Mathematical Modelling of Transmission and Control of Malaria

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The thesis presented in partial fulfillment of the requirements for the Degree of Master of Science in Mathematics at the University of Venda

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Declaration

I declare that the Dissertation hereby submitted to the University of Venda for the Master of Science in Mathematical Dissertation (MSCMAD) degree has not previously been submitted by me for a degree at this University, that it is my own work in design and in execution, and that all material contained therein has been duly acknowledged.

Signed: ....

Mulaudzi Matodzi Stanley

Date:.....14.....APRIL.....2011.......................................

Dedication

I dedicate this work to all individuals and organisations around the world involved in the formulation of malaria control policy, SACEMA and my younger brother.

Abstract

Malaria starts with plasmodium sporozoites infection of the host liver, where development into blood stage parasites occurs. A number of deterministic models are developed in this thesis. The release of modified mosquitoes aims to displace gradually the wild (natural) mosquito from the habitat.We discuss the suitability of this technique when applied to pre-domestically adapted plasmodium falciparum mosquitoes which are transmissor of malaria disease. The dynamics of interaction of sporozoites, liver cells, merozoites and red blood cells which cause the symptoms and pathology of the disease is comprehensively studied. We then show how variability of host-parasite immunity is incorporated in the model which are constructed to include liver and blood compartments by subdividing the host population into various mutually exclusive compartments. The increase in eggs, larval and pupal stages of mosquitoes increase the vector mosquito population and transmission of the disease, hence the suggestion that immature and adult mosquitoes be controlled extensively. The models which are in the form of nonlinear ordinary differential equations are rigorously analysed using extensively analytic and numerical techniques to determine important epidemiological thresholds, stability of the steady states and the persistence of infection in the respective populations. Conclusions are made based on the results obtained from the analyses of the models of malaria that have been developed.

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May the Lord bless you all

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Introduction

1.1. Background

Infectious diseases remain a leading cause of morbidity and mortality worldwide, with HIV, malaria and tuberculosis estimated to be 68.5% of all deaths each year (World Malaria Report, 2005). Malaria is a mosquito-borne and a potentially fatal blood disease caused by a parasite that is transmitted to human hosts by the bite of female *Anopheles* mosquito when they feed on human blood. Malaria still remains one of the major impediments to health and development in Africa and it is a complex disease in different parts of the world. In Africa today, malaria is understood to be both a disease of poverty and a cause of poverty. In South Africa malaria is not exempted from the potential ravages with its debilitating effects on communities and development. Malaria occurs in almost all of Sub-Sahara Africa. Malaria got into South Africa at its very fringe, but now is only in low altitude areas in the northern part of the country (Mpumalanga, Limpopo and Northeastern part of the Kwazulu-Natal). The four species that cause malaria in humans are the protozoan parasites of the genus *Plasmodium*: Human malaria in South Africa is caused mainly by the parasite *plasmodium*, the most deadly of the human parasites (Busenberg, 1991), is the most widespread in tropics. The other three *plasmodium* species are also causative agents for malaria in humans but they are rare in South Africa: *Plasmodium vivax* is a major cause of clinical malaria but is rarely fatal. *Plasmodium malariae* and *Plasmodium ovale* are an infrequent cause of clinical malaria, often persisting as low grade parasitaemia with other species and relapse many years after apparent cure. *Plasmodium falciparum* accounts for the most severe and often potentially lethal forms of malaria. Chronic infections persisting over 2-3 years do occur but relapses are uncommon, since no dormant stages, viz. hyponozoites exist in liver. Although there are four species of plasmodium that infect humans, only two (*Plasmodium vivax* and *Plasmodium falciparum*) cause this disease, with nearly all deaths being caused by *Plasmodium falciparum* (Aide *et al.*, 2007). Our focus in thesis, will be centered on *Plasmodium falciparum.* Studies have shown that in areas where sprinkler irrigation scheme is practised there is potential transmission of malaria (Chimbari *et al.*, 2004). The associated of irrigation and vectors that transmit malaria is well documented (Keiser *et al.*, 2004, Mutero *et al.*, 2000, Hunter *et al.*, 1993).

In South Africa malaria slows economic growth to 1.1% each year (WHO, 2000). Malaria cases are also being exacerbated by the high levels of HIV infection, that weakens the immune system rendering people with HIV more susceptible to contracting the disease (Bush *et al.*, 2001). There are no simple solutions to the world's malaria problem and it is unlikely that a single strategy for control will be applicable to all countries and all epidemiological situations. Therefore, expansion of our understanding of the biological, epidemiology, pathogenesis and clinical manifestations of this complex, heterogeneous disease will be critical to the development and additional strategies for control.

1.2. Overall Aim

To develop mathematical models that can be used to inform the development of a policy frame work for control and implementation of successful malaria control programmes.

