KWAME NKRUMAH UNIVERSITY OF SCIENCE AND TECHNOLOGY

A MATHEMATICAL MODEL TO CONTROL THE SPREAD OF MALARIA IN GHANA

BY

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(BSc. MATHEMATICS, CERTIFICATE IN EDUCATION)

A Thesis submitted to the Department of Mathematics

in partial fulfillment of the requirements for the award of the degree

of

MASTER OF PHILOSOPHY IN MATHEMATICS

COLLEGE OF SCIENCE

JUNE, 2012

DECLARATION

I hereby declare that this submission is my own work towards the Master of Philosophy (MPhil) and that, to the best of my knowledge, it contains no material previously published by another person nor material which has been accepted for the award of any other degree of the University, except where due acknowledgement has been made in the text.

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ABSTRACT

Malaria is a serious health problem in Ghana and is reported by the Ministry of Health to be responsible for more than 44 percent of outpatient visits and approximately 22 percent of deaths in children under the age of five, which means there is a lot of work to be done if the country wants to achieve the goals set by Roll Back Malaria Partnership (RBM), a global initiative that coordinates actions against malaria. The goal of this thesis is to use clinical malaria data from Ghana Health Service to develop a mathematical model to help control the spread of malaria in Ghana in order to perhaps meet the target year given by RBM programme. The model consists of seven non-linear differential equations which describe the dynamics of malaria with 4 variables for humans and 3 variables for mosquitoes. We perform stability analysis of the model and the next generation method is used to derive the basic reproduction number R_0. We have proved that the disease-free equilibrium is locally asymptotically stable if $R_0 < 1$ and unstable when $R_0 > 1$. The Centre Manifold theorem is used to show that the model has a unique endemic equilibrium which is locally asymptotically stable when $R_0 < 1$. The basic reproduction number for Ghana is found to be $R_0 = 0.8939$. Numerical simulation of the model suggests that the most effective strategy for controlling or eradicating malaria is to combine the use of insecticide-treated bed nets, indoor residual spraying and chemotherapy, but the best strategy is to reduce the biting rate of the female anopheles mosquito through the use of insecticide-treated bed nets and indoor residual spraying since the malaria parasite has developed resistance to some of the antimalarial drugs.

ACKNOWLEDGEMENTS

I am eternally indebted to Yahweh God, Yeshua Messiah and The Holy Spirit who will never leave nor forsake those who diligently trust in HIM no matter what happens.

My most sincere thanks also go to my supervisor Dr. Francis T. Oduro for his patience in me while I was trying to learn so many things within a short time. Thanks for reading the thesis and your useful comments. I would never have finished the thesis without you. Thanks for everything! My deepest appreciation goes to all the lecturers (both classical and contemporary) at the Department of Mathematics in Kwame Nkrumah University of Science and Technology, Kumasi. If today I can teach mathematics, then it is because of the good tuition I have received from the Department of Mathematics. My sincere thanks go to Prof. B.W.L. Lawson at the Department of Biological Sciences for given me insights into transmission dynamics of malaria in Ghana.

My deepest gratitude goes to my wife, Pearl and children Ephraim and Angel for their love, support and patience as I spent time away while pursuing my studies. I am forever thankful to my parents and family members for their love and support.

I am grateful to Hilary Atiawu and Joseph Nana Wodzebeyew and all those who assisted me in diverse ways during the completion of this thesis. I would also like to thank the postgraduate students at the Department of Mathematics, for their contribution and encouragement during the whole period of my study.

Finally, I am indebted to the Headmaster and staff of Saint Martin's Senior High School in Nsawam for their support, not forgetting the immediate past Headmaster of the school, Rev. Fr. John Acheampong.

DEDICATION

To my wife, children, extended family and all those who inspired me.

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CHAPTER 1

INTRODUCTION

1.0 BACKGROUND TO THE STUDY

Malaria is a life-threatening disease caused by a protozoan parasite called Plasmodium, which lives part of its life in humans and part in Anopheles mosquitoes. The development of malaria parasites in a human host commences in the liver cells where the malaria parasites undergo asexual multiplication to produce merozoites that are eventually released into the blood stream to invade red blood cells. The infected red blood cells burst after 2–3 days to release merozoites and gametocytes into the blood stream. This is associated with the clinical symptoms of the disease. Anopheles mosquitoes become infected when they feed and ingest human blood that contains mature gametocytes. The gametocytes develop into male and female gametes that fertilize to become zygotes in the mid-gut wall of the mosquito. The zygote elongates to become ookinete and penetrates the mid-gut epithelium that later develop and ultimately produce sporozoites which become infective when they migrate to the salivary glands (Tumwiine et al, 2007).

The disease is endemic in tropical and subtropical regions, including Africa, Asia, Latin America, the Middle East and some parts of Europe. According to the WHO report 2010, it is estimated that the number of cases of malaria rose from 233 million in 2000 to 244 million in 2005 but decreased to 225 million in 2009 and the number of deaths due to malaria is estimated to have decreased from 985 000 in 2000 to 781 000 in 2009. Most of the malaria related deaths occur mostly in sub-Saharan Africa and in children less than five years.

There are more than 100 different species of Plasmodium parasites, but only four species of parasites can cause infections in humans, namely Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae and Plasmodium ovale (Understanding Malaria, Fighting an Ancient Scourge, February 2007, www.niaid.nih.gov). The following three species are found in Ghana: Plasmodium falciparum, Plasmodium malariae and Plasmodium ovale. Plasmodium falciparum is responsible for most of the deaths and morbidity associated with malaria in Ghana, accounting for about (90- 98) % of malaria cases. Only infected female Anopheles mosquitoes can transmit malaria and they must have been infected through a previous blood meal taken on an infected person. When a mosquito bites an infected person, a small amount of blood is taken in which contains microscopic malaria parasites. About 1 week later, when the mosquito takes its next blood meal, these parasites mix with the mosquito's saliva and are injected into the person being bitten. There are three species that transmit the disease in Ghana: Anopheles gambiae, Anopheles arabiensis and Anopheles funestus (Ministry of Health, 2009).

Because the malaria parasite is found in red blood cells of an infected person, malaria can also be transmitted through blood transfusion, organ transplant, or the shared use of needles or syringes contaminated with blood. Malaria may also be transmitted from a mother to her unborn infant before or during delivery ("congenital" malaria) (Malaria.com, 2011).

The early people attributed the malaria fevers to evil spirits, angered deities, demons, or the black magic of sorcerers. The ancient Chinese believed the frightening symptoms and signs to be the work of three demons, one with a hammer, one with a bucket of cold water, and a third with a stove. The ancient Romans worshiped a fever goddess, three demons rolled into one. Babylonian cuneiform script attributes malaria to a god, pictured as a mosquito-like insect. In

800 BCE the Indian sage Dhanvantari wrote that bites of mosquitoes could causes diseases, fever, shivering etc. In 1696 Morton presented the first detailed description of the clinical picture of malaria and its treatment with cinchona. Fransesco Torti, professor of medicine at Modena, accurately described the intricate course of the disease that was curable by the cinchona in 1712. One American physician, James K. Mitchell, wrote that malaria was due to certain spores present in marshy regions. This possible relationship was so firmly established that it gave the two most frequently used names to the disease *mal'aria*, which later shortened to one word '*malaria'*. The term malaria is derived from the Italian words mala "bad" and aria "air" which was used by the Italians to describe the cause of intermittent fevers associated with exposure to marsh air or miasma. Up to that point the various intermittent fevers had been called jungle fever, marsh fever, paludal fever, or swamp fever.

In 1884, Russian physiologist, Basil Danielewsky identified parasites of malaria in the blood of wild birds and in the same year, Marchiafava and Celli demonstrated active amoeboid ring in unstained blood and named it Plasmodium. The name chosen for the parasite by them turned out to be an incorrect one, since the organism is not actually a plasmodium. But the name stuck despite years of haggling. On August 20, 1897, Ronald Ross demonstrated oocysts in the gut of anopheline mosquito at Secunderabad, India, proving that mosquito was the vector for malaria. In September 1898, Italian physician Giovanni Battista Grassi was able to report that this insect, Anopheles claviger, was the carrier of human malaria.

In 1973 human protection from malaria by vaccination was first reported. For about 20 years, progress occurred mainly in experimental models rather than in human vaccine trials. In 1987, Dr. Manuel Elkin Patarroyo, a Colombian biochemist, developed the first synthetic Spf66 vaccine against P. falciparum parasite. But phase III trials showed that lacked efficacy. During

the past 5 years, many candidate vaccine approaches have been tested in clinical trials. The genome sequences of Anopheles gambiae and Plasmodium falciparum were published in 2002 and those of P. vivax and P. knowlesi in 2008.

Research information on history of malaria in Ghana can be traced back to the 1950s, that is, Gold Coast era. In 1946, Beet suggested that the sickle-cell trait might protect the bearer from the effects of malaria in hyper endemic malarial areas, thus accounting for the high incidence of the trait in certain parts of Africa. Therefore, in 1954-5, two doctors M.J. Colbourne and G.M. Edingiton from the Medical Research Institute in Accra carried out sickling tests during routine malaria surveys on two groups: Frafras in the Northern Territories of the Gold Coast then and inhabitants of Accra (mainly Ga). They investigated 680 Frafras inhabiting the small village of Yorugu and 1,015 inhabitants of Accra. In Accra the sickle-cell trait appeared partially to protect the bearer against P. falciparum infection in all age groups, whereas no protection over the age of 1 year was noted in sicklers in the North. The sickle-cell trait was not found to give protection against P. malariae infection in either district. A group of Accra schoolchildren was also observed, and it was found that malaria was responsible for morbidity in both sicklers and non-sicklers.

In Ghana traditional herbalists were using medicinal plants to treat malaria before the introduction of orthodox medicine. Some of the plants species commonly used are Neem tree and its leaves, pawpaw leaves, etc. In 1950s, Ghana with the support from WHO, added indoor residual spraying using DDT as one of the measures to control mosquitoes. Many households in Volta and Northern regions benefited. Accra and its surrounding areas also had aerial spraying. During the same period, Chloroquine was added to salt and sold at various Post Offices. From

the 1970 onwards the use of Chloroquine as malaria drug was intensified at all health facilities in Ghana (Action Alert, 2007).

Malaria is normally referred to fever and its names in some Ghanaian languages are, in Twi is called 'hurae' or 'etiridii' (fever), Dangme is 'asra' (fever) or 'asraku' (very high fever), Buli and Kasim is 'pua' (Adongo et al, 2005) and Ga is 'atridii' (fever). According to the Anti-Malaria Drug Policy for Ghana document in 2009, Malaria remains hyper endemic in Ghana and is the single most important cause of mortality and morbidity especially among children under five years, pregnant women and the poor. In 2006, the disease accounted for 38.6% of all outpatient illnesses and 36.9% of all admissions. Malaria prevalence per thousand populations was 171 and 2,835 malaria-attributable deaths (all ages) representing 19% of all deaths were recorded. Infection rates are high in children peaking at more than 80% in those aged (5 – 9) years and falling to low levels in adults. Malaria infection during pregnancy causes maternal anaemia and placental parasitemia both of which are responsible for miscarriages and low birth weight babies among pregnant women. It accounts for 13.7% of all admissions of pregnant women in 2006 and 9.0% of them died. According to UNICEF Ghana Fact Sheet July 2007 report , 3.5 million people contract malaria every year and approximately 20,000 children die from Malaria every year (25 per cent of the deaths of children under the age of five). Even if a child survives, the consequences from severe malaria such as convulsions or brain dysfunction can hamper long-term development and schooling.

According to Martcheva and Hoppensteadt (2010), WHO, the World Bank and several charitable organizations launched in 1998 the Roll Back Malaria Partnership (RBM), a global initiative that coordinates actions against malaria. The mission of the RBM Partnership has more recently been outlined in its Global Malaria Action Plan. Some of the major goals of the Partnership are (1) Reduce global malaria cases from 2000 levels by 50% in 2010 and by 75% in 2015; (2) Reduce

global malaria deaths from 2000 levels by 50% in 2010, and to near zero by 2015; (3) Eliminate malaria in 8-10 countries by 2015; and eventually (4) Achieve eradication of malaria world-wide.

Since 1998, Ghana has committed itself to the RBM Initiative. The country drew up a 'Medium Term Strategic Plan for Malaria Control in Ghana' (1998-2002), which sought to improve the coverage of malaria control activities by adopting an inter-sectoral approach involving and promoting partnership with the private sector and the community. It has also committed itself to the Abuja Declaration on Roll Back Malaria in Africa, which similarly seeks to achieve specific targets on malaria prevention and control.

In Ghana, as well as globally, the P. falciparum parasite has developed resistance to commonly used antimalarials such as Chloroquine which poses a serious challenge to the mono therapies. In this regard, in 2002 Ghana initiated the process of using Artemisinin based combination therapies (ACTs) following WHO recommendations for all countries experiencing resistance to mono-therapies in the treatment of falciparum malaria. Artesunate-Amodiaquine was selected as the first line drug for the treatment of uncomplicated malaria, but due to the challenges such as adverse drug reactions, lack of other treatment options and safety concerns faced by the Health sector, two additional ACTs namely; Artemether-Lumefantrine and Dihydroartemisinin/Piperaquine were also added. Quinine or Intramuscular Artemether is the drugs of choice for treating complicated malaria. Pregnant women with severe malaria are put on parenteral Quinine (Intravenous or Intramuscular in all trimesters) until the patient can take oral preparations.

According to UNICEF Ghana Fact Sheet July 2007 report, as part of the measures to prevent Malaria, Ghana health Service (GHS) in cooperation with local government authorities and UNICEF has distributed Insecticide Treated Nets (ITNs) to over 20 per cent of children below 5

and pregnant women through community bed nets sales agents, antenatal clinics and child immunization clinics in the Upper East, Upper West and Northern Regions.

Malaria has a huge social, economic and health burden on the world, particularly in the tropical countries. According to World Health Organization (WHO) report 2010, the amount estimated for malaria control in 2010 was more than US$6 billion, but received US$1.8 billion from the international sources, which represents less than 30% of the amount aiming at. It is therefore means that, the government of malaria endemic country will receive less financial support from WHO and rest of the budget for malaria will come from country's Gross Domestic Product (GDP) , which will negatively affect the country's economic growth. In 2009, Ghana's Minister of Health then, Dr. George Sipa-Adjah Yankey said that the government of Ghana spends over $760 million every year treating malaria which is almost the entire budget for the health sector and an amount of over GH¢921 million was allocated for the health sector that year (Ghana Business News, 2009).

1.1 STATEMENT OF THE PROBLEM

Malaria is a serious health problem in Ghana which is responsible for up to 40% of daily out-patient consultations at hospitals and clinics and over 23% of deaths in children under five years of age (Buabeng et al, 2007), which means there is more work to be done if the country wants to achieve the goals set by RBM Initiative. The disease also affects majority of the labour force especially the poor; therefore, the cost of treatment is indirectly transferred to the government, because they cannot afford it. So apart from the health consequences; malaria puts a heavy burden on productivity and hence economic development. Although, a lot of Malaria Control Programs are going on in the country, yet the disease seems to be still raging on. Hence, it is time

we introduce mathematical models into the fight against malaria in the country and that is the goal of this thesis. It has become necessary for the decision makers in Malaria Control Programs to understand the main parameters in the transmission of the disease and develop effective solution strategies for its prevention and control. We intend to use existing malaria data from Ghana Health Service to develop a mathematical model to understand the disease dynamics in Ghana and assist decision makers to formulate the best ideas to prevent, control and eradicate the disease. It is non-linear ordinary differential equations that will be used to form the model based on epidemiological compartmental modelling.

1.2 OBJECTIVES

The objectives of this thesis are the following:

1. To develop a mathematical model of the spread of malaria in Ghana taking both host and vector populations into account.
2. To perform stability analysis of the model.
3. To perform simulations in respect of various scenarios.
4. To interpret the results in view of management issues.

1.3 METHODOLOGY

We intend to use deterministic differential equation approach to model malaria where humans and mosquitoes interact and infect each other. The model will be based on the important intervention strategies we have in country such as clinical treatment and the death of the female Anopheles mosquito which is caused by natural death rate, indoor residual spraying (IRS),

insecticide treated bed nets (ITNs), etc. Temporary (time dependent) immunity will also be considered for human population. The model divides the human population into four classes: susceptible, exposed, infectious and recovered. There are also three classes for the mosquito population: susceptible, exposed, and infectious. Both species follow the logistic model for their population growth. Data for the thesis is obtained from the World Malaria Report 2010 under the aegis of WHO Global Malaria Programme through the internet. The data covers the period

2000 to 2009 and represents clinical cases of malaria in Ghana. The simulations will be conducted using MATLAB's ode45.

1.4 JUSTIFICATION

This thesis will assist Ghana's Malaria Control Programmes tremendously, because it will give decision makers and stakeholders a mathematical model to understand the transmission and spread of malaria in order to make precise policy interventions.

The thesis may also assist research scientists, mathematicians, etc to further develop suitable models to help public health professionals make better strategies for controlling the disease.

Finally, it will assist to measure the performance of the interventions the country has made in controlling the disease.

1.5 THESIS ORGANIZATION

The first chapter of the thesis talks about the introduction to the topic. It contains the background to the study, problem statement and objectives. The chapter two discusses literature review

(work done by other researchers in mathematical modelling of malaria and the methods applied). The third chapter provides the methodology the researchers intend to use model the problem or the topic. That is, formulation and analysis of the model. The fourth chapter is the results analysis (that is, computational procedure, discussion, significance and relating the results to the literature). Finally, chapter five provides conclusion on the model and findings of the study. It also gives recommendation to areas that can be researched in the future by other researchers.

CHAPTER 2

LITERATURE REVIEW

1.0 INTRODUCTION

For the last 100 years, different people have developed many mathematical models for malaria. In this chapter, we review the ones that are directly related to the objectives of this study.

Mathematical modeling of malaria began with Sir Ronald Ross while working at the Indian Medical Service in 1911, (Johansson and Leander, 2010). He developed a simple model, now known as the classical "Ross model" (Ross, 1915), which explained the relationship between the number of mosquitoes and incidence of malaria in humans. From the Ross's model, several models have been developed by researchers who extended his model by considering different factors such as latent period of infection in mosquitoes and humans, age-related differential susceptibility to malaria in human population, acquired immunity and genetic heterogeneity of host and parasite.

