yet there remains a debate as to the best method of ensuring they are universally utilized. Mueller et al., [78] and Stevens et al., [114] studied cost-effectiveness analysis of an intervention in Malawi in which the costs were calculated retrospectively through analysis of expenditure data. Costs and effects were measured as cost per treat-net year (cost/TNY) and cost per distributed nets. Combining targeting and social marketing has the potential of being both cost-effective and capable of achieving high levels of coverage.

The debate as to the best way to achieve long-term shifts in levels of ITN utilization in malaria endemic countries has centered on the trade-off between the need for immediate health impact and the need for long-term sustainability of such a change in coverage. Those who advocate the universal distribution of free nets have prioritized the need for immediate results in terms of health gain, whereas those who argue for the development of domestic markets for ITNs wish to ensure

the long term sustainability of utilization of ITNs. The third way combines traditional social marketing with heavily subsidized highly-targeted distribution through the nationwide network of public health facilities. Social marketing has been defined as the application of commercial marketing technologies to the analysis, planning, execution, and evaluation of programmes designed to influence the voluntary behavior of target audiences in order to improve their personal welfare and their society [3, 114]. Currently the literature on the cost-effectiveness of ITN distribution interventions is measured using only the immediate, directly relevant health outcomes, and ignores any benefits from developing the market for future accessibility. This is understandable as conventional forms of economic evaluation tend to over-look issues of sustainability. Nevertheless its value comes in practicality, in the ability to make comparisons between different methodologies with broadly similar goals.

Also, during the study of impact of malaria morbidity on gross domestic product (GDP) in Uganda by Orem et al., [92], the impact of malaria was categorized from three dimensions namely: health, social and economic. The impact of malaria morbidity on GDP of Uganda was estimated using a double-log econometric model. The results showed that malaria morbidity comes out in a substantive loss in GDP of Uganda. The high burden of malaria leads to decreased long-term economic growth, and works against poverty eradication efforts and socio-economic development of the country. This is also true in Malawi whereby socio-economic and poverty eradication efforts are hindered by the burden of health challenges including malaria.

Unprecedented efforts are now underway to eliminate malaria from many regions. Despite the enormous financial resources committed, if malaria elimination is perceived as failing it is likely that this funding will not be sustained. It is

imperative that methods are developed to use the limited data available to design site-specific, cost-effective elimination programmes. Mathematical modeling is a way of including mechanistic understanding to use available data to make predictions. Different strategies can be evaluated much more rapidly than is possible through trial and error in the field. Mathematical modeling has great potential as a tool to guide and inform current elimination efforts. Economic modeling weighs costs against characterized effects or predicted benefits in order to determine the most cost-efficient strategy but has traditionally used static models of disease not suitable for elimination [69]. In this study dynamic mathematical modeling and economic modeling techniques are to be combined to contribute most effectively to the intervention strategies.

2.5 Optimal control strategies and cost-effective analysis

Optimal control theory is a powerful mathematical tool to make decisions involving complex dynamical systems, while optimal control is a set of ordinary differential equations describing the paths of the control variables that minimize the cost function [57]. 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., [103] 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, and in some cases, to prevent the emergence

of drug resistance. It deals with the problem of finding a control law for a given system such that a certain optimality criterion is achieved. It is one of the primary reasons for studying infectious diseases such as malaria in order to improve control and ultimately to eradicate the infection from the population. The percentage of the population which uses ITNs as a means of prevention from acquiring Plasmodium, those who stay in indoor sprayed houses as well as those given or who seek treatment are considered in order to minimize the number of individuals who are exposed to and infected with malaria and the cost of implementing the intervention strategies.

Studies have shown that epidemiological models may provide some basic guidelines for public health practitioners to compare the effectiveness of different potential management strategies. The cost functional equation with weights related to the costs of intervention strategies and implementation is used. Optimal control functions were used in the study of optimal control applied to a vector borne disease related to Dengue disease in order to determine the best intervention methods [102]. 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. Kar and Jana [48] developed and analyzed a theoretical study on a mathematical epidemic problem on infectious disease with application of optimal control. They aimed at minimizing the infected population as well as the costs required to control the disease. It was observed that the simultaneous use of vaccination and treatment control was the most favorable case to prevent the disease from being epidemic. Furthermore, the researchers considered controls as time dependent and obtained the optimal control strategy to minimize both the infected populations and the associated costs. Vaccination and treatment were the only interventions considered. Vaccination is not practised in Malawi as a

means of malaria intervention. Therefore, this study aims to minimize the exposed and infected individuals as well as the costs required to control the disease through preventive strategies (ITNs and IRS) and treatment.

Kong et. al., [53] presented a vector-host epidemic model with control measures to assess the impact of control measures on the prevalence of the vector-host diseases. Mosquito-reduction strategy and host medical treatment were incorporated into the model. One control strategy, i.e. ITNs for reduction of contact between host and vector was investigated. This is one of the strategies which is intensely used in Karonga District, Malawi. Using optimal control theory, the optimal levels of the two controls are characterized, and then existence and uniqueness for the optimal control pair are established. Numerical results suggested that optimal multi-control strategy is a more beneficial choice in fighting the outbreak of the vector-host diseases. Culshaw et. al., [21] presented an optimal control model of drug treatment of the human immunodeficiency virus (HIV). Yan and Zou [128] discussed the application of optimal and sub-optimal controls to a SEQIJR SARS model via Pontryagin's Maximum Principle.

Optimal control approach is also applied during the study of vaccination models of Dengue disease [101]. The researchers observed that using the optimal strategy of vaccination produced better costs for the disease when compared to not being vaccinated. The optimal control problem was solved using direct and indirect methods. In another study, the dynamic model is described by a set of nonlinear ordinary differential equations that depend on the dynamics of Dengue mosquito, the number of infected individuals, and people's motivation to combat the mosquito [104]. The cost functional did not only depend on the costs of medical treatment of the infected people but also on the costs related to educational and sanitation

campaigns. The researchers used optimal control theory and nonlinear programming after discretizing the problem. The cost functional reflected a compromise between financial spending on insecticides and educational campaigns and the population's health.

The mathematical model which included the dynamics of the Dengue mosquito, the affected persons, the people's motivation to combat the mosquito and the inherent social cost of the disease, such as cost to ill individuals, education and sanitary campaigns were incorporated during the research of optimizing the Dengue epidemics: a test case with different discretization schemes was considered [105]. The problem was discretized through Euler and Runge Kutta schemes. An optimal control problem was solved by direct methods using nonlinear optimization software.

The impact of antimalaria control measures can be assessed by formulating the model as an optimal control problem. The nonlinear optimal control framework is used. Then, it is approached by establishing a characterization of the optimal control via adjoint variables. Lashari et. al., [55] used a competitive Gauss-Seidel-like implicit difference method to solve the optimality system numerically during the study of malaria epidemics using multiple optimal controls. Optimal control problems are generally nonlinear and therefore, generally do not have analytic solutions. As a result, it is necessary to employ numerical methods to solve optimal control problems. Using this principle, Makinde and Okosun, [62] established the optimal strategies for malaria control with infected immigrants. Okosun, [87], Makinde and Okosun, [62], and Okosun et. al., [91] applied optimal control theory to a continuous malaria model that includes treatment and vaccination with waning immunity to study the impact of possible vaccination with treatment strategies in controlling the spread of malaria. Silva and Torres [111] presented an optimal control

approach to malaria prevention via ITNs in which supervision control was introduced representing information, education, communication (IEC) campaigns for improving the ITN usage. The optimal control problem was developed and solved with the aim of minimizing the number of infected humans while keeping the cost low. The numerical results showed the effectiveness of the optimal control interventions. Only one prevention strategy, i.e. ITN, was investigated.

Lashari and Zaman, [56] argued that the optimal combination of intervention strategy scheme for patients remains the subject of intense debate. The desired outcome depends on the particular situation. The application of optimal control to investigate the most economical use of active and passive immunization in controlling infectious disease is reported in Gupta and Rink, [35]. Kbenesh et al., [49], and Makinde and Okosun, [62] presented an autonomous ordinary differential equation model with vector-control and treatment model and time dependent version of the model involving an optimal control of vector-borne diseases with treatment and prevention as control measures. Thome et al., [118] present a mathematical model to describe the dynamics of a mosquito population when male mosquitoes produced by irradiation are introduced as a biological control, besides the application of insecticide. The optimal control was used by considering the cost of insecticide application, the cost of the production of irradiated mosquitoes and their delivery as well as the social cost in order to analyze the minimal effort to reduce the fertile female mosquitoes. In addition, Yan et al., [129] applied optimal control methods to study the outbreak of severe acute respiratory syndrome (SARS) using Pontryagins Maximum Principle and genetic algorithm. Also Rafikov et al., [100] and Okosun et. al., [91] formulated a continuous model for malaria vector control with the aim of studying how genetically modified mosquitoes should be introduced in the environment using optimal control problem strategies. When providing vaccines to a

susceptible population, consequences of the SIR epidemic model (where SIR means Susceptible Infected Recovered) have received much attention from researchers whose main concerns are control and eradication of diseases. Kar and Batabyal, [47] looked at the consequences of providing vaccination to the susceptible population on the SIR dynamics. Optimal control strategies were used in the form of vaccination to control the number of infected individuals and increase the number of recovered individuals. Further, although optimal control methods have been used to study the dynamics of some diseases such as dengue fever, HIV/AIDS [9, 45], these studies did not consider the use of ITNs and IRS. To the best of the researcher's knowledge, no such methods have been used in Malawi to determine the optimal combination of intervention strategies for malaria epidemic with direct transmission.

Okosun et al., [91] showed that a possible vaccination combined with an effective treatment regime would reduce the spread of the disease. Their research based on the combined vaccination and treatment strategy, ruled out insecticide treated bed-nets (ITNs) and indoor residual spraying (IRS) which are highly practised as a means of malaria interventions in Malawi.

Optimal control strategy for Plasmodium vivax malaria transmission in Korea was investigated using a deterministic system of differential equations. If the cost of reducing the reproduction rate of the mosquito population is more than that of prevention measures to minimize mosquito-human contacts, the control of mosquito-human contacts needs to be taken for a longer period of time, comparing the other situations [51]. Mathematical model and numerical simulations suggested that the use of mosquito-reduction strategies was more effective than personal protection in some cases but not always. More knowledge about the actual effectiveness and costs of control intervention measures would provide more realistic strategies.

Magombedze et al., [61] studied optimal control of malaria chemotherapy in which an intra-host mathematical model of malaria that describes the interaction of the immune system with the blood stage malaria merozoites was presented. The model was modified by incorporating the effects of malaria drugs that target blood stage parasites. The optimal control represented percentage effects of the chemotherapy of chloroquine in combination with chlorpheniramine on the reproduction of merozoites in erythrocytes. Their results indicated that highly toxic drugs and small dosage sizes have the potential of improving the quality of life and reduce economic costs of therapy.

2.6 Malaria mathematical models

Mathematical models that study transmission of malaria are based on the threshold number, which defines the most important aspects of transmission for any infectious disease. Specifically it is calculated by determining the expected number of infected organisms that can trace their infection directly back to a single organism after one disease generation. The solution of controlling the disease is to arrive at a threshold number at which the disease-free state can be established and maintained. Previous studies used ordinary differential equations to model the transmission of malaria, in which human populations are classified as susceptible, exposed, infectious and recovered. Likewise, mosquito populations are divided into susceptible, exposed and infectious groups. The threshold below which the disease-free equilibrium can be maintained is determined by varying these parameters [120].

The key conclusions of several malaria mathematical models are reviewed in order to increase and influence the theory and practice with emphasis on disease management

and relevance for control. This is because they can assist in figuring out decisions that are of significant importance on the outcomes and provide comprehensive examinations that enter into decisions in a way that human reasoning debate cannot. The Ross-Macdonald model of malaria transmission [108] originates many studies of malaria control and other diseases, and has had major influences. A mathematical model showed that bringing a mosquito population below a certain threshold was sufficient to eliminate malaria. This threshold naturally depends on biological factors such as the biting rate and vectorial capacity. Furthermore, mathematical models are used to provide an explicit framework for understanding malaria transmission dynamics in human and mosquito populations. Mandal et. al., [65] made a critical assessment of the existing models in order to explore their evolution and efficacy in describing the host-parasite biology. Deaths and disabilities caused by malaria due to change in environmental and socio-economic conditions prompted researchers to carry out a review of different mathematical models of malaria. The emphasis was more on the evolution of the deterministic differential equation based on epidemiological compartment models and a discussion on data based statistical models. The approach has summarized the modeling activity so that it helps reach a wider range of researchers working on epidemiology, transmission and other aspects of malaria so that it facilitates mathematicians to develop suitable models relevant to the present scenario. This will assist biologists and public health personnel to adopt a better understanding of modeling strategies to control the disease.

Mathematical models have been widely used by epidemiologists as tools to predict the occurrence of epidemics of infectious diseases, and also as a tool for guiding research for eradication of malaria at the present time [65]. There is a vast amount of literature available for malaria and it has been studied for a long time from all angles.

Different modeling methodologies have been adopted in addition to differential equation-based models, for instance habitat-based models [33], individual-based models [32] and integrated models [59, 113]. The major modeling approach still remains the transmission of infection through the epidemiological compartments of human and vector populations in spite of the wide range of these models and methodologies. Sir Ronald Ross is among the first to publish papers in which in one of his papers a simple model termed the Ross Model was developed [108]. The simple model highlighted the relationship between the number of vectors and incidence of malaria in humans. These types of models cannot accommodate more complex interactions of the population compartments and give limited predictions. Therefore several models have been developed extending the Ross model by incorporating different factors such as latent period of infection in mosquito and human populations [116], age-related differential susceptibility to malaria in human population [2, 24] antimalarial drug resistance [117], and spatial and genetic heterogeneity of parasite and host [36, 37]. Different approaches are helpful in guiding different stages of disease through synthesizing available information and extrapolating it.

Some malaria interventions are based on personal protection, house spraying, treatment, and possible vaccination. Chiyaka et. al., [19] formulated a mathematical deterministic model in order to theoretically assess the potential impact of personal protection, treatment and vaccination strategies on the transmission dynamics of malaria. They deduced from analysis that personal protection has a positive impact on disease control but to eradicate the disease in the absence of any other control measures, efficacy and compliance should be very high. Their results showed that vaccination and personal protection can suppress the transmission rate of parasite from human to vector and vice-versa. Further they argued that if the treated

population are infectious then certain conditions should be satisfied for treatment to reduce the spread of malaria in the community.

It is important to evaluate the effectiveness of malaria control interventions on the basis of their impact on transmission as countries move from malaria control to pre-elimination programs. Mathematical modeling can examine relationships between malaria indicators, allowing translation of easily measured data into measures of transmission, and addressing key concerns with traditional methods for quantifying transmission [115]. Results from such models can provide public health officials with accurate estimates of transmission, by seasonal patterns, that are necessary for assessing and tailoring malaria control and elimination programs to specific settings.

A deterministic mathematical model for the transmission of malaria formulated by Ducrot et. al., [25] considered two host types in the human population. The first type is called "non-immune" comprising all humans who have never acquired immunity against malaria and the second type is called "semi-immune". Here the possibility of a control of malaria through a specific sub-group such as non-immune or semi-immune or mosquitoes was explored. Mathematical modeling combines mechanical understanding with available data from multiple sources to make predictions. It could potentially be used for preliminary evaluation of different strategies for malaria elimination in different epidemiological contexts much more rapidly and a lower cost than is possible through trial and error in the field [70]. This can assist with preliminary optimization of local malaria elimination strategies before commitment of valuable resources.

The main goal of this research is to formulate the malaria model with intervention strategies aiming to set the disease management question into an optimal control

problem requiring the maximization or minimization of some objective function that depends on the biological issues and economic issues subject to initial conditions. The model is based on the combined insecticide treated bed-nets (ITNs), indoor residual spraying (IRS) and treatment strategies on mass action form of infection. The cost functions will be incorporated into the model in order to study and determine the possible impacts of these three intervention measures in controlling the disease in Karonga District, Malawi. This will allow us to propose practical control measures to the authorities to assess and forecast the disease burden such as progression rate, hospitalization, morbidity and mortality.

Chapter 3

Formulation of malaria model with prevention and control strategies

3.1 Formulation of malaria model

The optimal control model for malaria disease is formulated in order to derive optimal control strategies with minimal implementation cost. We formulate the model with the population under study being subdivided into compartments according to individuals' disease status. The total host population $N_h(t)$ at time t is partitioned into the populations of susceptible $S_h(t)$, exposed $E_h(t)$, infected $I_h(t)$, and recovered $R_h(t)$. $S_h(t)$ represents the number of individuals not yet infected with the malaria parasite at time t, or those susceptible to the disease. Many diseases like malaria have what is termed a latent or exposed phase, $E_h(t)$, during which an individual is said to be infected but not infectious. $I_h(t)$ denotes the number of individuals who have been infected with malaria and are capable of spreading the disease to those in the susceptible category, and this is done through infecting the susceptible mosquitoes. The dynamic transmission of the malaria parasite between

and among individuals in both species is driven by the biting habit of the mosquito. $R_h(t)$ is the compartment of individuals who have temporarily recovered from the disease. These humans cannot transmit the infection to the mosquitoes as we assume that they have no plasmodium parasites in their bodies. We assume that the human and mosquito population are non-constant, and that the infectious humans recover without any immunity against reinfection.

The transfer rates between the sub-classes are composed of several epidemiological parameters. Killeen et al., [50] explained that a susceptible human bitten by an infectious Anopheles mosquito may become infected with a finite probability that depends on the abundance of infectious mosquitoes and human hosts. The model assumes a horizontal standard incidence with homogeneous mixing meaning that susceptible individuals become infected through contact with infected mosquitoes. The susceptible human population is increased by recruitment. Some individuals are recruited through birth by Λ_h, where all newborns are susceptible to infection and there is no vertical transmission, while the immigrants are generated through $(1-\kappa_1)\theta$, where κ_1 is the proportion of exposed immigrants into the exposed class, and θ is the rate at which people migrate into the Karonga District. Karonga District has many migrants from Tanzania, and Zambia through the neighboring Chitipa District. Individuals migrate from other districts of Malawi to Karonga to seek employment in different companies found in the district such as the Kayerekera Uranium Mine and Mwaulambo Coal Mine. We assume that the infectious people will not migrate, and that most humans who are sick will not travel. Hence this inflow does not enter the infectious class.

When an infectious female Anopheles mosquito bites a susceptible human, there is some finite probability, β_{vh} that the parasites (in the form of sporozoites) will

be passed onto the humans. The parasites then move to the liver where they develop into their next life stage, merozoites. Susceptible individuals acquire malaria through contact with infectious mosquitoes at biting probability ϑ such that $\frac{\vartheta N_v}{N_h}$ is the contact rate of mosquitoes per individual in unit time where N_v denotes the total mosquito population. The proportion of infectious mosquitoes is $\frac{I_v}{N_v}$ such that $\frac{\vartheta N_v}{N_h}\frac{I_v}{N_v}S_h$ is the total number of contacts between the infectious mosquitoes and individuals per unit time. Thereafter the infection rate of humans is $\lambda_h = \beta_{vh}\frac{\vartheta N_v}{N_h}\frac{I_v}{N_v}S_h = \frac{\beta_{vh}\vartheta I_v S_h}{N_h}$. The infected person moves to the exposed class at rate $(1-u_1)\lambda_h S_h$ where $1-u_1(t)$ describes the failure rate of using ITNs. The preventive variable $u_1(t) \in [0,1]$ represents the use of ITNs as a means of minimizing or eliminating mosquito-human contacts.

After a certain period of time, the parasite (in the form of merozoites) enters the bloodstream, usually signaling the clinical onset of malaria. Then the exposed individuals become infectious and progress to the infected state at a constant rate α_h. The proportion of individuals ρ who have experienced infection recover with immunity and move to the recovered class while some infectious humans after recovery without immunity become immediately susceptible again. Infectious individuals recover due to rate of effective treatment η whose effect is influenced by control function $u_2(t) \in [0,1]$ representing the control effort on treatment of infectious individuals; and ϕ is the spontaneous recovery rate from infectious class to recovered class of the human population. We assume that the recovered humans have temporary immunity to malaria and they do not harbor parasite in their bloodstream and cannot pass the infection to mosquitoes. After some period of time, they lose their immunity and return to the susceptible class at the rate ψ. The natural and disease induced death rates are μ_h and δ_h respectively. The disease induced death rate is very small in comparison to the recovery rate in order to

maintain the population.

The mosquito population N_v is divided into three compartments: susceptible $S_v(t)$, exposed $E_v(t)$, and infectious $I_v(t)$. Female Anopheles mosquitoes (the male Anopheles mosquito is not included in the model because only the female mosquito bites animals for blood meals) enter the susceptible class through birth at a rate Λ_v. The parasites in the form of gametocytes enter the susceptible mosquito with probability β_{hv} after being in contact with the infectious individuals. As we assume that the mosquito population is infected only by contacting infectious humans and with the proportion of infectious individuals $\frac{I_v}{N_h}$, then the term $\lambda_v = \Lambda\frac{\beta_{hv}\vartheta I_h S_v}{N_h}$ describes the infection rate of mosquitoes through contact with infectious individuals. This happens when the mosquito bites an infectious human and the mosquito moves from the susceptible to the exposed. The susceptible mosquito acquires malaria through contact with infected humans at a force of infection λ_v and progresses to the exposed class. Mosquitoes are assumed to suffer death due to natural causes at a rate μ_v. The exposed class of the mosquitoes progresses to the class of symptomatic mosquitoes, I_v, at a rate α_v. The prevention rate of using IRS τ whose effect is affected by the effort of using IRS house $u_3(t)$ affect the whole mosquito population.

The model's force of infections, λ_h and λ_v, depend on the total population of humans N_h because we assume that mosquitoes bite human hosts randomly. In Chitnis et. al., [18] the total number of mosquito bites on humans depends on both the human and mosquito population sizes, while in our model, the total number of bites depends only on the number of mosquitoes. The effective contact rates between individual and mosquito populations depend on the biting rate of the mosquitoes, the transmission probabilities between the species and the number of individuals in

both populations. If ϑ is the biting rate of the mosquito, then there are $\vartheta N_v/N_h$ bites per human per time. The percentage of the total number of bites that are possibly infectious to individuals is I_v/N_v since there are S_h susceptible individuals, and the number of potentially infectious bites given to susceptible individuals is $\vartheta I_v S_h/N_h$ bites per time. Hence we have

$$\text{exposed rate of individuals} = \frac{\beta_{vh}\vartheta I_v}{N_h} S_h,$$

and

$$\text{exposed rate of mosquitoes} = \lambda_V = \frac{\beta_{hv}\vartheta I_h}{N_h} S_v.$$

Malaria control is an increasingly important focus for the international body concerned with public health and disease control [6]. ITNs and IRS are the most available effective prevention strategies for malaria vector control in Africa. ITNs are being promoted throughout Africa as fundamental preventive strategies to Roll Back Malaria [106]. The ITNs are nets that need to be treated once a year with a special chemical solution that ensures their effectiveness. The chemical used to treat ITNs (LLINs) kills the mosquito without harming the person underneath the net. Currently permethrin is the chemical most commonly used to treat mosquito nets. ITNs help to reduce human-mosquito contacts, a decrease in the number of mosquitoes and a reduction in malaria transmission which leads to a decline in malaria -related morbidity and mortality. In addition, ITNs provide protection against nuisance mosquitoes and kill head lice and bedbugs. The IRS is the organized spraying of an insecticide on the inside walls of houses prior to peak malaria transmission. It is designed to interrupt malaria transmission by either killing adult female mosquitoes when they enter houses and rest on the walls after feeding or by repelling mosquitoes from entering houses. This method leads to increase in mortality of the mosquitoes. But malaria control in Africa is less successful because of the occurrence of drug resistant parasites and insecticide resistant vectors.

The model flow is shown in Figure 3.1.

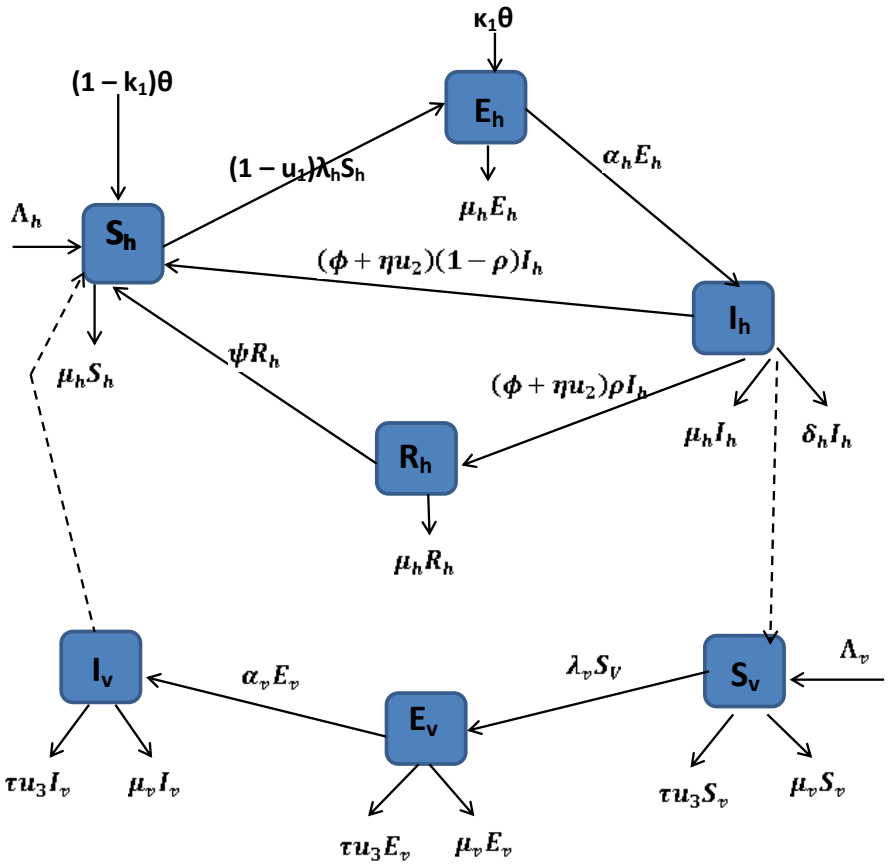


Figure 3.1: The malaria model with interventions flowchart

The dash line from the infected human class, I_h, to the susceptible mosquito population, S_v, shows that the infected human individuals infect the susceptible mosquito population whilst the dash line from the infected mosquito population, I_v, to the susceptible human population, S_h, shows the transfer of Plasmodium parasites from the infected mosquito population to susceptible individuals. The state variables in the compartmental model are represented in Table 3.1. Table 3.2

Symbol	**Description**
$S_h(t)$	Number of susceptible individuals at time t
$E_h(t)$	Number of exposed individuals at time t
$I_h(t)$	Number of infectious humans at time t
$R_h(t)$	Number of recovered humans at time t
$S_v(t)$	Number of susceptible mosquitoes at time t
$E_v(t)$	Number of infected mosquitoes at time t
$I_v(t)$	Number of infectious mosquitoes at time t
$N_h(t)$	Total number of individuals at time t
$N_v(t)$	Total mosquito population at time t

Table 3.1: State variables of the malaria model

represents prevention and control strategies practised in the district.

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)
τ	Prevention rate of effective use of indoor residual spraying
η	Treatment recovery rate

Table 3.2: Prevention and control variables in the model

Table 3.3 shows parameters of the model.

Symbol	Description
Λ_h	Recruitment rate of individuals
Λ_v	Recruitment rate of mosquitoes
κ_1	Proportion of exposed immigrants into exposed class
θ	Rate at which people migrate into Karonga District
μ_h	Per capita natural death rate of humans
μ_v	Per capita natural death rate of mosquitoes
δ_h	Per capita disease-induced death rate for humans
α_h	Progression rate of exposed humans to the infectious state
α_h	Progression rate of exposed mosquitoes to infectious state
β_{vh}	Probability that a bite results in transmission of infection to human
β_{hv}	Probability that a bite results in transmission of the parasite from an infectious human to the susceptible mosquitoes
ϑ	Average biting rate of a mosquito on an individual
λ_h	Rate at which individuals get infected by infected mosquitoes
λ_v	Rate at which susceptible mosquitoes are infected by infected individuals
ρ	Proportion of individuals who recover with immunity
ϕ	Spontaneous individual recovery rate
ψ	Loss temporary immunity by recovered individuals
α_v	Progression of exposed mosquitoes into infected mosquitoes

Table 3.3: Parameters variables of the malaria model

The state variables in Table 3.1, the prevention and control parameters in Table 3.2 and the parameters in Table 3.3 for the malaria model satisfy equations (3.2). It is assumed that all state variables and parameters of the model which monitor human and mosquito populations are positive for all $t \geq 0$, we will therefore analyse the model in a suitable region.