1.3. Objectives

The objectives of this thesis are:

(*a*) To investigate the control of malaria using transgenic mosquito population using a mathematical model of the interaction of transgenic and wild type mosquitoes. (Transgenic mathematical model).

(b) To compare malaria control measures that target the vector population in water and those that target the adult mosquito population using an age-structure mathematical model of vector population dynamics.

(c) To develop a more elaborate understanding of host pathogen interaction in malaria infection using a new mathematical model that incorporates the liver and blood stages of malaria infection.

1.4. Problem Statement

The life of *Anopheles* species causes the transmission of malaria between infected humans and mosquitoes. No vaccines are available for the mosquito-borne disease. One effective way to prevent the malaria epidemic and other mosquito-borne disease is to control mosquitoes, which has been one of the major efforts for many years.

The research intends to investigate the control of malaria by mathematically targeting the vector mosquito population in aerial and aquatic environments, and also to gain more understanding on how malaria parasites in the human body can be reduced before affecting the human host blood. Despite the availability of drugs for the control of malaria disease, its incidence still continues to rise. In this research we want to investigate the control of malaria using transgenic mosquito population to interact with wild mosquitoes in their breeding site aiming to reduce the number of wild mosquito which causes the malaria in human host population. The wild mosquito is the natural mosquito population which transmit the parasite that cause malaria when it feeds on human blood; this project seeks to reduce the number of wild mosquitoes as the alternative way of malaria control technique. This technique aims to release male modified loaded gene that intergrate malaria resistance directly into mosquitoes DNA, which makes it impossible for those mosquitoes to transmit the parasites that cause malaria. These mosquitoes are released once in the environment to mate with wild mosquitoes, when they mate the resulting offspring is modified mosquito. When these proposed new species of mosquito population feed on human blood they won't transmit parasites that cause malaria.

The number of adult mosquito population is increasing every day in the environment due to higher number of immature mosquitoes developing into adult mosquitoes which causes the malaria infection to increase worldwide. The number of malaria infections is determined by the number of adult mosquito population and these adult mosquitoes which transmit parasites develop from the immature mosquito population. In this research we want to show mathematically that when small number of immature mosquitoes develop, the number of malaria cases is also small. We want to control malaria by targeting mosquito population in water and the adult mosquito using an age-structure mathematical model of vector mosquito population dynamics. Reducing immature mosquito population will have an effect on adult mosquito population as the cases of malaria infection decreases with the decrease in the number of adult mosquito.

Further, we will attempt to gain more understanding of host pathogen interaction in malaria infection, because when infected anopheles mosquito feeds on human blood the parasites in the form of sporozoites parasites is injected into human host to infect the human blood. The sporozoites parasites when injected into human body circulate in the blood in order to reach and destroy the human liver cells; once liver cells become infected they rapture to release merozoites into blood which increase the number of merozoites parasites in the blood which make impossible for immune system to destroy the merozoites parasites. In this research we will try to elaborate on control of malaria by targeting sporozoites parasites in the liver before it affects the blood stages.

These three issues will be investigated mathematically as the alternative way of malaria control technique. These techniques are not potentially yet possible, but advances are being made and mathematical modelling can shed light on the potentials of these approaches.

1.5. Transmission

There are several ways in which malaria can be transmitted in humans and these are:

(*a*) The bite of an infected female *Anopheles* mosquito. In this thesis, we will consider this type of transmission.

(*b*) Malaria can be transmitted through blood transmission. Among people living in malarious areas, partial (semi) immunity to malaria allows donors to have parasitaemia without any fever or other clinical manifestations.

(*c*) Organ transplantation may transmit malaria.

(*d*) Transplacental malaria can be significant in populations which are partially immune to malaria. The mother may have placental parasitaemia, peripheral parasitaemia, or both without any fever or other clinical manifestations. Vertical transmission of this infestation is associated with anaemia in the baby (WHO, 1999).

The incidence of direct human to human transmission is significantly lower than that from mosquitoes to human. There are about 3500 species of mosquito worldwide, of which 430 are in the genus anopheles (Baker, 1966). Of the approximately 430 only 30-40 species of *Anopheles* are capable of transmitting malaria (they are suitable for the development of malaria). The susceptibility of these mosquitoes to the malaria parasite is known to be variable with some mosquitoes permissive to the infection than others (Hume *et al.*, 2007). The *anopheles* mosquito are easy to recognise because of the characteristic stance. They rest with their head down and their abdomen sticking out, while other mosquitoes rest with their bodies parallel to the resting surface (Parry and Parms, 2007).