Ross in his first mathematical model of malaria used the word "pathometry" to mean "quantitative study of a disease either in the individual or in the community". Through his model, he showed that reduction of mosquito numbers "below a certain figure" (Transmission threshold) was sufficient to counter malaria, (Ross, 1915). The major advantage in Ross's models was his ability to provide a suitable control strategy through the Transmission threshold criterion which is based on the reproductive capacity of the parasite and is termed as basic reproductive number(R_0). Although the idea of threshold was first introduced by Ross, it originated from Fisher's "net reproductive value" for a parasite, (Fisher, 1930 and Mandal et al, 2011).

The figure 2.1 below is a piece of work done by Mandal et al. (2011). It gives the grouping of different types of malaria models developed by researchers in mathematical modelling of malaria. It will provide a pictorial background which would make the discussion easier to understand.

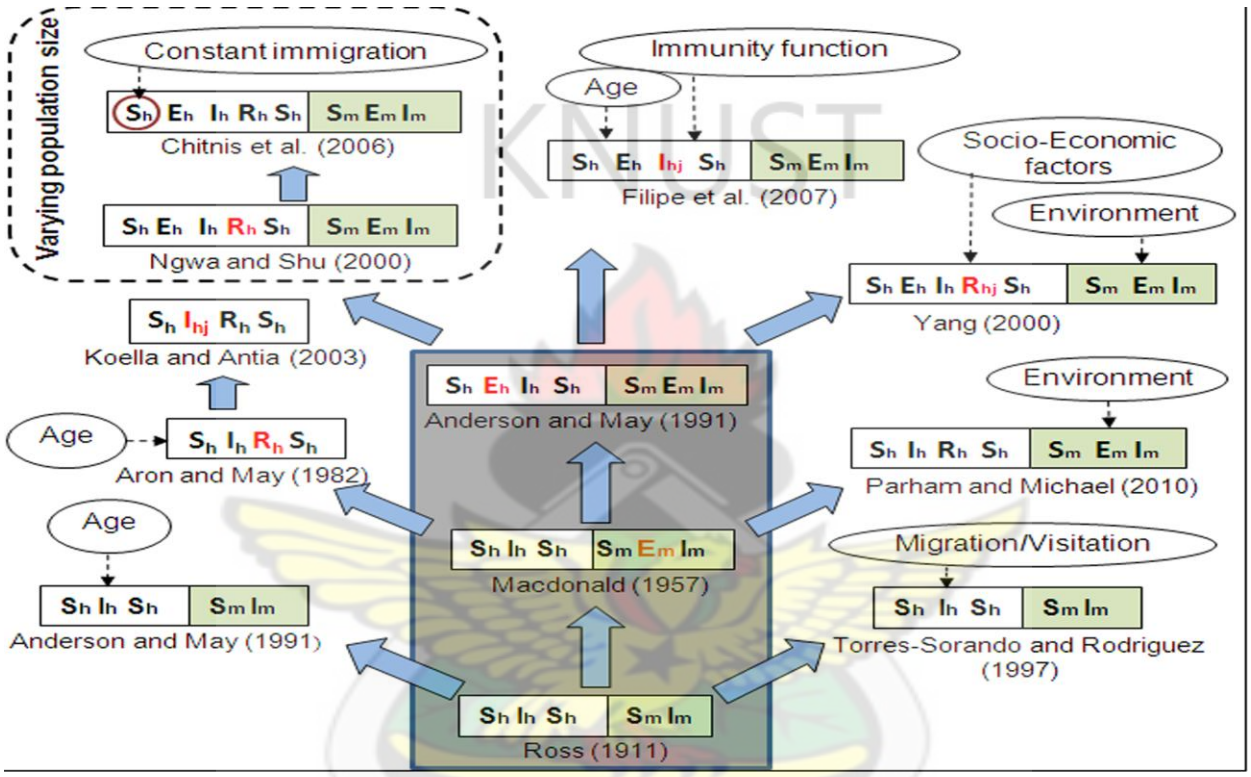

Figure 2.1 Evolution and grouping of different types of SEIR malaria models. Subscripts 'h' and 'm' stands for human and mosquito. Doublefolded boxes are for both human & mosquito population, and single fold boxes are only for human. First time addition of a new compartment is shown in red. The subscript 'j' (= 1, 2, 3) indicates further subdivision of the corresponding compartment. Three models inside the big grey box are considered as the Basic malaria models in this paper. Dotted arrows show the incorporation of complex factors in different models or specific compartment (red circle). Total population size is constant for all models, except the ones inside the dashed box.

In 1911, Ross introduced the first deterministic differential equation model of malaria by dividing the human population into susceptible (S_h) and infected (I_h) compartments, with the infected class returning to susceptible class again leading to the SIS structure. The mosquito population also has only two compartments (S_m, I_m), but they do not recover from infection due to their short life span, and thereby follow the SI structure. In the next section we will consider the introduction of latent or exposed class in mosquito population by George Macdonald.

2.1 INTRODUCTION OF EXPOSED CLASS IN MOSQUITO POPULATION

Ross did not consider the latency period of the parasite in mosquitoes and their survival during that period in his model. This resulted in the model predicting a rapid progress of the epidemic in human and a higher equilibrium prevalence of infectious mosquitoes. After about 40 years, George Macdonald, in the 1950s, reasserted the value of mathematical epidemiology based on 20 years of fieldwork. He modified Ross's model by integrating biological information of latency in the mosquito due to malaria parasite development, and concerned the survivorship of adult female mosquito as the weakest element in the malaria cycle. This provided the basis for a massive World Health Organization (WHO) coordinated campaign, which focused on using the insecticide dichlorodiphenyltrichloroethane (DDT) that killed mosquitoes, which resulted in the elimination of malaria transmission among 500 million people in Africa, (Macdonald, 1956 and Pampana, 1969).

Macdonald termed the latency period as t_m , and introduced the Exposed (E_m) class in the mosquitoes. Therefore, in his model the mosquito population is divided into three compartments

(SEI), and the model studies the time evolution of the exposed (E_m) and infected (I_m) classes in mosquito, (Macdonald, 1957).

2.2 AGE AND IMMUNITY IN HUMAN POPULATION

Aron and May (1982) added various characteristics of malaria to the Ross-Macdonald model, such as an incubation period in the mosquito, a periodically fluctuating density of mosquitoes, super infection and a period of immunity in humans. Aron and May proposed an age-specific immunity model with a new compartment - Immune (R_h) - in humans. This model, thus, consists of three compartments in humans: Susceptible(S_h), Infected (I_h) and Immune(R_h), and is a $SIRS$ model. They also include a continuum model for immunity where the dynamical variables are the population of asexual blood stages of Plasmodium in humans, the population of gametocytes (sexual stages of Plasmodium in humans), and the level of human immunity. In this system of partial differential equations, the variables depend on both time and age. The mosquitoes are modeled through V , the vectorial capacity, which is proportional to the mosquito density. This model is a significant deviation from the Ross-Macdonald model as it does not keep track of the number of infected humans and mosquitoes. Instead, this continuum model measures the number of parasites and level of immunity in the average human. This is useful for malaria because there can be a large difference in the parasitemia load in different humans, that the Ross-Macdonald model ignores, (Danso-Addo, 2009).

2.3 AGE AND EXPOSED CLASS IN HUMAN POPULATION

Anderson and May (1991) revisited many of the ideas discussed by Aron and May. Anderson and May in this addition, compile numerous data sets for parameter values, including the latent

period in mosquitoes and humans, the rate of recovery for humans, the expected adult lifespan of mosquitoes and malaria prevalence data across age distributions for humans. Anderson and May also studied the effect of adding age structure to the basic Ross model. Age structure was included by Anderson and May in the simple Ross model by considering the human population density. Finally, they looked at different control strategies, discussing the effects of a vaccine and the reduction of transmission rates on the malaria age-prevalence profile of the human population, (Anderson and May 1991).

2.4 MIGRATION AND VISITATION

The main two types of mobility patterns that can spread an infection to newer areas are migration, i.e., when the people move from one region to another with no returns and visitation, when the people return to their original region after visiting other regions. The effects of migration and visitation on transmission of malaria were shown by Torres-Sorando and Rodriguez by modifying the basic Ross model to include space that is split into A number of patches. Only humans are assumed to move among the patches and mosquitoes are evenly distributed. Their model results show that increase in mobility between patches enhances the persistence of the disease. Even though migration of humans does not change the equilibrium prevalence, equilibrium is reached faster for higher levels of migration. When there is visitation, the equilibrium prevalence increases with visitation time, and the time to reach the equilibrium decreases with increase in the intensity of visitation, (Torres-Sorando and Rodriguez, 1997).

2.5 SOCIAL AND ECONOMIC FACTORS

Yang (2000) showed how the basic reproductive number(R_0) of malaria transmission changes with global warming and local social and economic conditions (Yang and Ferreira, 2000). In his model good, intermediate and poor economic conditions among human community were considered and each condition was further divided into three temperature zones. A host of factors controlling disease transmission rates in his model are differential immunity, endemicity, resistance, economic conditions and temperature dependence of mosquito development. These lead to different (R_0) for three temperature zones with different socio-economic structures. These modelling results point out the requirement of proper management of the surrounding environment, along with good health care system, in disease transmission. From the point of view of designing field research, it is shown in a mosquito based model (Chitnis et al, 2010), that the effectiveness of malaria control through different types of intervention methods (insecticide-treated nets and indoor residual spraying) can have differential protection, with the former being more protective. The socio-economic situation for large scale deployment of interventions at the population level has also been addressed using modelling studies, (Killeen and Smith, 2007).

2.6 VARYING POPULATION SIZE

Total population size was assumed to be constant for all malaria models which came before Ngwa and Shu's model, (Mandal et al, 2011). Ngwa and Shu (1999) proposed an immunity model in which disease related death rate is considered to be significantly high, and the total population is not constant. The Ngwa-Shu model consists of four compartments in humans – Susceptible (S_h), Exposed(E_h), Infected (I_h) and Immune (R_h) and three compartments in mosquitoes – Susceptible(S_m), Exposed (E_m) and Infected(I_m). Mathematical analysis of the

model shows that the Basic Reproductive Number, R_0 , can describe the malaria transmission dynamics of the disease, where a globally stable disease-free state exists if $R_0 < 1$, while for $R_0 > 1$, the endemic equilibrium becomes globally stable. This model explicitly shows the role of inclusion of demographic effects (net population growth) in predicting the number of fatalities that may arise as a result of the disease.

In a similar theme, Chitins (2005) and Chitins et al (2006) included constant immigration of susceptible human population in their model. Considering immigration of people and excluding direct human recovery from the infectious to susceptible class as considered in Ngwa and Shu's model and other models. They showed that the population approaches the locally asymptotically stable endemic equilibrium point, or stable disease-free equilibrium point, depending on the initial size of the susceptible class.

2.7 OTHER IMMUNITY MODELS

Immunity can be described as a continuum of different levels of protection rather than a single class, as anti-malarial immunity develops slowly among people exposed to continuous and intense malaria transmission. Yang (2000) divided the immune class (R_h) in human population into immune(R_{h1}) , partially immune (R_{h2}) and non-immune but with immunologic memory(R_{h3}) , with each class having differential immunity. The mathematical analysis of Yang model shows that the effects of these three types of immune responses lead to delay in the reappearance of the individuals, who already had experienced malaria, to the susceptible population. Hence the community under high threat of malaria (high R_0) shows low prevalence of individuals with asexual blood-stage infection and without infectious gametocytes, whereas,

the same community is relatively free of severe infection due to the increase in immunity by re-infection.

Due to lack of confirmed markers of immunological protection, different processes that determine the immunity acquisition to clinical disease and to asymptomatic carriage of malaria parasites are poorly understood. The models discussed in the earlier section consider the immune individuals as a separate class, with no consideration of the types of processes that drive acquisition of immunity and its role in disease progression, (Mandal et al, 2011). In an insightful approach, Filipe et al (2007) introduced three age-specific "immunity-functions" in their SEI model for the human host, in which the infected humans are divided into three classes – infected with severe disease (I_{h1}), asymptomatic patent infection (I_{h2}), and infected with undetectable parasite density (I_{h3}). The effect of mosquito density is incorporated through the force of infection (h). The three immunity functions (IF) introduced in the Filipe model are - (1) Reducing the susceptibility to clinical disease, φ $(IF1)$, (2) speeding up of the clearance of detectable parasites, r_A $(IF2)$, and (3) increasing tolerance to sub-patent infections, r_{ij} $(IF3)$. These functions depend on age and disease transmission intensity (i.e., Entomological Inoculation Rate) in a complex manner.

They base their model assumptions on the fact that the rates at which both types of immunity - clinical and anti-parasite - develop are different. All these processes have widely varied time scales, which make the disease transmission in this age-structured population quite complex. The first two types of immune functions reproduced the epidemiological age-prevalence curves seen in empirical data better. The third one i.e. the tolerance to sub-patent infections, is not required to explain the empirical data.

2.8 HOST-PATHOGEN VARIABILITY AND RESISTANT STRAIN MODELS

Several mathematical models have been developed with pathogen population structure and heterogeneous host population to explain variable antigenic response, immune selection, pathogen strain structure, (Gupta and Galvani, 1999; Gupta and Anderson, 1999; and Recker et al, 2004). Addition of evolution of drug resistance, along with other factors, in the models can assist in the design of rational strategies for the control of drug resistance, (Hastings, 1997; Dye and Williams, 1997; Mackinnon, 2005). A number of resistant-strain models have been developed based on evolution of drug resistance through host immunity,(Koella and Antia (2003) and Chiyaka et al ,2009), and by considering the practical implications of the Artemisinin combination therapy (ACT) drug policies adopted by a lot of countries,(Pongtavornpinyo et al ,2008). Population genetic considerations of the cost of resistance are also included in this type of models, (Koella, 1998; and Boëte and Koella, 2002). More recent work elaborates the complexity of the process of drug resistance by considering the interaction of several environmental, pharmacological and genetic factors, (Antao and Hastings, 2011). In general, these resistant-Strain models divide the infected host population (I_h) into two compartments, i.e., infected by drug-sensitive strain and drug-resistant strain of the parasite. The model proposed by Koella and Antia (Koella and Antia, 2003), further divides the host population infected by drug-sensitive strain into two compartments - treated and untreated.

So this model consists of five compartments of human: susceptible(S_h) , sensitive, infected, and treated(I_{h1}), sensitive, infected, and untreated(I_{h2}), infected with the resistant strain(I_{h3}), and the recovered(R_h). The role of mosquito vector is included through inoculation rates of sensitive and resistant parasites. The main prediction of this model indicates that there is a threshold

proportion of people(f_c) among the infected and treated (I_{h1}) classes, below which resistance cannot spread, and above which resistance will eventually become fixed in the population. The model also shows that, in the absence of drug or treatment, the fitness of resistant parasite reduces with respect to sensitive parasite; otherwise both the parasites have identical properties. In this case, sensitive and resistant parasites cannot co-exist.

2.9 ENVIRONMENTAL FACTORS

The basic reproductive numbers (R_0) for the early models depend crucially on the parameters related to mosquito density. Environmental factors, such as temperature, humidity, rainfall and wind patterns have great impact on mosquito reproduction, development and longevity and the parasite survival in its life cycle in mosquito. It is known that mosquito breeding is influenced by temperature – a change in temperature from 12°C to 31°C reduces the number of days required for breeding from 65 days to 7.3 days, (Li et al, 2002). The sporogony of the parasites in vector is completed in 55 days at 16°C, which reduces to 7 days at 28°C, (Martens et al, 1995). Influence of temperature and humidity change on the rate of transformation from juveniles to adults in the susceptible class of adult mosquitoes has been modelled, (Li et al, 2002). In addition, several mathematical studies have been performed to simulate the effect of environmental variability in the abundance of mosquito populations such as, random fluctuation in the form of colour noise in infected mosquito dynamics of Ross model,(Chattopadhyay et al,2004), periodic or noisy form of the force of infection,(Aron and May,1982 and Anderson and May ,1991). Several studies have also included the effect of environmental fluctuations in diverse ways with the aim to develop realistic and validated malaria modelling frameworks that are able to identify the crucial linkages between pathogen transmission processes and climactic

factors, (Martens et al, 1995; Yang, 2000; Yang and Ferreira, 2000; Hoshen and Morse, 2004 and Yé et al, 2009). In a recent study, Parham and Michael proposed a model (Parham and Michael, 2010), to study the dynamics of the mosquito population by considering simultaneous effects of rainfall and temperature. The model consists of three compartments in humans(S_h, I_h, R_h) with fixed duration of latency, and three compartments in mosquitoes(S_m, E_m, I_m) . Different environmental factors are introduced in this model through parameters related to mosquitoes. The birth rate of adult mosquito is considered to be a function of rainfall and temperature, whereas, mosquito mortality rate, biting rate, duration of sporogonic cycle and survival probability of infected mosquitoes over the incubation period of the parasite are considered to be dependent on temperature variation. The major finding of this model is that changes in rainfall patterns not only influence vector abundance, but also strongly govern malaria endemicity, invasion and extinction. However, when sufficient rainfall exists to sustain vector development and survival, then the temperature affects the pathogen life cycle, and has stronger influence on the rate of disease spread.

2.10 STOCHASTIC MODELS

Plasmodium life-cycle and mosquito population density are highly dependent on different internal processes and external environmental factors, which are probabilistic in nature. In many of the models discussed above, stochasticity has been included in different ways. Even when the main structure of the compartments is similar to the differential equation based models, stochasticity has been included through individual variability in individual based models (Gu et al, 2003, and Smith et al, 2008) and probabilistic variation in different variables and parameters of transmission processes and environmental factors (Smith, 2008; Saul, 1996; Craig et al, 1999

and Gaudart et al, 2009). Models integrating stochasticity with other factors such as, spatial contact structure and temporal forcing, also explain many interesting features of disease transmission (Dangerfield, 2009 and Parham and Michael, 2011).

2.11 CONCLUSION

From the public health point of view, decision makers will be more interested in knowing if the infection will die out, or persist in a population through the important parameter R_0 . In this literature review, efforts have been taken to group the epidemiological models of malaria in terms of the complexity of infection processes included in its description, which makes them more realistic. The age-specific distribution of infection due to differential immunity across age is one such case. The assumption is that more realistic models would enhance the understanding of the infection transmission process at the population level, which, in turn, may help in better prediction of intervention strategies. Pure mathematical analysis of the models, although not so popular among the biologists, is important. They provide clear understanding of the logic of the system behaviour in terms of the relationship among the parameters and variables, which are representative to real biological processes.

This literature review of different mathematical models of malaria would contribute to consolidate our understanding about the evolution of these models, and may also help in developing new models by incorporating features discussed above to improve predictions and deciding realistic control measures.