The above assumptions and the model flowchart together lead to the following deterministic system of nonlinear ordinary differential equations which describe the evolutionary dynamics of a malaria model with a combination of interventions:

$$\left.\begin{aligned}
\frac{dS_h}{dt} &= \Lambda_h + (1-\kappa_1)\theta + (\phi + \eta u_2)(1-\rho)I_h \\
&\quad - (1-u_1)\lambda_h S_h - \mu_h S_h + \psi R_h, \\
\frac{dE_h}{dt} &= (1-u_1)\lambda_h S_h + \kappa_1\theta - (\alpha_h + \mu_h)E_h, \\
\frac{dI_h}{dt} &= \alpha_h E_h - (\phi + \eta u_2 + \mu_h + \delta_h)I_h, \\
\frac{dR_h}{dt} &= (\phi + \eta u_2)\rho I_h - (\mu_h + \psi)R_h, \\
\frac{dS_v}{dt} &= \Lambda_v - \lambda_v S_v - (\mu_v + \tau u_3)S_v, \\
\frac{dE_v}{dt} &= \lambda_v S_v - (\alpha_v + \mu_v + \tau u_3)E_v, \\
\frac{dI_v}{dt} &= \alpha_v E_v - (\mu_v + \tau u_3)I_v,
\end{aligned}\right\} \tag{3.1}$$

where $\lambda_h = \dfrac{\beta_{vh}\vartheta I_v}{N_h}$, $\lambda_V = \dfrac{\beta_{hv}\vartheta I_h}{N_h}$.

The term $\dfrac{\beta_{vh}I_v S_h}{N_h}$ denotes the rate at which the human host, S_h, becomes infected by infected mosquitoes, I_v, and $\dfrac{\beta_{hv}S_v I_h}{N_h}$ refers to the rate at which the susceptible mosquitoes, S_v, are infected by the infected human hosts, I_h. It indicates that the rate of infection of susceptible human, S_h, by infected mosquito, I_v, is dependent on the total number of humans, N_h, available per vector.

3.2 Qualitative analysis of model

In this section, the basic properties of model system (3.1) such as invariant region and positivity, which are useful in the proofs of stability are studied using the autonomous model. The autonomous model is developed by considering the control functions in 3.1 as $u_1 = 0, u_2 = 0$ and $u_3 = 0$. Hence the system becomes

$$\left.\begin{aligned}
\frac{dS_h}{dt} &= \Lambda_h + (1-\kappa_1)\theta + \phi(1-\rho)I_h - \lambda_h S_h - \mu_h S_h + \psi R_h, \\
\frac{dE_h}{dt} &= \lambda_h S_h + \kappa_1\theta - (\alpha_h + \mu_h)E_h, \\
\frac{dI_h}{dt} &= \alpha_h E_h - (\phi + \mu_h + \delta_h)I_h, \\
\frac{dR_h}{dt} &= \phi\rho I_h - (\mu_h + \psi)R_h, \\
\frac{dS_v}{dt} &= \Lambda_v - \lambda_v S_v - \mu_v S_v, \\
\frac{dE_v}{dt} &= \lambda_v S_v - (\alpha_v + \mu_v)E_v, \\
\frac{dI_v}{dt} &= \alpha_v E_v - \mu_v I_v,
\end{aligned}\right\} \tag{3.2}$$

The invariant region describes the region in which the solutions of the system (3.2) make biological sense while positivity of the solutions describes nonnegativity of the solutions.

3.2.1 Invariant region

Since the malaria model displays human and mosquito populations, it is assumed that all the state variables are non-negative for all time $t \geq 0$ and that the solutions of the model (3.2) with positive initial data remain positive for all time $t \geq 0$. The associated parameters are assumed as non-negative for all time $t \geq 0$. The autonomous version of the model (3.2) will therefore be analyzed in a suitable feasible region, obtained as follows.

The model sub-divides the total human population at time t, denoted by $N_h(t)$, so that $N_h(t) = S_h(t) + E_h(t) + I_h(t) + R_h(t)$, and the total mosquito population $N_v(t)$ is also sub-divided so that $N_v(t) = S_v(t)+E_v(t)+I_v(t)$, or form the differential equations

$$\frac{dN_h}{dt} = \Lambda_h + \theta - \delta_h I_h - \mu_h N_h, \tag{3.3}$$

and

$$\frac{dN_v}{dt} = \Lambda_v - \mu_v N_v. \tag{3.4}$$

We show that all feasible solutions are uniformly bounded in a proper subset $\Phi = \Phi_h \times \Phi_v$.

Without loss of generality, we assume that the dynamics of system (3.2) without infection are asympotically stable. Hence

$$\frac{dN_h}{dt} \leq \Lambda_h + \theta - \mu_h N_h. \tag{3.5}$$

Applying Birkhoff and Rota's theorem [8] on differential inequality (3.5) gives

$$\frac{dN_h}{\Lambda_h + \theta - \mu_h N_h} \leq dt. \tag{3.6}$$

Integrating (3.6 on both sides gives

$$\left.\begin{aligned} \int \frac{dN_h}{\Lambda_h + \theta - \mu_h N_h} &\leq \int dt \\ \implies \frac{-1}{\mu_h} \ln(\Lambda_h + \theta - \mu_h N_h) &\leq t + c \\ \implies \ln(\Lambda_h + \theta - \mu_h N_h) &\geq -\mu_h(t + c) \end{aligned}\right\}. \tag{3.7}$$

Therefore,

$$\Lambda_h + \theta - \mu_h N_h \geq K e^{-\mu_h t}, \text{ where } K \text{ is constant.} \tag{3.8}$$

Furthermore, applying the initial conditions $N_h(0)$ in (3.8) we obtain

$$K = \Lambda_h + \theta - \mu_h N_h(0). \tag{3.9}$$

Substituting 3.9 into 3.8 gives

$$\Lambda_h + \theta - \mu_h N_h \quad \geq (\Lambda_h + \theta - \mu_h N_h(0))e^{-\mu_h t}. \tag{3.10}$$

Calculating for N_h in (3.10) gives

$$N_h \quad \leq \frac{\Lambda_h + \theta}{\mu_h} - \left[\frac{\Lambda_h + \theta - \mu_h N_h(0)}{\mu_h}\right] e^{-\mu_h t}. \tag{3.11}$$

As $t \to \infty$ in (3.11), the population size, N_h, approaches

$$0 \leq N_h \leq \frac{\Lambda_h + \theta}{\mu_h} \Longrightarrow N_h \longrightarrow \frac{\Lambda_h + \theta}{\mu_h}.$$

Therefore all feasible solutions of the human population of the model system (3.2) enter the region

$$\Phi_h = \left\{(S_h, E_h, I_h, R_h) \in \mathbb{R}^4_{\geq 0} : N_h(t) \leq \frac{\Lambda_h + \theta}{\mu_h}\right\}.$$

Similarly, the feasible solutions of the mosquito population only enter the region

$$\Phi_v = \left\{(S_v, E_v, I_v) \in \mathbb{R}^3_{\geq 0} : N_v(t) \leq \frac{\Lambda_v}{\mu_v}\right\}.$$

Hence the feasible solution set for the model system (3.2) is

$$\left.\begin{aligned} \Phi = \big\{(S_h, E_h, I_h, R_h, S_v, E_v, I_v) \in \mathbb{R}^7_+ : S_h, E_h, I_h, R_h, S_v, E_v, I_v \geq 0; \\ N_h \leq \frac{\Lambda_h + \theta}{\mu_h};\ N_v \leq \frac{\Lambda_v}{\mu_v}\Big\} \end{aligned}\right\}. \tag{3.12}$$

In this case, whenever $N_h > \dfrac{\Lambda_h + \theta}{\mu_h}$, then $\dfrac{dN_h}{dt} < 0$ (similarly whenever $N_v > \dfrac{\Lambda_v}{\mu_v}$ then $\dfrac{dN_v}{dt} < 0$) which means that the host population reduces asymptotically to its carrying capacity. Hence every solution with initial condition in $\mathbb{R}^7_+$ remains in that region for $t > 0$, which is a positively invariant set under the flow induced by the model (3.2). Hence the system (3.2) is epidemiologically meaningful and mathematically well-posed in the interior of domain Φ. Therefore, in this domain it is sufficient to consider the dynamics of the flow generated by model (3.2).

3.2.2 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 (3.2).

Lemma 1. *Let the initial data be*

$$\{S_h(0), S_v(0) > 0, (E_h(0), I_h(0), R_h(0), E_v(0), I_v(0)) \geq 0\} \in \Phi.$$

Then the solution set $\{S_h, E_h, I_h, R_h, S_v, E_v, I_v\}(t)$ *of the model system (3.2) is positive for all* $t > 0$.

Proof. Let that $\bar{t} = sup\{t > 0 : S_h > 0, E_h > 0, I_h > 0, R_h > 0,$
$S_v > 0, E_v > 0, I_v > 0\} \in [0, t]$, gives $\bar{t} > 0$. The first equation of the model (3.2) gives

$$\begin{aligned} \frac{dS_h}{dt} &= \Lambda_h + (1-\kappa_1)\theta + \phi(1-\rho)I_h - \lambda_h S_h - \mu_h S_h + \psi R_h \\ \frac{dS_h}{dt} &\geq -\left[\lambda_h + \mu_h\right] S_h, \end{aligned}$$

which on solving gives

$$\frac{d}{dt}\left[S_h(t) e^{\int_0^t \lambda_h(s)ds + \mu_h t}\right] \geq e^{\int_0^t \lambda_h(s)ds + \mu_h t}.$$

Therefore,

$$S_h(\bar{t}) e^{\int_0^{\bar{t}} \{\lambda_h(s)ds\} + \mu_h \bar{t}} - S_h(0) \geq \int_0^{\bar{t}} e^{\int_0^{t^*} \lambda_h(w)dw + u_h t^*} dt^*,$$

so that

$$\begin{aligned} S_h(\bar{t}) \geq\ & S_h(0) e^{-\left(\int_0^{\bar{t}} \lambda_h(s)ds + \mu_h \bar{t}\right)} + \\ & e^{-\left(\int_0^{\bar{t}} \lambda_h(s)ds + \mu_h \bar{t}\right)} \left\{ \int_0^{\bar{t}} e^{\int_0^{t^*} \lambda_h(w)dw + \mu_h t^*} dt^* \right\} > 0. \end{aligned}$$

Hence S_h is always positive for $t > 0$.

From the second equation of (3.2) we have

$$\begin{aligned} \frac{dE_h}{dt} &= \lambda_h S_h + \kappa_1 \theta - (\alpha_h + \mu_h) E_h \geq -(\alpha_h + \mu_h) E_h \\ \int \frac{1}{E_h} dE_h &\geq -\int (\alpha_h + \mu_h) dt. \\ \Longrightarrow E_h(t) &\geq E_h(0) e^{-(\alpha_h + \mu_h)dt} > 0. \end{aligned}$$

This shows that E_h is always positive for $t > 0$.

We also obtain the following from the third equation of (3.2)

$$\begin{aligned} \frac{dI_h}{dt} &= \alpha_h E_h - (\phi + \mu_h + \delta_h) I_h \geq -(\phi + \mu_h + \delta_h) I_h \\ \int \frac{1}{I_h} dI &\geq -\int (\phi + \mu_h + \delta_h) dt \\ \Longrightarrow I(t) &\geq I(0) e^{-(\phi + \mu_h + \delta_h)t} > 0. \end{aligned}$$

Therefore I_h is always positive for $t > 0$.

It follows also from the fourth equation of (3.2) that

$$\begin{aligned} \frac{dR_h}{dt} &= \phi \rho I_h - (\mu_h + \psi) R_h \geq -(\mu_h + \psi) R_h \\ \int \frac{1}{R} dR &\geq -\int (\mu_h + \psi) dt. \\ \Longrightarrow R(t) &\geq R(0) e^{-(\mu_h + \psi)t} > 0. \end{aligned}$$

Hence R_h is always posotive for $t > 0$.

Since we are dealing with two populations, it is important also to discuss (as in the human population) the state variables of the mosquito population. Determining $S_v(t)$, we consider the fifth equation of (3.2) which gives

$$\begin{aligned} \frac{dS_v}{dt} &= \Lambda_v - \lambda_v S_v - \mu_v S_v \\ &= \Lambda_v - (\lambda_v + \mu_v) S_v \geq -(\lambda_v + \mu_v) S_v \end{aligned}$$

which can be solved as

$$\frac{d}{dt}\left[S_v(t)e^{\left\{\mu_v t + \int_0^t \lambda_v(s)ds\right\}}\right] \geq e^{\left\{\mu_v t + \int_0^t \lambda_v(s)ds\right\}}.$$

Hence

$$S_v(\bar{t})e^{\left\{\mu_v \bar{t} + \int_0^{\bar{t}} \lambda_v(s)ds\right\}} - S_v(0) \geq \int_0^{\bar{t}} e^{\left\{\mu_v t^* + \int_0^{t^*} \lambda_v(w)dw\right\}} dt^*,$$

so that

$$S_v(\bar{t}) \geq e^{-\left\{\mu_v \bar{t} + \int_0^{\bar{t}} \lambda_v(s)ds\right\}} \left(S_v(0) + \int_0^{\bar{t}} e^{\left\{\mu_v t^* + \int_0^{t^*} \lambda_v(w)dw\right\}} dt^*\right) > 0.$$

Therefore S_v remains positive for $t > 0$.

Also the sixth equation of (3.2) gives

$$\begin{aligned} \frac{dE_v}{dt} &= \lambda_v S_v - (\alpha_v + \mu_v)E_v \geq -(\alpha_v + \mu_v)E_v. \\ \int \frac{1}{E_v} dE_v &\geq -\int (\alpha_v + \mu_v)dt. \\ \implies E_v(t) &\geq E_v(0)e^{-(\alpha_v+\mu_v)t} > 0. \end{aligned}$$

This gives the result that E_v is always positive for $t > 0$.

Lastly, the seventh equation of (3.2) gives

$$\begin{aligned} \frac{dI_v}{dt} &= \alpha_v E_v - \mu_v I_v \geq -\mu_v I_v. \\ \int \frac{1}{I_v} dI_v &\geq -\int \mu_v dt. \\ \implies I_v(t) &\geq I_v(0)e^{-\mu_v t} > 0. \end{aligned}$$

Hence I_v is always positive for $t > 0$.

Additionally, we need to show that the feasible region Φ is positively invariant so

that it satisfies the dynamics of the system. The right hand sides of equations (3.3) and (3.4) are both bounded by $\Lambda_h + \theta - \mu_h N_h$ and $\Lambda_v - \mu_v N_v$, respectively. It follows that

$$\frac{dN_h}{dt} < 0 \text{ if } N_h(t) > \frac{\Lambda_h + \theta}{\mu_h} \text{ and } \frac{dN_v}{dt} < 0 \text{ if } N_v(t) > \frac{\Lambda_v}{\mu_v}.$$

Using a standard comparison theorem [131], we have shown above that

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

and

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

In particular, if $N_h(0) < \frac{\Lambda_h + \theta}{\mu_h}$ then $N_h(t) \leq \frac{\Lambda_h + \theta}{\mu_h}$ and if $N_v(0) < \frac{\Lambda_v}{\mu_v}$ then $N_v(t) \leq \frac{\Lambda_v}{\mu_v}$. Therefore, Φ is positively invariant. If $N_h(0) > \frac{\Lambda_h + \theta}{\mu_h}$ and $N_v(0) > \frac{\Lambda_v}{\mu_v}$, then either the solution enters Φ in finite time, or $N_h(t) \to \frac{\Lambda_h + \theta}{\mu_h}$ and $N_v(t) \to \frac{\Lambda_v}{\mu_v}$ asymptotically, and the infected state variables $E_, I_h, R_h, E_v$ and I_v approach zero. □

3.2.3 Existence and stability of steady-state solutions

$\Pi = (S_h^*, E_h^*, I_h^*, R_h^*, S_v^*, E_v^*, I_v^*)$ is the steady-state solution of the system (3.2) which can be determined by setting the right hand side of the model (3.2) equal to zero.

Thus

$$\left.\begin{aligned}
\Lambda_h + (1-\kappa_1)\theta + \phi(1-\rho)I_h - \lambda_h S_h - \mu_h S_h + \psi R_h &= 0 \\
\lambda_h S_h + \kappa_1\theta - (\alpha_h + \mu_h)E_h &= 0 \\
\alpha_h E_h - (\phi + \mu_h + \delta_h)I_h &= 0 \\
\phi\rho I_h - (\mu_h + \psi)R_h &= 0 \\
\Lambda_v - \lambda_v S_v - \mu_v S_v &= 0 \\
\lambda_v S_v - (\alpha_v + \mu_v)E_v &= 0 \\
\alpha_v E_v - \mu_v I_v &= 0
\end{aligned}\right\}. \tag{3.13}$$

For as long as Λ_h the human recruitment term through birth, θ for immigrants and Λ_v the mosquito recruitment term are nonzero, the population will not be extinct. This implies that there is no trivial equilibrium, thus

$$(S_h^*, E_h^*, I_h^*, R_h^*, S_v^*, E_v^*, I_v^*) \neq (0,0,0,0,0,0,0).$$

Disease-free equilibrium

Disease-free equilibrium (DFE) of the disease model is the steady-state solution of the disease in the absence of infection or disease (malaria). We denote a disease-free equilibrium as E_0 and define the "diseased" classes as the human or mosquito populations that are either exposed or infected, that is, E_h, I_h, E_v and I_v in the system (3.2). Hence, the DFE of the malaria optimal control model with no immigration of infectious individuals (3.2) is given by

$$E_0 = (S_h^*, E_h^*, I_h^*, R_h^*, S_v^*, E_v^*, I_v^*) = \left(\frac{\Lambda_h + \theta}{\mu_h}, 0, 0, 0, \frac{\Lambda_v}{\mu_v}, 0, 0\right). \tag{3.14}$$

This represents the state in which there is no infection in the society and is known as the DFE.

3.2.4 The reproduction number $\mathcal{R}_0$

We use the next generation operator approach as described by Deikman, [23] to define the effective reproduction number, $\mathcal{R}_0$, as the number of secondary infections that one infectious individual would create during the infectious period, provided that everyone else is susceptible. It is an important parameter that plays a large role in the control of the malaria infection.

$\mathcal{R}_0 = 1$ is a threshold below which the generation of secondary cases is insufficient to maintain the infection within the human community. If $\mathcal{R}_0 < 1$, each individual produces on average, less than one new infected individual and hence the disease dies out while if $\mathcal{R}_0 > 1$, each individual produces more than one new infected individual and hence the disease is able to invade the susceptible population. It is therefore a useful quantity in the study of a disease as it sets the threshold for its establishment.

The effective reproduction number cannot be determined from the structure of the mathematical model alone, but depends on the definition of infected and uninfected compartments. We define X_s to be the set of all disease free states. That is

$$X_s = \{x \geq 0 \mid x_i = 0,\ i = 1, \ldots, m\},$$

where m is the number of diseased (infected) classes.
In order to compute $\mathcal{R}_0$ it is important to distinguish new infections from all other changes in the population. Let

- $\mathcal{F}_i$ be the rate of appearance of new infections in compartment i,
- $\mathcal{V}_i = \mathcal{V}_i^- - \mathcal{V}_i^+$ be the difference between the rate of transfer of individuals out of compartment i, $(\mathcal{V}_i^-)$, by all other means and the rate transfer of individuals in the compartment $i, (\mathcal{V}_i^+)$, by all other means.

- x_0 be the DFE.

It is assumed that each function is at least twice continuously differentiable in each variable. The disease transmission model consists of non-negative initial conditions together with the following system of equations

$$\dot{x} = f_i(x) = \mathcal{F}_i(x) - \mathcal{V}_i(x),\ i = 1, \cdots, n;$$

where n is number of compartments with new infection.
Let $F = \left[\frac{\partial \mathcal{F}_i}{\partial x_j}(x_0)\right]$ and $V = \left[\frac{\partial \mathcal{V}_i}{\partial x_j}(x_0)\right]$ with $1 \leq (i, j) \leq m$.

Further, F is non-negative, V is a non-singular M-matrix. Both are $m \times m$ matrices, where m is the number of infected classes. Hence $\mathcal{R}_0$ is the largest eigenvalue of FV^{-1}, where

- the (i, j) entry of F is the rate at which infected individuals in compartment j produce new infections in compartment i,
- the (j, k) entry of V^{-1} is the average length of time this individual spends in compartment j during its lifetime, assuming that the population remains near the DFE and barring reinfection.

Hence, the (i, k) entry of the product FV^{-1} is the expected number of new infections in compartment i produced by the infected individual originally introduced in compartment k. Following Diekmann et al., [22] FV^{-1} is termed the next generation matrix for the model and we set

$$\mathcal{R}_0 = \rho(FV^{-1}),$$

where $\rho(A)$ denotes the spectral radius of a matrix A.

Rewriting the system (3.2) starting with the infected compartments for both populations; E_h, I_h, E_v, I_v and followed by uninfected classes; S_h, R_h, S_v also from the two populations, results in

$$\left.\begin{aligned}
\frac{dE_h}{dt} &= \frac{\beta_{vh}\vartheta I_v S_h}{N_h} + \kappa_1\theta - (\alpha_h + \mu_h)E_h \\
\frac{dI_h}{dt} &= \alpha_h E_h - (\phi + \mu_h + \delta_h)I_h \\
\frac{dE_v}{dt} &= \frac{\beta_{hv}\vartheta I_h S_v}{N_h} - (\alpha_v + \mu_v)E_v \\
\frac{dI_v}{dt} &= \alpha_v E_v - \mu_v I_v \\
\frac{dS_h}{dt} &= \Lambda_h + (1-\kappa_1)\theta + \phi(1-\rho)I_h - \frac{\beta_{vh\vartheta I_v S_h}}{N_h} - \mu_h S_h + \psi R_h \\
\frac{dR_h}{dt} &= \phi\rho I_h - (\mu_h + \psi)R_h \\
\frac{dS_v}{dt} &= \Lambda_v - \frac{\beta_{hv\vartheta I_h S_h}}{N_h} - \mu_h S_v
\end{aligned}\right\}. \qquad (3.15)$$

The rate of appearance of a new infection in compartments E_h and E_v has been derived by using the method of next generation matrix, from the system (3.15) for

$$\mathcal{F} = \begin{bmatrix} \frac{\beta_{vh}\vartheta I_v S_h}{N_h} + \kappa_1\theta \\ 0 \\ \frac{\beta_{hv}\vartheta I_h S_v}{N_h} \\ 0 \end{bmatrix}.$$

The Jacobian matrix of $\mathcal{F}$ at the DFE E_0 (see equation (3.14)) where $0 \leq N_h \leq \frac{\Lambda_h + \theta}{\mu_h}$ and $N_v \leq \frac{\Lambda_v}{\mu_v}$ is

$$F = \begin{bmatrix} 0 & 0 & 0 & \beta_{vh}\vartheta \\ 0 & 0 & 0 & 0 \\ 0 & \frac{\beta_{hv}\vartheta\Lambda_v\mu_h}{(\Lambda_h+\theta)\mu_v} & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}, \qquad (3.16)$$

The transfer of individuals out of the compartments of the system (3.15) by all other means is

$$\mathcal{V} = \begin{bmatrix} (\alpha_h + \mu_h)E_h \\ (\phi + \mu_h + \delta_h)I_h - \alpha_h E_h \\ (\alpha_v + \mu_v)E_v \\ \mu_v I_v - \alpha_v E_v \end{bmatrix}.$$

The Jacobian matrix of $\mathcal{V}$ is given by

$$V = \begin{bmatrix} \alpha_h + \mu_h & 0 & 0 & 0 \\ -\alpha_h & \phi + \mu_h + \delta_h & 0 & 0 \\ 0 & 0 & \alpha_v + \mu_v & 0 \\ 0 & 0 & -\alpha_v & \mu_v \end{bmatrix}. \tag{3.17}$$

The inverse of V is

$$V^{-1} = \begin{bmatrix} \frac{1}{\alpha_h + \mu_h} & 0 & 0 & 0 \\ f & g & 0 & 0 \\ 0 & 0 & \frac{1}{(\alpha_v + \mu_v)} & 0 \\ 0 & 0 & h & \frac{1}{\mu_v} \end{bmatrix}, \tag{3.18}$$

where $f = \dfrac{\alpha_h}{(\alpha_h + \mu_h)(\phi + \mu_h + \delta_h)}$, $g = \dfrac{1}{(\phi + \mu_h + \delta_h)}$, $h = \dfrac{\alpha_v}{(\alpha_v + \mu_v)\mu_v}$.

Therefore

$$FV^{-1} = \begin{bmatrix} 0 & 0 & a & b \\ 0 & 0 & 0 & 0 \\ c & d & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}, \tag{3.19}$$

where $a = \dfrac{\beta_{vh}\vartheta\alpha_v}{(\alpha_v + \mu_v)\mu_v}$, $b = \dfrac{\beta_{vh}\vartheta}{\mu_v}$, $c = \dfrac{\beta_{hv}\vartheta\Lambda_v\mu_h\alpha_h}{(\Lambda_h + \theta)(\alpha_h + \mu_h)(\phi + \mu_h + \delta_h)\mu_v}$,

$$d = \frac{\beta_{hv}\vartheta\Lambda_v\mu_h}{(\Lambda_h+\theta)(\phi+\mu_h+\delta_h)\mu_v}.$$

The eigenvalues of FV^{-1} are calculated from $M = |FV^{-1} - \lambda I| = 0$, that is

$$M = \begin{vmatrix} -\lambda & 0 & a & b \\ 0 & -\lambda & 0 & 0 \\ 0 & 0 & -\lambda & 0 \\ c & d & 0 & -\lambda \end{vmatrix} = 0, \tag{3.20}$$

which gives

$$\lambda_i = \begin{bmatrix} 0 \\ 0 \\ 0 \\ \dfrac{\sqrt{(\alpha_h+\mu_h)(\phi+\mu_h+\delta_h)(\alpha_v+\mu_v)\mu_v\Theta^*\beta_{vh}\vartheta\alpha_h\alpha_v}}{(\alpha_h+\mu_h)(\phi+\mu_h+\delta_h)(\alpha_v+\mu_v)\mu_v} \\ -\dfrac{\sqrt{(\alpha_h+\mu_h)(\phi+\mu_h+\delta_h)(\alpha_v+\mu_v)\mu_v\Theta^*\beta_{vh}\vartheta\alpha_h\alpha_v}}{(\alpha_h+\mu_h)(\phi+\mu_h+\delta_h)(\alpha_v+\mu_v)\mu_v} \end{bmatrix},$$

where $\Theta^* = \left(\dfrac{\beta_{hv}\vartheta\Lambda_v\mu_h}{(\Lambda_h+\theta)\mu_v}\right)$, which can be simplified further

$$\lambda_i = \begin{bmatrix} 0 \\ 0 \\ 0 \\ \dfrac{\sqrt{(\alpha_h+\mu_h)(\phi+\mu_h+\delta_h)(\alpha_v+\mu_v)\mu_v\beta_{hv}\beta_{vh}\vartheta^2\alpha_h\alpha_v\Theta^{**}}}{(\alpha_h+\mu_h)(\phi+\mu_h+\delta_h)(\alpha_v+\mu_v)\mu_v} \\ -\dfrac{\sqrt{(\alpha_h+\mu_h)(\phi+\mu_h+\delta_h)(\alpha_v+\mu_v)\mu_v\beta_{hv}\beta_{vh}\vartheta^2\alpha_h\alpha_v\Theta^{**})}}{(\alpha_h+\mu_h)(\phi+\mu_h+\delta_h)(\alpha_v+\mu_v)\mu_v} \end{bmatrix}. \tag{3.21}$$

where $\Theta^{**} = \dfrac{\Lambda_v \mu_h}{\mu_v(\Lambda_h + \theta)}$.

Hence, the reproduction number, $\mathcal{R}_0$, is the dominant eigenvalue of FV^{-1} given by

$$\mathcal{R}_0 = \sqrt{\frac{(\alpha_h + \mu_h)(\phi + \mu_h + \delta_h)(\alpha_v + \mu_v)\mu_v \beta_{hv}\beta_{vh}\vartheta^2 \alpha_h \alpha_v \Lambda_v \mu_h}{(\alpha_h + \mu_h)^2(\phi + \mu_h + \delta_h)^2(\alpha_v + \mu_v)^2 \mu_v^3(\Lambda_h + \theta)}}.$$

After further simplification, the reproduction number $\mathcal{R}_e$ becomes

$$\mathcal{R}_0 = \sqrt{\frac{\beta_{hv}\beta_{vh}\vartheta^2 \alpha_h \alpha_v \Lambda_v \mu_h}{(\alpha_h + \mu_h)(\phi + \mu_h + \delta_h)(\alpha_v + \mu_v)(\Lambda_h + \theta)\mu_v^2}}, \tag{3.22}$$

where

- $\dfrac{\alpha_h}{\alpha_h + \mu_h}$ is the probability of survival of the individuals from the latent stage into the infectious stage.
- $\dfrac{\alpha_v}{\alpha_v + \mu_v}$ is the probability of survival of the mosquitoes from the exposed stage into the infectious stage of the mosquito population.

The expression for the reproduction number, $\mathcal{R}_0$, has a biological meaning that is readily interpreted by terms under the square root sign.

- The term $\dfrac{\beta_{vh}\vartheta\alpha_v}{(\alpha_v + \mu_v)\mu_v}$ describes the number of humans that one mosquito infects (through contacts) during the lifetime it survives as infectious, when all humans are susceptible.
- The term $\dfrac{\beta_{hv}\vartheta\alpha_h}{(\alpha_h + \mu_h)(\phi + \mu_h + \delta_h)}$ describes the number of mosquitoes that are infected through contacts with one infectious human, while the human survives as infectious, assuming no infection among vectors (female Anopheles mosquitoes). The reproduction number is given by

$$\mathcal{R}_0 = \sqrt{\mathcal{R}_{0v}\mathcal{R}_{0h}},$$

where

- $\mathcal{R}_{0v} = \dfrac{\beta_{hv}\alpha_v\vartheta\Lambda_v}{\mu_v^2(\alpha_v+\mu_v)}$ is the contribution of the mosquito population when it infects the humans, and
- $\mathcal{R}_{0h} = \dfrac{\beta_{vh}\vartheta\mu_h\alpha_h}{(\Lambda_h+\theta)(\alpha_h+\mu_h)(\phi+\mu_h+\delta_h)}$ is the human contribution when they infect the mosquitoes.