These vectors also differ in their biology and ecology, varied epidemiological patterns and capability to develop resistance to insecticides. Both female and male mosquitoes feed on nector, the female however requires a blood meal for the protein necessary for egg development (Klowden, 1995). Some species of the mosquito prefer human blood (Antropophilic) while others prefer animal blood (zoophilic). Some prefer to bite indoors (endophagic) and other prefer outdoors (exophagic). Similarly some rest indoors (endophilic), while other rest outdoors (exophagic). Once a good blood meal has been taken, the vector searches for a convenient breeding site. The *Anopheles* mosquito, like several other insect vectors, goes through several separate and distinct stages of development. The eggs are laid on water and after about 2-3 days, they hatch into larva. This process is temperature-dependent and can take-up to 2-3 weeks in cold water. In about 2-4 days, the larval changes into pupa. The pupa then changes into the adult mosquito in about 2-4 days. The duration of the whole cycle (form eggs laying to an adult mosquito) varies between 7 and 20 days, depending on the ambient temperature and the mosquito species (Gilles and warrel, 1993). In the process of interaction, the mosquito may loose its life. When a mosquito alight on the skin, it attempts to pierce a small blood vessel with its proboscis in order to suck blood. The mosquito first injects some saliva together with an anticoagulant (anti-clotting chemical) to prevent blood from clotting and closing the wound so the mosquito can drink it. If the mosquito is infected with malaria parasites then sporozoites are introduced into the human body together with saliva during the bite. The sporozoites leave the site of the bite fairly rapidly, penetrate capillary and travel through the bloodstream to gain access to hepatocytes. About minutes after being introduced into the blood stream these sporozoites enter the hepatocytes and form schizonts (McQueen and Mckenzie, 2004; Rouzine and Mckenzie, 2003; Bailey, 1982). Schizonts undergo a process of maturation and multiplication known as pre-erythrocytic or hepatic schizogony. In *plasmodium malariae* and *Plasmodium ovale*, some sporozoites convert to dormant forms called hypnozoites, which can cause disease after months or years. They further continue to differentiate and divide into exo-erythrocytic Schizonts, each containing thousands of infectious merozoites. The liver stage is also called the pre-erythrocytic stage. The sporozoites stage and the liver stage that follows subsequently are clinically silent stages of infection and parasite clearance or reduction in the parasites burden at these stages can markedly attenuate disease. 6 to 16 days after infection, the Schizont ruptures releasing merozoites is estimated as 2,000 for *plasmodium malariae*, 10,000 for *plasmodium vivax/ plasmodium ovale* and up to 30,000 for *plasmodium falciparum* (Garnham, 1996).

These merozoites released into the blood stream invade neighbouring or circulating erythrocytes and become first trophozoites and then erythrocytic Schizonts (by a phase of asexual reproduction). After about 48-72 hours (Diebner *et al.*, 2000; Hoshen *et al.*, 2000), depending on the plasmodium species, the infected erythrocytes burst releasing 16-32 merozoites and multiple antigenic and pyrogenic substances into the bloodstream. These merozoites quickly infect fresh erythrocytic incessantly propagating the parasites cycle. Some merozoites responding to diverse triggers (Bilker *et al.*, 1997), follow an alternative development pathway that yields the sexual form called the gametocytes (Diebner *et al.*, 2000). These gametocytes develop through morphologically distinct stages within red blood cells. Matured gametocytes enclosed within the red blood cell membrane, circulated in the host's body blood, awaiting up-take by mosquito vector during a blood meal. When the infection takes place symptoms begin 10 days to 4 weeks after an infective bite and symptoms start with high fever and flu-like illness with shaking chills, headache, sweating, muscle aches, tiredness and sometimes nausea, vomiting, and diarrhea (Diener *et al.*, 1994).

The male gametocyte nucleus divided into eight sperm-like flagellated microgametes each of which also leaves the erythrocytes the midgud and actively moves to fertilizer a macrogamete within 60 minutes of ingestion of blood (Simonetti,1996). The result of the fertilization process is the zygote, which develops into a motile ookinete within 10-25 hours from the blood meal. The ookinete invade the midgut wall of the mosquito where they develop into oocysts. The oocyst grow, rupture and release sporozoites, which make their way to the mosquitoes salivary glands over a period of 7-12 days. Here they stay for possible very long periods until injected into another vertebrate host when the next blood meal is taken (Carter and Graves, 1988; Sinden, 1984). Time required for the entire sexual development of the parasite in the body of the mosquito depends critically on the prevailing temperature and for *plasmodium falciparum* it is about 12 days within temperature range of 25-27^0C (Anderson and May, 1991). Inoculation of sporozoites into a new human host perpetuates the malaria life cycle. The cycle of blood meal and oviposition continues throughout the life of a female mosquito and requires repeated contacts with the vertebrate host, allowing for ingestion of malaria parasites, their multiplication and maturation, and transmission to other individual hosts during subsequent feedings. The life cycle of the malaria parasite, spanning its mosquito and human hosts, is shown in Figure 1.1.