CHAPTER 3

MODEL FORMULATION

3.0 INTRODUCTION

In this chapter, we will use deterministic differential equation approach to develop malaria model where humans and mosquitoes interact and infect each other. The model will be based on the important intervention strategies we have in country such as clinical treatment and the death of the female Anopheles mosquito which is caused by natural death rate, indoor residual spraying (IRS), insecticide treated bed nets (ITNs), etc.

3.1 FORMULATION OF THE MODEL

We formulate a model similar to that of Chitnis (2005) describing the transmission of malaria. The model (Figure 3.1) divides the human population into 4 classes: Susceptible, S_h , the fraction of host population that is susceptible to infection; then comes the Exposed, E_h , the fraction of population who are infected , but not infectious and they cannot transmit the infection . The next is infectious, I_h , people who have been infected with malaria and are capable of spreading the disease to those in the susceptible class and finally, the recovered (immune), R , people who recover from the infection through clinical treatment with temporary immunity . These humans can not transmit the infection to mosquitoes because we assume that they have no plasmodium parasites in their bodies. People enter the susceptible class, either through birth or immigration at a constant rate. When an infectious anopheles mosquito bites a susceptible human, there is some finite probability that the parasite (in the form of sporozoites) will be passed on to the human and the person will move to the exposed class. The parasite then travels to the liver where it develops into its next life stage. After a certain period of time, the parasite (in the form of merozoites)

enters the blood stream, usually signaling the clinical onset of malaria. Then the exposed people become infectious and progress to infectious class. After some time, the infectious humans recover and move to the recovered class. The recovered humans have some immunity to the disease and do not get clinically ill, but after some period of time, they lose their immunity and return to the susceptible class. Humans leave the population through natural death and those in the infectious class have additional disease-induced death rate.

We do not include the immigration of infectious humans because we assume that most people who are sick will not travel. The movement of Exposed humans are excluded because, given the short time of the exposed stage, the number of exposed people is small. We do make a simplifying assumption that there is no immigration of recovered humans.

The female Anopheles mosquito population is divided into 3 classes: Susceptible, S_m , Exposed E_m and Infectious I_m . Anopheles male mosquitoes are not included in the model because only female mosquitoes bite humans for blood meals. Female mosquitoes enter the susceptible class through birth. The parasite (in the form of gametocytes) enters the mosquito, with some probability, when the mosquito bites an infectious human and the mosquito moves from the Susceptible to the Exposed class. After some period of time, dependent on the ambient temperature and humidity, the parasite develops into sporozoites and enters the mosquito's salivary glands; and the mosquito moves from the exposed class to the infectious class. The mosquito remains infectious for life. Mosquitoes leave the population through natural death rate and death caused by insecticides. We assume that longevity of the female Anopheles mosquitoes is unaffected by the parasite infection and do not die from the infection. There is no super infection of the disease. Mosquitoes cannot survive without human host as they need human blood to feed their developing eggs.

The main differences of our model, from that of Chitnis (2005) is that we have excluded the infection of female Anopheles mosquito by recovered humans, because we assume that these humans do not have sufficient plasmodium parasites in their bodies to transmit the infection to mosquitoes. Also, in our model, the infectious humans recover with clinical treatment and the death of the female Anopheles mosquito is caused by natural death rate and insecticides.

The state variables in Table 3.1 and parameters in Table 3. 2 below are used figure 3.1 to formulate the malaria model (3.1).

Table 3.1: The state variables for the malaria model (3.1).

Parameter	Description
$S_h(t)$	Number of susceptible humans at time t .
$E_h(t)$	Number of exposed humans at time t .
$I_h(t)$	Number of infectious humans at time t .
$R(t)$	Number of recovered (immune) humans at time t .
$S_m(t)$	Number of susceptible mosquitoes at time t .
$E_m(t)$	Number of exposed mosquitoes at time t .
$I_m(t)$	Number of infectious mosquitoes at time t .
$N_h(t)$	Total human population at time t .
$N_m(t)$	Total mosquito population at time t .

Table 3.2 Model parameters and their interpretations for the malaria model (3.1).

Parameter	Description
ψ	Recruitment rate of humans.
ρ	Recruitment rate of mosquitoes.
α_h	Force of infection of humans from susceptible state to exposed state.
α_m	Force of infection of mosquitoes from susceptible state to exposed state.
β_h	Rate of progression of humans from the exposed state to the infectious state.
β_m	Rate of progression of mosquitoes from the exposed state to the infectious state.
τ	Clinical treatment -recovery rate of humans from the infectious state to the recovered state.
μ	Natural death rate for humans.
ω	Death of mosquitoes caused by natural death rate and insecticides
π	Disease-induced death rate for humans.
φ	Rate of loss of immunity for humans.
θ_{mh}	Probability of transmission of infection from an infectious mosquito to a susceptible human provided there is a bite.
θ_{hm}	The probability of transmission of infection from an infectious human to a susceptible mosquito provided there is a bite.
ϕ	Biting rate of mosquitoes.

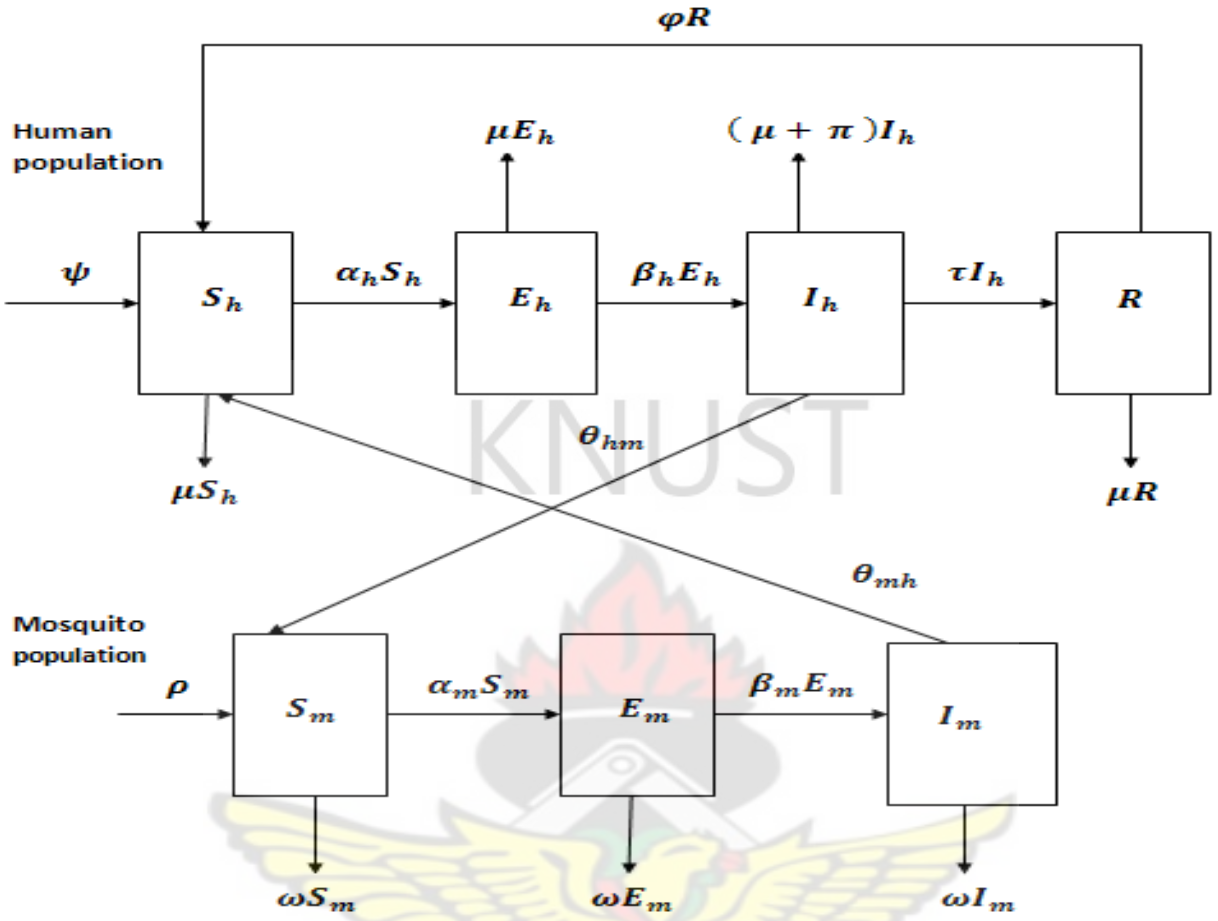

Figure (3 . 1): Schematic Diagram for the Malaria Model. Susceptible humans, S_h , get infected at a certain probability when they contact infectious mosquitoes. They then progress through the Exposed, E_h, Infectious, I_h and Recovered, R , classes, before reentering the susceptible class. Susceptible mosquitoes, S_m , get infected at a certain probability when they contact infectious humans and then move through the Exposed, E_m and Infectious, I_m , classes. Both species follow a logistic model for their population growth.

3. 2 EQUATIONS OF THE MODEL

Applying the assumptions, definitions of state variables and parameters above, the system of non-linear differential equations which describe the dynamics of malaria are formulated below:

$$\left.\begin{aligned}
\frac{dS_h}{dt} &= \psi + \varphi R - \alpha_h S_h - \mu S_h \\
\frac{dE_h}{dt} &= \alpha_h S_h - \beta_h E_h - \mu E_h \\
\frac{dI_h}{dt} &= \beta_h E_h - \tau I_h - (\mu + \pi) I_h \\
\frac{dR}{dt} &= \tau I_h - \varphi R - \mu R \\
\frac{dS_m}{dt} &= \rho - \alpha_m S_m - \omega S_m \\
\frac{dE_m}{dt} &= \alpha_m S_m - \beta_m E_m - \omega E_m \\
\frac{dI_m}{dt} &= \beta_m E_m - \omega I_m
\end{aligned}\right\} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.1)$$

with initial conditions

$S_h(0) = S_{h0}, E_h(0) = E_{h0}, I_h(0) = I_{h0}, R(0) = R_0, S_m(0) = S_{m0}, E_m(0) = E_{m0}, I_m(0) = I_{m0},$

where $\alpha_h = \frac{\theta_{mh}\phi I_m}{N_h}$ and $\alpha_m = \frac{\theta_{hm}\phi I_h}{N_h}$.

In the model, the term $\frac{\theta_{mh}\phi I_m S_h}{N_h}$ denotes the rate at which the susceptible humans S_h, become infected by infectious female Anopheles mosquitoes I_m and $\frac{\theta_{hm}\phi I_h S_m}{N_h}$ refers to the rate at which the susceptible mosquitoes S_m are infected by infectious humans I_h.

It is important to note that the rate of infection of susceptible human S_h by infected mosquito I_m is dependent on the total number of humans N_h available per vector, **(**Mwamtobe, 2010).

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

$$\left.\begin{aligned}\frac{dN_h}{dt} &= \frac{dS_h}{dt} + \frac{dE_h}{dt} + \frac{dI_h}{dt} + \frac{dR}{dt} \\ &= \psi - \mu N_h - \pi I_h\end{aligned}\right\} \ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.2)$$

$$\left.\begin{aligned}\frac{dN_m}{dt} &= \frac{dS_m}{dt} + \frac{dE_m}{dt} + \frac{dI_m}{dt} \\ &= \rho - \omega N_m\end{aligned}\right\} \ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.3)$$

3.3 ANALYSIS OF THE MODEL

We analyse the model to check if the intervention strategies have any impact on the diseases, that is, whether the disease be eradicated or not. The thresholds parameters which determine persistence or elimination of malaria will be determined and studied. Therefore, we start by determining the invariant region to check whether the model is biologically meaningful and showing that all solutions of (3.1) are positive for all $t \geq 0$ and are attracted in that region.

3.3.1 INVARIANT REGION

This region can be obtained by the following theorem.

Theorem 3. 1

The solutions of the system (3.1) are feasible for all t > 0 if they enter the invariant region $\Omega = \Omega_h \times \Omega_m$.

Proof:

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

In absence of the disease (malaria), that is, $I_h = 0$, equation (3.2) becomes

$$\frac{dN_h}{dt} \leq \psi - \mu N_h \ ,$$

$$\frac{dN_h}{dt} + \mu N_h \leq \psi \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.4)$$

The integrating factor for (3. 4) is $(IF) = e^{\int \mu dt} = e^{\mu t}$

Multiplying both sides of (3. 4) by $e^{\mu t}$ gives

$$e^{\mu t}\frac{dN_h}{dt} + \mu N_h e^{\mu t} \leq \psi e^{\mu t} \ ,$$

$$\frac{d}{dt}(N_h e^{\mu t}) \leq \psi e^{\mu t} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.5)$$

Integrating on both sides of (3. 5) we have

$$N_h e^{\mu t} \leq \frac{\psi}{\mu} e^{\mu t} + C \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.6)$$

where C is a constant of integration.

Dividing through (3. 6) by $e^{\mu t}$ gives

$$N_h \leq \frac{\psi}{\mu} + Ce^{-\mu t} \ ,$$

Using the initial conditions at $t = 0$, $N_h(0) = N_{h0}$:

$$N_{h0} \leq \frac{\psi}{\mu} + C \Longrightarrow N_{h0} - \frac{\psi}{\mu} \leq C \ ,$$

$$N_h \leq \frac{\psi}{\mu} + \left(N_{h0} - \frac{\psi}{\mu}\right)e^{-\mu t} \quad \ldots\ldots\ldots\ldots\ldots\ldots (3.7)$$

Applying the theorem of differential inequality (Birkhoff and Rota, 1982), we obtain

$$0 \leq N_h \leq \frac{\psi}{\mu} \ \ as \ t \longrightarrow \infty \ ,$$

Therefore, as $t \longrightarrow \infty$ in (3.7), the human population N_h approaches $K = \frac{\psi}{\mu}$ (that is, $N_h \longrightarrow K = \frac{\psi}{\mu}$), the parameter $K = \frac{\psi}{\mu}$ is usually called the carrying capacity, (Namawejje, 2011).

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

$$\Omega_h = \left\{ (S_h, E_h, I_h, R) \in R_+^4 : S_h > 0, E_h \geq 0, I_h \geq 0, R \geq 0, N_h \leq \frac{\psi}{\mu} \right\}.$$

Similarly, the feasible solutions set of the mosquito population enters the region

$$\Omega_m = \left\{ (S_m, E_m, I_m) \in R_+^3 : S_m > 0, E_m \geq 0, I_m \geq 0, N_m \leq \frac{\rho}{\omega} \right\}.$$

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

$$\Omega = \left\{ (S_h, E_h, I_h, R, S_m, E_m, I_m) \in R_+^7 : (S_h, S_m) > 0, (E_h, I_h, R, E_m, I_m) \geq 0 ; N_h \leq \frac{\psi}{\mu} ; N_m \leq \frac{\rho}{\omega} \right\}.$$

Therefore, the region Ω is positively-invariant (i.e. solutions remain positive for all times, t) and the model (3.1) is biologically meaningful and mathematically well-posed in the domain Ω.

3.3.2 POSITIVITY OF SOLUTIONS

Lemma 3. 1

Let the initial data be

$$\{(S_h(0), S_m(0)) > 0, (E_h(0), I_h(0), R(0), E_m(0), I_m(0)) \geq 0\} \in \Omega.$$

Then the solution set $\{S_h, E_h, I_h, R, S_m, E_m, I_m\}(t)$ of the system (3.1) is positive for all $t > 0$.

Proof

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

$$\frac{dS_h}{dt} = \psi + \varphi R - \alpha_h S_h - \mu S_h \geq -\alpha_h S_h - \mu S_h$$

$$\geq -(\alpha_h + \mu)S_h$$

Integrating by separation of variables gives

$$\int \frac{1}{S_h} dS_h \geq -\int (\alpha_h + \mu)\, dt \implies \ln S_h \geq -(\alpha_h + \mu)t + C \implies S_h(t) = e^{[-(\alpha_h+\mu)t + C]}$$

$$\implies S_h(t) \geq e^{-(\alpha_h+\mu)t} \times e^{C} = e^{-(\alpha_h+\mu)t} \times A = Ae^{-(\alpha_h+\mu)t}, \ \boldsymbol{A = e^{C}}$$

$$\implies S_h(t) \geq Ae^{-(\alpha_h+\mu)t}$$

$$At\ t = 0, \qquad S_h(0) \geq A \implies S_h(t) \geq S_h(0)e^{-(\alpha_h+\mu)t} \geq 0$$

Therefore,

$$S_h(t) \geq S_h(0)e^{-(\alpha_h+\mu)t} \geq 0 \ .$$

From the second equation,

$$\frac{dE_h}{dt} = \alpha_h S_h - \beta_h E_h - \mu E_h \geq -(\beta_h + \mu)E_h$$

$$\int \frac{1}{E_h} dE_h \geq \int -(\beta_h + \mu)dt$$

Therefore,

$$E_h(t) \geq E_h(0)e^{-(\beta_h+\mu)t} \geq 0 \ .$$

From the third equation,

$$\frac{dI_h}{dt} = \beta_h E_h - \tau I_h - (\mu + \pi)I_h \geq -(\tau + \mu + \pi)I_h$$

$$\int \frac{1}{I_h} dI_h \geq -(\tau + \mu + \pi)dt$$

Therefore,

$$I_h(t) \geq I_h(0)e^{-(\tau+\mu+\pi)t} \geq 0 \ .$$

Similarly, it can be shown that the remaining equations of system (3.1) are also positive for all $t > 0$, because $e^{\eta} > 0$ for all $\eta \in \mathbb{R}$.

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

3. 3. 3 EXISTENCE AND STABILITY OF STEADY-STATE SOLUTIONS

Steady state solutions or equilibrium points are the roots or solutions of the system of equations when the right-hand side of a nonlinear system is set to zero. That is, using the nonlinear system (3 . 1), we have

$$\left.\begin{aligned} \psi + \varphi R - \alpha_h S_h - \mu S_h &= 0 \\ \alpha_h S_h - \beta_h E_h - \mu E_h &= 0 \\ \beta_h E_h - \tau I_h - (\mu + \pi) I_h &= 0 \\ \tau I_h - \varphi R - \mu R &= 0 \\ \rho - \alpha_m S_m - \omega S_m &= 0 \\ \alpha_m S_m - \beta_m E_m - \omega E_m &= 0 \\ \beta_m E_m - \omega I_m &= 0 \end{aligned}\right\} \quad \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (3.8)$$

Let $(S_h^e, E_h^e, I_h^e, R^e, S_m^e, E_m^e, I_m^e)$ be the steady state of (3.1) which can be obtained by solving (3 . 8) .

3. 3. 4 EXISTENCE OF EQUILIBRIUM POINTS WITHOUT DISEASE

Disease-free equilibrium points (DFE) are steady state solutions where there is no malaria in the human population or Plasmodium parasite in the mosquito population.