The square root represents the geometric mean of the average number of secondary host infections produced by one vector, and the average number of secondary vector infections produced by one host. The reproduction number serves as an invasion threshold both for predicting outbreaks and evaluating control strategies that would reduce the spread of the disease.

The threshold quantity, $\mathcal{R}_e$, measures the average number of secondary cases generated by a single infected individual in a susceptible human population, where a fraction of the susceptible human population is under prevention through the use of ITNs and IRS, and the infected class is under treatment. The value of the effective reproduction number, $\mathcal{R}_e$, for the model (3.1) with $u_1 \neq u_2 \neq u_3 \neq 0$ is obtained from the expression of basic reproduction, $\mathcal{R}_0$, of the autonomous model (3.2). Hence the effective reproduction number of the model with intervention strategies is given by

$$\mathcal{R}_e = \sqrt{\frac{\beta_{hv}\beta_{vh}\vartheta^2\alpha_h(1-u_1)\alpha_v\Lambda_v\mu_h}{(\alpha_h+\mu_h)(\phi+\eta u_2+\mu_h+\delta_h)(\alpha_v+\mu_v+\tau u_3)(\tau u_3+\mu)_v^2(\Lambda_h+\theta)}}. \quad (3.23)$$

In the absence of any protective measure, the effective reproduction number, $\mathcal{R}_e$, with treatment is

$$\mathcal{R}_{et} = \sqrt{\frac{\beta_{hv}\beta_{vh}\vartheta^2\alpha_h\alpha_v\Lambda_v\mu_h}{(\alpha_h+\mu_h)(\phi+\eta u_2+\mu_h+\delta_h)(\alpha_v+\mu_v)\mu_v^2(\Lambda_h+\theta)}}.$$

Also if the protection by using ITNs as the only intervention strategy, then

$$\mathcal{R}_{eN} = \sqrt{\frac{\beta_{hv}\beta_{vh}\vartheta^2\alpha_h\alpha_v\Lambda_v\mu_h(1-u_1)}{(\alpha_h+\mu_h)(\phi+\mu_h+\delta_h)(\alpha_v+\mu_v)\mu_v^2(\Lambda_h+\theta)}}.$$

Similarly, if IRS is the only means of protection, then

$$\mathcal{R}_{es} = \sqrt{\frac{\beta_{hv}\beta_{vh}\vartheta^2\alpha_h\alpha_v\mu_h\Lambda_v}{(\alpha_h+\mu_h)(\phi+\mu_h+\delta_h)(\alpha_v+\mu_v+\tau u_3)(\mu_v+\tau u_3)^2(\Lambda_h+\theta)}}.$$

From the two reproduction numbers, it is easy to prove that

$$\mathcal{R}_e \leq \mathcal{R}_0,$$

for $0 \leq u_1, u_3 \leq 1$, due to reduction of likelihood of infection by using ITNs and IRS. This implies that ITNs and IRS have a positive impact on the malaria dynamics as they contribute to the reduction of secondary infections. Therefore, from Van den Driessche and Watmough [122], (Theorem 2), the following result holds;

Lemma 2. *The DFE, E_0, of the malaria model with intervention strategies (3.2) given by (3.14) is locally asymptotically stable if*
$\mathcal{R}_e < 1$, *and unstable if* $\mathcal{R}_e > 1$.

Proof. The Jacobian matrix of the model (3.2) with $S_h = N_h - (E_h + I_h + R_h)$ calculated at the DFE is given by

$$\begin{bmatrix} -(\alpha_h+\mu_h) & 0 & 0 & 0 & 0 & m_1 \\ \alpha_h & -n_1 & 0 & 0 & 0 & 0 \\ 0 & \phi\rho & -(\mu_h+\psi) & 0 & 0 & 0 \\ 0 & -p & 0 & -\mu_v & 0 & 0 \\ 0 & p & 0 & 0 & -f_1 & 0 \\ 0 & 0 & 0 & 0 & \alpha_v & -\mu_v \end{bmatrix},$$

where $m_1 = \beta_{vh}\vartheta,\ n_1 = (\phi+\mu_h+\delta_h),\ p = \dfrac{\beta_{hv}\vartheta\Lambda_v\mu_h}{(\Lambda_h+\theta)\mu_v}$,
$f_1 = (\alpha_v+\mu_v)$.
The third and fourth columns have diagonal entries. Hence, the diagonal entries

$-(\mu_h+\psi)$ and $-\mu_v$ are two eigenvalues of the Jacobian. Therefore, excluding these columns and the corresponding rows, we solve for the remaining eigenvalues using the following matrix;

$$\begin{bmatrix} -(\alpha_h+\mu_h) & 0 & 0 & \beta_{vh}\vartheta \\ \alpha_h & -(\phi+\mu_h+\delta_h) & 0 & 0 \\ 0 & \dfrac{\beta_{hv}\vartheta\Lambda_v\mu_h}{(\Lambda_h+\theta)\mu_v} & -(\alpha_v+\mu_v) & 0 \\ 0 & 0 & \alpha_v & -\mu_v \end{bmatrix}.$$

These eigenvalues are the solutions of the characteristic equation of the reduced matrix of dimension four which is given by

$$(x+\mu_v)(x+\alpha_h+\mu_h)(x+\phi+\mu_h+\delta_h)(x\ +\alpha_v+\mu_v)-\frac{\beta_{vh}\beta_{hv}\alpha_v\alpha_h\vartheta^2\Lambda_v\mu_h}{(\Lambda_h+\theta)\mu_v}=0. \tag{3.24}$$

For simplicity, let $B_0=\mu_v^2,\ B_1=\alpha_h+\mu_h,\ B_2=\alpha_v+\mu_v,\ B_3=\phi+\mu_h+\delta_h$. This reduces the effective reproduction number to $\mathcal{R}_e^2=\dfrac{\beta_{vh}\beta_{hv}\vartheta^2\alpha_v\alpha_h\Lambda_v\alpha_h}{(\Lambda_h+\theta)B_0B_1B_2B_3}$ and equation (3.24) to

$$x^4+A_3x^3+A_2x^2+A_1x+A_0=0, \tag{3.25}$$

where

$$\left.\begin{aligned} A_3 &= B_1+B_3+2B_0+\alpha_v \\ A_2 &= (B_3+B_1)(2B_0+\alpha_v)+B_0B_2+B_1B_3 \\ A_1 &= B_0B_3B_2+B_1B_3(2B_0+\alpha_v)+B_0B_1B_2 \\ A_0 &= B_0B_1B_2B_3-\alpha_v\alpha_h\vartheta^2\beta_{vh}\beta_{hv}\frac{\Lambda_v\mu_h}{(\Lambda_h+\theta)\mu_v} \end{aligned}\right\}.$$

The Routh-Hurwitz conditions [95], which usually have different forms, are the sufficient and necessary conditions on the coefficients of the polynomial in equation (3.25). These conditions ensure that all roots of the polynomial given by equation (3.25) have negative real parts. For this polynomial, the Routh-Hurwitz conditions

are $A_0 > 0,\ A_1 > 0,\ A_2 > 0,\ A_3 > 0,\ H_1 = A_3 > 0,$

$$H_2 = \begin{vmatrix} A_3 & 1 \\ A_1 & A_2 \end{vmatrix} > 0,$$

$$H_3 = \begin{vmatrix} A_3 & 1 & 0 \\ A_1 & A_2 & A_3 \\ 0 & A_0 & A_1 \end{vmatrix} > 0,$$

$$H_4 = \begin{vmatrix} A_3 & 1 & 0 & 0 \\ A_1 & A_2 & A_3 & 1 \\ 0 & A_0 & A_1 & A_2 \\ 0 & 0 & 0 & A_0 \end{vmatrix} > 0.$$

Clearly $H_4 = A_0 H_3$. Since $B_0 > 0,\ B_1 > 0,\ B_2 > 0,\ B_3 > 0$, we have $A_i > 0$, $i = 1, 2, 3$. Moreover, if $\mathcal{R}_e < 0$, it follows that $A_0 > 0$. Thus, it is sufficient to prove that $H_2 > 0$ and $H_3 > 0$. Clearly $H_3 = A_1(A_3A_2 - A_1) - A_0A_3^2$ and $H_2 = A_3A_2 - A_1$. Hence checking the positivity, we have

$$\left.\begin{aligned} H_2 &= A_3A_2 - A_1 \\ &= B_3^2(B_0 + B_2 + B_1) + B_2B_3(2B_0 + B_2 + 2B_1) \\ &\quad + B_0^2(B_3 + B_1 + B_2) + B_1^2(B_0 + B_2 + B_3) \\ &\quad + 2B_0B_1(B_3 + B_2) + B_2^2(B_1 + B_0) \end{aligned}\right\},$$

which is positive. We can also see that

$$\left.\begin{aligned} H_3 &= A_1(A_3A_2 - A_1) - A_0A_3^2 \\ &= (B_3 + B_0)(B_0 + B_2)(B_3 + B_2)(B_1 + B_0)(B_3 + B_1) \\ &\quad (B_1 + B_2) + \alpha_h\vartheta^2\alpha_v\beta_{vh}\beta_{hv}\frac{\Lambda_v\mu_h}{(\Lambda_h + \theta)\mu_v} \end{aligned}\right\},$$

which is clearly a positive quantity. Therefore, all the eigenvalues of the Jacobian matrix have negative real parts when $\mathcal{R}_e < 1$. However, $\mathcal{R}_e > 1$ implies that $A_0 < 0$,

and since all of coefficients (A_1, A_2 and A_3) of the polynomial in equation (3.25) are positive, not all roots of this polynomial can have negative real parts. This means, when $\mathcal{R}_e > 1$, the DFE is unstable. □

Note that the results in Lemma 2 are local, that is we can only conclude that solutions with fairly small initial size in the invariant set Φ are attracted to the DFE. It is possible to further reduce the dimension of the Jacobian in the proof of Lemma 2 by using $S_v = N_v - (E_v + I_v)$ and
$S_h = N_h - (E_h + I_h + R_h)$ without any technical difficulty.

The following theorem establishes the global stability of the DFE E_0;

Theorem 1. *The DFE E_0 of system of equations (3.2) is globally asymptotically stable if $\mathcal{R}_e \leq 1$ and unstable if $\mathcal{R}_e > 1$.*

Proof. Let us define the new variables and break the system given by (3.2) into subsystems. We use notation $X_1 = (S_h, R_h, S_v)$ which denotes the numbers of susceptible and recovered individuals, and susceptible mosquitoes. In addition the notation $Y_1 = E_h, I_h, E_v, I_v$ denotes the numbers of latent and infectious individuals and mosquitoes in different compartments. The system can be presented as

$$\left.\begin{array}{rcl} \dfrac{dX_1}{dt} & = & F(X_1, Y_1) \\ \dfrac{dY_1}{dt} & = & G(X_1, Y_1) \end{array}\right\} \text{ where } X_1 \in \mathbb{R}^3_+,\ Y_1 \in \mathbb{R}^4_+.$$

Then the two vector-valued functions are

$$\left.\begin{array}{rcl} F(X_1, Y_1) & = & \Big(\Lambda_h + (1-\kappa_1)\theta + \phi(1-\rho)I_h - \dfrac{\beta_{vh}\vartheta I_v S_h}{N_h} - \mu_h S_h + \psi R_h, \\ & & \phi\rho I_h - (\mu_h + \psi)R_h,\ \Lambda_v - \dfrac{\beta_{hv}\vartheta I_h S_v}{N_h} - \mu_h S_v\Big)^T \\ G(X_1, Y_1) & = & \Big(\dfrac{\beta_{vh}\vartheta I_v S_h}{N_h} + \kappa_1\theta - (\alpha_h + \mu_h)E_h,\ \alpha_h E_h - (\phi + \mu_h + \delta_h)I_h, \\ & & \dfrac{\beta_{hv}\vartheta I_h S_v}{N_h} - (\alpha_v + \mu_v)E_v,\ \alpha_v E_v - \mu_v I_v\Big)^T \end{array}\right\}$$

where T denotes the transpose. For simplicity we identify X_1 with $(X_1, 0)$ and Y_1 with $(0, Y_1)$ in $\mathbb{R}^3_+ \times \mathbb{R}^4_+$. Hence the reduced system: $\dfrac{dX_1}{dt} = F(X_1, 0)$;

$$\left.\begin{array}{rcl} \dfrac{dS_h}{dt} & = & \Lambda_h + (1-\kappa_1)\theta - \mu_h S_h + \psi R_h \\ \dfrac{dR_h}{dt} & = & -(\mu_h + \psi)R_h \\ \dfrac{dS_v}{dt} & = & \Lambda_v - \mu_v S_v \end{array}\right\} \tag{3.26}$$

and $X^* = (S_h^{**}, R_h^{**}, S_v^{**}) = \left(\dfrac{\Lambda_h + (1-\kappa_1)\theta}{\mu_h},\ 0,\ \dfrac{\Lambda_v}{\mu_v}\right)$ is a global asymptotically stable equilibrium point for the reduced system $\dfrac{dX_1}{dt} = F(X_1, 0)$. This can easily be shown by solving the second equation in (3.26) by integrating

$$\left.\begin{array}{rcl} \dfrac{dR_h}{dt} & = & -(\mu_h + \psi)R_h \\ \Longrightarrow R_h(t) & = & R_h(0)e^{-(\mu_h+\psi)t} \end{array}\right\}. \tag{3.27}$$

It approaches zero as $t \longrightarrow \infty$. Similarly integrating and simplifying the third equation in (3.26) gives $S_v(t) = \dfrac{\Lambda_v}{\mu_v} + \left(S_v(0) - \dfrac{\Lambda_v}{\mu_v}\right)e^{-\mu_v t}$ which approaches $\dfrac{\Lambda_v}{\mu_v}$ as $t \longrightarrow \infty$. Finally integrating and simplifying the first equation in (3.26) gives $S_h = \dfrac{\Lambda_h + (1-\kappa_1)\theta}{\mu_h} - R_h(0)e^{-(\mu_h+\psi)t} + \left(S_h(0) + R_h(0) - \dfrac{\Lambda_h + (1-\kappa_1)\theta}{\mu_h}\right)e^{-\mu_h t}$ which approaches to $\dfrac{\Lambda_h + (1-\kappa_1)\theta}{\mu_h}$ as $t \longrightarrow \infty$. These asymptotic dynamics are independent of initial conditions in Φ. Clearly $G(X_1, Y_1)$ satisfies the following two conditions given as assumptions H3 and H4 in [46] namely;

$G(X_1, 0) = 0$ and $G(X_1, Y_1) = A^* Y_1 - \bar{G}(X_1, Y_1),\ \bar{G}(X_1, Y_1) \geq 0$ in Φ, where

$$A^* = D_Y G(X_1, 0) = \begin{bmatrix} -(\alpha_h + \mu_h) & 0 & 0 & \beta_{vh}\vartheta \\ \alpha_h & -(\phi + \mu_h + \delta_h) & 0 & 0 \\ 0 & \dfrac{\beta_{hv}\vartheta\Lambda_v\mu_h}{(\Lambda_h + \theta)\mu_v} & -(\alpha_v + \mu_v) & 0 \\ 0 & 0 & \alpha_v & -\mu_v \end{bmatrix}$$

and

$$\bar{G}(X_1, Y_1) = \begin{bmatrix} \beta_{vh}\vartheta I_v(1 - \dfrac{S_h}{N_h}) \\ 0 \\ \beta_{hv}\vartheta I_h \left(\dfrac{\Lambda_v \mu_h}{\mu_v(\Lambda_h + (1-\kappa_1)\theta)} - \dfrac{S_v}{N_h} \right) \\ 0 \end{bmatrix}.$$

Note that since the human and the mosquito populations assume a steady-state value $N_h = \dfrac{\Lambda_h + (1-\kappa_1)\theta}{\mu_h}$ and $N_v = \dfrac{\Lambda_v}{\mu_v}$, then term $\beta_{hv}\vartheta I_h \left[\dfrac{\Lambda_v \mu_h}{\mu_v(\Lambda_h + (1-\kappa_1)\theta)} - \dfrac{S_v}{N_h} \right]$ in $\bar{G}(X_1, Y_1)$ is nonegative. Moreover by Lemma 2 the DFE is locally asymptotically stable for $\mathcal{R}_e < 1$.

□

We have shown that the DFE E_0 is globally asymptotically stable if $\mathcal{R}_e \leq 1$. This concludes that the infected mosquitoes and humans eventually vanish and the disease dies out.

Theorem 2. *The malaria model 3.2 has a unique endemic equilibrium in* Φ *if* $\mathcal{R}_e > 1$.

Proof. The equilibrium equations for S_h, E_h, I_h and R_h, with
$S_h = N_h - (E_h + I_h + R_h)$ on which (from system of equation (3.2))
$\dfrac{\beta_{vh}\vartheta I_v S_h}{N_h} = (\alpha_h + \mu_h)E_h - \kappa_1\theta,$
for I_h : $I_h = \dfrac{\alpha_h E_h}{\phi + \mu_h + \delta_h}$ and
for R_h : $R_h = \dfrac{\phi\rho I_h}{\mu_h + \psi} = \dfrac{\phi\rho\alpha_h E_h}{(\mu_h + \psi)(\phi + \mu_h + \delta_h)}$, yield

$$\frac{\beta_{vh}\vartheta I_v S_h}{N_h} = \frac{\beta_{vh}\vartheta I_v}{N_h}(N_h - (E_h + I_h + R_h)) = (\alpha_h + \mu_h)E_h - \kappa_1\theta.$$

Simplifying further we get

$$\begin{aligned}&\frac{\beta_{vh}\vartheta I_v}{N_h}\left[N_h-\left[E_h+\frac{\alpha_h E_h}{\phi+\mu_h+\delta_h}+\frac{\phi\rho\alpha_h E_h}{(\mu_h+\psi)(\phi+\mu_h+\delta_h)}\right]\right]\\&+\kappa_1\theta-(\alpha_h+\mu_h)E_h=0.\end{aligned}\tag{3.28}$$

Also, from steady-state equations for S_v, E_v and I_v, with $S_v = N_v - (E_v + I_v)$ where

$$I_v=\frac{\alpha_v E_v}{\mu_v}\text{ and }\frac{\beta_{hv}\vartheta I_h S_v}{N_h}=(\alpha_v+\mu_v)E_v\tag{3.29}$$

yield

$$\begin{aligned}\frac{\beta_{hv}\vartheta I_h}{N_h}=\frac{\beta_{hv}\vartheta I_h S_v}{N_h}(N_v-(E_v+I_v))=(\alpha_v+\mu_v)E_v,\\\frac{\beta_{hv}\vartheta I_h}{N_h}\left[N_v-\frac{\mu_v+\alpha_v}{\mu_v}E_v\right]-(\alpha_v+\mu_v)E_v=0.\end{aligned}\tag{3.30}$$

But $I_h=\dfrac{\alpha_h E_h}{\phi+\mu_h+\delta_h}$, and substituting in (3.30), we get

$$\frac{\beta_{hv}\vartheta\alpha_h E_h}{N_h(\phi+\mu_h+\delta_h)}\left[N_v-\frac{\mu_v+\alpha_v}{\mu_v}E_v\right]-(\alpha_v+\mu_v)E_v=0.\tag{3.31}$$

Using notations $A_E=\dfrac{\beta_{hv}\vartheta}{N_h(\phi+\mu_h+\delta_h)}$ and $B_E=\dfrac{\mu_v+\alpha_v}{\mu_v}$, the equation 3.31 becomes

$$\begin{aligned}A_E\alpha_h E_h(N_v-B_E E_v)-\mu_v B_E E_v=0,\\E_h=\frac{\mu_v B_E E_v}{A_E\alpha_h(N_v-B_E E_v)}.\end{aligned}\tag{3.32}$$

The equation (3.28) is transformed by replacing I_v with its new value (see the first equation in 3.29) to

$$\begin{aligned}&\frac{\beta_{vh}\vartheta\alpha_v E_v}{N_h}(N_h-C_E E_h)+\kappa_1\theta-(\alpha_h+\mu_h)E_h=0,\text{ where}\\&C_E=1+\frac{\alpha_h}{\phi+\mu_h+\delta_h}\left(1+\frac{\phi\rho}{\mu_h+\psi}\right).\end{aligned}\tag{3.33}$$

We can deduce that if $N_v - B_E E_v = 0$, then $E_v + I_v = N_v$ which leads to $S_v = 0$ because $S_v + E_v + I_v = N_v$. As a results of this, we notice that $\dfrac{dS_v}{dt} = 0 \Longrightarrow \Lambda_v = 0$, which means that $N_v = 0$. This is true only if $E_v = I_v = 0$, which is not of interest

to us because there are vectors in the environment. Thus, $S_v > 0$ and $N_v > E_v + I_v = B_E E_v$ at equilibrium. Furthermore, as $N_v - B_E E_v > 0$ we have $E_h > 0$ as long as $E_v > 0$, which we verify in the next argument. Using the notations introduced in this proof and equation (3.32), the equation (3.33) becomes

$$\frac{\beta_{vh}\vartheta\alpha_v E_v}{N_h}\left[N_h - \frac{C_E\mu_v B_E E_v}{A_E\alpha_h(N_v - B_E E_v)}\right] + \kappa_1\theta - \frac{[\alpha_h+\mu_h]\mu_v B_E E_v}{A_E\alpha_h(N_v - B_E E_v)} = 0.$$

A unique nonzero solution of this equation satisfies

$$\begin{aligned} E_v &= \frac{\alpha_h\vartheta\beta_{vh}\alpha_v N_v A_E N_h - (\alpha_h+\mu_h)(\alpha_v+\mu_v)\mu_v N_h}{\dfrac{B_E\alpha_h A_E\alpha_v N_v\beta_{vh}\vartheta}{\mu_v} + \beta_{vh}\vartheta\alpha_v C_E B_E} \\ &= \frac{(\mathcal{R}_e^2 - 1)(\alpha_h+\mu_h)(\alpha_v+\mu_v)\mu_v N_h}{\dfrac{B_E\alpha_h A_E\alpha_v N_v\beta_{vh}\vartheta}{\mu_v} + \beta_{vh}\vartheta\alpha_v C_E B_E}. \end{aligned}$$

Note that $E_v > 0$ if and only if

$\Phi_3 = \dfrac{\beta_{hv}\beta_{vh}\vartheta^2\alpha_h\alpha_v\Lambda_v\mu_h}{(\alpha_h+\mu_h)(\phi+\mu_h+\delta_h)(\alpha_v+\mu_v)\mu_v^2(\Lambda_h+\theta)} > 1$, but

$\mathcal{R}_e^2 = \Phi_3$. Thus, a unique endemic equilibrium point is possible only if $\mathcal{R}_e > 1$. □

3.2.5 Global stability of the endemic equilibrium

Herein, we investigate the global behavior of the endemic equilibrium of the model (3.2) for the special case when there is no loss of immunity ($\psi = 0$). It can be shown that the region

$$\tilde{\Phi} = \tilde{\Phi}_h \cup \tilde{\Phi}_v \subset \mathbb{R}_+^4 \times \mathbb{R}_+^3$$

where

$$\left.\begin{aligned} \tilde{\Phi}_h &= \{(S_h, E_h, I_h, R_h) \subset \Phi_h : S_h \leq S_h^*\} \\ \tilde{\Phi}_v &= \{(S_v, E_v, I_v) \subset \Phi_v : S_v \leq S_v^*\} \end{aligned}\right\},$$

is positively-invariant for the special case of the system (3.2). It is appropriate to define

$$\tilde{\Phi} = \{(S_h, E_h, I_h, R_h, S_v, E_v, I_v) \in \Phi : E_h = I_h = R_h = E_v = I_v = 0\}.$$

Theorem 3. *The unique endemic equilibrium of the malaria model (3.2) is globally asymptotically stable in* $\tilde{\Phi}\backslash\{E_h = I_h = R_h = E_v = I_v = 0\}$ *whenever* $\tilde{\mathcal{R}}_{e|_{\psi=0}} > 1$.

Proof. Let $\tilde{\mathcal{R}}_e > 1$ so that the unique endemic equilibrium of the model exists. Consider the following non-linear Lyapunov function

$$\left.\begin{aligned} L_f &= S_h^*\left(\frac{S_h}{S_h^*} - \ln\frac{S_h}{S_h^*}\right) + E_h^*\left(\frac{E_h}{E_h^*} - \ln\frac{E_h}{E_h^*}\right) + \frac{a_1}{\alpha_h} I_h^*\left(\frac{I_h}{I_h^*} - \ln\frac{I_h}{I_h^*}\right) \\ &+ \frac{a_2 a_1}{\alpha_h \gamma_1} R_h^*\left(\frac{R_h}{R_h^*} - \ln\frac{R_h}{R_h^*}\right) + S_v^*\left(\frac{S_v}{S_v^*} - \ln\frac{S_v}{S_v^*}\right) + E_v^*\left(\frac{E_v}{E_v^*} - \ln\frac{E_v}{E_v^*}\right) \\ &+ \frac{a_4}{\alpha_v} I_v^*\left(\frac{I_v}{I_v^*} - \ln\frac{I_v}{I_v^*}\right) \end{aligned}\right\},$$

where $a_1 = \alpha_h + \mu_h,\ a_2 = \phi + \mu_h + \delta_h,\ \gamma_1 = \phi\rho,\ a_3 = \mu_h + \psi$ and $a_4 = \alpha_v + \mu_v$. The derivative of Lyapunov function is

$$\left.\begin{aligned} \dot{L}_f &= \left(1 - \frac{S_h^*}{S_h}\right)\dot{S}_h + \left(1 - \frac{E_h^*}{E_h}\right)\dot{E}_h + \frac{a_1}{\alpha_h}\left(1 - \frac{I_h^*}{I_h}\right)\dot{I}_h + \frac{a_2 a_1}{\alpha_h \gamma_1}\left(1 - \frac{R_h^*}{R_h}\right)\dot{R}_h \\ &+ \left(1 - \frac{S_v^*}{S_v}\right)\dot{S}_v + \left(1 - \frac{E_v^*}{E_v}\right)\dot{E}_v + \frac{a_4}{\alpha_v}\left(1 - \frac{I_v^*}{I_v}\right)\dot{I}_v \end{aligned}\right\}. \tag{3.34}$$

Substituting the derivatives from (3.2) with $\psi = 0$ into (3.34) gives

$$\left.\begin{aligned} \dot{L}_f &= \Lambda_h + (1-\kappa_1)\theta - \lambda_h S_h - \mu_h S_h - \frac{S_h^*}{S_h}(\Lambda_h + (1-\kappa_1)\theta - \lambda_h S_h - \mu_h S_h) \\ &+ \lambda_h S_h + \kappa_1\theta - a_1 E_h - \frac{E_h^*}{E_h}(\lambda_h S_h + \kappa_1\theta - a_1 E_h) \\ &+ \frac{a_1}{\alpha_h}(\alpha_h E_h - a_2 I_h) - \frac{a_1}{\alpha_h}\frac{I_h^*}{I_h}(\alpha_h E_h - a_2 I_h) \\ &+ \frac{a_2 a_1}{\alpha_h\gamma_1}(\gamma_1 I_h - a_3 R_h) - \frac{a_2 a_1}{\alpha_h\gamma_1}\frac{R_h^*}{R_h}(\gamma_1 I_h - a_3 R_h) \\ &+ \Lambda_v - \lambda_v S_v - \mu_v S_v - \frac{S_v^*}{S_v}(\Lambda_v - \lambda_v S_v - \mu_v S_v) \\ &+ \lambda_v S_v - a_4 E_v - \frac{E_v^*}{E_v}(\lambda_v S_v - a_4 E_v) \\ &+ \frac{a_4}{\alpha_v}(\alpha_v E_v - \mu_v I_v) - \frac{a_4}{\alpha_v}\frac{I_v^*}{I_v}(\alpha_v E_v - \mu_v I_v) \end{aligned}\right\}.$$

Hence

$$\left.\begin{aligned}\dot{L}_f &= \lambda_h S_h^*\left(1-\frac{S_h^*}{S_h}\right)+\mu_h S_h^*\left(2-\frac{S_h}{S_h^*}-\frac{S_h^*}{S_h}\right)+\lambda_h S_h^*-\frac{E_h^*}{E_h}\lambda_h S_h\\ &+ a_1E_h^*-a_1\frac{I_h^*}{I_h}E_h+\frac{a_2a_1}{\alpha_h}I_h^*-\frac{a_2a_1}{\alpha_h}\frac{R_h^*}{R_h}I_h+\frac{a_3a_2a_1}{\alpha_h\gamma_1}R_h\\ &- \frac{a_3a_2a_1}{\alpha_h\gamma_1}R_h+\lambda_v S_v^*\left(1-\frac{S_v^*}{S_v}\right)+\mu_v S_v^*\left(2-\frac{S_v}{S_v^*}-\frac{S_v^*}{S_v}\right)\\ &+ \lambda_v S_v^*-\frac{E_v^*}{E_v}\lambda_v S_v+a_4E_v^*-a_4\frac{I_v^*}{I_v}E_v+\frac{a_4\mu_v}{\alpha_v}I_v^*-\frac{a_4\mu_v}{\alpha_v}I_v^*\end{aligned}\right\}. \quad (3.35)$$

The Lyapunov equation (3.35) is simplified further to become

$$\left.\begin{aligned}\dot{L}_f &= \mu_h S_h^*\left(2-\frac{S_h^*}{S_h}-\frac{S_h}{S_h^*}\right)+a_2E_h^*\left(5-\frac{S_h^*}{S_h}-\frac{E_h^*}{E_h}-\frac{E_h}{E_h^*}\frac{I_h^*}{I_h}\right.\\ &\left.- \frac{I_h}{I_h^*}\frac{R_h^*}{R_h}-\frac{R_h}{R_h^*}\right)+\mu_v S_v^*\left(2-\frac{S_v^*}{S_v}-\frac{S_v}{S_v^*}\right)\\ &+ a_4E_v^*\left(4-\frac{S_v^*}{S_v}-\frac{E_v^*}{E_v}-\frac{E_v}{E_v^*}\frac{I_v^*}{I_v}-\frac{I_v}{I_v^*}\right)\end{aligned}\right\}.$$

We find that the arithmetic mean exceeds the geometric mean, then it follows that

$$\left.\begin{aligned}&2-\frac{S_h^*}{S_h}-\frac{S_h}{S_h^*}\le 0,\ 2-\frac{S_v^*}{S_v}-\frac{S_v}{S_v^*}\le 0,\\ &5-\frac{S_h^*}{S_h}-\frac{E_h^*}{E_h}-\frac{E_h}{E_h^*}\frac{I_h^*}{I_h}-\frac{I_h}{I_h^*}\frac{R_h^*}{R_h}-\frac{R_h}{R_h^*}\le 0,\\ &4-\frac{S_v^*}{S_v}-\frac{E_v^*}{E_v}-\frac{E_v}{E_v^*}\frac{I_v^*}{I_v}-\frac{I_v}{I_v^*}\le 0\end{aligned}\right\}.$$

Since the model parameters are assumed to be non-negative, it follows that $\dot{L}_f \le 0$ for $\tilde{\mathcal{R}}_{e|_{\psi=0}} > 1$. Hence, from LaSalles' Invariance Principle, we conclude that every solution to the equations in the model (3.2) with initial conditions in $\tilde{\Phi}\backslash\{E_h = I_h = R_h = E_v = I_v = 0\}$ approaches the endemic equilibrium point as $t \longrightarrow \infty$ whenever $\tilde{\mathcal{R}}_{e|_{\psi=0}} > 1$. □

The malaria model has a locally asymptotically stable DFE whenever $\mathcal{R}_e < 1$, and a unique endemic equilibrium is possible whenever $\mathcal{R}_e > 1$. In addition, the unique endemic equilibrium is globally asymptotically stable for the case

$\psi = 0$ if $\mathcal{R}_e > 1$.