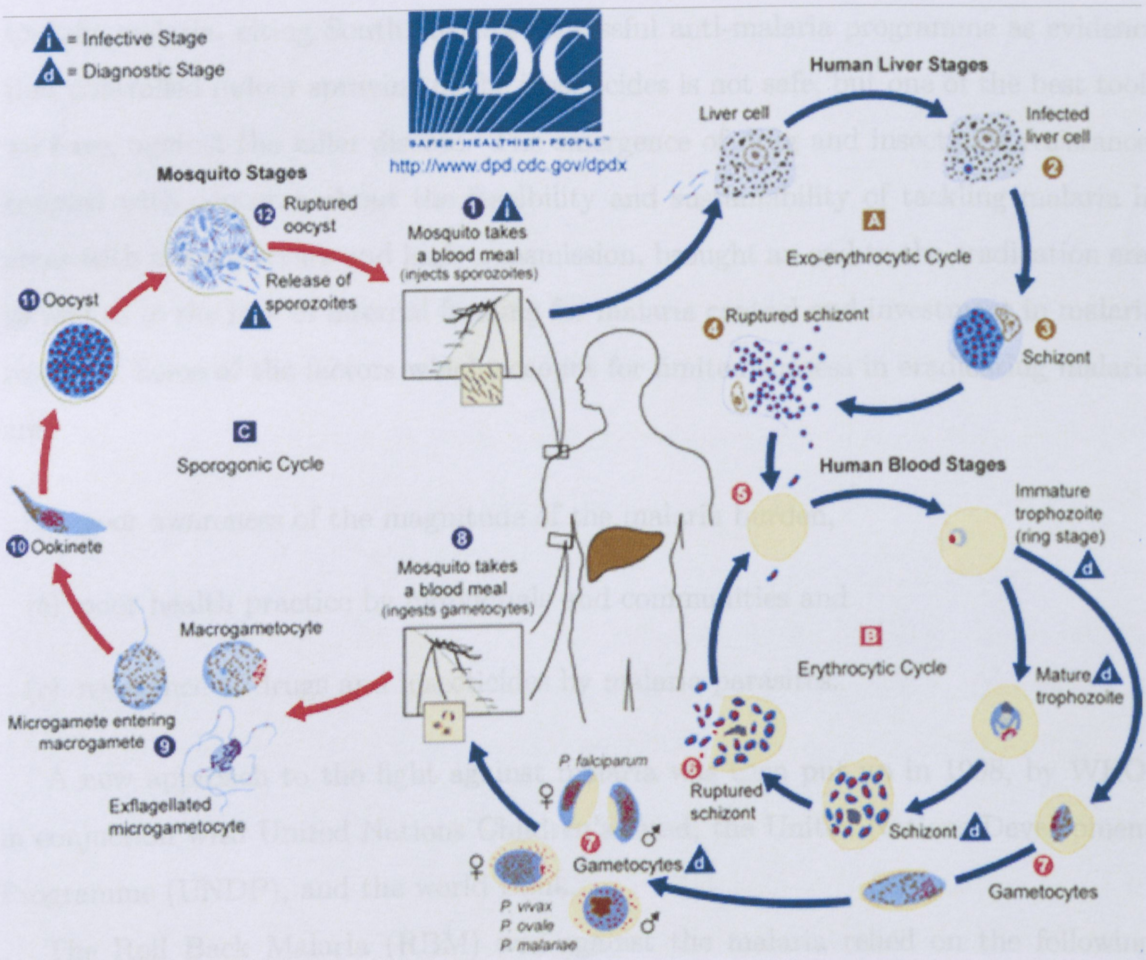


Figure 1.1: Life cycle of malaria parasites adapted from CDC, (2004).

1.6. Control strategies

The global malaria eradication campaign successfully eliminated or controlled the disease in countries with temperate climates used in some countries where malaria transmission was low or moderate. One of the projects on the study of epidemiology and control of malaria was conducted by World health Organization (WHO) and the government of Nigeria in Garki, Nigeria, from 1969 to 1979 (Nedelman, 1983). The results of the study have been reported by the WHO in a monograph (Molineaux and Gramiccia, 1980).

In 2006, the WHO turned on the use of Dichloro-Diphenyl-Tricholoethane (DDT) to fight malaria, citing South Africa's successful anti-malaria programme as evidence that controlled indoor spraying of the insecticides is not safe, but one of the best tools we have, against the killer disease. The emergence of drug and insecticide resistance, coupled with concerns about the feasibility and sustainability of tackling malaria in areas with infrastructure and high transmission, brought an end to the eradication era, as well as to the lack of internal funding for malaria control and investment in malaria research. Some of the factors which account for limited success in eradicating malaria are:

(a) poor awareness of the magnitude of the malaria burden,

(b) poor health practice by individuals and communities and

(c) resistance of drugs and insecticides by malaria parasites.