Let define the "diseased" classes as the human or mosquito populations that are either exposed or infectious; that is, E_h , I_h , E_m and I_m .

In absence of the disease, this implies that ($E_h = I_h = E_m = I_m = 0$) , therefore (3 . 8) reduces to

$$\left.\begin{aligned} \psi - \mu S_h^{e_0} &= 0 \\ \rho - \omega S_m^{e_0} &= 0 \end{aligned}\right\} \quad \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (3 . 9)$$

which implies that

$$\left.\begin{aligned} S_h^{e_0} &= \frac{\psi}{\mu} \\ S_m^{e_0} &= \frac{\rho}{\omega} \end{aligned}\right\} \quad \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (3 . 10)$$

Therefore, the disease-free equilibrium point of the malaria model (3 . 1) is given by,

$$E_0 = \left(S_h^{e_0} , E_h^{e_0} , I_h^{e_0} , R^{e_0} , S_m^{e_0} , E_m^{e_0} , I_m^{e_0} \right) = \left(\frac{\psi}{\mu} , 0 , 0 , 0 , \frac{\rho}{\omega} , 0 , 0 \right) \dots\dots (3 . 11)$$

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

3. 3. 5 BASIC REPRODUCTION NUMBER R_0

We use the next generation operator approach as described by Diekmann et al. (1990) to define the basic reproduction number, R_0 , as the number of secondary infections that one infectious individual would create over the duration of the infectious period, provided that everyone else is susceptible.

Reproduction number R_0 is the threshold for many epidemiology models, it determines whether a disease can invade a population or not. When $R_0 < 1$, each infected individual produces on average less than one new infected individual, so we would expect the disease to die out. On the other hand, if $R_0 > 1$, each individual produces more than one new infected

individual, so we would expect the disease to spread in the population. This means that the threshold quantity for eradicating the disease is to reduce the value of R_0 to value less than one.

Let us outline the steps needed to compute the basic reproduction number.

The basic reproduction number cannot be determined from the structure of the mathematical model alone, but depends on the definition of infected and uninfected compartments. Let us assume that there are n compartments of which the first m compartments correspond to infected individuals.

Let

$\mathcal{F}_i(x)$ be the rate of appearance of new infections in compartment i,

$\mathcal{V}_i(x) = \mathcal{V}_i^-(x) - \mathcal{V}_i^+(x)$, where $\mathcal{V}_i^+$ is the rate of transfer of individuals into compartment i by all other means and $\mathcal{V}_i^-$ is the rate of transfer of individual out of the i th compartment.

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

$$\dot{x}_i = h_i(x) = \mathcal{F}_i(x) - \mathcal{V}_i(x), \quad i = 1, \dots n.$$

Where $\dot{x}$ is the rate of change of x.

The next step is the computation of the square matrices F and V of order ($m \times m$), where m is the number of infected classes, defined by $F = \left[\frac{\partial \mathcal{F}_i}{\partial x_j}(x_0)\right]$ and $V = \left[\frac{\partial \mathcal{V}_i}{\partial x_j}(x_0)\right]$ with $1 \leq i, j \leq m$, such that F is nonnegative, V is a nonsingular M-matrix and x_0 is the disease-free equilibrium point (DFE). Since F is nonnegative and V is nonsingular, then of V^{-1} is nonnegative and also of FV^{-1} is nonnegative. Hence the matrix of FV^{-1} is called as the next

generation matrix for the model. Finally, the basic reproduction number (reproduction ratio) R_0 is given by

$$R_0 = \gamma(FV^{-1}),$$

where $\gamma(A)$ denotes the spectral radius of a matrix A and The spectral radius, $\gamma(FV^{-1})$, is the biggest nonnegative eigenvalue of the next generation matrix .

Rewriting the system (3. 1) starting with the infected compartments for both populations; E_h, I_h, E_m, I_m and then followed by uninfected classes; S_h, R, S_m also from the two populations, then the model system becomes:

$$\left.\begin{aligned}
\frac{dE_h}{dt} &= \frac{\theta_{mh}\phi I_m S_h}{N_h} - (\beta_h + \mu)E_h \\
\frac{dI_h}{dt} &= \beta_h E_h - (\tau + \mu + \pi)I_h \\
\frac{dE_m}{dt} &= \frac{\theta_{hm}\phi I_h S_m}{N_h} - (\beta_m + \omega)E_m \\
\frac{dI_m}{dt} &= \beta_m E_m - \omega I_m \\
\frac{dS_h}{dt} &= \psi + \varphi R - \frac{\theta_{mh}\phi I_m S_h}{N_h} - \mu S_h \\
\frac{dR}{dt} &= \tau I_h - (\varphi + \mu)R \\
\frac{dS_m}{dt} &= \rho - \frac{\theta_{hm}\phi I_h S_m}{N_h} - \omega S_m
\end{aligned}\right\} \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (3.12)$$

From the system (3. 12), $\mathcal{F}_i$ and $\mathcal{V}_i$ are defined as:

$$\mathcal{F}_i = \begin{bmatrix} \frac{\theta_{mh}\phi I_m S_h}{N_h} \\ 0 \\ \frac{\theta_{hm}\phi I_h S_m}{N_h} \\ 0 \end{bmatrix} \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (3.13)$$

and

$$\mathcal{V}_i = \begin{bmatrix} (\beta_h + \mu)E_h \\ (\tau + \mu + \pi)I_h - \beta_h E_h \\ (\beta_m + \omega)E_m \\ \omega I_m - \beta_m E_m \end{bmatrix} \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (3.14)$$

The partial derivatives of (3.13) with respect to (I_h, I_m) and the Jacobian matrix of $\mathcal{F}_i$ at the disease-free equilibrium point (3.11) is:

$$F = \begin{bmatrix} 0 & 0 & 0 & \theta_{mh}\phi \\ 0 & 0 & 0 & 0 \\ 0 & \frac{\theta_{hm}\phi\mu\rho}{\psi\omega} & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} \dots\dots\dots\dots\dots\dots\dots\dots\dots (3.15)$$

Similarly, the partial derivatives of (3.14) with respect to (E_h, I_h, E_m, I_m) and the Jacobian matrix of $\mathcal{V}_i$ is:

$$V = \begin{bmatrix} (\beta_h + \mu) & 0 & 0 & 0 \\ -\beta_h & (\tau + \mu + \pi) & 0 & 0 \\ 0 & 0 & (\beta_m + \omega) & 0 \\ 0 & 0 & -\beta_m & \omega \end{bmatrix} \dots\dots\dots\dots\dots\dots\dots (3.16)$$

The inverse of the matrix V is given as:

$$V^{-1} = \begin{bmatrix} \frac{1}{(\beta_h + \mu)} & 0 & 0 & 0 \\ \frac{\beta_h}{(\beta_h + \mu)(\tau + \mu + \pi)} & \frac{1}{(\tau + \mu + \pi)} & 0 & 0 \\ 0 & 0 & \frac{1}{(\beta_m + \omega)} & 0 \\ 0 & 0 & \frac{\beta_m}{\omega(\beta_m + \omega)} & \frac{1}{\omega} \end{bmatrix} \dots\dots\dots\dots\dots (3.17)$$

Now we have to compute FV^{-1},

$$FV^{-1} = \begin{bmatrix} 0 & 0 & 0 & \theta_{mh}\phi \\ 0 & 0 & 0 & 0 \\ 0 & \frac{\theta_{hm}\phi\mu\rho}{\psi\omega} & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} \frac{1}{(\beta_h + \mu)} & 0 & 0 & 0 \\ \frac{\beta_h}{(\beta_h + \mu)(\tau + \mu + \pi)} & \frac{1}{(\tau + \mu + \pi)} & 0 & 0 \\ 0 & 0 & \frac{1}{(\beta_m + \omega)} & 0 \\ 0 & 0 & \frac{\beta_m}{\omega(\beta_m + \omega)} & \frac{1}{\omega} \end{bmatrix}$$

$$= \begin{bmatrix} 0 & 0 & \frac{\beta_m\theta_{mh}\phi}{\omega(\beta_m + \omega)} & \frac{\theta_{mh}\phi}{\omega} \\ 0 & 0 & 0 & 0 \\ \frac{\beta_h\theta_{hm}\phi\mu\rho}{\psi\omega(\beta_h + \mu)(\tau + \mu + \pi)} & \frac{\theta_{hm}\phi\mu\rho}{\psi\omega(\tau + \mu + \pi)} & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

Let $k = \frac{\beta_h\theta_{hm}\phi\mu\rho}{\psi\omega(\boldsymbol{\beta_h}+\boldsymbol{\mu})(\boldsymbol{\tau}+\boldsymbol{\mu}+\boldsymbol{\pi})}$, $l = \frac{\theta_{hm}\phi\mu\rho}{\psi\omega(\boldsymbol{\tau}+\boldsymbol{\mu}+\boldsymbol{\pi})}$, $m = \frac{\boldsymbol{\beta_m}\theta_{mh}\phi}{(\boldsymbol{\beta_m}+\boldsymbol{\omega})\omega}$ and $n = \frac{\theta_{mh}\phi}{\omega}$.

$$FV^{-1} = \begin{bmatrix} 0 & 0 & m & n \\ 0 & 0 & 0 & 0 \\ k & l & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} \dots\dots\dots\dots\dots\dots\dots\dots\dots (3.18)$$

From (3.18), we can now calculate the eigenvalues to determine the basic reproduction number R_0 by taking the spectral radius (dominant eigenvalue) of the matrix FV^{-1}.

Thus, it is computed by $|A - \lambda I| = 0$, we have

$$\begin{vmatrix} -\lambda & 0 & m & n \\ 0 & -\lambda & 0 & 0 \\ k & l & -\lambda & 0 \\ 0 & 0 & 0 & -\lambda \end{vmatrix} = 0$$

$$= -n\begin{vmatrix} 0 & -\lambda & 0 \\ k & l & -\lambda \\ 0 & 0 & 0 \end{vmatrix} - \lambda\begin{vmatrix} -\lambda & 0 & m \\ 0 & -\lambda & 0 \\ k & l & -\lambda \end{vmatrix} = -n(0) - \lambda(-\lambda^3 + \lambda km) = 0$$

$$\lambda^2(\lambda^2 - km) = 0 \implies \lambda^2 = 0 \ or \ \lambda^2 - km = 0$$

$$\implies \lambda = 0 \ or \ \lambda = \pm\sqrt{km} \ .$$

From the four eigenvalues, the dominant eigenvalue of the matrix FV^{-1} is $\lambda = \sqrt{km}$. Therefore the basic reproduction number $R_0 = \sqrt{km}$. Hence

$$R_0 = \sqrt{\frac{\phi^2 \rho \beta_h \beta_m \theta_{hm} \theta_{mh} \mu}{\psi \omega(\beta_h + \mu)(\tau + \mu + \pi)(\beta_m + \omega)\omega}} \ldots\ldots\ldots\ldots\ldots\ldots (3.19)$$

Where:

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

$\frac{\beta_m}{\beta_m + \omega}$ is the probability that a mosquito will survive the exposed state to become infectious.

$\frac{\beta_m \theta_{mh} \phi}{(\beta_m + \omega)\omega}$ is the number of humans that one mosquito infects during its infectious lifetime, provided all humans are susceptible.

$\frac{\beta_h \theta_{hm} \phi}{(\beta_h + \mu)(\tau + \mu + \pi)}$ is the number of mosquitoes that one human infects during the duration of the infectious period, provided all mosquitoes are susceptible.

The threshold parameter R_0 can be defined as square roots of the product of number of humans one mosquito infects during its infectious lifetime (R_{0h}) and number of mosquitoes one human

infects during the duration of the infectious period (R_{0m}), provided all humans and mosquitoes are susceptible. Therefore,

$$R_0 = \sqrt{R_{0h} \times R_{0m}}$$

$$= \sqrt{\frac{\beta_h \theta_{mh} \phi \mu}{\psi(\beta_h + \mu)(\tau + \mu + \pi)} \times \frac{\beta_m \theta_{hm} \phi \rho}{(\beta_m + \omega)\omega^2}} \quad \ldots\ldots\ldots(3.20)$$

Hence

$$R_{0h} = \frac{\beta_h \theta_{mh} \phi \mu}{\psi(\beta_h + \mu)(\tau + \mu + \pi)} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(3.21)$$

and

$$R_{0m} = \frac{\beta_m \theta_{hm} \phi \rho}{(\beta_m + \omega)\omega^2} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(3.22),$$

where

$\frac{\theta_{mh} \phi \mu}{\psi(\tau + \mu + \pi)}$ is the number of latent infections produced by a typical infectious individual during the mean infectious period.

$\frac{\theta_{hm} \phi \rho}{\omega^2}$ is the number of latent infections produced by a typical infectious mosquitoes during the mean infectious period.

The parameter ϕ appears in the both expressions because the mosquito biting rate controls the transmission from humans to mosquitoes and from mosquitoes to humans.

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

3. 3. 6 LOCAL STABILITY OF THE DISEASE-FREE EQUILIBRIUM

The local stability of the disease-free equilibrium can be analyzed using the Jacobian matrix of the malaria model (3 . 1) at the disease free equilibrium point. Using Van den Driessche P. and Watmough J., (2002), the following theorem holds.

Theorem 3. 2:

The disease free equilibrium point for system (3 . 1) is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

Proof:

The Jacobian matrix (J) of the malaria model (3 . 1) with $S_h = N_h - (E_h + I_h + R)$ and $S_m = N_m - (E_m + I_m)$ at the disease-free equilibrium point is given by

$$\begin{bmatrix} -(\beta_h + \mu) & 0 & 0 & 0 & \theta_{mh}\phi \\ \beta_h & -(\tau + \mu + \pi) & 0 & 0 & 0 \\ 0 & \tau & -(\varphi + \mu) & 0 & 0 \\ 0 & \frac{\theta_{hm}\phi\mu\rho}{\psi\omega} & 0 & -(\beta_m + \omega) & 0 \\ 0 & 0 & 0 & \beta_m & -\omega \end{bmatrix} \ldots\ldots (3 . 23)$$

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

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

That is

$$\begin{vmatrix} -(\beta_h + \mu + \lambda) & 0 & 0 & 0 & \theta_{mh}\phi \\ \beta_h & -(\tau + \mu + \pi + \lambda) & 0 & 0 & 0 \\ 0 & \tau & -(\varphi + \mu + \lambda) & 0 & 0 \\ 0 & \frac{\theta_{hm}\phi\mu\rho}{\psi\omega} & 0 & -(\beta_m + \omega + \lambda) & 0 \\ 0 & 0 & 0 & \beta_m & -(\omega + \lambda) \end{vmatrix} = 0$$

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

The remaining eigenvalues can be obtained as follows:

$$\begin{vmatrix} -(\beta_h + \mu + \lambda) & 0 & 0 & \theta_{mh}\phi \\ \beta_h & -(\tau + \mu + \pi + \lambda) & 0 & 0 \\ 0 & \frac{\theta_{hm}\phi\mu\rho}{\psi\omega} & -(\beta_m + \omega + \lambda) & 0 \\ 0 & 0 & \beta_m & -(\omega + \lambda) \end{vmatrix} = 0$$

$$(\beta_h + \mu + \lambda)(\tau + \mu + \pi + \lambda)(\beta_m + \omega + \lambda)(\omega + \lambda) - \frac{\phi^2\rho\theta_{hm}\theta_{mh}\beta_h\beta_m\mu}{\psi\omega} = 0 \quad \ldots(3.24)$$

To simplify the equation, let $A_1 = \omega$, $A_2 = (\beta_m + \omega)$, $A_3 = (\tau + \mu + \pi)$, $A_4 = (\beta_h + \mu)$ and $K = \frac{\phi^2\rho\theta_{hm}\theta_{mh}\beta_h\beta_m\mu}{\psi\omega}$. This implies

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

$$\lambda^4 + B_1\lambda^3 + B_2\lambda^2 + B_3\lambda + B_4 = 0 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(3.25)$$

where

$$\left.\begin{aligned} B_1 &= A_4 + A_3 + A_2 + A_1 \\ B_2 &= A_4(A_3 + A_2 + A_1) + A_3(A_2 + A_1) + A_2A_1 \\ B_3 &= A_4A_3A_2 + A_4A_3A_1 + A_4A_2A_1 + A_3A_2A_1 \\ B_4 &= A_4A_3A_2A_1 - K \end{aligned}\right\} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(3.26)$$

The expression for R_0 (3. 19) can be written, in terms of A_i as

$$R_0^2 = \frac{\phi^2\rho\beta_h\beta_m\theta_{hm}\theta_{mh}\mu_h}{\psi A_3A_4A_2A_1^2} \quad \ldots\ldots\ldots\ldots\ldots\ldots(3.27)$$

Using the Routh-Hurwitz Criteria on (3. 25), we can prove that all roots of the polynomial (3. 25) have negative real parts. The Routh-Hurwitz Criteria is stated as follows: Important criteria that give necessary and sufficient conditions for all of the roots of the characteristic polynomial (with real coefficients) to lie in the left half of the complex plane are known as Routh-Hurwitz criteria (Flores, 2011).

Theorem 3. 3: Routh-Hurwitz Criteria.

Given the polynomial

$$P(\lambda) = \lambda^n + B_1\lambda^{n-1} + \cdots + B_{n-1}\lambda + B_n ,$$

where the coefficients B_i are real constants, $i = 1, \ldots, n$, define the n Hurwitz matrices using the coefficients B_i of the characteristic polynomial:

$$H_1 = (B_1) \quad , \quad H_2 = \begin{pmatrix} B_1 & 1 \\ B_3 & B_2 \end{pmatrix} \quad , \quad H_3 = \begin{pmatrix} B_1 & 1 & 0 \\ B_3 & B_2 & B_1 \\ B_5 & B_4 & B_3 \end{pmatrix}$$

and

$$H_n = \begin{pmatrix} B_1 & 1 & 0 & 0 & \cdots & 0 \\ B_3 & B_2 & B_1 & 1 & \cdots & 0 \\ B_5 & B_4 & B_3 & B_2 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \cdots & \vdots \\ 0 & 0 & 0 & 0 & \cdots & B_n \end{pmatrix}$$

where $B_j = 0$ if $j > n$. All of the roots of the polynomial $P(\lambda)$ are negatives or have negative real parts if and only if the determinants of all Hurwitz matrices are positive:

$$det(H_j) > 0 , \; j = 1 , \; 2 , \ldots , n .$$

For the characteristic polynomial in (3 . 25) , when $n = 4$, the Routh-Hurwitz criteria are

$B_1 > 0$, $B_2 > 0$, $B_3 > 0$, $B_4 > 0$ and $det(H_1) = B_1 > 0$,

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

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

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

Now we show that all determinants of the Hurwitz matrices are positive, which means all the eigenvalues of the Jacobian (3.25) have negative real part. Therefore, disease-free equilibrium point is stable.