The DFE is achieved if the intervention strategies for malaria (ITNs, IRS and treatment) are effectively implemented and followed. When the $\mathcal{R}_0 > 1$, the health personnel need to check if the ITNs are still effective, usability of the ITNs and if every member of the households is sleeping under the ITNs. On the other hand, the IRS chemical effectiveness must be verified. In addition, the available treatment should be checked and verified if the procedures of taking the pills are followed. The monitoring of treatment should be extended to the type of treatment given to the malaria patients taking into account parasite resistance to some medicines. If all these are checked and made available to the members of the society, it is likely that the effective reproduction number $\mathcal{R}_e < 1$, showing the reduction of malaria in the community.

In chapter 4, we apply the optimal control method using Pontryagin's Maximum Principle to determine the necessary conditions for the combined optimal control of ITNs, IRS and treatment effort which are being practised in Karonga District, Malawi.

Chapter 4

Optimal control analysis

In this chapter we investigate the analytical part of the optimal control of the intervention strategies and its numerical analysis. Optimal control has been applied to vector-borne disease problems and it has proved to be a good method for determining how best to prevent and treat a disease. We formulate an optimal control model for malaria disease in order to determine optimal prevention (ITNs and IRS) and treatment strategies with minimal implementation cost.

4.1 Analysis of optimal control of the malaria model with intervention strategies

The force of infection in the human population in the model (3.1) is reduced by a factor $(1 - u_1(t))$ where $u_1(t)$ represents the fraction of susceptible individuals who make use of ITNs as a means of minimizing or eliminating mosquito-human contacts. The control function $u_2(t) \in [0, 1]$ represents the control effort on treatment of infectious individuals. This indeed represents the situation when individuals in the

community seek treatment after visiting the hospitals or dispensary in their areas. For the mosquito population, we have a third control variable, $u_3(t)$. The use of IRS affects the whole mosquito population by increasing its mortality rate by $u_3(t)$. The control functions are practised on the time interval $[0, T_f]$. In this study we will use Pontryagin's Maximum Principle to determine the conditions under which eradication of the disease can be achieved in finite time. Following the dynamics of the model system (3.1) with appropriate initial conditions, the bounded Lebesgue measurable control is used with the objective functional defined as

$$\Gamma(u_1, u_2, u_3) = \int_0^{T_f} (C_1 E_h + C_2 I_h + C_3 N_v + \frac{1}{2}(A_1 u_1^2 + A_2 u_2^2 + A_3 u_3^2))dt, \qquad (4.1)$$

subject to the differential equations in (3.1), where T_f is the final time, $C_1, C_2,$ and C_3, positive weights to balance the factors of the exposed individuals, infected individuals and total mosquito population respectively, while A_1, A_2 and A_3 are positive weight constants for use with ITNs, treatment effort and IRS effort respectively which regularize the optimal control. The total mosquito population ($N_v = S_v + E_v + I_v$) is part of the objective function because it is affected by the use of IRS. 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 and treatment respectively. We choose a quadratic cost on the controls in line with what is known in the literature on epidemic controls for example Okosun et al., [91], Lashari and Zaman [56], Thome et al., [118]. The objective is to minimize the cost functional (4.1) which includes the exposed and infectious human population and the total mosquito population. In addition, it includes the cost of implementing personal protection using ITNs, $A_1 u_1^2$, treatment of infected individuals, $A_2 u_2^2$, and spraying of houses, $A_3 u_3^2$. A linear function has been chosen for the cost incurred by exposed individuals $C_1 E_h$, infected individuals, $C_2 I_h$ and the mosquito population, $C_3 N_v$. A quadratic form is used for the cost on the controls $A_1 u_1^2,\ A_2 u_2^2$ and $A_3 u_3^2$, such that the terms $\frac{1}{2} A_1 u_1^2,\ \frac{1}{2} A_2 u_2^2$ and $\frac{1}{2} A_3 u_3^2$ describe the cost associated with the ITNs, treatment and mosquito control (IRS)

respectively. The weights A_1, A_2 and A_3 depend on the relative importance of each of the control efforts in vindicating the spread of the disease as well as the cost of implementing each of the control strategies per unit time. The cost of treatment could be from cost of drugs, surveillance and follow up of drug management and fighting emergence of drug-resistance strains. The cost of prevention is related to cost of pesticide sprays, cost of ITNS and educating the community about personal protection. Our aim is to minimize the number of latent humans $E_h(t)$ and infected humans $I_h(t)$ while minimizing the cost of control $u_1(t), u_2(t)$ and $u_3(t)$. We select to model the control efforts via a linear combination of quadratic terms $u_i^2(t)$, constants C_i and A_i, where $i = (1, 2, 3)$, represent a measure of the relative cost of the interventions over $[0, T_f]$. We seek an optimal control $u_1^*(t)$, $u_2^*(t)$ and $u_3^*(t)$ such that

$$\Gamma(u_1^*, u_2^*, u_3^*) = \min_{(u_1,u_2,u_3)\in\Phi_2} \Gamma(u_1, u_2, u_3),$$

where

$$\begin{aligned} \Phi_2 &= \{u = (u_1, u_2, u_3) | u_i(t) \text{ is Lebesgue measurable, } 0 \leq u_i(t) \leq u_{i\ max}(t) \leq 1 \\ &\quad \text{for } t \in [0, T_f] \to [0, 1], i = 1, 2, 3\} \end{aligned}$$

is the control set, subject to the system (3.1) and appropriate initial conditions. Thus $u_1, u_2,$ and u_3 lie between 0 and 1 while $u_{i\ max}(t)$ depend on the amount of resources available to implement each of the control strategies. The basic framework of an optimal control problem is to prove the existence of the optimal control and then characterize the optimal control through the optimality system. We develop the optimal system for which the necessary conditions that an optimal control must satisfy come from Pontryagin's Maximum Principle.

4.2 Existence of an optimal control problem

Pontryagin's Maximum Principle converts the state system (3.1) and objective functional (4.1) into a problem of minimizing pointwise the Lagrangian L, and Hamiltonian H, with respect to u_1, u_2 and u_3. The Lagrangian of the control problem which is the Hamiltonian augmented with penalty terms for control constraints consists of the integrand of the objective functional and is given by

$$L = C_1 E_h + C_2 I_h + C_3 N_v + \frac{1}{2}(A_1 u_1^2 + A_2 u_2^2 + A_3 u_3^2).$$

We search for the minimum value of the Lagrangian. This can be achieved by defining the Hamiltonian H for the control problem which consists of the integrand of the objective functional (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

$$
\begin{aligned}
H &= L + \lambda_1 \frac{dS_h}{dt} + \lambda_2 \frac{dE_h}{dt} + \lambda_3 \frac{dI_h}{dt} + \lambda_4 \frac{dR_h}{dt} + \lambda_5 \frac{dS_v}{dt} + \lambda_6 \frac{dE_v}{dt} + \lambda_7 \frac{dI_v}{dt} \\
&= C_1 E_h + C_2 I_h + C_3 N_v + \frac{1}{2}(A_1 u_1^2 + A_2 u_2^2 + A_3 u_3^2) + \lambda_1 \frac{dS_h}{dt} + \lambda_2 \frac{dE_h}{dt} \\
&\quad + \lambda_3 \frac{dI_h}{dt} + \lambda_4 \frac{dR_h}{dt} + \lambda_5 \frac{dS_v}{dt} + \lambda_6 \frac{dE_v}{dt} + \lambda_7 \frac{dI_v}{dt} \\
&= C_1 E_h + C_2 I_h + C_3 N_v + \frac{1}{2}(A_1 u_1^2 + A_2 u_2^2 + A_3 u_3^2) \\
&\quad + \lambda_1 \left[\Lambda_h + (1-\kappa_1)\theta + (\phi + \eta u_2)(1-\rho) I_h - \frac{(1-u_1)\beta_{vh} \vartheta I_v S_h}{N_h} \right. \\
&\quad \left. - \mu_h S_h + \psi R_h \right] \\
&\quad + \lambda_2 \left[\frac{(1-u_1)\beta_{vh} \vartheta I_v S_h}{N_h} + \kappa_1 \theta - (\alpha_h + \mu_h) E_h \right] \\
&\quad + \lambda_3 \left[\alpha_h E_h - (\phi + \eta u_2 + \mu_h + \delta_h) I_h \right] \\
&\quad + \lambda_4 \left[(\phi + \eta u_2)\rho I_h - (\mu_h + \psi) R_h \right] \\
&\quad + \lambda_5 \left[\Lambda_v - \frac{\beta_{hv} \vartheta I_h S_v}{N_h} - (\mu_v + \tau u_3) S_v \right] \\
&\quad + \lambda_6 \left[\frac{\beta_{hv} \vartheta I_h S_v}{N_h} - (\alpha_v + \mu_v + \tau u_3) E_v \right] \\
&\quad + \lambda_7 \left[\alpha_v E_v - (\mu_v + \tau u_3) I_v \right]
\end{aligned}
\tag{4.2}
$$

The state and the control variables of the system (3.1) are non-negative values. The control set Φ_2 is closed and convex. Corollary 4.1 in Fleming [29] shows that the existence of optimal control due to the closeness and convexity of the integrand of the objective cost function Φ_2 expressed by (3.1) is a convex function of (u_1, u_2, u_3) on the control set Φ_2. Therefore, there exist positive numbers ξ_1, ξ_2 and a constant $\epsilon > 1$ such that

$$\Gamma(u_1, u_2, u_3) \geq \xi_1(|u_1|^2 + |u_2|^2, |u_3|^2)^{\epsilon/2} - \xi_2 \text{ where } \xi_1 > 0, \xi_2 > 0, \text{ and } \epsilon > 1.$$

The state and the control variables of the system (3.1) are non-negative values and non-empty. The control set Φ_2 is closed and convex. The integrand of the objective cost function Γ expressed by (3.1) is a convex function of (u_1, u_2, u_3) on the control set Φ_2. 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 $\epsilon > 1$ such that

$$\Gamma(u_1, u_2, u_3) \geq \xi_1(|u_1|^2 + |u_2|^2, |u_3|^2)^{\epsilon/2} - \xi_2.$$

This concludes existence of an optimal control since the state variables are bounded.

4.3 Classification of the optimal control problem

We use Pontryagin's Maximum Principle to develop the necessary conditions for this optimal control since there exists an optimal control for maximizing the functional (4.1) subject to the system of equations (3.1). Using the approach similar of Mwamtobe et. al., [79] that if (χ, u) is an optimal solution of an optimal control problem, then there exists a non trivial vector function $\lambda^* = (\lambda_1^*, \lambda_2^*, \lambda_3^*, \cdots, \lambda_n^*)$ satisfying the following equations;

$$\left.\begin{aligned} 0 &= \frac{\partial H(t, \chi, u, \lambda^*)}{\partial u} \\ \lambda^{*\prime} &= \frac{\partial H(t, \chi, u, \lambda^*)}{\partial \chi} \\ \frac{d\chi}{dt} &= -\frac{\partial H(t, \chi, u, \lambda^*)}{\partial \lambda^*} \end{aligned}\right\}. \tag{4.3}$$

Hence the necessary conditions of Hamiltonian, H, and Pontryagin's Maximum Principle can be applied in the system of equations (4.2).

Theorem 4. *For the optimal control triple (u_1^*, u_2^*, u_3^*) with their optimal state*

solutions $(S_h^*, E_h^*, I_h^*, R_h^*, S_v^*, E_v^*, I_v^*)$ *that minimize* $\Gamma(u_1, u_2, u_3)$ *over* Φ_2, *there exist adjoint variables* $(\lambda_1^*, \lambda_2^*, \lambda_3^*, \lambda_4^*, \lambda_5^*, \lambda_6^*, \lambda_7^*)$ *satisfying*

$$
\left.
\begin{aligned}
-\lambda_1^{*\prime} &= \left[\frac{-(1-u_1)\beta_{vh}\vartheta I_v}{N_h} + \frac{(1-u_1)\beta_{vh}\vartheta I_v S_h}{N_h^2} - \mu_h\right]\lambda_1 \\
&+ \left[\frac{(1-u_1)\beta_{vh}\vartheta I_v}{N_h} - \frac{(1-u_1)\beta_{vh}\vartheta I_v S_h}{N_h^2}\right]\lambda_2 + \frac{\beta_{hv}\vartheta I_h S_v}{N_h^2}\lambda_5 \\
&- \frac{\beta_{hv}\vartheta I_h S_v}{N_h^2}\lambda_6 \\
-\lambda_2^{*\prime} &= \frac{(1-u_1)\beta_{vh}\vartheta I_v S_h}{N_h^2}\lambda_1 - \left[\frac{(1-u_1)\beta_{vh}\vartheta I_v S_h}{N_h^2} + (\alpha_h + \mu_h)\right]\lambda_2 \\
&+ \alpha_h\lambda_3 + \frac{\beta_{hv}\vartheta I_h S_v}{N_h^2}\lambda_5 - \frac{\beta_{hv}\vartheta I_h S_v}{N_h^2}\lambda_6 + C_1 \\
-\lambda_3^{*\prime} &= \left[(\phi + \eta u_2)(1-\rho) + \frac{(1-u_1)\beta_{vh}\vartheta I_v S_h}{N_h^2}\right]\lambda_1 \\
&- \frac{(1-u_1)\beta_{vh} I_v S_h}{N_h^2}\lambda_2 - (\phi + \eta u_2 + \mu_h + \delta_h)\lambda_3 \\
&+ (\phi + \eta u_2)\rho\lambda_4 + \left[\frac{\beta_{hv}\vartheta I_h S_v}{N_h^2} - \frac{\beta_{hv}\vartheta S_v}{N_h}\right]\lambda_5 \\
&+ \left[\frac{\beta_{hv}\vartheta S_v}{N_h} - \frac{\beta_{hv}\vartheta I_h S_v}{N_h^2}\right]\lambda_6 + C_2 \\
-\lambda_4^{*\prime} &= \left[\frac{(1-u_1)\beta_{vh}\vartheta I_v S_h}{N_h^2} + \psi\right]\lambda_1 - \frac{(1-u_1)\beta_{vh}\vartheta I_v S_h}{N_h^2}\lambda_2 \\
&+ (\mu_h + \psi)\lambda_4 + \frac{\beta_{hv}\vartheta I_h S_v}{N_h^2}\lambda_5 - \frac{\beta_{hv}\vartheta I_h S_v}{N_h^2}\lambda_6 \\
-\lambda_5^{*\prime} &= \left[\frac{-\beta_{hv}\vartheta I_h}{N_h} - (\mu_v + \tau u_3)\right]\lambda_5 + \frac{\beta_{hv}\vartheta I_h}{N_h}\lambda_6 + C_3 \\
-\lambda_6^{*\prime} &= -(\alpha_v + \mu_v + \tau u_3)\lambda_6 + \alpha_v\lambda_7 + C_3 \\
-\lambda_7^{*\prime} &= \frac{-(1-u_1)\beta_{vh}\vartheta S_h}{N_h}\lambda_1 + \frac{(1-u_1)\beta_{vh}\vartheta S_h}{N_h}\lambda_2 \\
&- (\mu_v + \tau u_3)\lambda_7 + C_3
\end{aligned}
\right\}, \quad (4.4)
$$

with transversality conditions

$$\lambda_1^*(T_f) = \lambda_2^*(T_f) = \lambda_3^*(T_f) = \lambda_4^*(T_f) = \lambda_5^*(T_f) = \lambda_6^*(T_f) = \lambda_7^*(T_f) = 0. \tag{4.5}$$

Additionally, the optimal control triple (u_1^*, u_2^*, u_3^*) *that minimize* Γ *over* Φ_2 *satisfy the optimality condition*

$$\left.\begin{aligned} u_1^* &= \max\left\{0, \min\left(1, \frac{\beta_{vh}\vartheta(\lambda_2^* - \lambda_1^*)I_v^* S_h^*}{A_1}\right)\right\} \\ u_2^* &= \max\left\{0, \min\left(1, \frac{\eta(\lambda_3^* + \rho(\lambda_1^* - \lambda_4^*) - \lambda_1^*)I_h^*}{A_2}\right)\right\} \\ u_3^* &= \max\left\{0, \min\left(1, \frac{\tau(\lambda_5^* S_v^* + \lambda_6^* E_v^* + \lambda_7^* I_v^*)}{A_3}\right)\right\} \end{aligned}\right\}. \tag{4.6}$$

Proof. The adjoint equations can be determined by using the differential equations governing the adjoint variables. The Hamiltonian function H, is differentiated with respect to $S_h, E_h, I_h, R_h, S_v, E_v$ and I_v and evaluated at the optimal control. The

adjoint equations are given by

$$\left.\begin{aligned}
-\frac{d\lambda_1^*}{dt} = \frac{\partial H}{\partial S_h} &= \left[\frac{-(1-u_1)\beta_{vh}\vartheta I_v}{N_h} + \frac{(1-u_1)\beta_{vh}\vartheta I_v S_h}{N_h^2} - \mu_1\right]\lambda_1 \\
&+ \left[\frac{(1-u_1)\beta_{vh}\vartheta I_v}{N_h} - \frac{(1-u_1)\beta_{vh}\vartheta I_v S_h}{N_h^2}\right]\lambda_2 + \frac{\beta_{hv}\vartheta I_h S_v}{N_h^2}\lambda_5 \\
&- \frac{\beta_{hv}\vartheta I_h S_v}{N_h^2}\lambda_6 \\
-\frac{d\lambda_2^*}{dt} = \frac{\partial H}{\partial E_h} &= \frac{(1-u_1)\beta_{vh}\vartheta I_v S_h}{N_h^2}\lambda_1 - \left[\frac{(1-u_1)\beta_{vh}\vartheta I_v S_h}{N_h^2} + (\alpha_h+\mu_h)\right]\lambda_2 \\
&+ \alpha_h\lambda_3 + \frac{\beta_{hv}\vartheta I_h S_v}{N_h^2}\lambda_5 - \frac{\beta_{hv}\vartheta I_h S_v}{N_h^2}\lambda_6 + C_1 \\
-\frac{d\lambda_3^*}{dt} = \frac{\partial H}{\partial I_h} &= \left[(\phi+\eta u_2)(1-\rho) + \frac{(1-u_1)\beta_{vh}\vartheta I_v S_h}{N_h^2}\right]\lambda_1 \\
&- \frac{(1-u_1)\beta_{vh} I_v S_h}{N_h^2}\lambda_2 - (\phi+\eta u_2+\mu_h+\delta_h)\lambda_3 \\
&+ (\phi+\eta u_2)\rho\lambda_4 + \left[\frac{\beta_{hv}\vartheta I_h S_v}{N_h^2} - \frac{\beta_{hv}\vartheta S_v}{N_h}\right]\lambda_5 \\
&+ \left[\frac{\beta_{hv}\vartheta S_v}{N_h} - \frac{\beta_{hv}\vartheta I_h S_v}{N_h^2}\right]\lambda_6 + C_2 \\
-\frac{d\lambda_4^*}{dt} = \frac{\partial H}{\partial R_h} &= \left[\frac{(1-u_1)\beta_{vh}\vartheta I_v S_h}{N_h^2} + \psi\right]\lambda_1 - \frac{(1-u_1)\beta_{vh}\vartheta I_v S_h}{N_h^2}\lambda_2 \\
&+ (\mu_h+\psi)\lambda_4 + \frac{\beta_{hv}\vartheta I_h S_v}{N_h^2}\lambda_5 - \frac{\beta_{hv}\vartheta I_h S_v}{N_h^2}\lambda_6 \\
-\frac{d\lambda_5^*}{dt} = \frac{\partial H}{\partial S_v} &= \left[\frac{-(1-u_1)\beta_{hv}\vartheta I_h}{N_h} - (\mu_v+\tau u_3)\right]\lambda_5 + \frac{\beta_{hv}\vartheta I_h}{N_h}\lambda_6 + C_3 \\
-\frac{d\lambda_6^*}{dt} = \frac{\partial H}{\partial E_v} &= -(\alpha_h+\mu_v+\tau u_3)\lambda_6 + \alpha_v\lambda_7 + C_3 \\
-\frac{d\lambda_7^*}{dt} = \frac{\partial H}{\partial I_v} &= \frac{-(1-u_1)\beta_{vh}\vartheta S_h}{N_h}\lambda_1 + \frac{(1-u_1)\beta_{vh}\vartheta S_h}{N_h}\lambda_2 - (\mu_v+\tau u_3)\lambda_7 + C_3
\end{aligned}\right\},$$

with the transversality conditions

$$\lambda_1^*(T_f) = \lambda_2^*(T_f) = \lambda_3^*(T_f) = \lambda_4^*(T_f) = \lambda_5^*(T_f) = \lambda_6^*(T_f) = \lambda_7^*(T_f) = 0.$$

Solving $\dfrac{\partial H}{\partial u_1} = 0$, $\dfrac{\partial H}{\partial u_2} = 0$ and $\dfrac{\partial H}{\partial u_3} = 0$, and evaluating at the optimal control on the interior of the control set, where $0 < u_i < 1$, for $i = 1, 2, 3$ and letting

$S_h = S_h^*,\ E_h = E_h^*,\ I_h = I_h^*,\ R_h = R_h^*,\ S_v = S_v^*,\ E_v = E_v^*,\ I_v = I_v^*$ yields

$$\left.\begin{aligned} \frac{\partial H}{\partial u_1} &= A u_1^* + \beta_{vh}\vartheta\lambda_1^* I_v^* S_h^* - \beta_{vh}\vartheta\lambda_2^* I_v^* S_h^* = 0 \\ \frac{\partial H}{\partial u_2} &= A_2 u_2 + (1-\rho)\eta\lambda_1^* I_h^* - \eta\lambda_3^* I_h^* + \eta\rho\lambda_4^* I_h^* = 0 \\ \frac{\partial H}{\partial u_3} &= A_3 u_3^* - \tau\lambda_5^* S_v^* - \tau\lambda_6^* E_v^* - \tau\lambda_7^* I_v^* = 0 \end{aligned}\right\}, \tag{4.7}$$

from which we obtain the following optimal controls

$$\left.\begin{aligned} u_1^* &= \frac{\beta_{vh}\vartheta(\lambda_2^* - \lambda_1^*) I_v^* S_h^*}{A_1} \\ u_2^* &= \frac{\eta(\lambda_3^* + \rho(\lambda_1^* - \lambda_4^*) - \lambda_1^*) I_h^*}{A_2} \\ u_3 &= \frac{\tau(\lambda_5^* S_v^* + \lambda_6^* E_v^* + \lambda_7^* I_v^*)}{A_3} \end{aligned}\right\}. \tag{4.8}$$

Then the optimal controls are characterized as

$$\left.\begin{aligned} u_1^* &= \max\left\{0, \min\left(1, \frac{\beta_{vh}\vartheta(\lambda_2^* - \lambda_1^*) I_v^* S_h^*}{A_1}\right)\right\} \\ u_2^* &= \max\left\{0, \min\left(1, \frac{\eta(\lambda_3^* + \rho(\lambda_1^* - \lambda_4^*) - \lambda_1^*) I_h^*}{A_2}\right)\right\} \\ u_3^* &= \max\left\{0, \min\left(1, \frac{\tau(\lambda_5^* S_v^* + \lambda_6^* E_v^* + \lambda_7^* I_v^*)}{A_3}\right)\right\} \end{aligned}\right\}.$$

We achieve the uniqueness of the optimal control for small T_f due to the prior boundedness of the state system, adjoint functions and the resulting Lipschitz structure of the ordinary differential equations. The uniqueness of the optimal control triple trails from the uniqueness of the optimal system, which consists of the state system (3.1), with initial conditions, the co-state (adjoint) system (4.4), with the terminal conditions (4.5), with characterization of the optimal control conditions (4.6). □

The optimality system is comprised of the state system (3.1), the adjoint system (4.4), initial conditions at $t = 0$, boundary conditions (4.5), and the characterization

of the optimal control (4.6). Therefore 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, and u_3 respectively are positive indicates that the optimal problem is a minimum at controls u_1^*, u_2^* and u_3^*. Substituting u_1^*, u_2^* and u_3^* in the system (3.1), we obtain strategies:

$$\left.\begin{aligned}
\frac{dS_h^*}{dt} &= \Lambda_h + (1-\kappa_1)\theta + (\phi+\eta u_2)(1-\rho)I_h^* \\
&\quad - \beta_{vh}\vartheta I_v^* S_h^* \left(1 - \max\left\{0, \min\left(1, \frac{\beta_{vh}\vartheta(\lambda_2^* - \lambda_1^*)I_v^* S_h^*}{A_1}\right)\right\}\right) \\
&\quad - \mu_h S_h^* + \psi R_h^* \\
\frac{dE_h^*}{dt} &= \beta_{vh}\vartheta I_v^* S_h^* \left(1 - \max\left\{0, \min\left(1, \frac{\beta_{vh}\vartheta(\lambda_2^* - \lambda_1^*)I_v^* S_h^*}{A_1}\right)\right\}\right) \\
&\quad + \kappa_1\theta - \alpha_h E_h^* - \mu_h E_h^* \\
\frac{dI_h^*}{dt} &= \alpha_h E_h^* - \left(\phi + \eta\left(\max\left\{0, \min\left(1, \frac{\eta(\lambda_3^* + \rho(\lambda_1^* - \lambda_4^*) - \lambda_1^*)I_h^*}{A_2}\right)\right\}\right)\right. \\
&\quad \left. + \mu_h + \delta_h\right) I_h^* \\
\frac{dR_h^*}{dt} &= \left(\phi + \eta\left(\max\left\{0, \min\left(1, \frac{\eta(\lambda_3^* + \rho(\lambda_1^* - \lambda_4^*) - \lambda_1^*)I_h^*}{A_2}\right)\right\}\right)\right)\rho I_h \\
&\quad - (\mu_h + \psi)R_h \\
\frac{dS_v^*}{dt} &= \Lambda_v - \left(\mu_v + \tau\left(\max\left\{0, \min\left(1, \frac{\tau(\lambda_5^* S_v^* + \lambda_6^* E_v^* + \lambda_7^* I_v^*)}{A_3}\right)\right\}\right)\right) S_v^* \\
&\quad - \beta_{hv}\vartheta I_h^* S_v^* \\
\frac{dE_v^*}{dt} &= \beta_{hv}\vartheta I_h^* S_v^* - \left(\mu_v + \tau\left(\max\left\{0, \min\left(1, \frac{\tau(\lambda_5^* S_v^* + \lambda_6^* E_v^* + \lambda_7^* I_v^*)}{A_3}\right)\right\}\right)\right) \\
&\quad E_v^* - \alpha_v E_v^* \\
\frac{dI_v^*}{dt} &= \alpha_v E_v - \left(\mu_v + \tau\left(\max\left\{0, \min\left(1, \frac{\tau(\lambda_5^* S_v^* + \lambda_6^* E_v^* + \lambda_7^* I_v^*)}{A_3}\right)\right\}\right)\right) I_v^*
\end{aligned}\right\}, \tag{4.9}$$

with H^* at $(t, S_h^*, E_h^*, I_h^*, R_h^*, u_1^*, u_2^*, u_3^*, \lambda_1^*, \lambda_2^*, \cdots, \lambda_7^*)$:

$$\left.\begin{aligned} H^* &= C_1 E_h + C_2 I_h + C_3 N_v \\ &\quad + \frac{1}{2}\left[A_1 \left(\max\left\{0, \min\left(1, \frac{\beta_{vh}\vartheta(\lambda_2^* - \lambda_1^*) I_v^* S_h^*}{A_1}\right)\right\}\right)^2 \right. \\ &\quad + A_2 \left(\max\left\{0, \min\left(1, \frac{\eta(\lambda_3^* + \rho(\lambda_1^* - \lambda_4^*) - \lambda_1^*) I_h^*}{A_2}\right)\right\}\right)^2 \\ &\quad \left. + A_3 \left(\max\left\{0, \min\left(1, \frac{\tau(\lambda_5^* S_v^* + \lambda_6^* E_v^* + \lambda_7^* I_v^*)}{A_3}\right)\right\}\right)^2 \right] \\ &\quad + \lambda_1^* \frac{dS_h^*}{dt} + \lambda_2^* \frac{dE_h^*}{dt} + \lambda_3^* \frac{dI_h^*}{dt} + \lambda_4^* \frac{dR_h^*}{dt} + \lambda_5^* \frac{dS_v^*}{dt} \\ &\quad + \lambda_6^* \frac{dE_v^*}{dt} + \lambda_7^* \frac{dI_v^*}{dt} \end{aligned}\right\}. \quad (4.10)$$

We solve the system (4.9) and (4.10) numerically to determine the optimal control and the state.