A new approach to the fight against malaria was then put up in 1998, by WHO, in conjuction with United Nations Children's Fund, the United Nations Development Programme (UNDP), and the world Bank.

The Roll Back Malaria (RBM) war against the malaria relied on the following strategies:

(a) Curative measure based on research and evidence

(b) early diagnoses

(c) multiple prevention methods

(d) dynamic global movement against the problem.

The Roll Back Malaria (RBM) and other organisations, recommended some of the strategies that have been documented previously (Munday, 2007; Sharp *et al.*, 2007; WHO, 2006; Alonso *et al.*, 1998) these are:

(a) Egg-larval-pupa control: This strategy includes methods such as the destruction of mosquito breeding sites, to reduce the number of mosquitoes.

(b) Indoor residual spraying: Spraying reduces mosquito longevity. This strategy is also likely to kill mosquitoes that rest indoors after feeding so it increases the chances of killing infected mosquitoes.

(c) Insecticides-treated bed nets (ITNS): Roll Back Malaria (RBM) has been promoting the use of insecticides treated bed nets in many regions of Africa to reduce the transmission of malaria, and has succeeded in doing so in many regions.

(d) Transgenically mosquitoes: 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 facilitating malaria transmission. This is a promising area of research, although still in its early stages. There would be need for strict control to ensure that the new mosquitoes created are not accidentally given the capability of transmitting other disease such as influenza or AIDS. As these mosquitoes would be immune to malaria, having a population of only transgenically modified mosquitoes would eliminate the transmission of malaria. However, we would expect some wild-type mosquitoes to persist in the population of transgenic mosquitoes.

1.7. Genetically Modified Mosquitoes (Transgenic Mosquitoes)

Transgenic mosquito is the type of species of Anopheles mosquitoes that have an immune response that is unable to carry the plasmodium parasites. It blocks transmission of the malaria disease to humans, by preventing the human malaria microbe from getting into the mosquito's saliva and thus entering a human's bloodstream.

This genetically modified mosquito technique will work provided scientists can manage to get a foreign gene that could be loaded into male mosquito in order to be released into wild environment, it seems possible as scientists have already succeeded in genetically engineering mosquitoes that cannot transmit malaria to birds and mice (*http://www.vetmed.ucdavis.edu/ucmrp/index.html*).

Strategies of using the genetically modified mosquitoes to control mosquito borne disease are planned to be done by modifying male mosquito. The modified mosquitoes could be released into the wild mosquitoes by interbreeding and eventually transmit the beneficial gene to the mosquitoes offspring. This shows the feasibility of generating population of transgenic mosquitoes that have diminished potential to carry the malaria parasite. While these developments are promising and exciting, it seems that many questions have to be answered before such techniques can be implemented and transgenic mosquitoes can be deployed in the field (Enserink, 2001). The mating between heterozygous mosquitoes produce homozygous wild, and heterozygous transgenic mosquitoes and the mating between heterozygous transgenic and homozygous wild or transgenic mosquitoes (Jacom-Loren, 2002). The technique of sterile male were first used successfully in 1958 in Florida to control screwworm fly (cochliomyo omnivarax) (Knipling, 1979 and 1985). About 50 million flies of both sexes were released per week over an 18 months period, in a total of 2 billion flies over 85 000 square mile area. The pest was eradicated after this period of application, in which 40 tons of ground meat were required each week and 20 aircraft to release the sterile flies. Much research was carried out about 30 years ago, especially in India and El salvadar, on the application of sterile insect release method to mosquitoes. Unfortunately this technique virtually ended in the mid-1970s, not because the method was a technical failure, but because of political problems in India and intensifying civil wars in central America (Pates, 2005).

Much work has been done on genetically modified mosquitoes in the laboratory to hinder or block parasites transmission thus making the mosquitoes refractory. This is done by insertion of gene at appropriate sites to create a stable germline. The process research in this area is fairly recent.

Christophides (2005) studied the potential of the transgenic mosquitoes to suppress the transmission of malaria. He cites research on genetically modified mosquitoes that has been proposed for use in population suppression (via sterilization) and more recently for population replacement.

A collection of papers dealing with different aspects of genetically modified mosquito is given in Takken and Scott (2003), from genetic control of mosquito-borne disease, mosquito ecology, population genetics and pathogen transmission to consequences of releasing genetically modified mosquitoes into the environment.

The use of sterilization for trial releases of transgenic mosquitoes was proposed by Andreasen and Curtis (2005) and they study the optimal life stage for sterilizing anopheles males in order to reduce their fitness upon release. Lambrechts *et al.*, (2006) studied the effect of environmental factors on the resistance of mosquitoes to malaria infection. They concluded that environmental variation can significantly reduce the genetic component of resistance to malaria infection. They suggest that the influence of environmental factors should be studied in order to obtain a true assessment of the usefulness of transgenic mosquitoes.