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

$$\left.\begin{aligned} det(H_2) &= B_1B_2 \\ &= 3A_4A_3(A_1 + A_2) + 3A_2A_1(A_4 + A_3) + A_4^2(A_3 + A_2 + A_1) + \\ &\quad A_3^2(A_4 + A_2 + A_1) + A_2^2(A_4 + A_3 + A_1) + A_1^2(A_4 + A_3 + A_2) > 0 \end{aligned}\right\}$$

$$\left.\begin{aligned} det(H_3) &= B_1B_2 - B_3 \\ &= 2A_4A_3(A_1 + A_2) + 2A_2A_1(A_4 + A_3) + A_4^2(A_3 + A_2 + A_1) + \\ &\quad A_3^2(A_4 + A_2 + A_1) + A_2^2(A_4 + A_3 + A_1) + A_1^2(A_4 + A_3 + A_2) > 0 \end{aligned}\right\}$$

$$\left.\begin{aligned} det(H_4) &= B_3(B_2B_1 - B_3) - B_4B_1^2 \\ &= B_3C + KB_1^2 - A_4A_3A_2A_1\,B_1^2 \quad > 0 \end{aligned}\right\}$$

where $C = B_2B_1 - B_3$

Since all the determinants of the Hurwitz matrices are positive, then it means all the eigenvalues of the Jacobian (3.25) have negative real part and $R_0 < 1$. Therefore, disease-free equilibrium point is stable.

Conversely, if $R_0 > 1$ it implies that $B_4 < 0$, and since the remaining coefficients (B_1, B_2 and B_3) of the polynomial (3.25) are positive, then all the roots of this polynomial cannot have negative real parts. Therefore, the disease-free equilibrium point is unstable.

3. 3. 7 THE ENDEMIC EQUILIBRIUM POINT

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

$$EEP = \left(S_h^{e_1},\ E_h^{e_1},\ I_h^{e_1},\ R^{e_1},\ S_m^{e_1},\ E_m^{e_1},\ I_m^{e_1} \right),$$

where $\left(S_h^{e_1},\ E_h^{e_1},\ I_h^{e_1},\ R^{e_1},\ S_m^{e_1},\ E_m^{e_1},\ I_m^{e_1} \right) > 0.$

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

$$\left.\begin{aligned}
\psi + \varphi R - \frac{\theta_{mh}\phi I_m S_h}{N_h} - \mu S_h &= 0 \\
\frac{\theta_{mh}\phi I_m S_h}{N_h} - (\beta_h + \mu)E_h &= 0 \\
\beta_h E_h - (\tau + \mu + \pi)I_h &= 0 \\
\tau I_h - (\varphi + \mu)R &= 0 \\
\rho - \frac{\theta_{hm}\phi I_h S_m}{N_h} - \omega S_m &= 0 \\
\frac{\theta_{hm}\phi I_h S_m}{N_h} - (\beta_m + \omega)E_m &= 0 \\
\beta_m E_m - \omega I_m &= 0
\end{aligned}\right\} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.28)$$

From the seventh equation of(3.28), we have

$$I_m^{e_1} = \frac{\beta_m}{\omega} E_m^{e_1} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.29)$$

From the sixth equation, we have

$$E_m^{e_1} = \frac{\theta_{hm}\phi I_h^{e_1} S_m^{e_1}}{N_h(\beta_m + \omega)} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.30)$$

Substituting(3.30) into(3.29), we have

$$I_m^{e_1} = \frac{\beta_m \theta_{hm}\phi I_h^{e_1} S_m^{e_1}}{\omega N_h(\beta_m + \omega)} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.31)$$

From the fifth equation, we have

$$S_m^{e_1} = \frac{N_h \rho}{\theta_{hm} \phi I_h^{e_1} + \omega N_h} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.32)$$

Substituting the equation(3.32) into (3.31),we have

$$I_m^{e_1} = \frac{\rho \beta_m \theta_{hm} \phi I_h^{e_1}}{\omega(\beta_m + \omega)\left(\theta_{hm} \phi I_h^{e_1} + \omega N_h\right)} \quad \ldots\ldots\ldots\ldots\ldots\ldots (3.33)$$

$$I_m^{e_1} = \frac{R_{0m}\, \omega I_h^{e_1}}{\left(\theta_{hm} \phi I_h^{e_1} + \omega N_h\right)} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.34)$$

From the second equation, we have

$$\frac{\theta_{mh} \phi I_m^{e_1} S_h^{e_1}}{N_h} - (\beta_h + \mu) E_h^{e_1} = 0 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.35)$$

Substitute equation(3.34) into (3.35), we have

$$\frac{R_{0m}\, \omega \theta_{mh} \phi I_h^{e_1} S_h^{e_1}}{N_h\left(\theta_{hm} \phi I_h^{e_1} + \omega N_h\right)} - (\beta_h + \mu) E_h^{e_1} = 0 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.36)$$

From the third equation, we have

$$E_h^{e_1} = \frac{\tau + \mu + \pi}{\beta_h} I_h^{e_1} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.37)$$

Substitute equation(3.37) into (3.36), we have

$$\frac{R_{0m}\, \omega \theta_{mh} \phi I_h^{e_1} S_h^{e_1}}{N_h\left(\theta_{hm} \phi I_h^{e_1} + \omega N_h\right)} - \frac{(\beta_h + \mu)(\tau + \mu + \pi) I_h^{e_1}}{\beta_h} = 0 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.38)$$

$$\frac{\beta_h R_{0m}\, \omega \theta_{mh} \phi I_h^{e_1} S_h^{e_1} - N_h\left(\theta_{hm} \phi I_h^{e_1} + \omega N_h\right)(\beta_h + \mu)(\tau + \mu + \pi)\, I_h^{e_1}}{\beta_h N_h\left(\theta_{hm} \phi I_h^{e_1} + \omega N_h\right)} = 0$$

$$I_h^{e_1}\left[\beta_h R_{0m}\, \omega \theta_{mh} \phi S_h^{e_1} - N_h\left(\theta_{hm} \phi I_h^{e_1} + \omega N_h\right)(\beta_h + \mu)(\tau + \mu + \pi)\right] = 0$$

$$I_h^{e_1} = 0 \quad or \quad \left[\beta_h R_{0m}\, \omega \theta_{mh} \phi S_h^{e_1} - N_h\left(\theta_{hm} \phi I_h^{e_1} + \omega N_h\right)(\beta_h + \mu)(\tau + \mu + \pi)\right] = 0$$

$$\beta_h R_{0m}\, \omega \theta_{mh} \phi S_h^{e_1} - N_h\left(\theta_{hm} \phi I_h^{e_1} + \omega N_h\right)(\beta_h + \mu)(\tau + \mu + \pi) = 0 \quad \ldots\ldots\ldots (3.39)$$

Dividing (3 . 39) through by $N_h(\beta_h + \mu)(\tau + \mu + \pi)$, we have

$$\frac{\beta_h R_{0m}\,\omega\theta_{mh}\phi S_h^{e_1}}{N_h(\beta_h + \mu)(\tau + \mu + \pi)} - \left(\theta_{hm}\phi I_h^{e_1} + \omega N_h\right) = 0$$

$$\left[\frac{\beta_h\theta_{mh}\phi}{N_h(\beta_h + \mu)(\tau + \mu + \pi)}\right] R_{0m}\,\omega S_h^{e_1} - \left(\theta_{hm}\phi I_h^{e_1} + \omega N_h\right) = 0 \quad , \qquad N_h \le \frac{\psi}{\mu}$$

$$\left[\frac{\beta_h\theta_{mh}\phi\mu}{\psi(\beta_h + \mu)(\tau + \mu + \pi)}\right] R_{0m}\,\omega S_h^{e_1} - \left(\theta_{hm}\phi I_h^{e_1} + \omega\frac{\psi}{\mu}\right) = 0$$

$$R_{0h} \times R_{0m}\,\omega S_h^{e_1} - \left(\theta_{hm}\phi I_h^{e_1} + \frac{\psi\omega}{\mu}\right) = 0$$

$$R_{0h}R_{0m}\,\omega S_h^{e_1} = \left(\frac{\mu\theta_{hm}\phi I_h^{e_1} + \omega\psi}{\mu}\right) \Longrightarrow R_0^2\omega S_h^{e_1} = \frac{\mu\theta_{hm}\phi I_h^{e_1} + \omega\psi}{\mu}, \quad R_0^2 = R_{0h}R_{0m}$$

$$S_h^{e_1} = \frac{\mu\theta_{hm}\phi I_h^{e_1} + \omega\psi}{R_0^2\omega\mu} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3 . 40)$$

From the fourth equation of (3 . 28), we have

$$R^{e_1} = \frac{\tau}{\varphi + \mu} I_h^{e_1} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3 . 41)$$

Using the first equation of (3 . 28) we can solve for $I_h^{e_1}$,

$$\psi + \varphi R^{e_1} - \frac{\theta_{mh}\phi I_m^{e_1} S_h^{e_1}}{N_h} - \mu S_h^{e_1} = 0 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3 . 42)$$

Substitute equations (3 . 34) , (3 . 40) and (3 . 41) into (3 . 42) , we have

$$\psi + \varphi\left(\frac{\tau}{\varphi + \mu} I_h^{e_1}\right) - \frac{\theta_{mh}\phi}{N_h}\left[\frac{R_{0m}\,\omega I_h^{e_1}}{\left(\theta_{hm}\phi I_h^{e_1} + \omega N_h\right)}\right]\left[\frac{\mu\theta_{hm}\phi I_h^{e_1} + \omega\psi}{R_0^2\omega\mu}\right] - \mu\left(\frac{\mu\theta_{hm}\phi I_h^{e_1} + \omega\psi}{R_0^2\omega\mu}\right) = 0$$

Finally we get

$$A\left[I_h^{e_1}\right]^2 + BI_h^{e_1} + C = 0 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3 . 43)$$

$$\left[\begin{array}{l} A = R_0^2 L\omega\varphi\phi\tau - \phi^2\mu\theta_{hm}(\varphi+\mu)(M+L) \\ B = R_0^2\mu\omega^2 N_h^2\varphi\tau - \omega\phi(\varphi+\mu)[L(\psi R_0^2 - \psi - \mu N_h) - M\psi] \\ C = \mu\omega^2 N_h^2\psi(\varphi+\mu)[R_0^2 - 1] \end{array}\right]$$

where $L = \mu N_h\theta_{hm}$, $M = \omega\theta_{mh}R_{0m}$.

Using the quadratic formula

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

We have

$$I_h^{e_1} = \frac{-B \pm \sqrt{B^2 - 4AC}}{2A}$$

$$= \frac{-B + \sqrt{B^2 - 4AC}}{2A} \quad or \quad \frac{-B - \sqrt{B^2 - 4AC}}{2A}$$

$$\therefore \; I_h^{e_1} = \frac{-B + \sqrt{B^2 - 4AC}}{2A} = \frac{\sqrt{B^2 - 4AC} - B}{2A} = \Phi \;, \; I_h^{e_1} \geq 0 \quad \ldots\ldots\ldots\ldots (3.44)$$

Using the equation (3.40), we have

$$S_h^{e_1} = \frac{\mu\theta_{hm}\phi\,\Phi + \omega\psi}{R_0^2\omega\mu} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.45)$$

From the equation (3.37), we have

$$E_h^{e_1} = \frac{\tau + \mu + \pi}{\beta_h}\Phi \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.46)$$

From the equation (3.41),we have

$$R^{e_1} = \frac{\tau}{\varphi + \mu}\Phi \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.47)$$

Using(3.32), we have

$$S_m^{e_1} = \frac{N_h\rho}{\theta_{hm}\phi\,\Phi + \omega N_h} \qquad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.48)$$

Using (3 . 30) , we have

$$E_m^{e_1} = \frac{R_{0m}\,\omega^2\Phi}{\beta_m(\theta_{hm}\phi\,\Phi + \omega N_h)} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.49)$$

From (3 .34) ,we have

$$I_m^{e_1} = \frac{R_{0m}\,\omega\Phi}{(\theta_{hm}\phi\,\Phi + \omega N_h)} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.50)$$

We now consider the possibility of multiple endemic equilibria for the quadratic (3 . 43) . The equation (3 . 43) may indicate three distinct situations which we have to consider depending on the signs of B and C since A is always positive. The letter C is negative if $R_0 < 1$ and positive if $R_0 > 1$. Hence the three situations will form the following theorem.

. **Theorem 3. 4**

The malaria model (3 .1) has,

(i) Precisely one unique endemic equilibrium if $C < 0 \iff R_0 < 1$.

(ii) Precisely one unique endemic equilibrium if $B < 0$ and $C = 0$ or $B^2 - 4AC = 0$.

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

(iv) No endemic otherwise.

3. 3. 8 LOCAL STABILITY OF THE ENDEMIC EQUILIBRIUM

The stability of the endemic equilibrium of the model (3 . 1) can be analysed using the Centre Manifold Theory described by Castillo-Chavez and Song, 2004.

Theorem 3 . 5 ***Castillo-Chavez and Song***

Consider the following general system of ordinary differential equations with a parameter Ψ **.**

$$\frac{dx}{dt} = h(x, \Psi), \quad h: \mathbb{R}^n \times \mathbb{R} \longrightarrow \mathbb{R} \quad and \quad h \in \mathbb{C}^2(\mathbb{R}^n \times \mathbb{R}) \quad \ldots\ldots\ldots\ldots\ldots (3.59)$$

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

1 $A = D_x h(0,0) = \left(\frac{\partial h_i}{\partial x_i}(0, 0)\right)$ *is the linearization matrix of the system around the equilibrium* 0 *with* Ψ *evaluated at* 0 .

2 Zero is a simple eigenvalue of A *and other eigenvalues of* A *have negative real parts.*

3 Matrix A *has a nonnegative right eigenvector* w *and a left eigenvector* v *corresponding to the zero eigenvalue.*

Let h_k *be the* kth *component of* h *and*

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

and

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

then, the local dynamics of the system (3.59) *around* 0 *is totally determined by the sign of* a *and* b .

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

2 $a < 0$, $b < 0$. *When* $\Psi < 0$ *with* $|\Psi| << 1$, 0 *is unstable; when* $0 < \Psi << 1$, 0 *is locally asymptotically stable, and there exists a positive unstable equilibrium.*

3 $a > 0$, $b < 0$. *When* $\Psi < 0$ *with* $|\Psi| << 1$, 0 *is unstable, and there exists a locally asymptotically stable negative equilibrium; when* $0 < \Psi << 1$, 0 *is stable, and a positive unstable equilibrium appears.*

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

To apply this theorem we make the following change of variables in the system (3 . 1).

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

The system (3 . 1) is written in vector form as

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

Where $X_i = (x_1, x_2, \dots, x_7)^T$ and $H = (h_1, h_2, \dots h_7)^T$ are transposed matrices.

The system of equations (3 . 1) becomes

$$\left.\begin{aligned}
\frac{dx_1}{dt} &= \psi + \varphi x_4 - \frac{\Psi^* \phi \mu x_7 x_1}{\psi} - \mu x_1 = h_1 \\
\frac{dx_2}{dt} &= \frac{\Psi^* \phi \mu x_7 x_1}{\psi} - (\beta_h + \mu) x_2 = h_2 \\
\frac{dx_3}{dt} &= \beta_h x_2 - (\tau + \mu + \pi) x_3 = h_3 \\
\frac{dx_4}{dt} &= \tau x_3 - (\varphi + \mu) x_4 = h_4 \\
\frac{dx_5}{dt} &= \rho - \frac{\theta_{hm} \phi \mu x_3 x_5}{\psi} - \omega x_5 = h_5 \\
\frac{dx_6}{dt} &= \frac{\theta_{hm} \phi \mu x_3 x_5}{\psi} - (\beta_m + \omega) x_6 = h_6 \\
\frac{dx_7}{dt} &= \beta_m x_6 - \omega x_7 = h_7
\end{aligned}\right\} \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (3.51)$$

Where $N_h = x_1 + x_2 + x_3 + x_4$ and $N_m = x_5 + x_6 + x_7$ with $\Psi^* = \theta_{mh}$

Let Ψ^* be the bifurcation parameter, the system (3.51) is linearized at disease free equilibrium point when $\Psi = \Psi^*$ with $R_0 = 1$. Thus Ψ^* can be solved from (3.19) when $R_0 = 1$ as

$$R_0 = \sqrt{\frac{\phi^2 \rho \beta_h \beta_m \theta_{hm} \theta_{mh} \mu}{\psi(\beta_h + \mu)(\tau + \mu + \pi)(\beta_m + \omega)\omega^2}}$$

$$1^2 = \frac{\phi^2 \rho \beta_h \beta_m \theta_{hm} \Psi^* \mu}{\psi(\beta_h + \mu)(\tau + \mu + \pi)(\beta_m + \omega)\omega^2}$$

$$\Psi^* = \frac{\psi(\beta_h + \mu)(\tau + \mu + \pi)(\beta_m + \omega)\omega^2}{\phi^2 \rho \beta_h \beta_m \theta_{hm} \mu} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.52)$$

Then zero is a simple eigenvalue of the following Jacobian matrix, J_{bif} with the application of the bifurcation parameters.

$$\begin{bmatrix} -\mu & 0 & 0 & \varphi & 0 & 0 & -\Psi\phi \\ 0 & F_h & 0 & 0 & 0 & 0 & \Psi\phi \\ 0 & \beta_h & C & 0 & 0 & 0 & 0 \\ 0 & 0 & \tau & -(\varphi + \mu) & 0 & 0 & 0 \\ 0 & 0 & D & 0 & -\omega & 0 & 0 \\ 0 & 0 & E & 0 & 0 & F_m & 0 \\ 0 & 0 & 0 & 0 & 0 & \beta_m & -\omega \end{bmatrix} \quad \ldots\ldots (3.53)$$

Where $C = -(\tau + \mu + \pi)$, $D = -\frac{\theta_{hm}\phi\mu\rho}{\psi\omega}$, $E = \frac{\theta_{hm}\phi\mu\rho}{\psi\omega}$, $F_h = -(\beta_h + \mu)$ and $F_m = -(\beta_m + \omega)$.