4.4 Numerical results on optimal control analysis

In this section we discuss the method and present the results obtained from solving the optimality system numerically. The parameter values used in this section are from Table 6.12. The initial state variables are chosen as $S_h(0) = 360$, $E_h(0) = 30$, $I_h(0) = 10$, $R_h(0) = 10$, $S_v(0) = 960$, $E_v(0) = 30$, and $I_v(0) = 40$. The following weight factors $A_1 = 20, A_2 = 65, A_3 = 10, C_1 = 100, C_2 = 92$, and $C_3 = 20$ 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 4.1 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 $C_3 < C_2 < C_1$. We assign the weight factor u_1 when using ITNs greater than the weight factors for treatment u_2 and IRS u_3. This assumptions is based on the cost associated with u_1 which includes buying of

bed-nets, buying of insecticide chemicals, labor cost on treating bed-nets, educating the community on the importance of sleeping under the treated mosquito nets and expenses on the supplying of ITNs, the cost associated with treatment are medical examinations and antimalarial drugs. The prevention strategy IRS is associated with cost of insecticide chemical and labor cost on spraying the houses.

4.4.1 Effective reproduction numbers as functions of the intervention strategies

Here we consider the optimal control values of the three intervention strategies namely: ITNs, IRS and treatment which are common strategies in Karonga District, Malawi. The effective reproduction number 3.23 is plotted against the control functions 4.8 in which unity is regarded as perfect, effective prevention and treatment while zero is considered as unavailability of prevention and treatment in a community. The objective here is to determine, using the threshold quantity $\mathcal{R}_e$, (3.23) whether or not treating those in the infected malaria stage (modelled by u_2) can lead to elimination of the disease in the community. We also determine the effect of using preventive strategies such as long lasting insecticide treated nets (LLITNs) (modelled by u_1) and using indoor residual spraying (IRS) (modelled by u_3) on population growth.

$$\lim_{u_1 \to 1} \mathcal{R}_e = 0, \tag{4.11}$$

$$\lim_{u_2 \to 1} \mathcal{R}_e = 0, \tag{4.12}$$

$$\lim_{u_3 \to 1} \mathcal{R}_e = 0, \tag{4.13}$$

while

$$\lim_{u_1 \to 1} \mathcal{R}_e = 0, \tag{4.14}$$

$$\lim_{u_2 \to 1} \mathcal{R}_e = \sqrt{\frac{\alpha_h \alpha_v \beta_{hv} \beta_{vh} \Lambda_v \mu_h \left(1 - u_1\right) \vartheta^2}{(\alpha_h + \mu_h)(\theta + \Lambda_h) \left(\mu_v + \tau u_3\right)^2 (\delta_h + \eta + \mu_h + \phi) \left(\alpha_v + \mu_v + \tau u_3\right)}}, \tag{4.15}$$

$$\lim_{u_3 \to 1} \mathcal{R}_e = \sqrt{\frac{\alpha_h \alpha_v \beta_{hv} \beta_{vh} \Lambda_v \mu_h \left(1 - u_1\right) \vartheta^2}{(\alpha_h + \mu_h)(\theta + \Lambda_h)(\mu_v + \tau)^2 (\alpha_v + \mu_v + \tau) \left(\delta_h + \mu_h + \eta u_2 + \phi\right)}}. \tag{4.16}$$

Thus, a sufficient effective malaria treatment or preventive program that focuses on infected individuals (at a high rate, $u_2 \to 1$) or preventive strategy that focuses on the susceptible (at a rate $u_1 \to 1$), respectively, can lead to effective control. The profiles of $\mathcal{R}_e$ as a function of treatment rate u_2 and interventions u_1 with u_3, are shown in Figure 4.1. For the set of parameters used in the model simulation, it is evident that the insecticide treated nets (ITNs) or long lasting insecticide treated nets (LLTINs) can dramatically reduce $\mathcal{R}_e$. As we intensify treatment strategies ($u_1 \to 1$), $\mathcal{R}_e \to 0$. Figure 4.2 shows the comparisons of the intervention strategies strengths.

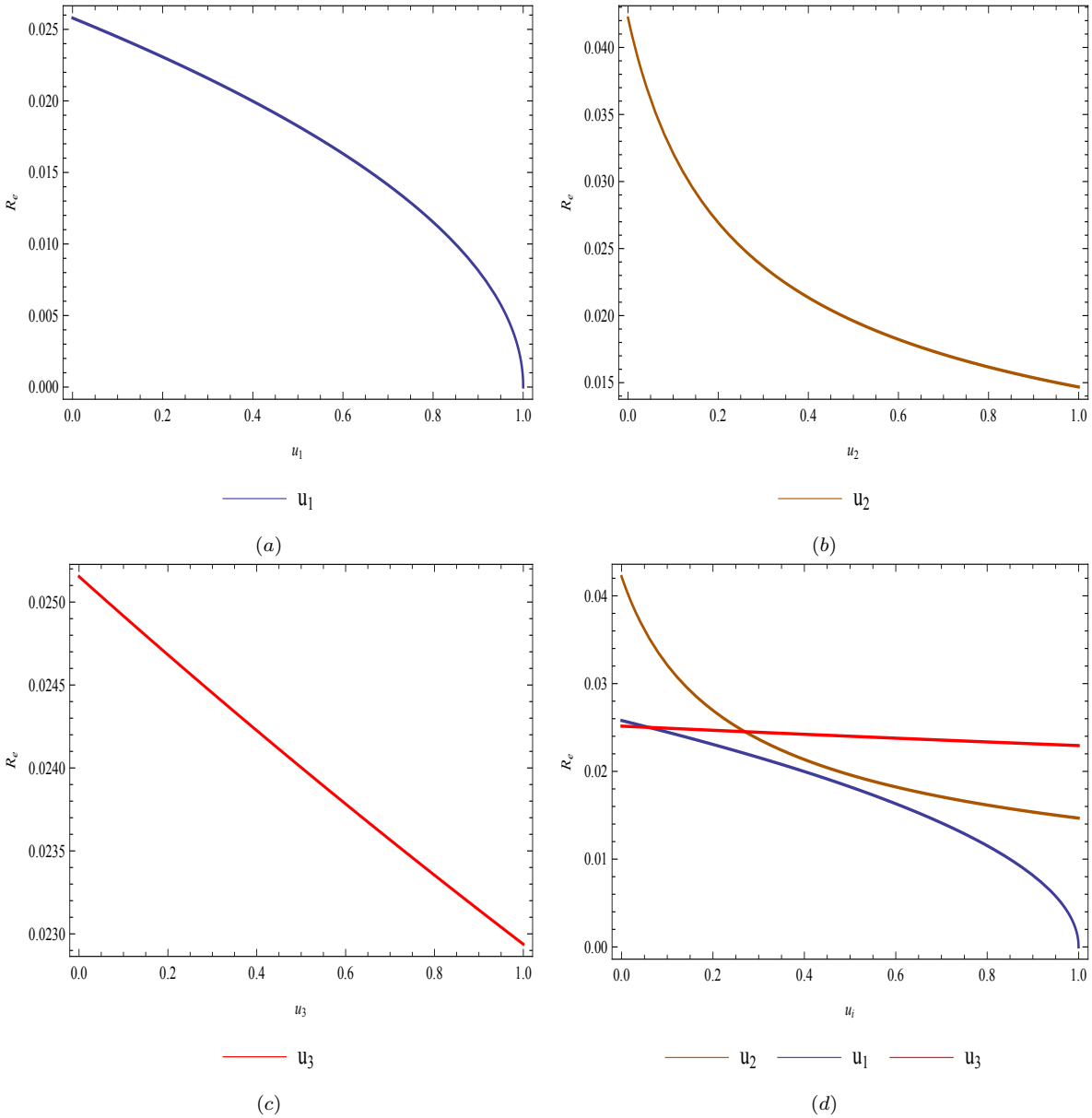


Figure 4.1: The malaria reproduction number $\mathcal{R}_e$ as a function of intervention. (a) strategy using LLITNs, (b) using treatment of malaria, (c) using IRS, and (d) all the strategies effectiveness with $i = (1, 2, 3)$. Plotted using parameters from Table 6.12.

The effectiveness of the intervention strategies is assessed in relation to the effective reproduction number. Different combination of the intervention strategies are set

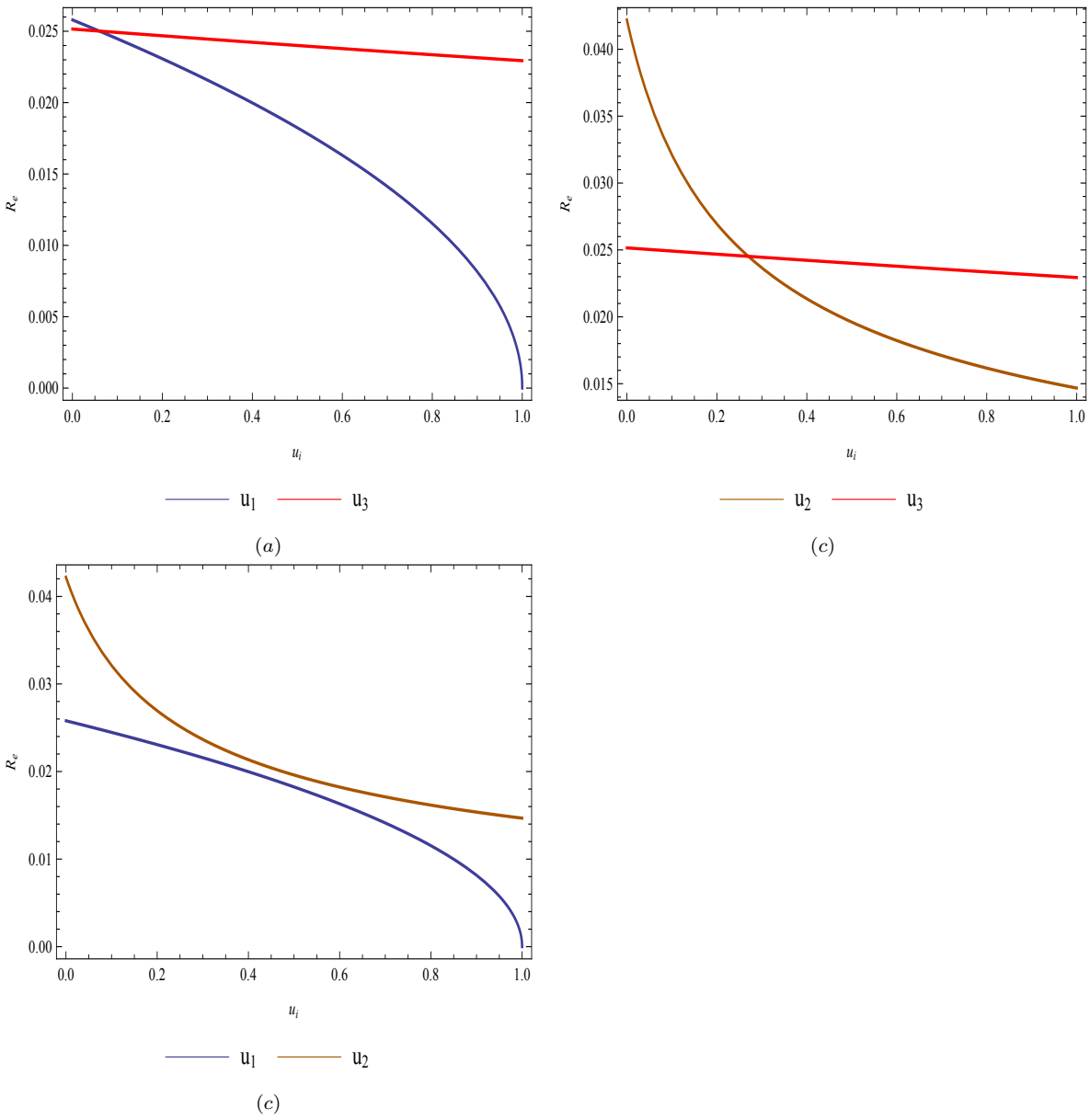


Figure 4.2: The malaria reproduction number $\mathcal{R}_e$ as a function of intervention. (a) LLITNs vs treatment with $i = (1, 3)$, (b) LLTINs vs IRS with $i = (2, 3)$, and (c) treatment vs IRS with $(i = 1, 2)$. The graphs are drawn using parameters from Table 6.12.

(see Figure 4.2 (a), (b), (c) and (d)). The combinations indicate that as the intervention demand increases, there is a decrease of the reproduction number, evidencing the decrease of malaria disease in the community. The most effective and needed intervention strategy can easily be identified within combination of the strategies. The results lead to the best strategy.

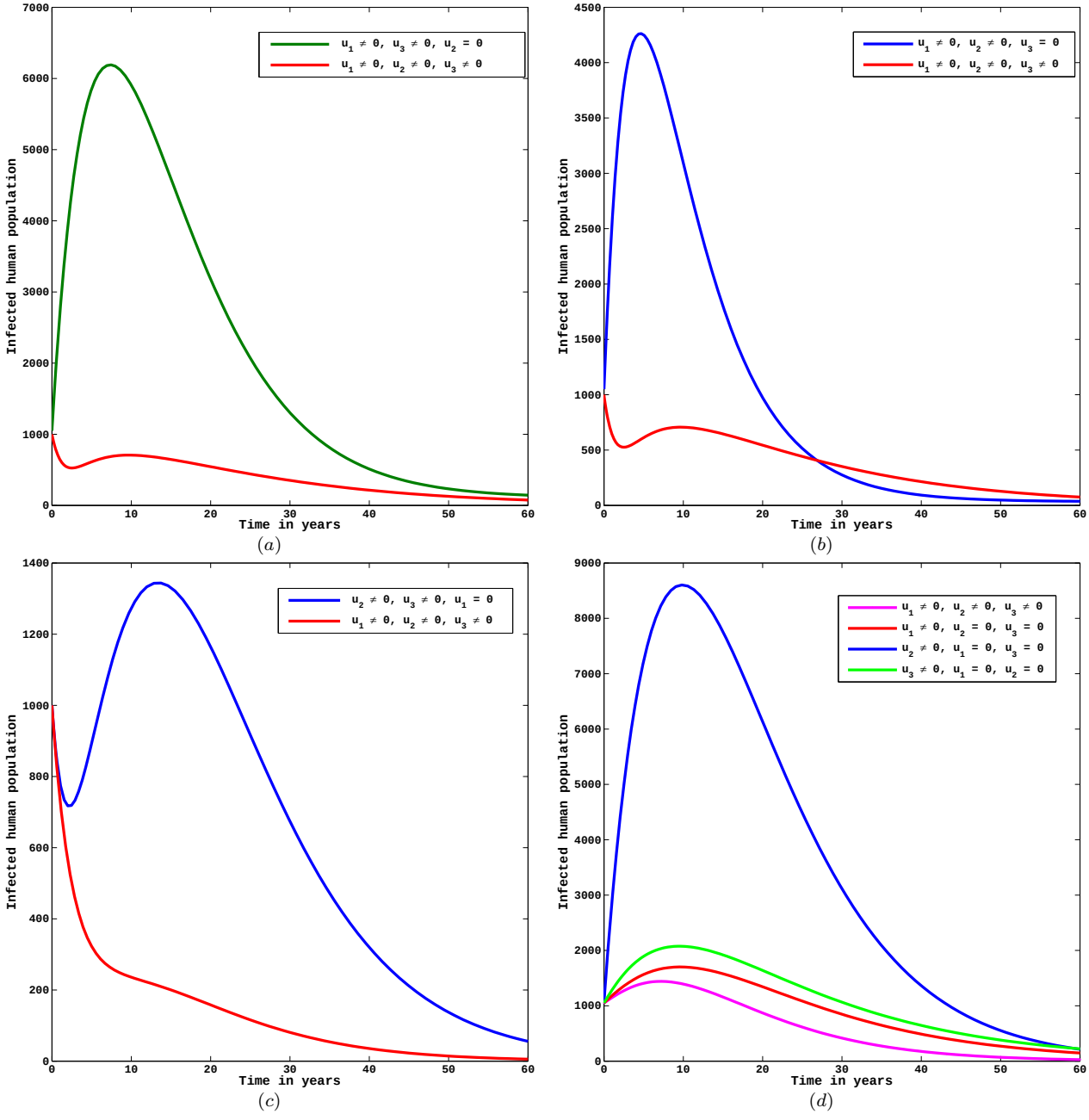


Figure 4.3: The model 3.2 is displaying effects of intervention measures with initial state variables $S_h(0) = 12000$, $E_h(0) = 1050$, $I_h(0) = 1000$, $R_h(0) = 800$, $S_v(0) = 1500$, $E_v(0) = 1100$, and $I_v(0) = 900$. The parameters remain the same as those in Table 6.12.

The model with intervention strategies (3.1) is analyzed with availability of one or

two intervention strategies and setting the other strategies equal to zero. Different initial values have been used in order to find the effects of intervention strategies in a large population with long time interval. We see that if the three intervention strategies are effectively implemented and used, the results show that there is positive impact compared to having ITNs and IRS (u_1 and u_3 respectively) as the only intervention strategies in the community (see Figure 4.3(a)). The initial increase in the infected human population in the graph with interventions of ITNs and IRS, may be due to the fact that some people refused to have their houses sprayed with insecticide chemicals due to their primitive traditional beliefs. In addition, as Karonga District is along the shore of Lake Malawi, some members of the community do not use ITNs owing to negative beliefs on the chemicals used and also due to hot weather in the districts. On the other hand, the district is waterlogged; hence this leads to an increase in the breeding of mosquitoes.

Similar results appear in Figure 4.3(b) where the impact of the campaigned intervention strategies are compared with the use of ITNs (u_1) and treatment (u_2). The results show that the concurrent administered intervention strategies lead to a decrease in the number of infected human population much faster than when ITNs and treatment are used as the only intervention strategies in the community. A similar occurrence is observed when IRS (u_3) and treatment (u_2) are used as the only means of intervention strategies in the society (see Figure 4.3(c)).

In addition, we also looked at the effects of these intervention measures as a stand alone approach of preventing or controlling malaria disease in the society. Figure 4.3(d) depicts the comparison of the effects of each intervention strategy and the effect of multi-intervention strategies. This figure indicates that if the three intervention measures are effectively practised, the infected human population is

much lower compared to a situation where only one intervention strategy is used. The graph of treatment (u_2) practised as the only means of intervention measure, shows a high number of infected human population owing to a number of reasons. One of the reasons is that in this situation, the mosquito population is unaffected; hence the infected mosquitoes will still be available in the community causing more infections to susceptible humans. Furthermore, most people in the area do not visit the nearby dispensary or hospital for medication when they observe signs or symptoms of malaria disease since they need to cover long distances to reach the hospital. The interview conducted revealed that some individuals opt for using the medication left by the previous patient or they buy medicines from the shops and use it before being diagnosed. Hence the reason why treatment needs to be consolidated with preventive measures such as ITNs and IRS for optimal control.

The epidemiological implication of the above result is that malaria could be eliminated from the community if prevention and treatment can lead to a situation where $\mathcal{R}_e$ is less than unity. However, other factors need to be considered.

In the chapter 5 we look at cost effective analysis by using optimal control theory by developing the objective function and the corresponding Hamiltonian equation.

Chapter 5

Cost effective analysis of malaria model with intervention strategies

After using the optimal control to investigate the optimality of the intervention strategies being practised in Karonga District, Malawi, we now carry out an economic evaluation of the strategies by performing a cost-effectiveness study to determine the most cost-effective combination of the three intervention strategies namely ITNs, treatment effort of infected individuals and IRS. Program evaluation can be effectively assessed by using the economic tools such cost-benefit analysis (CBA) and cost-effectiveness analysis (CEA). Cost-effectiveness analysis will be applied in this study as a tool or technique that relates the costs of a program such as the campaign for prevention and treatment of malaria to its key outcomes (health effects of an intervention strategies) such as a disease free and beneficial community or nation. The analysis is undertaken in order to assess the extent to which the intervention strategies are beneficial and cost effective. We aim at maximizing the level of benefits (health effects) relative to the level of resources available.

5.1 Economic assessment

The economic estimation for all three intervention techniques will be 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. This can be achieved by using the following cost objective function

$$\left.\begin{aligned} E_c(u_1,u_2,u_3) \;=\; & \min_{(u_1,u_2,u_3)\in\Phi_2} \int_0^{T_f} [b_1u_1(t)(S_h(t)+E_h(t)) + b_2\eta u_2(t)I_h(t) \\ & + b_3\tau u_3(t)N_v(t)]\, e^{-\varphi t}dt \end{aligned}\right\}, \tag{5.1}$$

subject to the system of differential equations (3.1), where b_1 denotes the per capita cost of ITNs u_1 which takes in account surveillance, the administration and educating the community; b_2 denotes the per capita cost of treating an individual who has malaria u_2 includes screening patients, administering drug intake and outpatients' conditions and patients in hospitals, and b_3 represents the per capita area cost of IRS effort u_3 which includes administrations and spraying houses. The compartments of the model which are highly affected by the use of ITNs 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 has been exponentially considered with a parameter φ. The Lagrangian of the cost objective function is

$$L_b = [b_1u_1(t)S_h(t) + b_1u_1(t)E_h(t) + b_2\eta u_2(t)I_h(t) + b_3\tau u_3(t)N_v(t)]\, e^{-\varphi t}.$$

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

$$H_b = L_b + \lambda_1^*\frac{dS_h}{dt} + \lambda_2^*\frac{dE_h}{dt} + \lambda_3^*\frac{dI_h}{dt} + \lambda_4^*\frac{dR_h}{dt} + \lambda_5^*\frac{dS_v}{dt} + \lambda_6^*\frac{dE_v}{dt} + \lambda_7^*\frac{dI_v}{dt}.$$

The developed corresponding Hamiltonian equation is as follows;

$$\left.\begin{aligned} H_b &= [b_1u_1(S_h(t)+E_h(t)) + b_2\eta u_2 I_h(t) + b_3\tau u_3 N_v(t)]\, e^{-\varphi t} \\ &+ \{\Lambda_h + (1-\kappa_1)\theta + (\phi+\eta u_2)(1-\rho)I_h(t) \\ &- \frac{(1-u_1)\beta_{vh}\vartheta I_v(t)S_h(t)}{N_h(t)} - \mu_h S_h(t) + \psi R_h(t)\Big\}\lambda_1^* \\ &+ \left\{\frac{(1-u_1)\beta_{vh}\vartheta I_v(t)S_h(t)}{N_h(t)} + \kappa_1\theta - (\alpha_h+\mu_h)E_h(t)\right\}\lambda_2^* \\ &+ \{\alpha_h E_h(t) - (\phi+\eta u_2+\mu_h+\delta_h)I_h(t)\}\,\lambda_3^* \\ &+ \{(\phi+\eta u_2)\rho I_h(t) - (\mu_h+\psi)R_h(t)\}\,\lambda_4^* \\ &+ \left\{\Lambda_v - \frac{\beta_{hv}\vartheta I_h(t)S_v(t)}{N_h(t)} - (\mu_v+\tau u_3)S_v(t)\right\}\lambda_5^* \\ &+ \left\{\frac{\beta_{hv}\vartheta I_h(t)S_h(t)}{N_h(t)} - (\alpha_h+\mu_v+\tau u_3)E_v(t)\right\}\lambda_6^* \\ &+ \{\alpha_v E_v(t) - (\mu_v+\tau u_3)I_v(t)\}\,\lambda_7^* \end{aligned}\right\}, \qquad (5.2)$$

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 $i = (1, 2, \ldots, 7)$ represent the changes in the objective value of an optimal solution of an optimization problem by relaxing the constraint by one unit [90]. These can be calculated by using Pontryagin's Maximum Principle as we did previously and give

$$\begin{aligned} \frac{d\lambda_1^*}{dt} &= -\frac{\partial H_b}{\partial S_h},\ \frac{d\lambda_2^*}{dt} = -\frac{\partial H_b}{\partial E_h},\ \frac{d\lambda_3^*}{dt} = -\frac{\partial H_b}{\partial I_h},\ \frac{d\lambda_4^*}{dt} = -\frac{\partial H_b}{\partial R_h}, \\ \frac{d\lambda_5^*}{dt} &= -\frac{\partial H_b}{\partial S_v},\ \frac{d\lambda_6^*}{dt} = -\frac{\partial H_b}{\partial E_v},\ \frac{d\lambda_7^*}{dt} = -\frac{\partial H_b}{\partial I_v}. \end{aligned}$$

Hence using the Hamiltonian equation (5.2) gives

$$\left.\begin{aligned}
\frac{d\lambda_1^*}{dt} &= -\frac{\partial H_b}{\partial S_h} = -\ b_1 u_1 e^{-\varphi t} \\
&+ \left(\frac{(1-u_1)\beta_{vh}\vartheta I_v}{N_h} - \frac{(1-u_1)\beta_{vh}\vartheta I_v S_h}{N_h^2} + \mu_h\right)\lambda_1^* \\
&- \left(1 - \frac{S_h}{N_h}\right)\frac{(1-u_1)\beta_{vh}\vartheta I_v}{N_h}\lambda_2^* - \frac{\beta_{hv}\vartheta I_h S_v}{N_h^2}(\lambda_5^* - \lambda_6^*) \\
\frac{d\lambda_2^*}{dt} &= -\frac{\partial H_b}{\partial E_h} = -\ b_1 u_1 e^{-\varphi t} - \frac{(1-u_1)\beta_{vh}\vartheta I_v S_h}{N_h^2}\lambda_1^* \\
&+ \left(\frac{(1-u_1)\beta_{vh}\vartheta I_v S_h}{N_h^2} + \alpha_h + \mu_h\right)\lambda_2^* - \frac{\beta_{hv}\vartheta I_h S_v}{N_h^2}(\lambda_5^* - \lambda_6^*) \\
\frac{d\lambda_3^*}{dt} &= -\frac{\partial H_b}{\partial I_h} = -\left((\phi + \eta u_2)(1-\rho) - \frac{(1-u_1)\beta_{vh}\vartheta I_v S_h}{N_h^2}\right)\lambda_1^* \\
&- b_2\eta u_2 e^{-\varphi t} + \left(\frac{\beta_{hv}\vartheta S_v}{N_h} - \frac{\beta_{hv}\vartheta I_h S_v}{N_h^2}\right)(\lambda_5^* - \lambda_6^*) \\
\frac{d\lambda_4^*}{dt} &= -\frac{\partial H_b}{\partial R_h} = -\left(\frac{(1-u_1)\beta_{vh}\vartheta I_v S_h}{N_h^2} - \psi\right)\lambda_1^* + (\mu_h + \psi)\lambda_3^* \\
&+ \frac{(1-u_1)\beta_{vh}\vartheta I_v S_h}{N_h^2}\lambda_2^* - \frac{\beta_{hv}\vartheta I_h S_v}{N_h^2}(\lambda_5^* - \lambda_6^*) \\
\frac{d\lambda_5^*}{dt} &= -\frac{\partial H_b}{\partial S_v} = -\ b_3\tau u_3 e^{-\varphi t} + \left(\frac{\beta_{hv}\vartheta I_h}{N_h} + \mu_v + \tau u_3\right)\lambda_5^* - \frac{\beta_{hv}\vartheta I_h}{N_h}\lambda_6^* \\
\frac{d\lambda_6^*}{dt} &= -\frac{\partial H_b}{\partial E_v} = -\ b_3\tau u_3 e^{-\varphi t} + (\alpha_v + \mu_v + \tau u_3)\lambda_6^* - \alpha_v\lambda_7^* \\
\frac{d\lambda_7^*}{dt} &= -\frac{\partial H_b}{\partial I_v} = -\ b_3\tau u_3 e^{-\varphi t} + \frac{(1 - u_1\beta_{vh}\vartheta S_h)}{N_h}(\lambda_1^* - \lambda_2^*) + (\mu_v + \tau u_3)\lambda_7^*
\end{aligned}\right\}.$$

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

5.1.1 Economic estimation 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

$$\frac{\partial H_b}{\partial u_1} = b_1 e^{-\varphi t}(S_h(t) + E_h(t)) + \frac{\beta_{vh}\vartheta I_v(t) S_h(t)}{N_h(t)}(\lambda_1^* - \lambda_2^*),$$

in which $\frac{\beta_{vh}\vartheta I_v(t) S_h(t)}{N_h(t)}(\lambda_1^* - \lambda_2^*)$ is the total marginal benefit due to the use of ITNs while $b_1(S_h(t) + E_h(t))$ 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;

$$u_1(t) = \begin{cases} 0 & \text{if} \quad b_1 e^{-\varphi t}(S_h + E_h) > \dfrac{\beta_{vh}\vartheta I_v S_h}{N_h}(\lambda_1^* - \lambda_2^*), \\ (0,1) & \text{if} \quad b_1 e^{-\varphi t}(S_h + E_h) = \dfrac{\beta_{vh}\vartheta I_v S_h}{N_h}(\lambda_1^* - \lambda_2^*), \\ 1 & \text{if} \quad b_1 e^{-\varphi t}(S_h + E_h) < \dfrac{\beta_{vh}\vartheta I_v S_h}{N_h}(\lambda_1^* - \lambda_2^*). \end{cases} \tag{5.3}$$

The third equation of (5.3), 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.