Turelli and Hoffman (1999) constructed mathematical models that accurately predict the dynamics and equilibria of *Wolbachia* infections as well as the associated spread of transgenes (mitochondrial DNA variants). They discuss strategies for using the rapid spread of *Wolbachia* to drive transgenes associated with disease control or pest abatement into mosquito populations.

Ribeiro and kidwell (1994) analyse the possible use of transposable elements as a mechanism for driving parasite-resistant genes into a vector population. Due to the high replicative ability of these DNA sequences and their broad distribution in eukaryotes and prokaryotes there is a high probability of finding elements with properties suitable for transforming vector populations. Their analysis is based on coupled Hassel-equations which are modified or generalized Beverton-Holt equations.

Esteva and yang (2005) study a continuous time mathematical model of the population dynamics of a system that includes male sterile insects. They show that for their model the technique of sterile insect release is completely successful if the average number of female insects produced by a single female is below a certain threshold which is a function of the ratio of the infertile to fertile matings.

Some of the work on genetic mosquito done by Jia Li (2004), proposed a discrete-time mathematical model for population consisting of wild and genetically altered mosquitoes. In that work a two species model having a hybrid Riccati/Ricker type nonlinearity and equal survival probabilities is developed and sufficient conditions are given guaranteeing the existence of a locally asymptotically stable fixed point. It was shown by Robert and Hubertus (2002) that under less restrictive conditions the fixed point is actually globally asymptotically stable with respect to initial populations in which both species are present.

One of the risks involved in the release of genetically altered mosquitoes is that of unanticipated phenotypic changes (Alphey *et al.*, 2002; Scott *et al.*, 2002 and Beijing-Chaina , 2002). Clarke (2002) state some of the possible drawbacks of releasing genetically modified mosquitoes. It could occur that transgenic mosquitoes could have the ability to transmit other disease that wild mosquitoes can not. The main concern is if the modifications are stable in the long run. Elimination of the disease for a short period could be devastating. Benedict and Rinson (2003) argue that to demonstrate the safety of releasing transgenic mosquitoes, one cloud first release transgenic sterile insects. Early studies such as Knipling (1959, 1968) proposes the release of sterile insects to control populations of targeted insects in the field. This approach has been successful in the elimination of the New World screwworm, *Cochliomyia hominivorax*, from southern USA, Mexico and central America (Wyss, 2000) and in North Africa as well, (Lindquist *et al.*, 1992).

Our work in Chapter 2 assess the same mosquitoes species considered by Jia Li (2004) as wild and genetically modified mosquito, but our work will employ the familiar epidemiology modells, SIR and SI which are explained well in Tables 1.1. and 1.2. while Jia Li uses discrete maps. The techniques here focus on the mating of wild mosquitoes and modified mosquitoes and also the interaction of these two types of mosquitoes with humans host population, aiming to show that the transgenic mosquito is a good fighter of malaria disease. The expectation is to see the rate of infection decrease and wild mosquitoes vacate the environment.

1.8. Mathematical Modelling

1.8.1. Introduction of Mathematical modelling

Mathematics is starting to play a greater role in the development of the life and social sciences, and these sciences are starting to influence the development of mathematics. Some people agree that real world problems can be translated and solved Mathematically, and this is where the name Mathematical modelling was born. Mathematical modelling is the process of using various mathematical structures such as graphs, equation, diagram, scatter plots, tree diagrams to represent real world situations. It essentially consists of translating real world problems into mathematical problems, solving the mathematical problems and interpreting these solutions in the language of the real world. This mathematical model is an abstract, simplified, mathematical construct related to a part of reality and created for a particular purpose.

Mathematical models can help us figure out which decision will have the largest impact on outcomes and can provide comprehensive examination of the assumptions that enter into decisions in a way that purely verbal reasoning and debate cannot.

Mathematics and Physics each had important effects on the development of the other. The constants, functions and so on are external and are referred to as exogenous variables (also called parameters, input, or independent variables). The things the model seeks to explain are endogenous variables (are also called output or dependent variable).

A mathematical model can take many forms, including but not limited to dynamical systems, statistical models, differential equations, or game theoretic models.

1.8.2. Mathematical Modelling of Diseases

Diseases are ubiquitous part of life. Many, such as the common cold, have minor symptoms and are purely an annoyance, but others, such as Malaria, Ebola or Aids, fill us with dread. It is unseen and seemingly unpredictable nature of the disease, infecting some individuals while others escape, that has gripped our imagination.