A right eigenvector associated with the eigenvalue zero is $w = (w_1, w_2, \ldots, w_7)$. We get

$$
\left.
\begin{aligned}
-\mu w_1 + \varphi w_4 - \Psi\phi w_7 &= 0 \\
-(\beta_h + \mu) w_2 + \Psi\phi w_7 &= 0 \\
\beta_h w_2 - (\tau + \mu + \pi) w_3 &= 0 \\
\tau w_3 - (\varphi + \mu) w_4 &= 0 \\
-\frac{\theta_{hm}\phi\mu\rho}{\psi\omega} w_3 - \omega w_5 &= 0 \\
\frac{\theta_{hm}\phi\mu\rho}{\psi\omega} w_3 - (\beta_m + \omega) w_6 &= 0 \\
\beta_m w_6 - \omega w_7 &= 0
\end{aligned}
\right\} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.54)
$$

Solving the systems (3.54), we have the following right eigenvector

$$
\left.
\begin{aligned}
w_1 &= \frac{\varphi w_4 - \Psi\phi w_7}{\mu} \\
w_2 &= \frac{\Psi\phi w_7}{\beta_h + \mu} \\
w_3 &= \frac{\beta_h w_2}{\tau + \mu + \pi} \\
w_4 &= \frac{\tau w_3}{\varphi + \mu} \\
w_5 &= -\frac{\theta_{hm}\phi\mu\rho w_3}{\psi\omega^2} \\
w_6 &= \frac{\theta_{hm}\phi\mu\rho w_3}{\psi\omega(\beta_m + \omega)} \\
w_7 &= w_7 > 0 \; free
\end{aligned}
\right\} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.55)
$$

and the left eigenvector satisfying $v \cdot w = 1$ is $v = (v_1, v_2, \ldots, v_7)$. To find these left eigenvector associated with the eigenvalue 0, the matrix (3.53) should be transposed and gives matrix, J_{left}

$$\begin{bmatrix} -\mu & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & F_h & \beta_h & 0 & 0 & 0 & 0 \\ 0 & 0 & C & \tau & D & E & 0 \\ \varphi & 0 & 0 & -(\varphi+\mu) & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\omega & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & F_m & \beta_m \\ -\Psi\phi & \Psi\phi & 0 & 0 & 0 & 0 & -\omega \end{bmatrix} \quad \ldots(3.56)$$

Where $C = -(\tau + \mu + \pi)$, $D = -\frac{\theta_{hm}\phi\mu\rho}{\psi\omega}$, $E = \frac{\theta_{hm}\phi\mu\rho}{\psi\omega}$, $F_h = -(\beta_h + \mu)$ and $F_m = -(\beta_m + \omega)$.

We have the following system

$$\left.\begin{aligned} -\mu_h v_1 &= 0 \\ -(\beta_h + \mu)v_2 + \beta_h v_3 &= 0 \\ -(\tau + \mu + \pi)v_3 + \tau v_4 - \frac{\theta_{hm}\phi\mu\rho v_5}{\psi\omega} + \frac{\theta_{hm}\phi\mu\rho v_6}{\psi\omega} &= 0 \\ \varphi v_1 - (\varphi + \mu)v_4 &= 0 \\ -\omega v_5 &= 0 \\ -(\beta_m + \omega)v_6 + \beta_m v_7 &= 0 \\ -\Psi\phi v_1 + \Psi\phi v_2 - \omega v_7 &= 0 \end{aligned}\right\} \quad \ldots\ldots(3.57)$$

From the left eigenvector we have the following results

$$\left.\begin{aligned} v_1 &= 0 \\ v_2 &= v_2 > 0 \ free \\ v_3 &= \frac{(\beta_h + \mu)v_2}{\beta_h} \\ v_4 &= 0 \\ v_5 &= 0 \\ v_6 &= \frac{\beta_m v_7}{\beta_m + \omega} \\ v_7 &= \frac{\Psi \phi v_2}{\omega} \end{aligned}\right\} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.58)$$

We now compute the sign of a and b as indicated in the theorem.

Computation of a and b

For the system (3.51), the associated non-zero second order partial derivatives (at DFE) are given by

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

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

Since $v_1 = v_4 = v_5 = 0$ for $k = 1, 4, 5$; then $k = 2, 3, 6, 7$ should be considered.

That is, the following functions will be used to compute a and b from the system (3.51).

$$h_2 = \frac{\Psi\phi\mu x_7 x_1}{\psi} - (\beta_h + \mu)x_2$$

$$= \frac{\Psi\phi\mu x_7}{\psi}(N_h - x_2 - x_3) - (\beta_h + \mu)x_2$$

$$= \frac{\Psi\phi\mu x_7 N_h}{\psi} - \frac{\Psi\phi\mu x_7 x_2}{\psi} - \frac{\Psi\phi\mu x_7 x_3}{\psi} - (\beta_h + \mu)x_2$$

$$h_6 = \frac{\theta_{hm}\phi\mu x_3 x_5}{\psi} - (\beta_m + \omega)x_6$$

$$= \frac{\theta_{hm}\phi\mu x_3}{\psi}(N_m - x_6 - x_7) - (\beta_m + \omega)x_6$$

$$= \frac{\theta_{hm}\phi\mu x_3 N_m}{\psi} - \frac{\theta_{hm}\phi\mu x_3 x_6}{\psi} - \frac{\theta_{hm}\phi\mu x_3 x_7}{\psi} - (\beta_m + \omega)x_6$$

Partial derivatives that are not zero at the disease-free equilibrium are

$$\frac{\partial^2 h_2}{\partial x_2 \partial x_7} = -\frac{\Psi\phi\mu}{\psi}, \quad \frac{\partial^2 h_2}{\partial x_3 \partial x_7} = -\frac{\Psi\phi\mu}{\psi}, \quad \frac{\partial^2 h_6}{\partial x_6 \partial x_3} = -\frac{\theta_{hm}\phi\mu}{\psi}, \quad \frac{\partial^2 h_6}{\partial x_7 \partial x_3} = -\frac{\theta_{hm}\phi\mu}{\psi}.$$

Hence

$$a = v_2 w_2 w_7 \frac{\partial^2 h_2}{\partial x_2 \partial x_7} + v_2 w_3 w_7 \frac{\partial^2 h_2}{\partial x_3 \partial x_7} + v_6 w_6 w_3 \frac{\partial^2 h_6}{\partial x_6 \partial x_3} + v_6 w_7 w_3 \frac{\partial^2 h_6}{\partial x_7 \partial x_3}$$

$$= v_2 w_2 w_7 \left(-\frac{\Psi\phi\mu}{\psi}\right) + v_2 w_3 w_7 \left(-\frac{\Psi\phi\mu}{\psi}\right) + v_6 w_6 w_3 \left(-\frac{\theta_{hm}\phi\mu}{\psi}\right) + v_6 w_7 w_3 \left(-\frac{\theta_{hm}\phi\mu}{\psi}\right)$$

$$= -\frac{\phi\mu}{\psi}[v_2 w_7 \Psi(w_2 + w_3) + v_6 w_3 \theta_{hm}(w_6 + w_7)]$$

$$= -\frac{\phi\mu}{\psi}\left[v_2 w_7^2 \Psi_7^2 \phi\left(\frac{\tau + \mu + \pi + \beta_h}{(\beta_h + \mu)(\tau + \mu + \pi)}\right) + v_6 w_3 \theta_{hm}\left(\frac{\theta_{hm}\phi^2\mu\rho\beta_h\Psi}{\psi\omega(\beta_m + \omega)(\tau + \mu + \pi)(\beta_h + \mu)} + 1\right)\right] < 0$$

Similarly partial derivatives that are not zero when calculating b are:

$$\frac{\partial h_2}{\partial \Psi} = \frac{\phi \mu x_7 x_1}{\psi} \quad , \quad \frac{\partial^2 h_2}{\partial x_7 \partial \Psi} = \frac{\phi \mu x_1}{\psi} = \frac{\phi \mu}{\psi}\left(\frac{\psi}{\mu}\right) = \phi$$

Therefore

$$b = v_2 w_7 \frac{\partial^2 h_2}{\partial x_7 \partial \Psi} = v_2 w_7 \phi > 0 \ .$$

Hence $a < 0$ and $b > 0$. Therefore the following theorem holds.

Theorem 3. 6

The model $(3 . 1)$ has a unique endemic equilibrium which is locally asymptotically stable when $R_0 < 1$ and unstable when $R_0 > 1$.

3. 4 SUMMARY

We analysed the system of seven non-linear differential equations which described the dynamics of malaria with 4 variables for humans and 3 variables for mosquitoes. We demonstrated that there exists a domain where the model (3.1) is epidemiologically and mathematically well-posed. We perform stability analysis of the model. The next generation method is used to derive the basic reproduction number, R_0 , a threshold quantity that determines whether a disease be eradicated or not. If $R_0 < 1$ then the disease-free equilibrium is stable and the disease can be eradicated from the population. We have proved that the disease-free equilibrium is locally asymptotically stable if $R_0 < 1$ and unstable when $R_0 > 1$. The Centre Manifold theorem is used to show that the endemic equilibrium point which is locally asymptotically stable when $R_0 < 1$.

CHAPTER 4

RESULTS

4.0 INTRODUCTION

In this chapter, we use the malaria model (3.1) in chapter three to analyse clinical malaria data in Ghana. We will also carry out numerical simulations using a fourth order Rung-Kutta scheme in Matlab ode45 and the final part will be the discussion on the results.

4.1 ESTIMATION OF PARAMETERS

The parameters in the model (3.1) were estimated using clinical malaria data and demographics statistics of Ghana. Those that were not available were obtained from literature published by researchers in malaria endemic countries which have similar environmental conditions compare to Ghana. The total population for Ghana in 2009 is 23837000 according to World Malaria Report 2010 and the population growth rate per year is also 1.855% (2010 est.) by 2011 CIA World Factbook and Other Sources. Furthermore, Life expectancy at birth in 2010 is 64years according to UNICEF, at a glance: Ghana, 2012. We estimate that it will take 7days for human to recover from malaria infection through chemotherapy and the incubation period of malaria in humans is from 10 to 14 days (Guidelines for Case Management of Malaria, 2009). Finally, the probability of transmission of malaria infection from infectious humans to susceptible mosquitoes is estimated to be 0.42 and we also assume that person who has completely recovered from malaria will lose his/her malaria acquired immunity after 3months based on information received from medical malaria researchers in Ghana.

4. 2 POPULATION DATA FOR MOSQUITOES

According to Ghana Living Standards Survey Report of the Fifth Round (GLSS 5), 2008, the estimated number of households in Ghana is 5.5 million with a higher proportion in the rural areas (3.1 million) than in the urban areas (2.4 million). Gimnig et al. (2003) provided quarterly data for the average number of Anopheles gambiae and Anopheles funestus mosquitoes in a region of Western Kenya (Asembo). From this data, Chitnis (2005) used an estimate of 2 Anopheles gambiae and 0.8 Anopheles funestus mosquitoes per house for his PhD thesis in high malaria transmission areas; therefore we can also conservatively estimate that we have 10 female Anopheles mosquitoes in each house in Ghana. Hence the female Anopheles mosquito population is approximately: $5500000 \times 10 = 55000000$ mosquitoes. We use an estimate of 0.40 bites on humans per mosquito per day in Ghana. The estimation of biting includes both, the dependence on the mosquito's gonotrophic cycle (the number of days a mosquito requires to produce eggs before it searches for a blood meal again), and the dependence on the mosquito's anthropophilic rate (the mosquito's preference for human blood as opposed to other mammalian blood). The probability of transmission of infection from an infectious mosquito to a susceptible human is estimated to be 0.0655. Latent period in mosquitoes is estimated to be 11 days for malaria endemic areas (Chitnis, 2005) and finally, the life expectancy of an adult anopheles mosquito is assumed to be 25days considering mortality of mosquitoes due to indoor residual spraying, mosquito coils and insecticide-treated bed nets.

The table 4.1 below shows the estimated parameters and their sources for the model (3.1). The rates are given per day.

Table 4. 1: Estimated parameter values and their sources for model (3.1)

Symbol	Value	Source
ψ	0.00005079	(2010 est.) by 2011 CIA World Factbook
ρ	0.071	Niger,2008
β_h	1/14	Malaria.com, 2011
β_m	1/11	Chitnis,2005
τ	1/7	Tumwiine et al (2004), Modelling the effect of treatment and mosquito control on Malaria transmission.
μ	$1/(64 \times 365.25)$	At a glance: Ghana, UNICEF, 2012
ω	1/25	Estimated
π	0.0000027	World Malaria Report 2010 for Ghana
φ	1/91.3125	Estimated
θ_{hm}	0.42	Estimated
θ_{mh}	0.0655	Estimated
ϕ	0.4	Chitnis,2005

4.3 EQUATIONS OF THE MODEL

After substituting the estimated parameter values in table 4.1 into model (3.1), we have following system of non-linear differential equations

$$\left.\begin{aligned}
\frac{dS_h}{dt} &= 0.00005079 + 0.0110R - 0.0262\frac{I_m S_h}{N_h} - 0.00004278S_h \\
\frac{dE_h}{dt} &= 0.0262\frac{I_m S_h}{N_h} - 0.07147E_h \\
\frac{dI_h}{dt} &= 0.07143E_h - 0.1429I_h \\
\frac{dR}{dt} &= 0.14286I_h - 0.010994R \\
\frac{dS_m}{dt} &= 0.071 - 0.168\frac{I_h S_m}{N_h} - 0.04S_m \\
\frac{dE_m}{dt} &= 0.168\frac{I_h S_m}{N_h} - 0.13091E_m \\
\frac{dI_m}{dt} &= 0.09091E_m - 0.04I_m
\end{aligned}\right\} \ldots (4.1)$$

with initial conditions $S_h(0) = 13413000$, $E_h(0) = 18000$, $I_h(0) = 3350000$, $R(0) = 3343000$, $S_m(0) = 16500000$, $E_m(0) = 500000$, $I_m(0) = 38000000$.

The total population sizes are $N_h = 20124000$ people and $N_m = 55000000$ mosquitoes. From equations (3.2) and (3.3) we have

$$\frac{dN_h}{dt} = 0.00005079 - 0.00004278N_h - 0.0000027\, I_h \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (4.2)$$

$$\frac{dN_m}{dt} = 0.071 - \frac{1}{25}N_m \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (4.3)$$

4.4 DISEASE-FREE EQUILIBRIUM POINTS

From (3.11) the disease-free equilibrium point of the malaria model is given by

$$E_0 = (\ 23892000\ ,\ 0\ ,\ 0\ ,\ 0\ ,\ 97625000\ ,\ 0\ ,\ 0\ ).$$

4.5 BASIC REPRODUCTION NUMBER R_0

The basic reproduction number is given by:

$$R_0 = \sqrt{\frac{\phi^2 \rho \beta_h \beta_m \theta_{hm} \theta_{mh} \mu}{\psi \omega (\beta_h + \mu)(\tau + \mu + \pi)(\beta_m + \omega)\omega}}$$

$$R_0 = \sqrt{\frac{(0.4)^2(0.071)(1/14)(1/11)(0.42)(0.0655)(0.00004278)}{(0.00005079)(1/25)^2(0.07147)(0.1429)(0.13091)}}$$

Therefore the basic reproduction number is $R_0 = 0.8939$.

Since $R_0 = 0.8939 < 1$, hence malaria disease can be eliminated or eradicated in the susceptible population in Ghana.

4.6 LOCAL STABILITY OF THE DISEASE-FREE EQUILIBRIUM

From (3.23), the Jacobian matrix (J) of the malaria model at disease-free equilibrium point is given by

$$\begin{bmatrix} -0.07147 & 0 & 0 & 0 & 0.0262 \\ 0.07143 & -0.1429 & 0 & 0 & 0 \\ 0 & 0.14286 & -0.01099 & 0 & 0 \\ 0 & 0.2512 & 0 & -0.1309 & 0 \\ 0 & 0 & 0 & 0.0909 & -0.04 \end{bmatrix}$$

Using (3.24), the characteristic equation of the Jacobian matrix above is given by

$$(0.07147 + \lambda)(0.1429 + \lambda)(0.01099 + \lambda)(0.04 + \lambda) - 0.00004273 = 0 \quad \ldots(4.4)$$

Simplifying (4.4), we have

$$\lambda^4 + 0.3853\lambda^3 + 0.05209\lambda^2 + 0.002868\lambda + 0.00001075 = 0$$

Since 0.3853 , 0.05209 , 0.002868 , $0.00001075 > 0$, therefore by the Routh-Hurwitz stability criteria the disease-free equilibrium point is asymptotically stable. This means that

malaria free society can be achieved.

4.7 THE ENDEMIC EQUILIBRIUM POINT

The endemic equilibrium point (EEP) of the model (4.1) is obtained given by solving the equations below:

$$\left.\begin{aligned} 0.00005079 + 0.0110R - 0.0262\frac{I_m S_h}{N_h} - 0.00004278S_h &= 0 \\ 0.0262\frac{I_m S_h}{N_h} - 0.07147E_h &= 0 \\ 0.07143E_h - 0.1429I_h &= 0 \\ 0.14286I_h - 0.010994R &= 0 \\ 0.071 - 0.168\frac{I_h S_m}{N_h} - 0.04S_m &= 0 \\ 0.168\frac{I_h S_m}{N_h} - 0.13091E_m &= 0 \\ 0.09091E_m - 0.04I_m &= 0 \end{aligned}\right\} \ldots (4.5)$$

The quadratic equation for calculating the value of $I_h^{e_1}$ from (3. 43) is given by (4.6) below:

$$0.0072\left[I_h^{e_1}\right]^2 + 34705I_h^{e_1} - 3.1111 = 0 \qquad \ldots\ldots\ldots\ldots\ldots\ldots\ldots (4.6)$$

$$I_h^{e_1} = \frac{\sqrt{B^2 - 4AC} - B}{2A} = \frac{\sqrt{(34705)^2 - 4(0.0072)(-3.1111)} - 34705}{2(0.0072)}$$

$$I_h^{e_1} = 0.00008964$$

We have

$$S_h^{e_1} = \frac{\mu\theta_{hm}\phi\,\Phi + \omega\psi}{R_0^2\omega\mu}$$

$$= \frac{(0.00004278)(0.42)(0.4)(0.00008964) + (1/25)(0.00005079)}{(0.8939)^2 \times (1/25)(0.00004278)} = 1.4864$$

$$E_h^{e_1} = \frac{\tau + \mu + \pi}{\beta_h} \Phi = \frac{0.1429}{(1/14)}(0.00008964) = 0.0001794$$

$$R^{e_1} = \frac{\tau}{\varphi + \mu}\Phi = \frac{(1/7)}{0.01099}(0.00008964) = 0.0012$$

$$S_m^{e_1} = \frac{N_h \rho}{\theta_{hm}\phi\,\Phi + \omega N_h} = \frac{(20124000)(0.071)}{(0.42)(0.4)(0.00008964) + (1/25)(20124000)} = 1.7750$$

$$E_m^{e_1} = \frac{R_{0m}\,\omega^2 \Phi}{\beta_m(\theta_{hm}\phi\,\Phi + \omega N_h)} = \frac{(5.1771)(1/25)^2(0.00008964)}{(1/11)(804960)} = 1.0147 \times 10^{-11}$$

$$I_m^{e_1} = \frac{R_{0m}\,\omega\Phi}{(\theta_{hm}\phi\,\Phi + \omega N_h)} = \frac{(5.1771)(1/25)(0.00008964)}{(804960)} = 2.3062 \times 10^{-11}$$

The endemic equilibrium point of the model (4.1) in terms actual population values is

$EEP = (1.961 \times 10^7,\ 8.964 \times 10^{-5},\ 601,\ 4012,\ 2.9288 \times 10^7,\ 5.0735 \times 10^{-6},\ 8.7631 \times 10^{-4})$

Since $C = -3.1111 < 0$ in (4.6) and also $R_0 < 1$, therefore the malaria model for Ghana has one unique endemic equilibrium point.