5.1.2 Economic appraisal 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, (5.2) is differentiated with respect to $u_2(t)$, giving;

$$\frac{\partial H_b}{\partial u_2} = b_2 \eta I_h e^{-\varphi t} + \eta I_h((1-\rho)\lambda_1^* - \lambda_3^* + \rho\lambda_4^*),$$

in which $b_2\eta I_h$ is the marginal cost and $\eta I_h((1-\rho)\lambda_1^* - \lambda_3^* + \rho\lambda_4^*)$ is the marginal benefit of treating infectious individuals. Hence;

$$u_2(t) = \begin{cases} 0 & \text{if} \quad b_2 \eta I_h e^{-\varphi t} > \eta I_h((1-\rho)\lambda_1^* - \lambda_3^* + \rho\lambda_4^*), \\ (0,1) & \text{if} \quad b_2 \eta I_h e^{-\varphi t} = \eta I_h((1-\rho)\lambda_1^* - \lambda_3^* + \rho\lambda_4^*), \\ 1 & \text{if} \quad b_2 \eta I_h e^{-\varphi t} < \eta I_h((1-\rho)\lambda_1^* - \lambda_3^* + \rho\lambda_4^*). \end{cases} \tag{5.4}$$

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 (5.4) all infected individuals must look for full treatment if the marginal benefit, $\eta I_h((1-\rho)\lambda_1^* - \lambda_3^* + \rho\lambda_4^*)$, must be greater than the marginal cost, $b_2\eta I_h e^{-\varphi t}$, for being treated. Otherwise, only few infected individuals will look for treatment.

5.1.3 Economic evaluation of IRS

Insecticide residual spraying (IRS) prevention parameter in the system (3.2) and in the Hamiltonian equation, H_b, (5.2) is $u_3(t)$. Then differentiating H_b with respect to u_3 gives

$$\frac{\partial H_b}{\partial u_3} = b_3\tau(S_v + E_v + I_v)e^{-\varphi t} - \tau(S_v\lambda_5^* + E_v\lambda_6^* + I_h\lambda_7^*),$$

where $b_3\tau(S_v + E_v + I_v)$ is the marginal cost for IRS and $\tau(S_v\lambda_5^* + E_v\lambda_6^* + I_h\lambda_7^*)$ 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

$$u_3(t) = \begin{cases} 0 & \text{if} \quad b_3\tau(S_v + E_v + I_v) > \tau(S_v\lambda_5^* + E_v\lambda_6^* + I_v\lambda_7^*), \\ (0,1) & \text{if} \quad b_3\tau(S_v + E_v + I_v) = \tau(S_v\lambda_5^* + E_v\lambda_6^* + I_v\lambda_7^*), \\ 1 & \text{if} \quad b_3\tau(S_v + E_v + I_v) < \tau(S_v\lambda_5^* + E_v\lambda_6^* + I_v\lambda_7^*). \end{cases} \tag{5.5}$$

The spraying of insecticides against mosquitoes is optimal for malaria disease control if the marginal cost $b_3\tau(S_v(t) + E_v(t) + I_v(t))$, is less than the marginal benefit, $\tau(S_v(t)\lambda_5^* + E_v(t)\lambda_6^* + I_v(t)\lambda_7^*)$.

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

5.1.4 Numerical evaluation of cost effectiveness analysis

Cost-effectiveness is only one of a number of criteria that should be employed in determining whether intervention strategies are made available. The cost-effectiveness analysis has been defined by the National Institute for Health and Clinical Excellence (NICE) [81] as an economic study in which consequences of different interventions are measured using a single outcome, usually in natural units such as life-years gained, death avoided, heart attacks avoided or cases detected. 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 [81, 94]. This analysis helps to decide the most cost effective measure to use against malaria (ITNs only, treatment only, IRS and combination of the strategies).

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. 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 our goal on the comparison of 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. The ICER provides an opportunity to help contain healthcare costs without adverse health consequences. It also provides policymakers with information on where resources should be allocated when these are limited. This technique requires 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 should be compared with the next less effective alternative intervention strategy when relating two or more competing intervention strategies. 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 for instance total number of infections avoided, number of susceptibility cases prevented. Hence mathematically

$$\text{ICER for Q} = \frac{\text{Cost of Intervention Q} - \text{Cost of Intervention P}}{\text{Effect of Intervention Q} - \text{Effect of Intervention P}} \tag{5.6}$$

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.

The intervention strategies practised in Karonga District are ranked in increasing order of effectiveness based on the model simulation results as follows: treatment and ITNs only (strategy A), treatment and IRS (strategy B), ITNs and IRS (strategy C) and combination of ITNs, IRS and treatment (strategy D).

The oral interviews conducted in June 2013 with the District Health Office at Karonga District Hospital in Karonga District revealed that on average the Karonga District Hospital spends US$0.407 per patient for treating patients who have malaria. This expenditure is minus laboratory costs, clinical examinations and household costs but this is the cost for screening patients, administering drug

intake and patients' conditions in hospital or as outpatients. In addition the cost per house spray for IRS is US$1.8722 on average for spraying the houses in the area. Furthermore the District Health Officer said that the ITNs cost US$0.1896 on average per net. The cost of prevention is associated with costs of pesticide sprays, educating the public about personal protection and supply of treated bed nets. The analysis in Table 6.2 in which 500 people were interviewed and the cost of each intervention given above is used to determine the cost-effectiveness of different combinations of the three intervention strategies.

Method	**Percentage interviewed**	**Infection averted**
Use of ITNs	90.4%	453.808
IRS	16.5%	82.83
Seek treatment	9.2%	46.184

Table 5.1: Percentage of people interviewed and its corresponding infection averted.

Different combinations of these intervention measures are developed from Table 5.1 in order to determine total infection averted. The combination of treatment and ITNs gives 499.992; of treatment and IRS gives 129.014; of ITNs and IRS gives 536.638 and the combination of treatment, ITNs and IRS gives 582.882. Then there is need of determining the total cost of the combined intervention strategies as follows: the combination of ITNs and treatment gives

$$\text{ITNs} \;\&\; \text{Treatment} = \left\{ \begin{array}{rcl} 453.808 \times 0.1896 & = & \$86.042 \\ 46.184 \times 0.407 & = & \$18.797 \end{array} \right\} = \$104.8389, \quad (5.7)$$

the combination of treatment and IRS gives

$$\text{Treatment} \;\&\; \text{IRS} = \left\{ \begin{array}{rcl} 46.184 \times 0.407 & = & \$18.797 \\ 82.83 \times 1.8731 & = & \$155.1528 \end{array} \right\} = \$173.9498, \quad (5.8)$$

the next combination is for ITNs and IRS gives

$$\text{ITNs} \ \& \ \text{IRS} = \left\{ \begin{array}{rcl} 453.808 \times 0.1896 & = & \$86.042 \\ 82.83 \times 1.8731 & = & \$155.1528 \end{array} \right\} = \$241.1948, \qquad (5.9)$$

and the final combination is for ITNs, treatment and IRS gives

$$\text{ITNs, Treatment} \ \& \ \text{IRS} = \left\{ \begin{array}{rcl} 453.808 \times 0.1896 & = & \$86.042 \\ 46.184 \times 0.407 & = & \$18.797 \\ 82.83 \times 1.8731 & = & \$155.1528 \end{array} \right\} = \$259.9918, \qquad (5.10)$$

The total number of infections averted as shown in Table 5.2 is determined by calculating the difference between the total of infectious humans without intervention strategies and the total of infectious humans with intervention strategies (see Table 5.7 and 5.8). Table 5.2 indicates the following values for the ICER;

Strategy	**Total infection averted**	**Total cost**($)
Strategy A	499.992	104.8389
Strategy B	129.014	173.9498

Table 5.2: Cost-effectiveness analysis of approaches A and B

$$\left. \begin{array}{rcl} \text{ICER(A)} & = & \dfrac{104.8389}{499.992} = 0.20968 \\ \text{ICER(B)} & = & \dfrac{173.9498 - 104.8389}{129.014 - 499.992} = -0.18629 \end{array} \right\}. \qquad (5.11)$$

The results of the comparison between ICER(A) and ICER(B) indicates a cost saving of 0.18629 for strategy B over strategy A. The negative ICER for strategy B indicates the strategy A is strongly dominated. This shows that strategy A is more costly and less effective than strategy B. Hence the strongly dominated strategy A, is excluded and we now compare strategies B and C using the values in Table 5.8 and 5.9. The table 5.3 leads to the following calculations for the ICER values;

Strategy	**Total infection averted**	**Total cost**($)
Strategy B	129.014	173.9498
Strategy C	536.638	241.1948

Table 5.3: Cost-effectiveness analysis of approaches B and C

$$\left.\begin{array}{rcl} \text{ICER(B)} & = & \dfrac{173.9498}{129.014} = 1.34830 \\ \text{ICER(C)} & = & \dfrac{241.1948 - 173.9498}{536.638 - 129.014} = 0.16497 \end{array}\right\}. \tag{5.12}$$

The comparison between ICER (B) for strategy B and the ICER (C) for strategy C displays a cost of 0.16497 for strategy C over strategy B. Similarly, the ICER for strategy C shows that strategy B strongly dominates which explains that strategy B is more costly and less effective than strategy C. Therefore, strategy B is excluded and then we compare the strategies C and D using the values in Table 5.9 and 5.10. Then calculating the ICER values using values in Table 5.4;

Strategy	**Total infection averted**	**Total cost**($)
Strategy C	536.638	241.1948
Strategy D	582.822	259.9918

Table 5.4: Cost-effectiveness analysis of approaches C and D

$$\left.\begin{array}{rcl} \text{ICER(C)} & = & \dfrac{241.1948}{536.638} = 0.44946 \\ \text{ICER(D)} & = & \dfrac{259.9918 - 241.1948}{582.822 - 536.638} = 0.40700 \end{array}\right\}. \tag{5.13}$$

The comparison between the ICER(C) and ICER(D) expresses a cost saving of 0.40700 for strategy D over strategy C. This means strategy C is more costly and less effective than strategy D. Therefore, strategy C which dominates strongly is excluded.

The cost-effectiveness calculations are further verified using the computation of incremental cost-effectiveness ratios in table form in order to have a complete overview of the outcome. In Table 5.5 the strategy B is associated with a negative

Strategy	**Cost** ($) [C]	**Strategy effects** [E]	**Incremental cost** $[\triangle C]$	**Incremental effect** $[\triangle E]$	**ICER** $[\triangle C]/[\triangle E]$
A	104.8389	499.9920	104.8389	499.9920	0.20968
B	173.9498	129.0140	69.1109	-370.9780	-0.18629
C	241.1948	536.6380	67.2450	407.6240	0.16497
D	259.9918	582.8220	18.7970	46.1840	0.40700

Table 5.5: Incremental cost-effectiveness ratios of all combined strategies.

ICER. In other words, strategy A is followed by strategy that has increased effectiveness and reduced cost. Therefore strategy A is excluded.

Having excluded strategy A, ICERs are recalculated for strategies B, C and D and are shown in Table 5.6. Strategy B is dominated by strategy C as the latter

Strategy	**Cost** ($) [C]	**Strategy effects** [E]	**Incremental cost** $[\triangle C]$	**Incremental effect** $[\triangle E]$	**ICER** $[\triangle C]/[\triangle E]$
B	173.9498	129.0140	173.9498	129.0140	1.34830
C	241.1948	536.6380	67.2450	407.6240	0.16497
D	259.9918	582.8220	18.7970	46.1840	0.40700

Table 5.6: Exclusion of more costly and less effective intervention strategies.

is more effective and costs less to produce an additional unit of effect ($0.16497 compared with $1.34830). The dominated strategy is then excluded and the ICERs are recalculated (see Table 5.7).

Strategy	**Cost** (\$) [C]	**Strategy effects** [E]	**Incremental cost** $[\triangle C]$	**Incremental effect** $[\triangle E]$	**ICER** $[\triangle C]/[\triangle E]$
C	241.1948	536.6380	241.1948	536.6380	0.44946
D	259.9918	582.8220	18.7970	46.1840	0.40700

Table 5.7: Exclusion of dominated intervention strategy.

In Table 5.7 strategy C is dominated by strategy D. Therefore strategy D is more effective and costs less

In deciding between strategy C and strategy D, the available budget must be brought to bear. If the available budget is \$241.1948, the intervention strategy C should be made available to the community members, while if the available budget is \$259.9918 the community members should have access to the more effective strategy D. However, if the budget is \$250, then since the cost difference between strategy C and strategy D is \$18.797 and the budget surplus is \$8.8052, it is possible to switch half of the need community members for intervention strategy to strategy D and still the expenditure remains within the budget.

From the above outcomes, we therefore conclude that strategy D which is the combination of the three strategies (treatment u_2, ITNs u_1 and IRS u_3,) is the most cost-effective of all the combined strategies developed in this study for malaria disease control and prevention. The result confirms the role which the three intervention strategies are playing in order to eradicate or minimize the spreading of the malaria disease. The ITNs help to increase the death of the mosquito population, and to reduce the contact rate between human and mosquito populations; IRS also increases the mortality rate of mosquito population; and treatment targets the

infected individuals. The outcome of calculations has also shown that strategy C (combination of ITNs and IRS) can be the second option to strategy D if treatment is expensive or not available or the parasite is resistance to available medicine.

Chapter 6

Numerical simulations and analysis

A structured questionnaire was developed and administered in Karonga District, Malawi in May - August, 2013 in order to determine how the intervention strategies of malaria disease are being practised and their effectiveness. The questionnaire was used to conduct a directed one to one interview, with the respondents who were randomly sampled with total size 500, which means that 500 questionnaires were administered. The enumerators were engaged in four days training on which they were trained questioning techniques and recording skills before they went to the field. The questionnaire was thoroughly discussed with the respondents.

We consider statistical results of how intervention strategies are practised. Different graphs and tables are depicted for all the prevention and treatment strategies.

6.1 Demographic results

As illustrated in Table 6.1 there were 500 respondents who participated in the study of which 205 were male and 295 were female.

Characteristic	**Number of people** ($N = 500$)	**Percentage**
Sex		
Male	205	41
Female	295	59
Marital status		
Married	432	86.4
Single	33	6.6
Divorced	35	7
Period of stay (years)		
Less than 1 year	6	1.2
1–2 years	20	4
3–4 years	18	3.6
More than 4 years	456	91.2

Table 6.1: Demographic characteristic of the participants.

Table 6.1 shows that about 86.4% of the respondents were married and 6.6% are single. Table 6.1 shows that approximately 91.2% of the respondents have stayed in the area of study for more than 4 years.

The respondents were asked about major diseases experienced in their community and malaria was mentioned by 93.2% of the respondents. Malaria was ranked highest common diseases that are encountered in the study community of Karonga District, Malawi. Tuberculosis (TB) is the least mentioned disease (about 8%, see Table 6.2).

Disease		**Number of people** ($N = 500$)	**Percentage**
Malaria	Yes	466	93.2
	No	34	6.8
Diarrhea	Yes	282	56.4
	No	218	43.6
Cough	Yes	268	53.6
	No	232	46.4
HIV/AIDS	Yes	200	40
	No	300	40
Bilharzia	Yes	72	14.4
	No	428	85.6
Tuberculosis	Yes	40	8
	No	460	92
Others (Flue, rushes)	Yes	82	16.4
	No	418	83.6

Table 6.2: Major diseases commonly experienced in the community.

6.1.1 Knowledge of transmission dynamics of malaria

Knowledge of malaria transmission is a key to malaria prevention [1]. Figure 6.1 shows that 409 respondents (81.8%) stated that malaria transmission occurs when bitten by an infected mosquito. Contrary to popular belief in developing countries [41] that someone may be infected with malaria when soaked in water, most respondents 97.2% answered "no". Table 6.3 shows the number of individuals who mentioned that malaria disease and malaria transmission is through a bite from

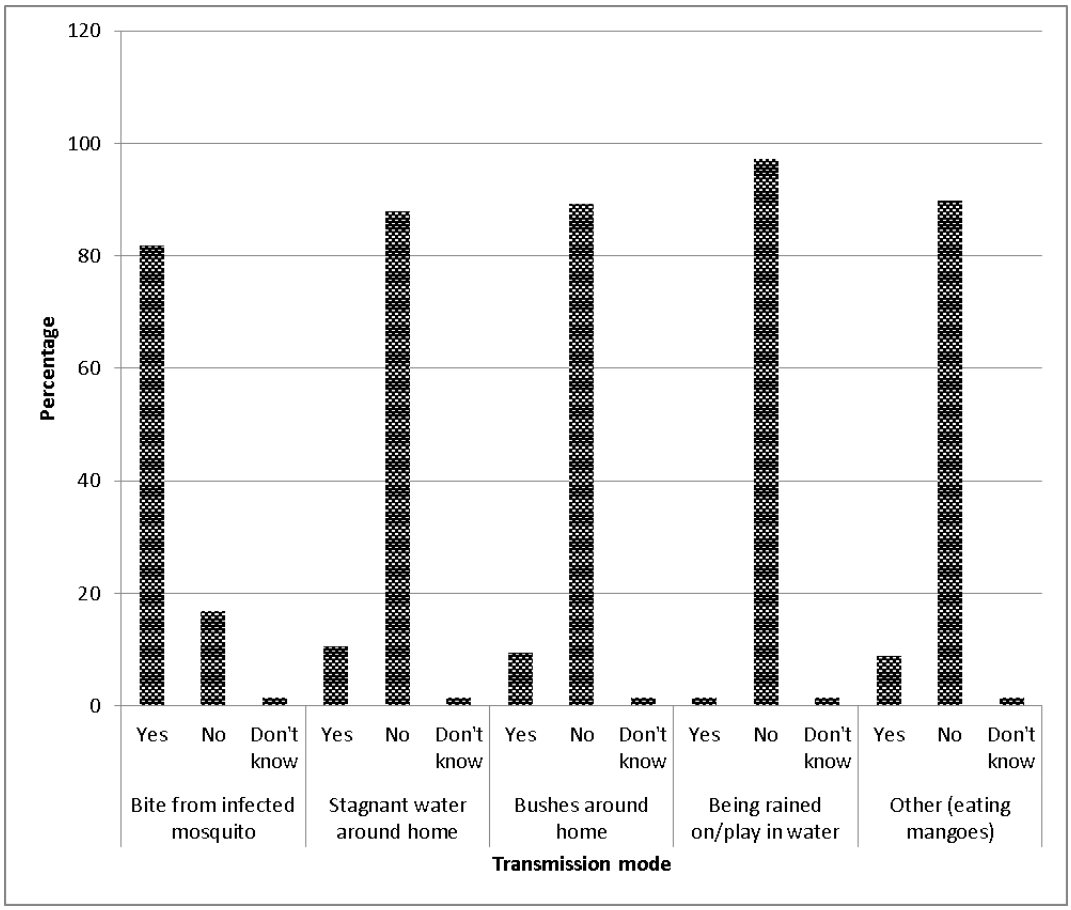


Figure 6.1: Knowledge of malaria transmission.

an infected mosquito; 79.9% responded "yes" to both malaria being a major disease and malaria transmission being acquired through a bite from an infected mosquito.

			Knowledge of malaria transmission		
			No	**Yes**	**Total**
Presence of malaria in the community	**No**	Count	11	15	26
		% of Total	2.3%	3.0%	5.3%
	Yes	Count	73	393	466
		% of Total	14.8%	79.9%	94%
Total		Count	84	408	492
		% of Total	17.1%	82.9%	100.0%

Table 6.3: Cross tabulation of presence of malaria in the community and Knowledge of malaria transmission.

6.1.2 Control and prevention measures

According to the Center for Disease Control and Prevention [14], prevention is better than cure and there are a number of methods which people can use to prevent malaria. Most of the respondents (90.4%) stated that they use ITN or long lasting insecticide treated bed-net (LLITN) as a method of preventing occurrence of malaria. Only 16.5% of the respondents mentioned that their houses are sprayed (IRS) and 9.2% are those who seek treatment when they are sick.

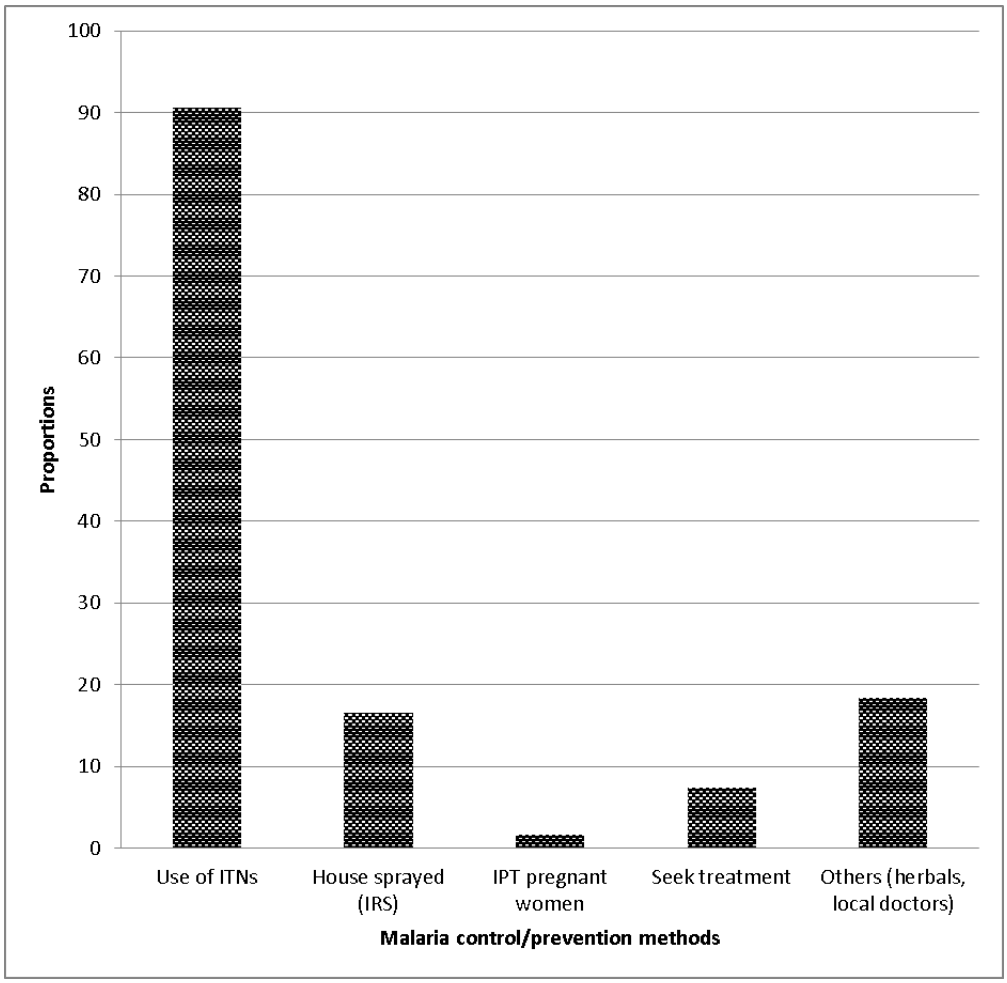


Figure 6.2: Method used in prevention and treatment of malaria.

Figure 6.3 illustrates that 93% of the respondents did not mention anything prioritizing who uses bed nets. Hence we conclude that everyone is prioritized to use the ITNs. However, 23 respondents (4.6%) mentioned that priority is given to children while 0.4% gave priority to pregnant women.

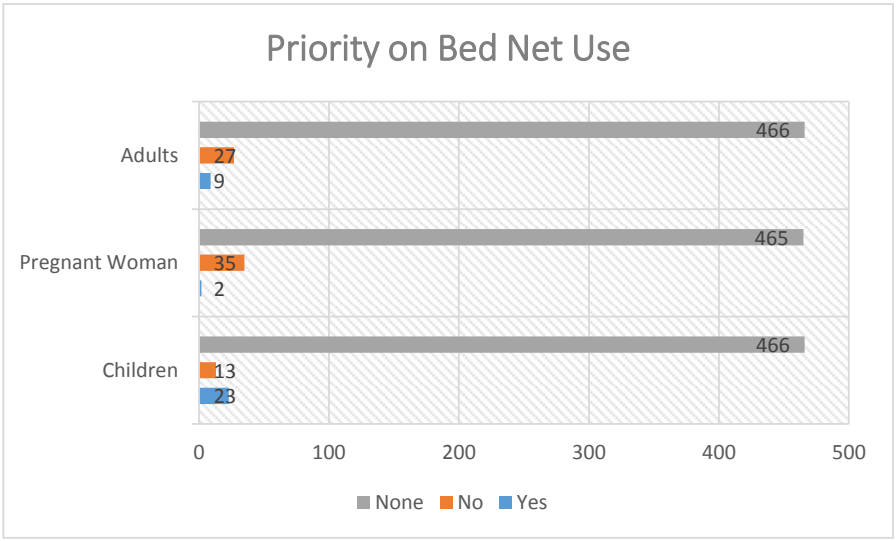


Figure 6.3: Priority on use of ITNs.

The interviewed members of the community gave different ways as a source of information on the importance of the IRS (see Figure 6.4). The health surveillance (HSA) and the village head played a role to educated the community on the importance of spraying their houses. The implementation of this campaign was well welcomed by the community just because the members of the community were involved.

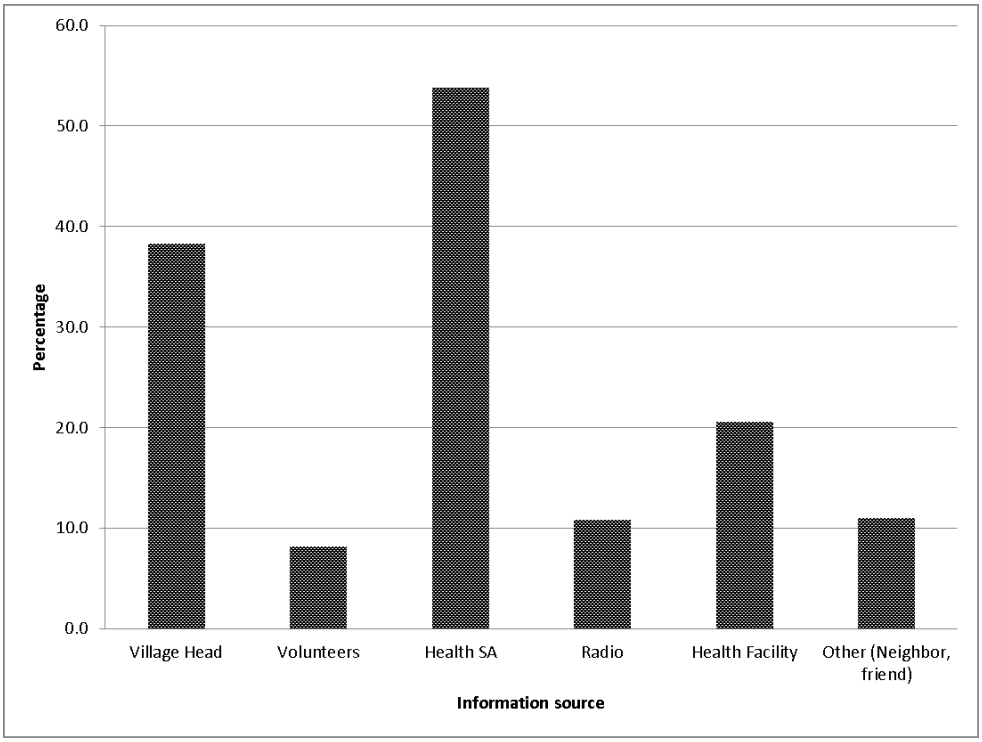


Figure 6.4: Source of information about IRS.

Figure 6.5 illustrates that 384 of the respondents who had heard about IRS had their houses sprayed as a preventive measure against malaria, thus reducing the number of female Anopheles mosquitoes. Two of the respondents had not heard anything about IRS but they have had their houses sprayed.