A model provides an abstraction that reduces a problem to its essential characteristics and it allows the user to eliminate the unimportant details so that the user can concentrate on the relevant decision variables that are present in a situation. This increases the opportunity to fully understand the problem and its solution. Once a model has been developed and used to answer a question, it should be critically examined and often modified to obtain a more accurate reflection of the observed reality of that phenomenon. Generally the success of a mathematical model depends on how easily it can be used and how accurate its predictions are.

Mathematical models can be used to:

(a) systematically compare alternate strategies,

(b) determine the key issues in decision-making,

(c) and identify gaps in current knowledge.

These models can be classified according to use (descriptive or optimization) degree of randomness (deterministic or stochastic) and degree of specificity (Specific or general).

Two types of modelling approaches are useful in the study of infectious disease: there are stochastic and deterministic modelling. Stochastic models rely on among-individual chance variation in risks of exposure, disease, and other factors. Stochastic model have several advantages one of which is that they allow follow-up of each individual in the population on a chance basis. Deterministic models, also known as compartmental models, attempt to describe and explain what happens. On the average at the population scale and they fit well in large populations. These models categories individuals into different subgroups (Compartments). Further, the models specify the transition rate between the compartments as susceptibles may become infected. Most models of infectious disease processes used until now are deterministic because they require less data, are relatively easy to set up, and because computer softwares are widely available and user-friendly. Many complex models exist in literature that can be modelled to incorporate stochastic elements, but these are not considered in this thesis.

The first step in deterministic modelling consists of having a complete and realistic picture of the biology of the disease (for example, the duration of the period of infectivity, incubation period, immune state after infection). The second step is to collect data on the demographical, epidemiological, and biological characteristics of the infection (transition rates) and the population (birth and death rates). Third, aparasimonous model is stated.

1.8.3. Development of Epidemiological Compartment Models

Since 1760, Daniel Bernoulli paved the way for mathematical modelling to the spread of infectious disease. Almost all modern epidemic models (Anderson and May, 1991; Daley and Gani, 1999, Hethcote), make use of multiple-state approach, segmenting the modelled population into a set of distinct compartments, each exhibiting different characteristics with respect to the disease. The states that are modelled include, passively immune (M), susceptible (S), exposed (E), infective (I), removed (R), and are also described in Table 1.2. The existence of each of these five states, together with the links between the respective states, is usually sufficient to provide a broad outline of the particular epidemic model being used, particularly in describing acute epidemics, which develop over a short period of time. However, models for more chronic and long-term epidemics would also need to consider births and deaths. A further enhancement for models dealing with disease for which vaccines have been immunised against a particular disease. Making use of the states outlined in Table 1.2, developed to name epidemic models after the states considered in the modelling process and the possible transitions between the various states. For example, SI models are the simplest possible because they are described with only two compartments (classes) that are susceptibles (S) and infectious (I). The models assume that the infective remains infectious for life. For SIS, there are still two subpopulations but in this type of model, it is assumed that the infectious individual has a chance to recover and become susceptible again. If the model considers the exposed period which is the time between being infected and becoming infectious then the SI and SIS models become SEI and $SEIS$ respectively where E is the exposed class. This means that the model accounts for the latent period of the disease; this model is needed when infected individuals (exposed) go through a latent period before being infectious. The latent period of measles, for example, is well known (about 8 days), and this information has to be translated in an appropriate model. An SIR model divides the population into susceptible (S), infectious (I), and recovered or removed (R). The recovered or removed class are those that have died, attained immunity or isolated. For example, the $SEIR$ model takes care of the exposed (E). If on the other hand, one deals with an infectious agent with no latent period then SIR would offer a relevant alternate model. The $SIRS$ and $SEIRS$ models rather posit that the recovered become susceptible as their immunity dies away. In this thesis, we will consider an SI type model in the mosquito population and either an SIR and $SIRS$ for the human population. Various other epidemic models, considering combinations of the above states are shown in Table 1.3.

Table 1.2: Full explanation of the categories of the populations, in the epidemic modelling. The sub-population are classified according to the disease status which are named M, S, E, I and R.

Symbol	Epidemic State	Description
M	Passively Immune	Lives that have acquired temporary immunity to a particular disease without having ever been infected. An example of this state would be new born infants with antibodies against the disease passed from their mother. These antibodies eventually disappear from the body at which time the infant moves into the susceptible state.
S	Susceptible	Lives that are healthy, but could potentially develop the disease.
E	Exposed	Lives that have been infected with the disease, but are still in the latent period and cannot transmit the disease to others.
I	Infective	Lives that are infected with the disease and are capable of transmitting the infection to others.
R	Removed	Lives that have either died or recovered from infectious thereby acquiring immunity (temporary to permanet) from infectious

Table 1.3: Different types of epidemic modells built up from the combination of the epidemic symbols (status) stated in Table 1.2.