4.8 LOCAL STABILITY OF THE ENDEMIC EQUILIBRIUM

The stability of the endemic equilibrium of the model (3.1) can be analysed using the Centre Manifold Theory described by Castillo-Chavez and Song, 2004.

From(3.52), the bifurcation parameter is given by

$$\Psi^* = \frac{\psi(\beta_h + \mu)(\tau + \mu + \pi)(\beta_m + \omega)\omega^2}{\phi^2 \rho \beta_h \beta_m \theta_{hm} \mu}$$

$$\Psi^* = \frac{0.00005079(0.07147)(0.1429)(0.13091)(0.04)^2}{(0.4)^2(0.071)(1/14)(1/11)(0.42)(0.00004278)} = 0.0820$$

The right eigenvector associated with the eigenvalue zero from (3.55) is

$$w_1 = \frac{\varphi w_4 - \Psi\phi w_7}{\mu} = \frac{(0.01095)(2.9817) - (0.082)(0.4)(1)}{0.00004278} = -3.5063$$

$$w_2 = \frac{\Psi\phi w_7}{\beta_h + \mu} = \frac{(0.0820)(0.4)(1)}{0.07147} = 0.4589$$

$$w_3 = \frac{\beta_h w_2}{\tau + \mu + \pi} = \frac{(1/14)(0.4589)}{0.1429} = 0.2294$$

$$w_4 = \frac{\tau w_3}{\varphi + \mu} = \frac{(0.1429)(0.2294)}{0.010994} = 2.9817$$

$$w_5 = -\frac{\theta_{hm}\phi\mu\rho w_3}{\psi\omega^2} = -\frac{(0.42)(0.4)(0.00004278)(0.071)(0.2294)}{(0.00005079)(1/25)^2} = -1.4405$$

$$w_6 = \frac{\theta_{hm}\phi\mu\rho w_3}{\psi\omega(\beta_m + \omega)} = \frac{(0.42)(0.4)(0.00004278)(0.071)(0.2294)}{(0.00005079)(1/25)(0.13091)} = 0.4401$$

$$w_7 = w_7 > 0 \; free$$

From (3.58) we have the following results for the left eigenvector

$$\left.\begin{aligned} v_1 &= 0 \\ v_2 &= v_2 > 0 \ free \\ v_3 &= \frac{(\beta_h + \mu)v_2}{\beta_h} = \frac{(0.07147)(1)}{(1/14)} = 1.0006 \\ v_4 &= 0 \\ v_5 &= 0 \\ v_6 &= \frac{\beta_m v_7}{\beta_m + \omega} = \frac{(1/11)(0.82)}{0.13091} = 0.5694 \\ v_7 &= \frac{\Psi\phi v_2}{\omega} = \frac{(0.0820)(0.4)(1)}{(1/25)} = 0.82 \end{aligned}\right\}$$

Computation of a and b

The parameter a is given by

$$a = -\frac{\phi\mu}{\psi}\left[v_2 w_7^2 \Psi_7^2 \phi\left(\frac{\tau + \mu + \pi + \beta_h}{(\beta_h + \mu)(\tau + \mu + \pi)}\right) + v_6 w_3 \theta_{hm}\left(\frac{\theta_{hm}\phi^2\mu\rho\beta_h\Psi}{\psi\omega(\beta_m + \omega)(\tau + \mu + \pi)(\beta_h + \mu)} + 1\right)\right]$$

$$v_2 w_7^2 \Psi_7^2 \phi\left(\frac{\tau + \mu + \pi + \beta_h}{(\beta_h + \mu)(\tau + \mu + \pi)}\right) = (1)(1)^2(0.082)^2(0.4)\left(\frac{0.2143}{(0.07147)(0.1429)}\right)$$

$$v_2 w_7^2 \Psi_7^2 \phi\left(\frac{\tau + \mu + \pi + \beta_h}{(\beta_h + \mu)(\tau + \mu + \pi)}\right) = 0.05644$$

$$v_6 w_3 \theta_{hm}\left(\frac{\theta_{hm}\phi^2\mu\rho\beta_h\Psi}{\psi\omega(\beta_m + \omega)(\tau + \mu + \pi)(\beta_h + \mu)} + 1\right)$$

$$= (0.5694)(0.2294)(0.42)\left(\frac{(0.42)(0.4)^2(0.00004278)(0.071)(1/14)(0.082)}{(0.00005079)(0.04)(0.13091)(0.1429)(0.07147)} + 1\right)$$

$$v_6 w_3 \theta_{hm}\left(\frac{\theta_{hm}\phi^2\mu\rho\beta_h\Psi}{\psi\omega(\beta_m + \omega)(\tau + \mu + \pi)(\beta_h + \mu)} + 1\right) = 0.07901$$

$$a = -\frac{(0.4)(0.00004278)}{(0.00005079)}[0.05644 + 0.07901] = -0.33692(0.13545) = -0.04564 < 0$$

Similarly the parameter b is given by

$$b = v_2 w_7 \frac{\partial^2 h_2}{\partial x_7 \partial \Psi} = v_2 w_7 \phi = (1)(1)(0.4) = 0.4 > 0$$

Since $a = -0.04564 < 0$ and $b = 0.4 > 0$, therefore by the Centre Manifold Theory described by Castillo-Chavez and Song (2004) the endemic equilibrium point is locally asymptotically stable. This means malaria will persist in Ghana.

4.9 NUMERICAL SIMULATIONS

In this section, we present the numerical analysis of the model. A numerical simulation of the model (4.1) is conducted to find out the dynamics of the disease in the human population. The simulations were conducted using MATLAB's ode45.The initial conditions used were $S_h(0) = 13413000$, $E_h(0) = 18000$, $I_h(0) = 3350000$, $R(0) = 3343000$, $S_m(0) = 16500000$, $E_m(0) = 500000$, $I_m(0) = 38000000$. The time-axes in all the phase portraits start from the year 2000. In figure 4.1, the system approaches an endemic equilibrium point as time increases, showing the existence of a stable endemic equilibrium. It tells us the impact of the current interventions we are practising in the country. If the country continues with the

current interventions, it will take Ghana almost six hundred years from now to attain malaria free nation; since the infectious human population ends somewhere 2565 on time-axis in figure 4. 1.

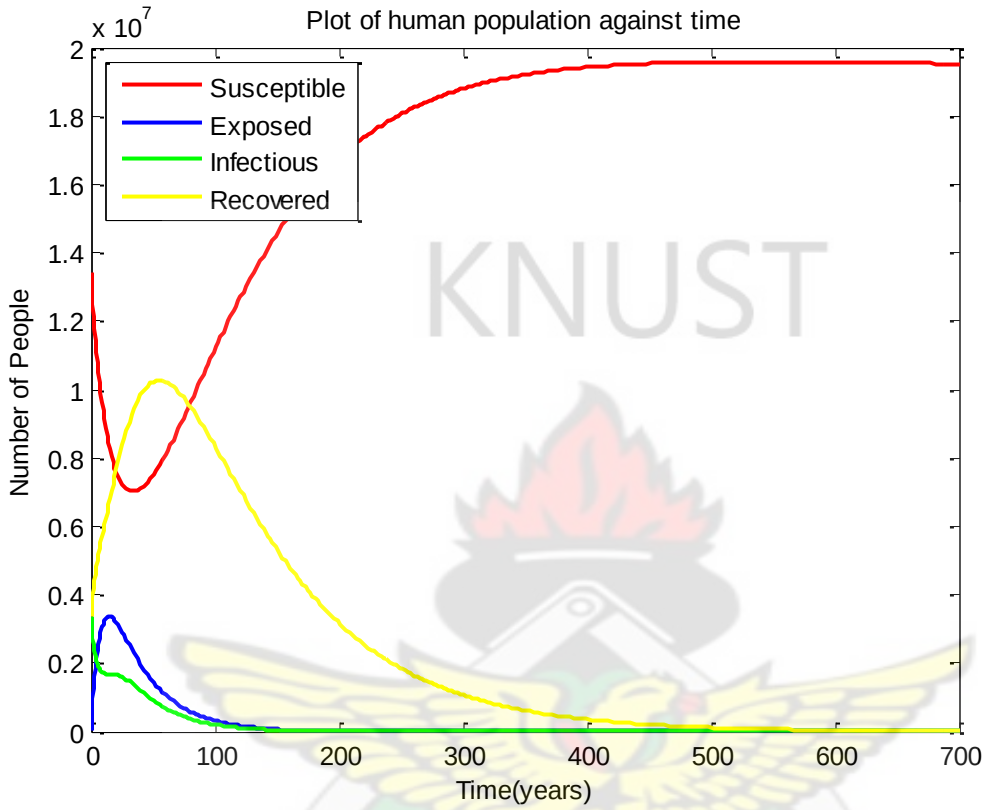

Figure 4.1: is a phase portrait illustrating the changes in the four state variables of the malaria model showing the dynamics with time, of susceptible humans, exposed humans, infected humans and shows the dynamics of recovered humans.

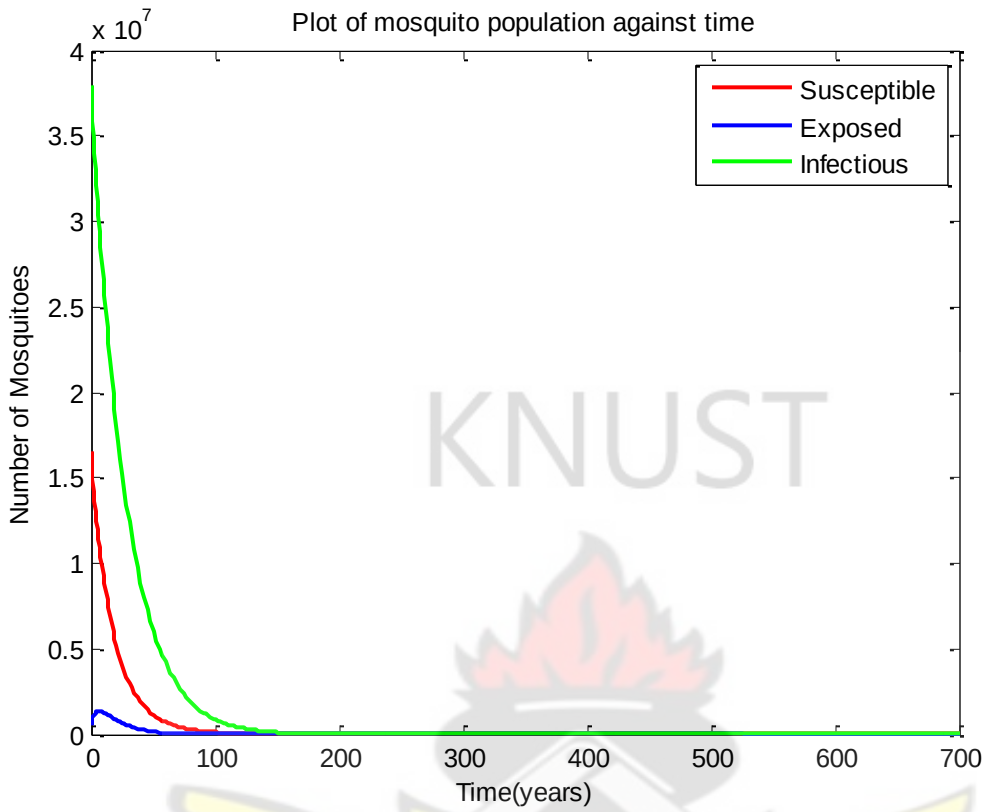

Figure 4. 2: Illustrates the changes in the three state variables of the malaria model showing the dynamics with time, of susceptible mosquitoes, exposed mosquitoes and infectious mosquitoes.

In figure 4.2 above, all the three curves are decreasing as time increases, which is positive for the current interventions in the mosquito population, but there is still more work to be done in the human population. Therefore, we will consider the effects of varying the main parameters responsible control malaria after considering malaria prevalence rate in the population now.

4.9.1 PREVALENCE IN THE MALARIA MODEL

Prevalence is defined as the ratio of which the number of cases of a disease in a population and with the number of individuals in a population at a given time.

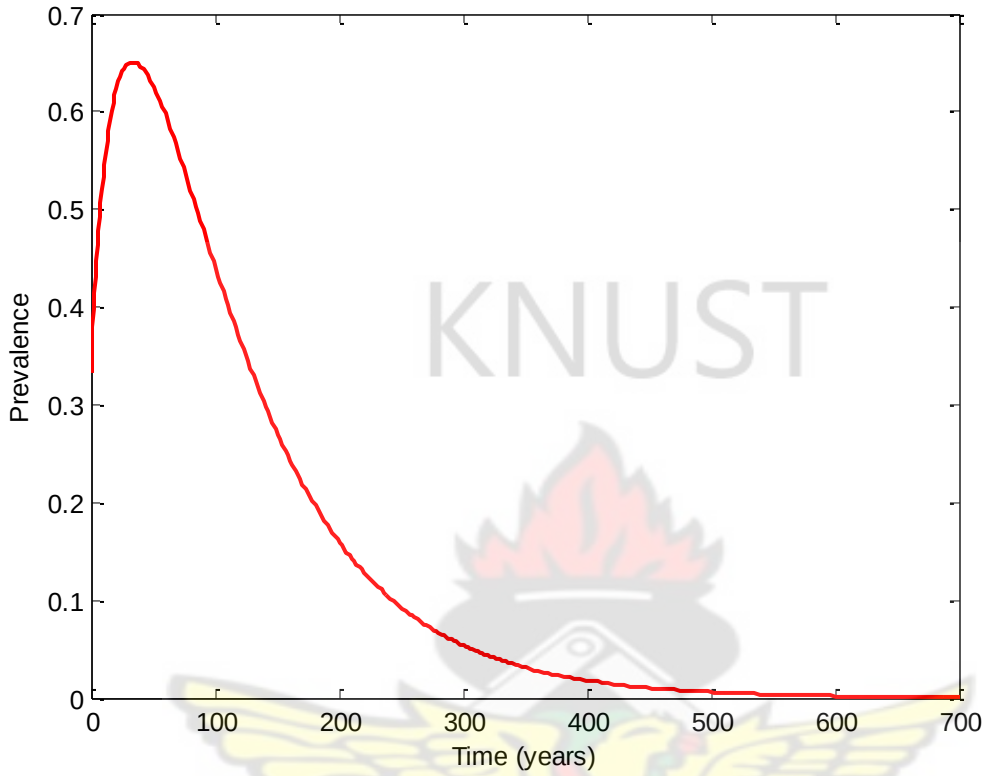

Figure 4.3: Represents changes of prevalence with time.

The prevalence graph shows that the prevalence rate as of now is high which confirms the figure 4.1 that there is more work to be done if we want to achieve malaria free society, because the prevalence rate reduces asymptotically to zero in the year 2600 on the time-axis in figure 4.3.

We now consider the effects of varying the main parameters responsible for controlling malaria. We consider the effect of:

- Reducing the biting rate of mosquitoes on the model.
- Increasing the treatment rate of infectious humans on model.

- Combining the reduction in the biting rate of mosquitoes and the increase in the treatment rate of infectious humans on model.

4.9.2 SIMULATION OF BITING RATE OF MOSQUITOES ON THE MODEL.

The biting rate of mosquitoes can be reduced by using the Insecticide-treated bed nets (ITN) and Indoor residual spraying (IRS). The values of the biting rate of mosquitoes, transmission rate of infection from an infectious mosquito to a susceptible human, rate of loss of immunity for humans and the mosquito population are reduced by $(1/16)$, while the values of the other parameters are maintained. This is illustrated in the figure 4.4.

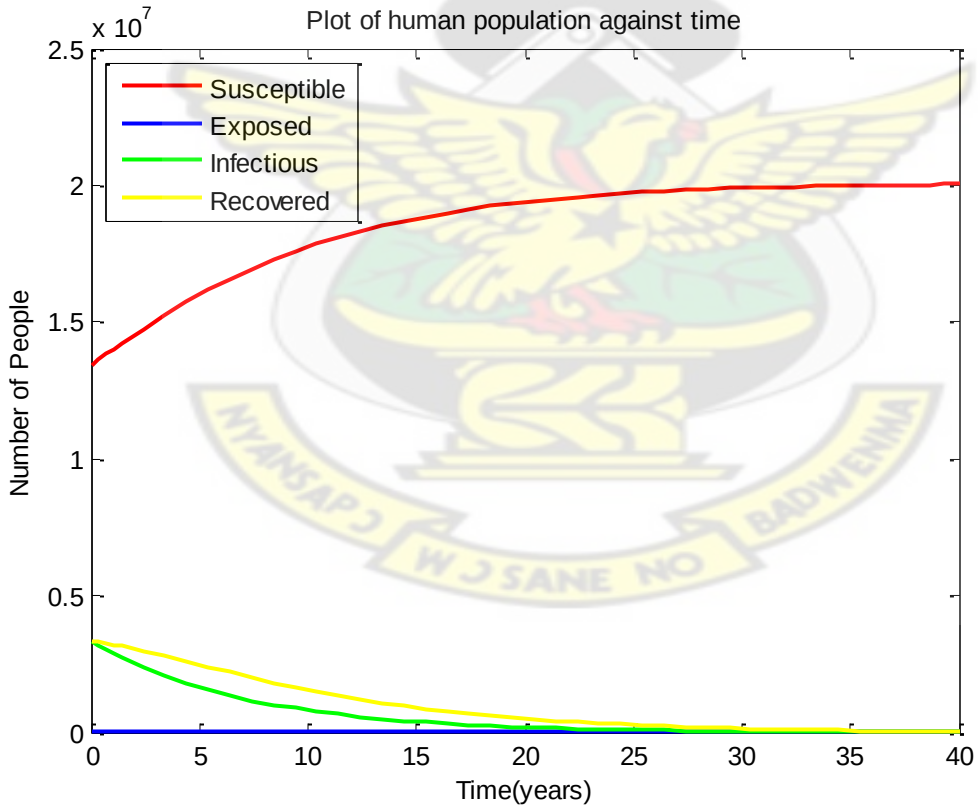

Figure 4.4: Represents of Effects of Reducing the Biting Rate of Mosquitoes on the Model

From figure 4.4 we can see infectious population ends in 2036 on the time-axis. Therefore the country can achieve malaria free status in the year 2037 if we reduce the initial values of the parameters mentioned above by $1/16$. Therefore, we can conclude that reducing biting rate has positive impact in controlling malaria disease on the model.