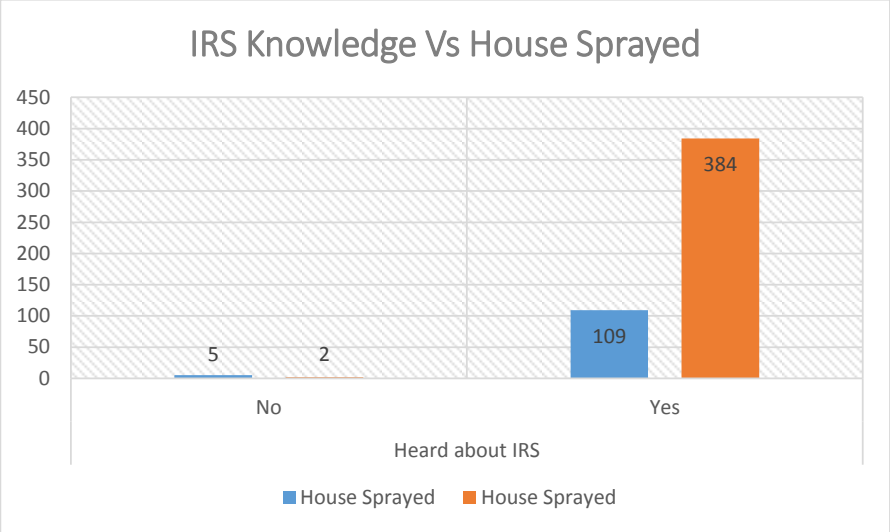


Figure 6.5: Knowledge about IRS versus house sprayed.

6.1.3 Malaria occurrence: assessing impact of interventions

Despite the use of ITN or LLITN and other preventive measures, cases of malaria are still evident. Table 6.4 shows that 49.2% of the respondents had experienced a malaria occurrence even though treated bed nets were in use.

	Number of people	**Percentage** (%)
No	231	46.2
Yes	246	49.2
Don't know	23	4.6
Total	**500**	**100.0**

Table 6.4: Use of net and malaria occurrence.

Furthermore, about 39.0% of malaria cases occur once in every four months as shown in Table 6.5.

	Number of people	**Percentage** (%)
Every month	55	22.4
Once in two months	46	18.7
Once in three months	49	19.9
Once in four months	96	39.0
Total	**246**	**100.0**

Table 6.5: Malaria occurence frequency despite use of net.

From Table 6.6, there are about 1% cases of malaria occurrences and about 2.2% respondents had not experienced any malaria cases after spraying their houses with IRS.

	Number of people	**Percentage** (%)
No	11	2.2
Yes	5	1.0
No response	484	96.8
Total	**500**	**100.0**

Table 6.6: Malaria occurance after spraying and without using net.

Some of the respondents used nets as well as sprayed their houses. Table 6.7 shows that 35.6% of the respondents had experienced malaria occurrence after their houses were sprayed and also used bed nets.

	Number of people	**Percentage** (%)
No	195	39.0
Yes	178	35.6
No response	127	25.4
Total	**500**	**100.0**

Table 6.7: Malaria occurrence after spraying and using net.

From the respondents who had been using ITNs or LLITNs, 44.9% did not have any malaria occurrence (see Table 6.8). However about 45.9% have had an occurrence of malaria despite the use of bed nets (see Table 6.8).

			Use of net and malaria occurrence		
			No	**Yes**	**Total**
Method of preventing -use of ITN or LLITN	**No**	Count	17	27	44
		% of Total	3.6%	5.7%	9.2%
	Yes	Count	214	219	433
		% of Total	44.9%	45.9%	90.8%
Total		Count	231	246	477
		% of Total	48.4%	51.6%	100.0%

Table 6.8: Method of preventing malaria - use of ITN or LLITN (Use of net and malaria occurrence cross tabulation).

A Chi-Square test of independence was conducted with a Chi-Square value of 1.454 since the cross tabulation is a two by two table. The assumption of no cells having an expected value less than 5 was not violated and hence the use of Chi-Square test. Table 6.9 shows that a calculated value of 1.454 was obtained. The level of significance used for the Chi-Square test was 0.05 which was compared to a p-value of 0.228. Since $0.228 > 0.05$, the null hypothesis was rejected hence there was an association between malaria occurrence and preventive methods (use of ITNs or LLITNs) and their proportions are not significantly different.

	Value	df	Asymp. sig. (2-sided)
Pearson Chi-Square	1.861^a	1	0.173
Continuity Correction^b	1.454	1	0.228

Table 6.9: Chi-Square of use of ITN or LLITN and use of net and malaria occurrence where a indicates the number of cells with expected count less than 5 while b shows the Yates continuity correction which is calculated for 2 by 2 table.

The relationship of indoor residual spraying (IRS) against the occurrence of malaria after the house was sprayed and use of bed nets was examined. From Table 6.10 the respondents who had not had their houses sprayed, 42.5% did not have an occurrence of malaria, while for those respondents who had had their houses sprayed, 38.4% had an occurrence of malaria.

			Malaria occurrence after spraying and using net		
			No	**Yes**	**Total**
Method of preventing -house spray (IRS)	**No**	Count	158	143	301
		% of Total	42.5%	38.4%	80.9%
	Yes	Count	36	35	71
		% of Total	9.7%	9.4%	19.1%
Total		Count	194	178	372
		% of Total	52.2%	47.8%	100.0%

Table 6.10: Method of preventing malaria-house sprayed (IRS): (Malaria occurrence after spraying and using net cross tabulation).

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	0.074^a	1	0.786
Continuity Correction^b	0.019	1	0.889

Table 6.11: House sprayed (IRS): Malaria occurrence after spraying and using net where a indicates the number of cells with expected count less than 5 while b shows the Yates continuity correction which is calculated for 2 by 2 table.

A Chi-Square test of independence was conducted with a Chi-Square value of 0.019. The assumption of no cells having an expected value less than 5 was not violated hence the use of Chi-Square test. The level of significance used for the Chi-Square test was 0.05 which was compared to a p-value of 0.889. Table 6.11 shows that the p-value of $0.889 > 0.05$, which means there was an association between preventive method (IRS) and malaria occurrence after spraying and using ITNs. However there were no significant differences in proportions between preventive methods and malaria occurrence after spraying.

6.2 Demographic findings summary

Malaria is a disease that causes morbidity and claims many lives in a year, more especially in the sub Saharan Africa region [126]. This is confirmed by the outcome of this study where about 93% of the respondents in Karonga district, Malawi stated that malaria is a major disease in their community. According to Center for Disease Control and Prevention [14], malaria has forced a change in treatment owing to resistance to previously prescribed medication.

Malaria transmission is assumed to occur by means of a bite of an infected female Anopheles mosquito. Ninety three respondents knew how malaria is transmitted. However 409 respondents out of 500 were able to state that the transmission of malaria is caused through the bite of infected mosquitoes. Contrary to old beliefs that one is infected with malaria when soaked in rain water, 486 respondents mentioned this as a mode of malaria transmission.

Malaria prevention is a key to reducing morbidity and deaths [44]. Knowledge of the use of treated bed nets was mentioned by 454 respondents in Karonga district as a preventive measure of the occurrence of malaria. Other respondents (418) also mentioned spraying their homes (IRS) as another means of getting rid of mosquitoes. However preventive measures like getting rid of the breeding sources of malaria were not mentioned by any of the respondents. This is in line with the heavy campaigns done by the government of Malawi against use of such means of intervention practices due to biological and environmental issues.

Despite knowledge of malaria transmission and prevention, malaria cases still occur [64]. About 50% of the respondents who used ITNs mentioned that malaria still

occurred and they still had malaria cases in their households. This is probably because bed nets are only used when going to bed and hence the vulnerability. Furthermore the proportion of those respondents who used ITNs or LLITNs and suffered from malaria was not significantly different from those who did not use ITN or LLITNs but suffer from malaria ($\chi^2 = 1.454,$ calculated value $= 0.228,$ and level of significance $= 0.05$). Of the respondents who had had their houses sprayed (about 3.2%), 1% experienced an occurrence of malaria. Those respondents who had their houses sprayed and suffered from malaria even though they had used ITNs or LLITNs had no significant difference with those respondents who had had their houses sprayed and had not suffered from malaria even though they had used ITNs or LLITNs ($\chi^2 = 0.019,$ calculated value $= 0.889,$ level of significance $= 0.05$).

6.3 Numerical results

The numerical simulations and analysis were carried out using a fourth order Runge-Kutta scheme in Matlab. Our aim was to determine and verify the analytic results and the stability of the model system (3.1). Some of the parameter values were calculated from the data collected in Karonga District, Malawi between the months of January to September, 2013. The other parameter values were obtained from the National Statistical Office (NSO) in Zomba, Malawi, some have been assumed, and very few have been taken from the literature (see Table 6.12). The assumed model parameters are considered based on malaria disease. The Government of Malawi has organized a number of intervention strategies in order to fight malaria in the country through the National Malaria Control Program (NMCP) [82].

6.3.1 Calculations and estimation of parameters

The simulations of the malaria model incorporate the average values of parameters such as incubation period, infection rate, length of infection period in host and mosquito populations, natural death rate, recovery rate, biting rate and contact rate between the host and mosquito populations. Table 6.12 provides a summary of the estimated values of all parameters. The parameters are explained and described as given by World Health Organization and Center for Disease and Prevention.

- Most malaria parasites are not highly fatal therefore we keep the disease induced death rate δ_h small.
- The duration of a mosquito's stay in the community is $1/\mu_v$ until it dies or migrates elsewhere. Hence the life expectancy of an adult mosquito $1/\mu_v$ is estimated based on the range 15 to 20 days.
- For humans, the natural death rate is estimated based on life of 60 years in Malawi.
- Humans become infectious 10 to 30 days after being bitten by female infectious anopheles mosquitoes and the average period is 20 days. [15]. Therefore the incubation period is approximated in the range $0.05479 \leq \alpha_h \leq 0.08219$.
- The recovered individuals can become susceptible within 1 to 20 days after treatment. Therefore, we assume that the recovered individuals lose temporary immunity at a value ranging between $1/365$ and $1/(20 \times 365)$.
- Malaria parasite takes 10 to 26 days to develop in the female Anopheles mosquito's salivary gland after a blood meal from infectious individuals [14]. The progression rate value α_v from latent mosquitoes to infectious mosquitoes ranges from $1/26$ to $1/10$.

6.3.2 Sensitivity analysis and model simulation

Simulations are carried out to monitor the dynamics of the full malaria model for various values of the associated reproduction threshold. In an attempt to reduce human mortality and morbidity due to malaria, we need to know the relative importance of the different factors responsible for its transmission and prevalence. Initial disease transmission is directly related to $\mathcal{R}_e$, and disease prevalence is directly related to the endemic equilibrium. We also compute sensitivity indices of the reproduction number which enable us to single out parameters that have a high impact on $\mathcal{R}_e$ and which are used to enhance the intervention strategies. We assume that the time unit for parameters with small initial values of state variables used in the analysis is days.

Parameter	Value	Source	Parameter	Value	Source
μ_h	$1/(58 \times 365)$	[83]	Λ_h	60	Assumed
μ_v	0.1429	[62]	Λ_v	1000	[9]
α_h	1/17	[9]	ϕ	0.005	Assumed
α_v	1/18	[9]	η	0.4	Assumed
β_{hv}	0.09	[9]	δ_h	0.05	[83]
β_{vh}	0.8333	[73]	τ	0.01	Assumed
ϑ	0.5 – 0.6502	[18]	θ	0.3	Assumed
κ_1	0.003	Assumed	ρ	0.035	Assumed
ψ	1/365	[82]			

Table 6.12: Values and ranges for parameters for the full malaria model.

In addition the units for parameters values for analysis of model with higher initials values are years and estimated as follows, $\Lambda_v = 1000$ year^{-1}, $\Lambda_h = 60$ year^{-1},

$\mu_v = 17.5$ year^{-1}, $\mu_h = 0.01667$ year^{-1}, $\vartheta = 209.9115$ year^{-1}, $\phi = 1.825$ year^{-1}, $\alpha_v = 20.27778$ year^{-1} and $\alpha_h = 21.47056$ year^{-1}.

6.3.3 Sensitive indices of $\mathcal{R}_e$

The sensitivity indices allow us to measure the relative change in a state variable when a parameter changes. When the state variable is a differentiable function of a certain parameter, the sensitivity index may be defined using partial derivatives.

Definition 6.1. The normalized forward sensitivity index of a variable ψ that depends differentiably on a parameter p is defined as:

$$\Upsilon_p^{\psi} = \frac{\partial \psi}{\partial p}.\frac{p}{\psi} \tag{6.1}$$

Since we have an explicit formula for $\mathcal{R}_e$, we derive an analytical expression for the sensitivity of $\mathcal{R}_e$, $\Upsilon_{p_i}^{\psi} = \partial\psi/\partial p_i \times p_i/\psi$, to each of the different parameters. For instance, the sensitivity of $\mathcal{R}_M$ with respect to β_{hv} and ϕ, respectively, is

$$\Upsilon_{\beta_{hv}}^{\mathcal{R}_e} = \frac{\partial \mathcal{R}_e}{\partial \beta_{hv}}.\frac{\beta_{hv}}{\mathcal{R}_e} = \frac{1}{2}, \tag{6.2}$$

$$\Upsilon_{\phi}^{\mathcal{R}_e} = \frac{\partial \mathcal{R}_e}{\partial \phi}.\frac{\phi}{\mathcal{R}_e} = -\frac{\phi}{2\left(\delta_h + \mu_h + \eta u_2 + \phi\right)}. \tag{6.3}$$

Note that the sensitivity with respect to β_{hv} does not depend on any parameter values. Similarly, the sensitivity values with respect to β_{vh}, ϑ and Λ_v do not depend on any parameter.

Most of the expressions for the sensitivity indices are complex with little obvious structure. We therefore evaluate the sensitivity indices at the parameter values given

in Table 6.12. Worth noting is the fact that the particular values of the sensitivity indices of the various reproductive numbers to different parameters depend on the parameter values chosen and on the assumptions upon which the model is based. The resulting sensitivity indices of $\mathcal{R}_e$ to the different parameters in the model are shown in Table 6.13.

The most sensitive parameter to $\mathcal{R}_e$ is the mosquito's natural death rate, μ_v ($\Upsilon_{\mu_v}^{\mathcal{R}_e} = -1.35959$). This is followed by the mosquito per capita biting rate, ϑ, ($\Upsilon_{\vartheta}^{\mathcal{R}_e} = 1$). Further, this is followed by the transmission probability per bite from infectious human to susceptible mosquito, β_{hv}, the transmission probability of infection to humans per bite, βvh, and the recruitment rate of mosquitoes, Λ_v. Other key parameters include the recruitment rate of individuals, Λ_h. With $\Upsilon_{\alpha_h}^{\mathcal{R}_e} = 0.0003398$, the progression rate of individuals from the exposed to infectious malaria state, α_h, is the least sensitive. We have that $\Upsilon_{\vartheta}^{\mathcal{R}_e} = 1$, then decreasing (or increasing) ϑ by 10% decreases (or increases) $\mathcal{R}_e$ by 10%. Similarly, as $\Upsilon_{\mu_h}^{\mathcal{R}_e} = 0.499531$, increasing (or decreasing) μ_h by 10% increases (or decreases) $\mathcal{R}_M$ by 4.99%.

For some parameters, $\Upsilon^{\mathcal{R}_e}$ depends on the human and mosquito demographic parameters. For instance, $\Upsilon_{\mu_v}^{\mathcal{R}_e}$ depends on α_h, τ, δ_h and ϕ. Hence, changing the equilibrium sizes would affect the sensitivity indices for the human and mosquito biting rates. Therefore, we would need a thorough knowledge of the demographic parameters to estimate their importance. However, for some parameters such as β_{hv}, β_{vh}, ϑ and Λ_v, $\Upsilon^{\mathcal{R}_M}$ does not depend on other parameter values. Reducing any of these parameters would have a huge effect on disease transmission regardless of other parameters.

For most of the parameters, the signs of the sensitivity indices of $\mathcal{R}_e$ agree with

intuitive expectations. For instance, for the mosquito recruitment rate Λ_v, the malaria reproduction number $\mathcal{R}_e$ increases as Λ_v increases. The understanding is, as Λ_v increases and the number of mosquitoes increases, the death rate also increases because the environment can only support a certain number of mosquitoes. Further, when the mosquito recruitment rate, Λ_v, is equal to the death rate μ_v, the mosquito population is at equilibrium. Thus, at equilibrium the recruitment rate, Λ_v, is also the per capita death rate. If $1/\Lambda_v$ is the life span of the mosquitoes, then increasing Λ_v reduces the life span. Reducing the life span of the vector population reduces $\mathcal{R}_e$ as more infected mosquitoes die before they become infectious.

Effective reproduction number $\mathcal{R}_e$			
Parameter	Sensitivity Indices SI	Parameter	Sensitivity Indices SI
μ_h	0.499531	Λ_h	-0.498504
μ_v	-1.53959	Λ_v	0.5
α_h	0.000339769	ϕ	-0.0161249
α_v	0.360065	η	-0.322497
β_{hv}	0.5	δ_h	-0.161249
β_{vh}	0.5	τ	-0.000475714
ϑ	1	θ	-0.00149551

Table 6.13: Sensitivity indices (SI) of $\mathcal{R}_e$ to parameters for the malaria model, evaluated at the parameter values given in Table 6.12.

6.3.4 Model simulation

The autonomous malaria model 3.2 was simulated. This was done with the absence of any intervention strategies. Thereafter, the simulation of the optimal malaria

model with intervention strategies was carried out.

Karonga District is the busy district harboring people who come to work for uranium and coal mines. The district is also a precious Kilombero rice growing district and situated along the lake-shore area. Karonga District is flat, prone to flooding and it is highly populated. The district has many mosquitoes due to good breeding sites caused by rice schemes and flooding. Hence it is a malaria endemic area. Therefore, the following estimated initial conditions for the state variables were used: $S_{h0} = 12000$, $E_{h0} = 1050$, $I_{h0} = 1000$, $R_{h0} = 800$, $S_{v0} = 1500$, $E_{v0} = 1100$, and $I_{v0} = 9000$. These values are an average of estimated values of the individuals who participated in the malaria survey in Karonga District, Malawi.

6.3.5 Dynamics of malaria model without intervention measures

The analysis of the model without intervention strategies was carried out in order to determine the dynamics of the disease in the population. The simulation was generated in a four year time frame since the first campaign of malaria intervention strategies in Karonga District was performed in the year 2010. The susceptible human population is decreasing exponentially (see Figure 6.6 (a)) showing that most susceptible humans are exposed to the disease due to unavailability of intervention strategies. This has led to an exponential increase in the exposed human population (Figure 6.6 (b)) and the infected population (Figure 6.6 (c)) with $\mathcal{R}_0 = 1.8894$. The infected human population increases due to an increase in the exposure of susceptible individuals to Plasmodium falciparum. This means that Plasmodium falciparum will continue to multiply in the human and mosquito populations since there are no intervention strategies to reduce or eradicate the disease. The outcome

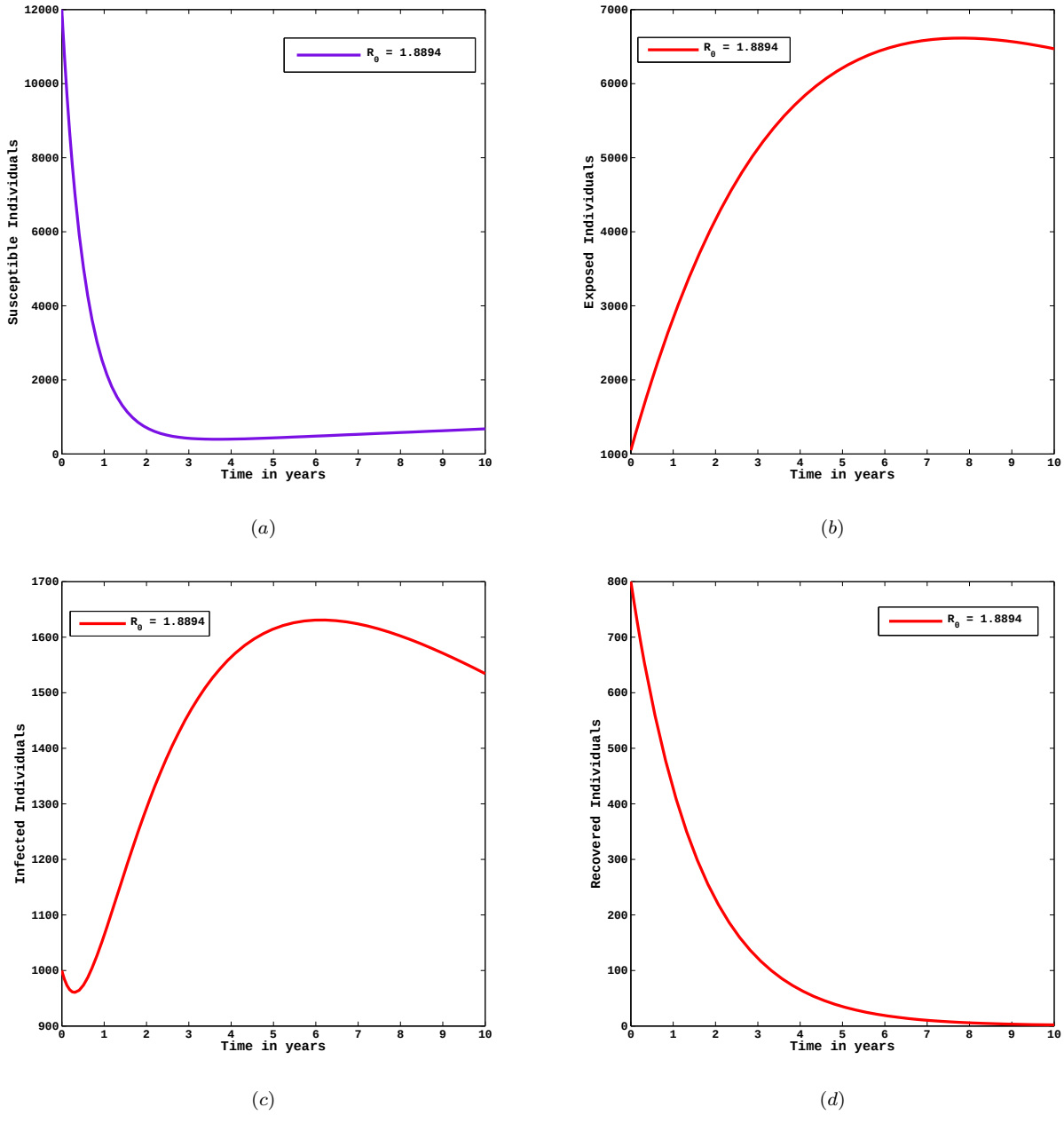


Figure 6.6: Shows the dynamics of (a) susceptible humans, (b) exposed humans, (c) infected humans and (d) recovered humans in the model without intervention strategies, with time. The parameter values are those in Table 6.12.

of this analysis supports Lemma 2 that the disease is endemic when $\mathcal{R}_0 > 1$. The recovered individual population (Figure 6.6(d)) decreases exponentially due to the steady increase in the infected human population. Figure 6.6(d) at its initial stage shows some individuals recovering, which might be due to natural immunity. Hence there is a need for intervention strategies in order to reduce or eradicate this malaria disease epidemic.

6.3.6 Prevalence in the malaria model without intervention strategies

Prevalence is defined as the ratio of the number of cases of the disease in a population to the total number of individuals in population at a given time.

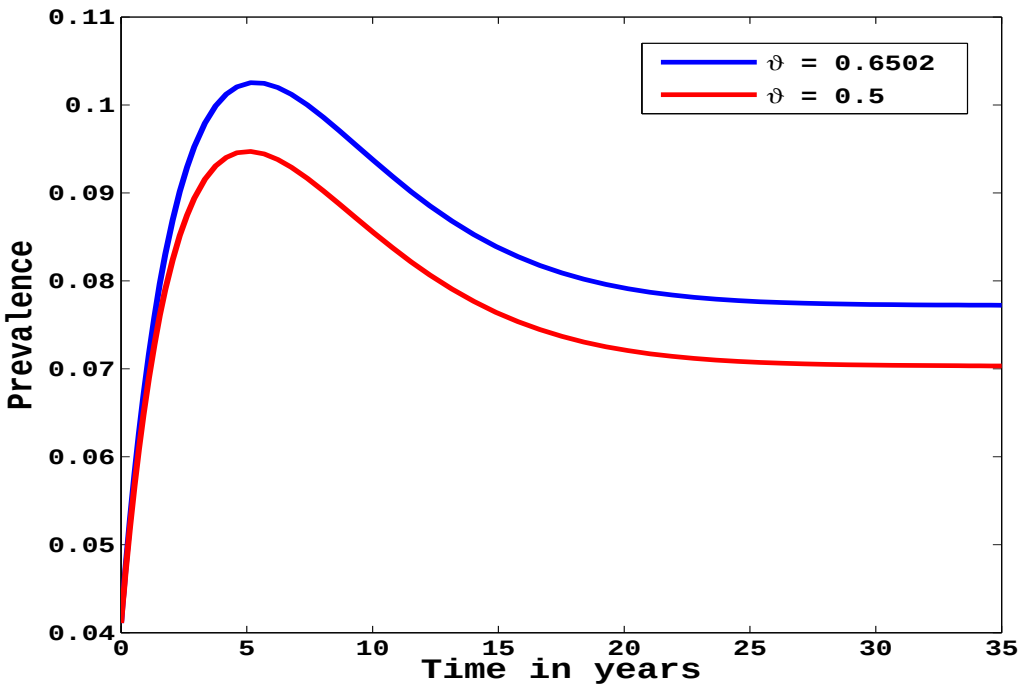


Figure 6.7: Prevalence of infection in humans as a function of time in years with two different levels of force of infection due to different values of biting probability rate and other parameter values are in Table 6.12.

The disease prevalence of infection in Figure 6.7 shows a steady increase during the first days of infection due to a high number of cases of individuals with Plasmodium falciparum. The graph drops asymptotically due to a reduced number of susceptible human population and thereafter the prevalence becomes constant. This might be due to increased immunity in some individuals as they are repeatedly exposed to Plasmodium. In addition, the campaigned intervention strategies have effects on the

transmission of the parasite. Interestingly, the graph drops when the probability of biting rate is low, ($\vartheta = 0.5$).

Some numerical simulations of the full model are carried out to illustrate some of the analytical results. Table 6.12 gives the parameter values used in the simulations, some of which were obtained from the literature while others were assumed (within realistic range) for the purpose of simulations. Some of the parameters were introduced for the first time to mosquito population. For instance, the effective use of LLITNs helps to increase the mortality of mosquitoes and this is ignored in most models. These parameter values were assumed in accordance with their intuitive functions. For example, the mosquitoes' death rate due to use of IRS is assumed to be $\tau = 0.01$. The idea is that some but not all of the mosquitoes that come into contact with the IRS fumes die. There are some mosquitoes that are resistant/immune to such sprays or just that individuals are using expired sprays. Malaria thrives in conditions of poverty and worsens poverty. With malaria being a disease of poverty, a higher value of τ would mean that people can afford effective and sophisticated IRS.