4.9.3 SIMULATION OF TREATMENT RATE OF INFECTIOUS HUMANS ON THE MODEL.

Increasing the treatment rate will reduce the transmission rate of infection from an infectious human to a susceptible mosquito and the rate of loss of immunity for humans. Therefore increasing the treatment rate to $1/3$ and reducing the transmission rate (θ_{hm}) and rate of loss of immunity to 0.18 and $1/39.1339$ respectively, give the phase portrait diagram below.

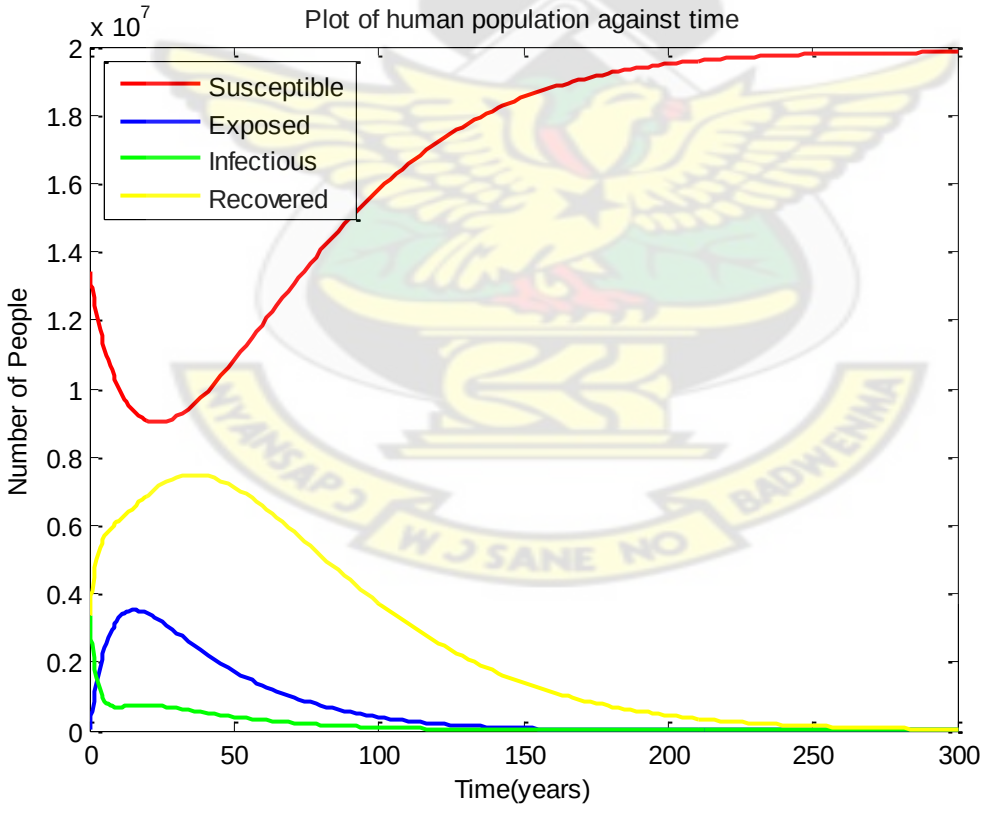

Figure 4.5: Represents Effects of Increasing the Treatment Rate of Infectious Humans on Model

From figure 4.5, if the treatment rate is increased to $1/3$, then Ghana will achieve malaria free status by the year 2285. Clinical treatment rate could be increased if the pharmaceutical industry produces antimalarial drug(s) that will reduce the number of days it takes to recover from malaria infection. Comparing the two interventions, we conclude that the most influential parameter in controlling the disease (malaria) is to reduce the mosquito biting rate, because even the malaria parasite has developed resistance to mono-therapies treatment of falciparum malaria (Anti-Malaria Drug Policy for Ghana,2009).

4.9.4 SIMULATION OF COMBINING BITING AND TREATMENT RATES OF INFECTIOUS HUMANS ON MODEL.

We consider the effects of combining the two interventions in controlling malaria disease.

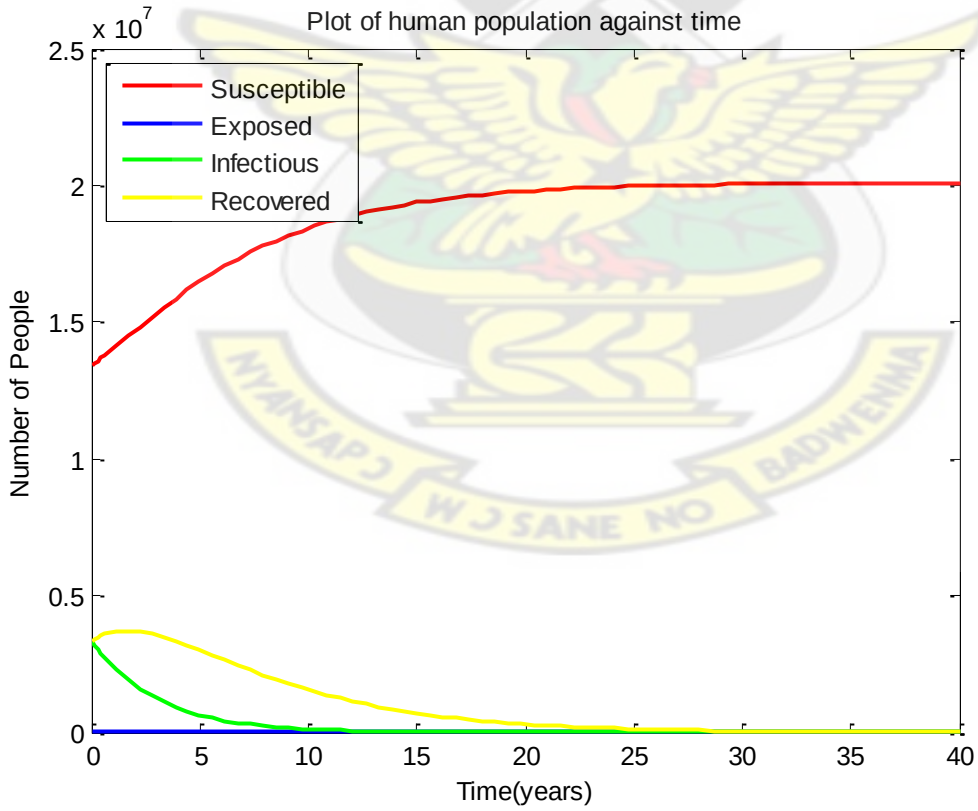

Figure 4.6: Represents the effects of combining the two interventions in controlling malaria disease.

The effects of combining the two interventions in controlling malaria disease are shown in figure 4.6. When the two interventions are combined in Ghana, we will have malaria free status by 2029. Our conclusion from this is that intervention practices that involve both prevention and treatment controls yield a relatively better result. It shows that the combination of these interventions can play a positive role in reducing or eradicating the disease in the country.

4.10 DISCUSSION

We have derived and analysed a mathematical model for the transmission and spread of malaria in Ghana. We computed the basic reproduction number R_0 for model. If $R_0 < 1$, the disease can not persist in the country and when $R_0 > 1$ the disease can persist. We have also shown that the model has both a disease-free and endemic equilibria, and the two equilibrium points are locally asymptotically stable. Simulation of the model has been carried out.

Following results was obtained from the analysis of the model. Therefore the basic reproduction number is $R_0 = 0.8939$. The disease-free equilibrium point is $(23892000, 0, 0, 0, 97625000, 0, 0)$ and the endemic equilibrium point is $(1.9937 \times 10^7, 3.2292, 300, 4012, 2.9288 \times 10^7, 5.0735 \times 10^{-6}, 8.7636 \times 10^{-4})$.

After the numerical simulation it has been revealed the most effective strategies to eliminate or eradicate malaria in Ghana is the combination of the two interventions in 4.6, but we conclude that the most influential parameter in controlling the disease (malaria) is to reduce the mosquito biting rate through the use of Insecticide-treated bed nets (ITN) and Indoor residual spraying (IRS) in figure 4.4 ; because the malaria parasite has developed resistance to mono-therapies treatment of falciparum malaria

CHAPTER 5

CONCLUSION AND RECOMMENDATION

5.0 INTRODUCTION

In this chapter, we present the conclusion of the study. We also present some recommendations based on the work done for further research.

5.1 CONCLUSION

We derived and analysed a mathematical model to better understand the transmission dynamics of malaria in Ghana. The model considered a varying total human population that incorporated recruitment of new individuals into the susceptible class through either birth or immigration. Our model incorporated features that are effective to control the transmission of malaria disease in Ghana.

Mathematically, we modelled malaria as a 7-dimensional system of ordinary differential equations. We first showed that there exists a domain where the model is epidemiologically and mathematically well-posed. We defined the basic reproduction number, R_0 , which provides the expected number of new infections (in mosquitoes or humans) from one infectious individual (human or mosquito) over the duration of the infectious period given that all other members of the population are susceptible. We proved if $R_0 < 1$, the disease can not persist in the country and when $R_0 > 1$ the disease can persist. We perform stability analysis of the model. We have proved that the disease-free equilibrium is locally asymptotically stable if $R_0 < 1$ and unstable when $R_0 > 1$. The Centre Manifold theorem is used to show that the model has a unique endemic equilibrium which is locally asymptotically stable when $R_0 < 1$.

In chapter four, the analysis of Ghana clinical data for malaria showed that the disease-free and endemic equilibrium points are asymptotically stable. The numerical analysis of the model suggested that the most effective strategies for controlling or eradicating malaria are the use of insecticide-treated bed nets and indoor residual spraying and prompt and effective diagnosis and treatment of infected individuals in figure 4.6. This study concurs with the Chavez (2008) suggestion that the intervention using insecticide-treated bed nets represents an excellent example of implementing an infectious disease control programme, and Smith et al, (2008)'s 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 case in humans. Hence the effect of reducing mosquito bites in figure 4.4 has great impact in the reduction of the spreading of the disease (malaria), but the combination of two interventions in figure 4.6 can play a bigger role in reducing or eradicating the transmission of the disease and malaria related deaths in Ghana.

5.2 RECOMMENDATIONS

Malaria eradication remains a big challenge to National Malaria Control Programme in most developing countries, hence there is need to strengthen the control strategies at hand as well as looking for some new ones since, in Ghana, malaria is responsible for more than 44 percent of outpatient visits at hospitals and clinics and approximately 22 percent of deaths in children under the age of five (President's Malaria Initiative, 2011). Thus, from the results of this work, it is recommended that:

1. Mosquito biting rate should be reduced as seen in figure 4.4, because we have proved that the country can achieve malaria free nation in 2037 if the country reduces the biting rate

by $1/16$. Mosquito biting rate can be reduced if the susceptible population sleeps under an insecticide-treated bed nets every night, stays in rooms with screened windows, uses mosquito repellants and coils, and reduces time spent outdoors after dark. Indoor residual spraying should also be encouraged, because it does not only reduce mosquito biting rate; but it has greater chances of reducing the mosquito population by killing mosquitoes that rest indoors after feeding. This strategy is likely to increase the chances of killing infected mosquitoes.

2. People who are ill should seek early clinical treatment at health centres, because in figure 4.5 we can see that increasing clinical treatment rate has positive impact in controlling the disease. Prompt and effective diagnosis and treatment of infected individuals can avoid severe or complicated malaria and reduce malaria related deaths. Intermittent prophylactic treatment should be encouraged during pregnancy and for infants.

3. Research institutions should commence researching into genetically modified mosquitoes that would be incapable of transmitting malaria, because if reducing the mosquito biting rates by $1/16$ could achieve malaria free nation in 2037 in figure 4.4. Then if the probability of transmission of infection from an infectious human to a susceptible mosquito and vice versa are made permanently to zero, then we can have the genetically modified mosquitoes existing without malaria infection in human population.

5.3 FUTURE WORK

As there are some species of Anopheles mosquitoes that have an immune response to kill the Plasmodium parasites, there is hope that genetically modified mosquitoes could be introduced into the wild that would be incapable of transmitting malaria. Having a population of only transgenetically modified mosquitoes would be the solution to eliminate the transmission of malaria. Li (2004) and (2005) examined some population models for the introduction of transgenic mosquitoes (Chitnis, 2005). Therefore, we would like to recommend that future work in malaria research should include the effects of the transgenic mosquitoes on the spread of malaria in our research works or models.

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APPENDIX A

Matlab codes used for simulating the malaria model (3.1)

(i) The M-function files

```
function dydt = malaria (t,y)

dydt = zeros (size(y));

a1=0.00005079;a2=0.071;b1=(1/14);b2=(1/11);c=(1/7);

d1=0.00004278;d2=(1/25);e1=(0.0000027);e2=(1/91.3125); f1=0.42;f2=0.0655;f3=0.40;

Sh=y(1);

Eh=y(2);

Ih=y(3);

R=y(4);

Sm=y(5);

Em=y(6);

Im=y(7);

Nh = Sh + Eh + Ih + R;

k1=(f2*f3)/Nh; k2=(f1*f3)/Nh;

%The malaria model

dydt(1) = a1 +e2*R - k1*Im*Sh  - d1*Sh;

dydt(2) = k1*Im*Sh - (b1 + d1)*Eh;

dydt(3) = b1*Eh - (c + d1 + e1)*Ih;

dydt(4) = c*Ih - (e2 +d1)*R;

dydt(5) = a2 - k2*Ih*Sm - d2*Sm;

dydt(6) = k2*Ih*Sm - (b2 + d2)*Em;
```

```
dydt(7) = b2*Em - d2*Im;

%The basic reproduction number for the malaria model

R0 = sqrt(((f3^2)*a2*b1*b2*f1*f2*d1)/(a1*(d2^2)*(b1+d1)*(c + d1 + e1)*(b2 + d2)));

disp(R0)
```

(ii)The executable file for plotting the line graph of human population against time

```
tspan = [0 700];

y0 = [13413000 18000 3350000 3343000 16500000 500000 38000000];

[t,y] = ode45(@malaria,tspan,y0);

plot(t,y(:,1),'r',t,y(:,2),'b',t,y(:,3),'g',t,y(:,4),'y','Linewidth',2)

title('Plot of human population against time')

xlabel('Time(years)')

ylabel('Number of People')

legend('Susceptible ','Exposed ','Infectious ','Recovered ',2)
```

(iii)The executable file for plotting the line graph of mosquito population against time

```
tspan = [0 700];

y0 = [13413000 18000 3350000 3343000 16500000 500000 38000000];

[t,y] = ode45(@malaria,tspan,y0);

plot(t,y(:,5),'r',t,y(:,6),'b',t,y(:,7),'g','Linewidth',2)

title('Plot of mosquito population against time')

xlabel('Time(years)')

ylabel('Number of Mosquitoes')
```

```
legend('Susceptible ','Exposed ','Infectious ')
```

(iv)The executable file for plotting the line graph of prevalence against time

```
tspan = [0 700];
y0 = [13413000 18000 3350000 3343000 16500000 500000 38000000];
[t,y] = ode45(@malaria,tspan,y0);
N1=(y(:,1)+y(:,2)+y(:,3)+y(:,4));
plot(t,(y(:,2)+y(:,3)+y(:,4))./N1,'r','Linewidth',2)
xlabel('Time (years)')
ylabel('Prevalence')
```

(v)The executable file for plotting the line graph of Simulation of Biting Rate of Mosquitoes on the Model

```
tspan = [0 40];
y0 = [13413000 18000 3350000 3343000 1031250 31250 2375000];
[t,y] = ode45(@malaria,tspan,y0);
plot(t,y(:,1),'r',t,y(:,2),'b',t,y(:,3),'g',t,y(:,4),'y','Linewidth',2)
title('Plot of human population against time')
xlabel('Time(years)')
ylabel('Number of People')
legend('Susceptible ','Exposed ','Infectious ','Recovered ' , 2 )
```

(vi)The executable file for plotting the line graph of Simulation of Treatment Rate of Infectious Humans on the Model

```
tspan = [0 300];
y0 = [13413000 18000 3350000 3343000 16500000 500000 38000000];
[t,y] = ode45(@malaria,tspan,y0);
plot(t,y(:,1),'r',t,y(:,2),'b',t,y(:,3),'g',t,y(:,4),'y','Linewidth',2)
title('Plot of human population against time')
xlabel('Time(years)')
ylabel('Number of People')
legend('Susceptible ','Exposed ','Infectious ','Recovered ')
```

(vii)The executable file for plotting the line graph of Simulation of Biting and Treatment Rates of Infectious Humans on Model.

```
tspan = [0 40];
y0 = [13413000 18000 3350000 3343000 1031250 31250 2375000];
[t,y] = ode45(@malaria,tspan,y0);
plot(t,y(:,1),'r',t,y(:,2),'b',t,y(:,3),'g',t,y(:,4),'y','Linewidth',2)
title('Plot of human population against time')
xlabel('Time(years)')
ylabel('Number of People')
legend('Susceptible ','Exposed ','Infectious ','Recovered ')
```

APPENDIX B

The table below shows the susceptible-exposed-infectious-recovered population of Ghana.

Year	Susceptible(S_h)	Exposed(E_h)	Infectious(I_h)	Recovered(R)	Total(N_h)
2000	13413000	18000	3350000	3343000	20124000
2001	14409000	17000	3045000	3043000	20514000
2002	14604000	17000	3141000	3139000	20901000
2003	14173000	20000	3553000	3551000	21297000
2004	14852000	19000	3416000	3414000	21701000
2005	15187000	19000	3453000	3451000	22110000
2006	15482000	19000	3511000	3508000	22520000
2007	16688000	17000	3123000	3119000	22947000
2008	17263000	17000	3051000	3047000	23378000
2009	20019000	5000	1900000	1896000	23820000