The baseline control parameter values chosen for the simulations in Figure 6.8 are $u_1 = 0.5,\ u_2 = 0.5$ and $u_3 = 0.5$. The values of u_i chosen above have no significant meanings but chosen merely for simulation purposes. Different values of u_i will result in different equilibrium rates. Figure 6.8 shows the dynamics of human and mosquito populations illustrating the effects of intervention strategies on the whole population. The susceptible individuals increase with time due to positive impact of LLITNs, IRS and treatment (see Figure 6.8(a)). At the same time Figure 6.8(d) shows the decrease of the exposed and infected mosquito population, hence evidencing the reduction of Plasmodium in the population. The analysis of Figure 6.8 is different from other figures on the initial state variables with the idea of seeing the impact of

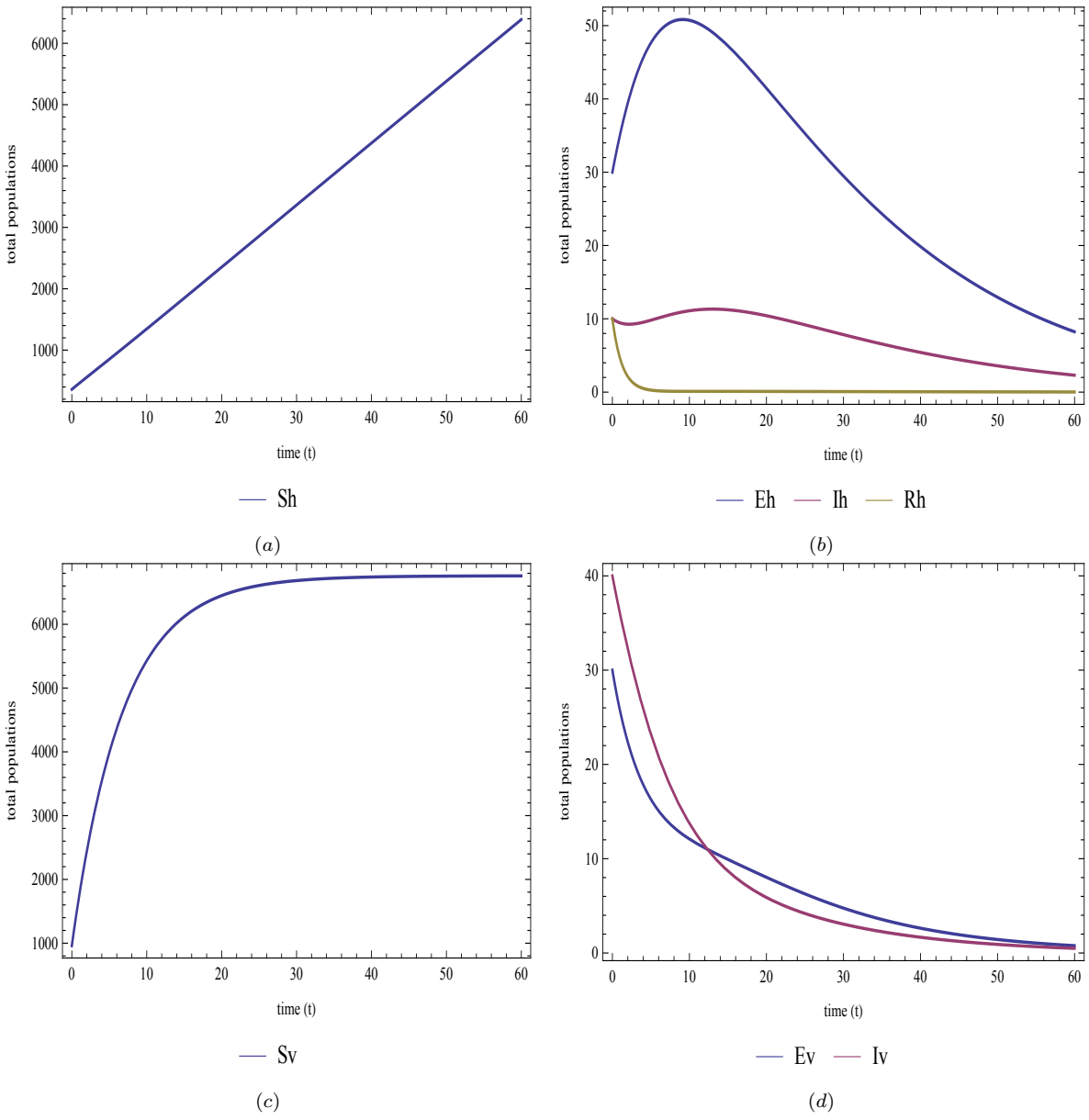
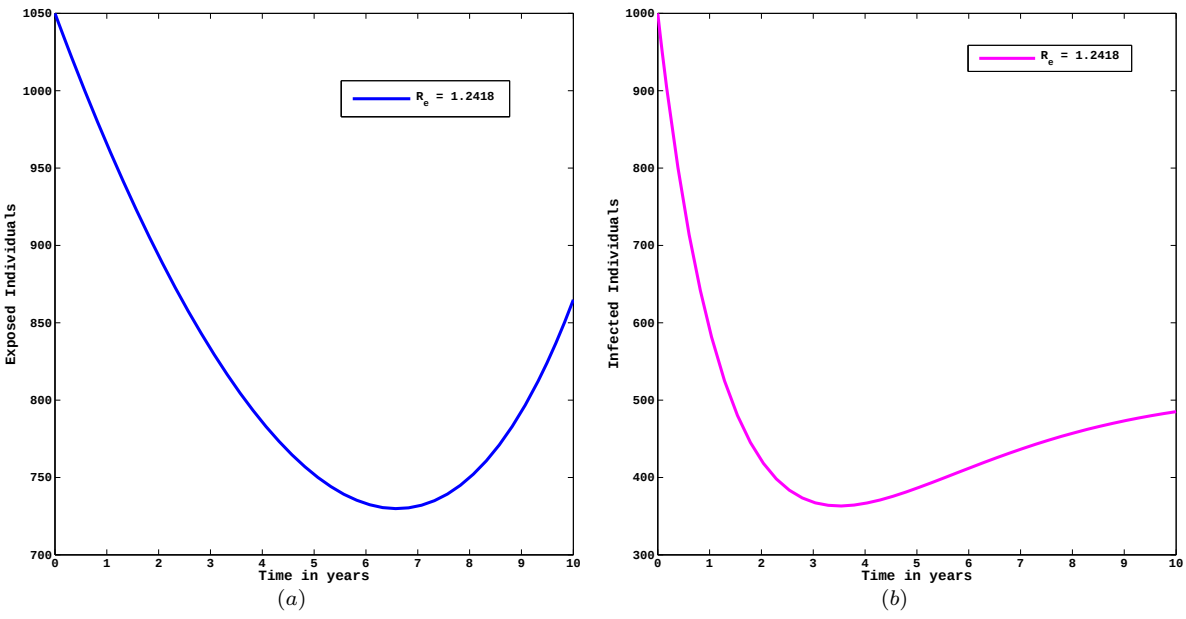


Figure 6.8: Simulations of the model (3.1) in years with parameter values from Table 6.12 and initial state variables $S_h(0) = 360, E_h(0) = 30, I_h(0) = 10, R_h(0) = 10, S_v(0) = 960, E_v(0) = 30, I_v(0) = 40$. (a) shows the susceptible individuals evolution over time, (b) shows the plots of the susceptible and infected human population over time, (c) shows the susceptible mosquitoes, and (d) shows the evolution of the infected and susceptible vector population over time.

having different initial values.

6.3.7 Dynamics of malaria model with intervention measures

Simulations were carried out in order to determine the impact of the intervention strategies practised in Karonga District, Malawi and to investigate how parameter values affect the dynamics of human population state variables over time. The analysis of the sub-model of malaria and treated infected individuals, malaria and individuals using ITNs, malaria and individuals living in IRS was performed. We also carried out simulation of the optimal control malaria model with all the three intervention strategies. With the introduction of better treatment to malaria in the

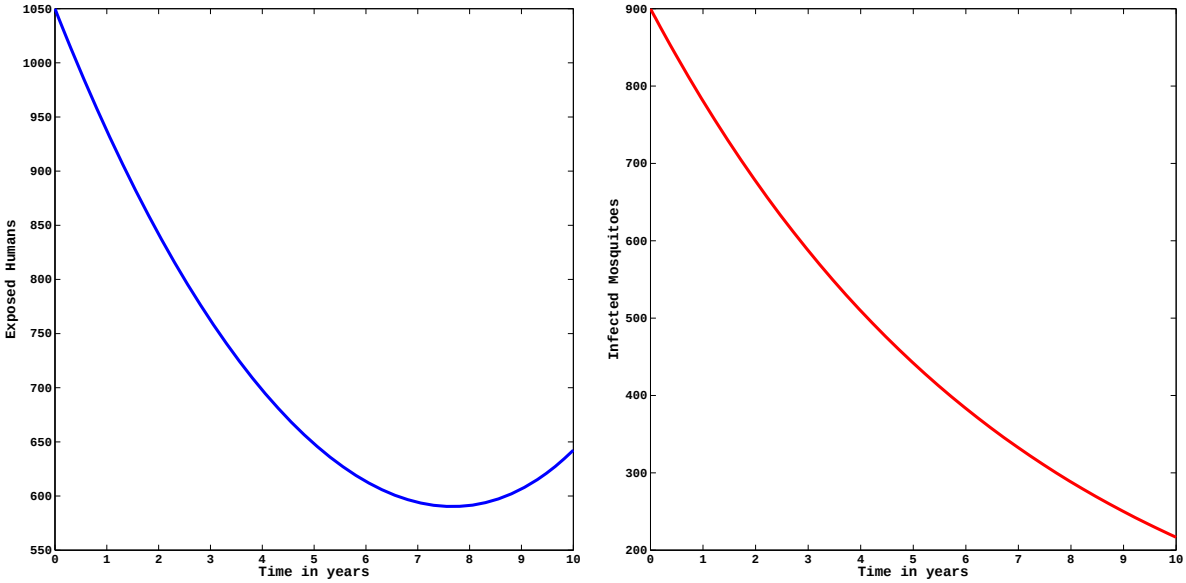


(a) (b)

Figure 6.9: Shows the changes in the (a) exposed and (b) infected individuals' state variables of the malaria model with treatment as the only intervention strategies, with time, where $u_1 = u_3 = 0$ and parameter values are from Table 6.12.

area, the number of the exposed individuals dropped exponentially and then picked

up again with a sharp gradient. This might be due to availability of Plasmodium falciparum in the female Anopheles mosquitoes and the people who do not seek treatment. In addition, the parasite may be resistance to medication being given to patients. The targeted group with treatment are people who have shown signs of malaria disease but nothing is done in this case to the mosquito population which is a carrier of this parasite. Hence the recurrence of the disease in the society as shown in Figure 6.9(b). Therefore prevention strategies are needed which target the mosquito population or which can reduce contact between the human and mosquito populations. Here we assume the situation whereby IRS is the only means

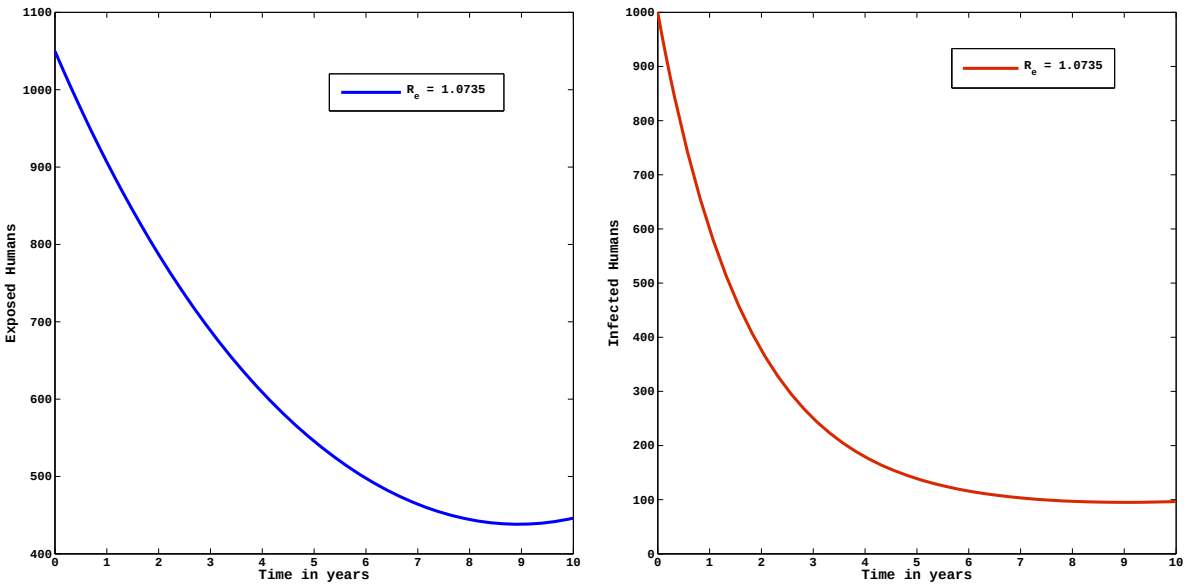


(a) (b)

Figure 6.10: Represents the phase plane of the exposed humans and infected mosquitoes with the use of IRS as the only means of intervention strategy for which $u_1 = u_2 = 0$. The parameter values are from Table 6.12.

of intervention strategy practised in the area. Figure 6.10(a) shows a decrease in exposure to the disease by exposed individuals. Thereafter, the graph shows an increase of the exposed individual to the disease. This might be due to reduction of

effectiveness of the insecticide chemical sprayed with time. The additional reason might be due to unavailability of the ITNs which reduces contact between the two population. The effectiveness of the intervention is indicated by the asymptotically dropping number of exposed individuals (see Figure 6.10(a)). The number of infected mosquito population decreases exponentially due to IRS intervention strategy which aims at eradicating those mosquitoes which land on the walls of the house (see Figure 6.10(b)). This prevention strategy to be effective needs to be accompanied by other intervention strategies, taking into account of resistance to insecticides by mosquito population, some mosquitoes might find its way to individuals without landing on the walls of the house, and the effectiveness period of the insecticide sprayed. With



(a) (b)

Figure 6.11: Indicates the dynamics of the exposed and infected individuals using ITNs as malaria prevention strategy while $u_2 = u_3 = 0$. The parameter values are in Table 6.12.

the use of ITNs as the only intervention in the community, Figure 6.11(a) shows a decrease to exposure to the disease or Plasmodium falciparum to a certain level without reaching zero. The contact between the ITNs and the female Anopheles

mosquitoes increases with time due to mosquitoes looking for blood meal and leads to an increase in the death of the mosquitoes, and the same time there is reduction in contact between the human and mosquito populations. Hence the number of infected mosquitoes in the society get reduced. This results in an exponential drop of the exposure of the human population to the disease (see Figure 6.11(a)). The graph could not drop further may be because other members of the society were not using the ITNs. This is evidenced in the demographic results in which the outcome shows that 88.4% of the household members interviewed use ITNs. Furthermore, there is exposure of human beings to the female Anopheles mosquitoes outside the ITNs. The same behavior of graphical outcome is observed in the infected human population (see Figure 6.11(b)) where the number of infected humans drops and remains constant thereafter. Hence there is need of other two or more different intervention strategies to help in reducing or eradicating malaria. We now consider the effects of the three intervention strategies (ITNs, IRS and treatment) which are campaigned concurrently in Karonga District, Malawi. It appears that if the three intervention strategies are effectively monitored and implemented, then there is a positive impact of combating malaria in the society. Figure 6.12 shows a steady decrease in the susceptible human population at the initial period as the exposure of humans to disease increases. Thereafter the graph of susceptible humans increases as the exposed and infected human population decrease due to positive effects of the intervention strategies implemented. This is evidenced that during this period chemicals which are available in the ITNs and sprayed in the houses are effective in reducing the mosquito population and at the same time reducing the contact rate between the human population and the mosquito population. Treatment strategy has also played an important role in reducing the number of infected individuals thus leading to an increase in susceptible individuals.

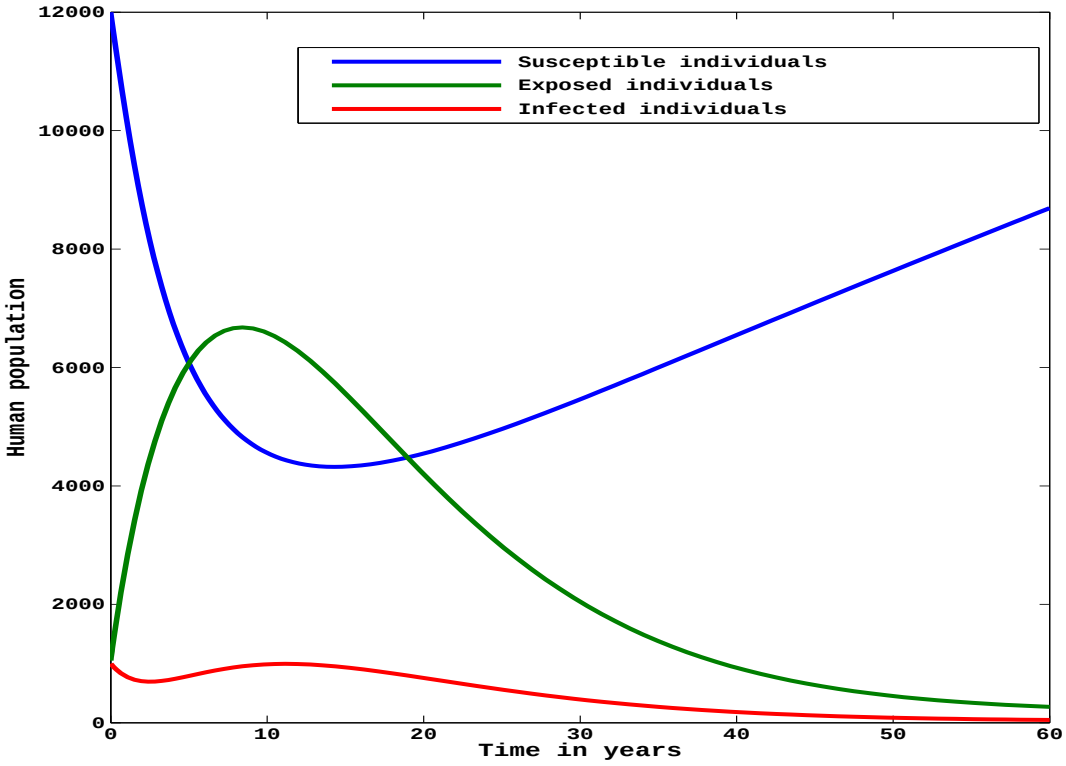


Figure 6.12: Illustrates the dynamics of susceptible, latent and infected humans in malaria model with intervention strategies using parameters in Table 6.12.

Despite being given ITNs and spraying long lasting chemicals in the houses, the campaign needs to be revisited to confirm whether the chemicals are still effective. The initial decrease of the graph explains that the effectiveness of the ITNs and the IRS deteriorates with time. Hence it is necessary to assess the right time interval to carry out the respraying of the houses and the resupply of ITNs.

Chapter 7

Conclusion and recommendations

7.1 Conclusion

An optimal control model (using a deterministic system of nonlinear ordinary differential equations) for the transmission dynamics of malaria in Karonga District, Malawi was presented. The model considered a varying total human population that incorporated recruitment of new individuals into the susceptible class through birth or immigration, and those immigrant individuals who were exposed to the disease were recruited into the exposed class. The prevention (IRS and ITNs) and other treatment intervention strategies were included in the model to assess the potential impact of these strategies on the transmission dynamics of the disease.

Our model incorporated features that were effective in controlling or reducing the transmission of malaria disease in Malawi. Analysis of the optimal control model revealed that there exists a domain where the model is epidemiologically and mathematically well-posed. We also computed the effective reproduction number, $\mathcal{R}_e$, then qualitatively analyzed the existence and stability of the model equilibria.

The basic reproduction number, $\mathcal{R}_0$, was obtained from the threshold reproduction number by eliminating all the intervention strategies. Then it was proved that if $\mathcal{R}_e < 1$, the disease cannot survive in the district. Hence the effective reproduction number, $\mathcal{R}_e$, is an essential indication of the effort required to eliminate the disease. It was also found that $\mathcal{R}_e \leq \mathcal{R}_0$ which implied that increased preventive and control intervention practices had a positive impact on the reduction of $\mathcal{R}_e$. Thus, malaria can be eradicated in the district by deployment of a combination of intervention strategies such as effective mass drug administration and vector control (LLITNs or ITNs and IRS) to combat and eventually eliminate the disease.

Analysis of the model supported that effective control or eradication of malaria can be achieved by the combination of protection and treatment measures. We have seen that when the three intervention strategies are combined, there is a greater reduction in the number of exposed and infected individuals. The prevention strategies played a greater role in reducing the number of infected individuals by lowering the contact rate between the mosquito and human populations for instance through the use of ITNs or LLITNs. On the other hand both prevention strategies led to the reduction of the mosquito population, hence lowering the infected mosquito population. Effective treatment consolidated the prevention strategies. Hence making control strategies readily available to both populations can play an important role in reducing or eradicating malaria disease in Karonga District, Malawi or in the country.

This study agrees with Chavez et al. [16] who suggested that the intervention strategy of using ITNs represents an excellent example of implementing an infectious disease control programme, and the Smith and Hay [112] study, which showed that both regular and non-fixed spraying resulted in a significant reduction in

the overall number of mosquitoes, as well as the number of malaria cases in the human population. Hence the combination of these two findings, and treatment as an additional intervention measure, showed great impact in the reduction of the spreading of the disease. Therefore the combination of these intervention strategies can play a more important role in reducing or eradicating the transmission of malaria disease in the district. This study provides useful tools for assessing the effectiveness of a combination of the three intervention strategies and analyzing the potential impact of prevention with treatment.

Malaria is a common disease in sub-Saharan Africa which most people suffer from despite their knowledge of how it is transmitted as well as the preventive measures [1]. The probable reasons for malaria mortality are that the preventive measures are only within an individual's home. As such when an individual is not within their home environment then they are vulnerable to mosquito bites.

Demographic findings also showed that the preventive measures namely ITNs and IRS if effectively practised, can help to reduce malaria transmission. These primary health intervention strategies are very important as they reduce the mosquito population, and contacts between the human and mosquito populations. These practices will lead to a reduction in the transfer of Plasmodium between the host and the vector. However, Dzinjalamala [26] states that malaria control in Malawi is still heavily reliant on chemotherapy. Hence the approach needs to change and effectively accommodate the campaign strategy taking place in Karonga District in order to combat the disease. Therefore, the presumptive treatment for fever and the primary health intervention practices (LLITNs and IRS) should both be effectively implemented or practised in order to reduce or eliminate malaria disease.

Using the optimal values of the three intervention practices (LLITNs, IRS and presumptive treatment), the results showed that the combination of the three intervention strategies has a positive and greater impact in eliminating or reducing the epidemic of malaria. This can be achieved when the measures are effectively implemented by the suppliers and effectively practised by the beneficiaries (the community members). Therefore the results indicate that treatment needs to be consolidated with preventive measures (ITNs and IRS) to circumvent the malaria epidemic effectively.

The combination of the three strategies has also shown that the approach is cost-effective compared to the other combinations of the three intervention measures such as the combination of ITNs and IRS, treatment and IRS, and treatment and ITNs. The second in the effectiveness and less costs in order to overcome the malaria epidemic is the combination of LLITNs and IRS. Therefore from the results obtained, it can be deduced that the intervention strategy of combining two preventive measures (ITNs and IRS) and presumptive treatment is the best and cost-effective method when carried out well in order to eliminate or eradicate malaria disease. This can be well achieved with the positive response and active participation of the community members in control programs in order to succeed in this malaria control strategy in Karonga District, Malawi.

In order to have a realistic chance of effectively controlling and eradicating the spread of malaria, the treatment programs must be complemented with other intervention strategies such as vector reduction and personal protection. Intervention practices that involve both prevention and treatment controls yield relatively better results. The combination of these strategies can play a positive role in Karonga District in reducing or eradicating malaria disease. Therefore, control and prevention efforts

aimed at lowering the infectivity of infected individuals to the mosquito vector will contribute greatly to the reduction of malaria transmission and this will eventually lower the prevalence of malaria and the incidence of the disease in the community. This can be achieved by prompt provision of effective prevention measures and antimalarial drugs for treatment to reduce transmission and death.

Other preventive measures need also to be considered. Individuals need to eliminate the existence of mosquitoes by eradicating breeding grounds for mosquitoes such as stagnant water and bushes by using biological and environmentally friendly preventive measures. If every home in a community could clear bushes and remove stagnant water within their surroundings, they could move away breeding grounds for mosquitoes to a significant distance away so that they are unable to reach the houses of the population.

7.2 Recommendations

As the resurgence of malaria continues to take its toll on individuals and communities in Karonga District and in Malawi as a whole, the policy makers need to be informed about the research results. The following recommendations should be taken into consideration:

1. Community participation and health education strategies promote awareness of malaria and the importance of control measures. Hence the community members should be aware of the intervention strategy being supplied to them and they should also take part during the implementation. This helps to reduce the incidence of malaria.

2. Since most of the reductions in transmission come from the protection of a few

humans, it is far more important to improve the elimination effects of LLITNs and the IRS around those who are mostly exposed to malaria. However, complete coverage and improved elimination effects may be necessary to reach control goals.

3. Vector control intervention strategies such as ITNs and IRS are proving effective in combating and preventing the disease in Karonga District, Malawi. The ITNS and IRS with insecticidal and diversionary properties, would reduce the availability of hosts, and kill mosquitoes that are attempting to feed on human blood, and thus reduce malaria transmission.

4. Since the set of intervention strategies is appropriate for the transmission regime, such as a combination of prevention and treatment, and it is implemented at the appropriate targeted scale in many endemic areas in the district or in the country, the malaria related millennium development goals can be achieved well before an effective vaccine is available.

5. Optimal control programs lead to effectively reduce the number of infectious individuals in all cases. Numerical simulations of the malaria model suggest that the use of of mosquito-reduction strategies (ITNs and IRS) is more effective in reducing the disease cost than person protection. Hence much emphasis needs to be put forward on the mosquito-reduction strategies to get rid of Plasmodium and thereafter treatment should follow to deal with those affected. Therefore the campaign of the combination of preventive-reduction and treatment which is taking place in Karonga District should be implemented in all districts in the country if the government commits itself to eradicate the malaria epidemic.

6. Because of the complications of measuring malaria at different transmission levels with different immunological status prevalent in different age and gender

groups, and across different locations, some guidelines should be developed to give researchers and health professionals a more accurate foundation on which to select indicators.

7.3 Future work

The proposed model has some limitations. We did not consider infective immigrants. Also, the population was not stratified by vulnerable groups such as children and pregnant women as it is well-known that malaria disproportionately affects children under the age of five years and pregnant women [41]. Hence the inclusion of immigrants and vulnerable groups in the model could shed more light on which intervention strategy to prioritize to specific groups.

In addition, the model can be extended by including the effects of environment such as the impact of climatic change on the spread of malaria. Seasonal environmental factors such as temperature, rainfall and humidity affect some parameters in the model, such as, the incubation period of mosquitoes and birth rate of mosquito population. The parameters can be modeled as periodic functions of time.

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Appendix A

University ethical approval

Research Office

HUMAN RESEARCH ETHICS COMMITTEE (NON MEDICAL)
R14/49 Mwantobe

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER H13/03/04**
PROJECT TITLE	Optimal control of intervention strategies for malaria epidemic in Karonga District, Malawi
INVESTIGATOR(S)	Mr PMM Mwantobe
SCHOOL/DEPARTMENT	Computational & Applied Mathematics/
DATE CONSIDERED	15/03/2013
DECISION OF THE COMMITTEE	Approved unconditionally
EXPIRY DATE	21/04/2015
DATE 22/04/2013	**CHAIRPERSON** (Professor M Williams, Acting Chairperson)

cc: Supervisor : Professor S Abelman

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.

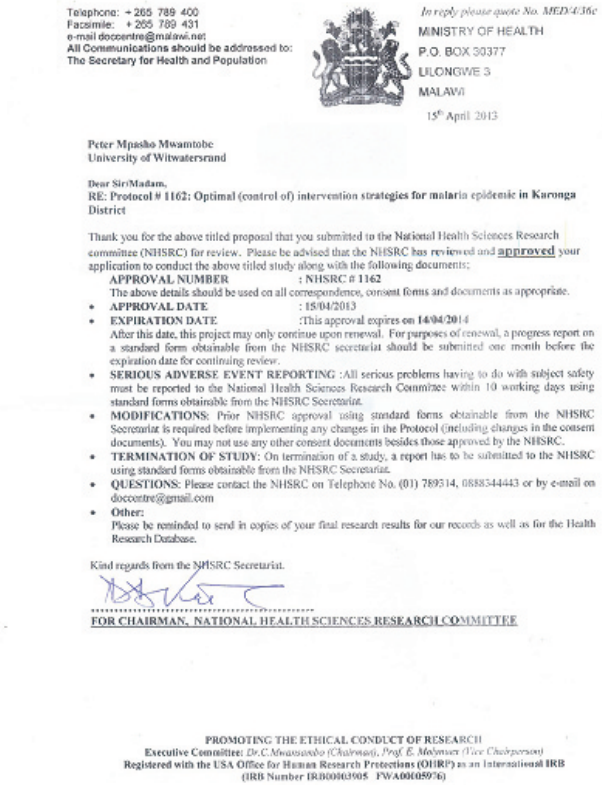
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to completion of a yearly progress report.**

Signature _____ Date _____/_____/_____

PLEASE QUOTE THE PROTOCOL NUMBER ON ALL ENQUIRIES

Appendix B

Malawi ethical approval



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All Communications should be addressed to:
The Secretary for Health and Population

In reply please quote No. MED/4/36c

MINISTRY OF HEALTH
P.O. BOX 30377
LILONGWE 3
MALAWI

15th April 2013

Peter Mpasho Mwamtobe
University of Witwatersrand

Dear Sir/Madam,

RE: Protocol # 1162: Optimal (control of) intervention strategies for malaria epidemic in Karonga District

Thank you for the above titled proposal that you submitted to the National Health Sciences Research committee (NHSRC) for review. Please be advised that the NHSRC has reviewed and **approved** your application to conduct the above titled study along with the following documents:

APPROVAL NUMBER : NHSRC # 1162

The above details should be used on all correspondence, consent forms and documents as appropriate.

- **APPROVAL DATE** : 15/04/2013
- **EXPIRATION DATE** :This approval expires on 14/04/2014
  After this date, this project may only continue upon renewal. For purposes of renewal, a progress report on a standard form obtainable from the NHSRC secretariat should be submitted one month before the expiration date for continuing review.
- **SERIOUS ADVERSE EVENT REPORTING** :All serious problems having to do with subject safety must be reported to the National Health Sciences Research Committee within 10 working days using standard forms obtainable from the NHSRC Secretariat.
- **MODIFICATIONS**: Prior NHSRC approval using standard forms obtainable from the NHSRC Secretariat is required before implementing any changes in the Protocol (including changes in the consent documents). You may not use any other consent documents besides those approved by the NHSRC.
- **TERMINATION OF STUDY**: On termination of a study, a report has to be submitted to the NHSRC using standard forms obtainable from the NHSRC Secretariat.
- **QUESTIONS**: Please contact the NHSRC on Telephone No. (01) 789314, 0888344443 or by e-mail on doccentre@gmail.com
- **Other:**
  Please be reminded to send in copies of your final research results for our records as well as for the Health Research Database.

Kind regards from the NHSRC Secretariat.

.....
FOR CHAIRMAN, NATIONAL HEALTH SCIENCES RESEARCH COMMITTEE

PROMOTING THE ETHICAL CONDUCT OF RESEARCH
Executive Committee: *Dr.C.Mwansambo (Chairman), Prof. E. Malamsen (Vice Chairperson)*
Registered with the USA Office for Human Research Protections (OHRP) as an International IRB
(IRB Number IRB00003905 FWA00005976)