Model	Characteristics
SI	Once a susceptible member of the population (S) has been infected with disease, he or she is immediately infective (I) and capable of transmitting the infection to others. No recovery from the disease is possible.
SIS	Same as the SI model, except that recovery from the disease is possible. However, upon recovery, a life is immediately susceptible (S) once again. That is, recovery fromthe disease does not confer any immunity against future infection.
SEI	Same as the SI model, except that, following initial exposure (E) to the disease leaing to infection, there is latent or incubation period during which the disease cannot be passed on to others.
$SEIS$	Same as the SIS model, except that, following initial exposure(E) to the disease leading to infection, there is a latent or incubation period during which the disease cannot be passed on to others.
SIR	Same as the SI model, except the recovery (R) from the disease is possible. Once recovered from the disease, there is lifelong immunity from reinfection.
$SIRS$	Same as the SIR model, except that postrecovery immunity is only temporary. Following a period of immunity, a life may become susceptible (S) once again.
$SEIR$	Same as the SIR model, except the following initial exposure (E) to the disease leading to infection, there is a latent or incubation period during which the disease cannot be passed on to others.
$SEIRS$	Same as the $SEIR$ model, except the postrecovery immunity is only temporary.
$MSEIR$	Same as the $SEIR$ model, with the addition of lives who are passively immune (M) from infection when they enter the population.
$MSEIRS$	Same as the $MSEIR$ model, except that postrecovery immunity is only temporary.

We will consider SI type model in the mosquito population and either an SIR and $SEIR$ for the human population.

1.8.4. Background on analysis of mathematical models

In this section we provide the necessary background to the mathematical analysis of non-linear systems of ordinary differential equations that are used in formulation of the epidemiological models in this thesis.

An ordinary differential system is a system of equations of the form

$$\begin{aligned} \frac{dz_1}{dt} &= f_1(z_1, z_2, \cdots z_n), \\ \frac{dz_2}{dt} &= f_2(z_1, z_2, \cdots z_n), \\ &\vdots \\ \frac{dz_n}{dt} &= f_n(z_1, z_2, \cdots z_n), \end{aligned} \tag{1.1}$$

which can be written more concisely in vector notation

$$\frac{d\mathbf{z}}{dt} = \mathbf{f}(\mathbf{z}), \tag{1.2}$$

where $\mathbf{z}$ and $\mathbf{f}$ are vectors with components z_i and f_i respectively, and the function f is assumed to be smooth enough so that through each point $\overline{z}$ there passes a unique solution of (1.1).

Definition 1.1. *An equilibrium point of a dynamical system generated by an autonomous system of ordinary differential equations (ODEs) (1.1) is a solution that does not change with time t.*

More precisely, the $ODEs$ (1.1) has an equilibrium solution $z(t) = \overline{z}$ if $f(\overline{z}) = 0$. Finding equilibria, i.e., solving the equation $f(z) = 0$ is only possible in a few special cases. Equilibria are sometimes called fixed point or steady states. Most mathematicians refer to equilibria as time-independent solutions of $ODEs$, and to fixed points as time-independent solutions of iterated maps $z(t+1) = f(z(t))$. The stability of typical equilibria of smooth $ODEs$ is determined by the sign of real part of eigenvalues of the Jacobian matrix. These eigenvalues are often referred to as the eigenvalues of the equilibrium point.

Definition 1.2. *An equilibrium is asymptotically stable if all eigenvalues of the ODE system have negative real parts; it is unstable if at least one eigenvalue has positive real part.*

In disease modelling the variables represent numbers of individuals, or fractions of the whole population, therefore they should be positive or zero for all times $t \geq 0$, and if this fails then the model should be discarded since it violates a basic aspect of the biological reality.

Let $\mathbb{R}^n$ be an $n-$ dimensional space ($n \geq 1$), and let Ω be a subset of $\mathbb{R}^n$. We say that Ω is positive invariant for (1.1) if, when $(z_1(0), z_2(0), \ldots, z_n(0))$ is in Ω, the solution starting with these initial conditions has the property that the trajectory $(z_1(t), z_2(t), \ldots, z_n(t))$ is in Ω, for all $t \geq 0$. Let

$$\mathbb{R}^n_+ = \{(z_1, z_2, \ldots z_n) : z_1 \geq, z_2 \geq 0, \ldots z_n \geq 0\}.$$

Positive invariance of the non-negative orthant $\mathbb{R}^n_+$ for any given system (1.1) will be assured if no trajectory can leave $\mathbb{R}^n_+$ crossing through one of its faces.

We now give the analyses of the system (1.1). Often the first step is to determine whether there are steady states or equilibria. An equilibrium is a constant vector $\overline{z}$ (that is, $z_i = \overline{z}_i, i = 1, \ldots, n$ are constant) that satisfies the equations (1.1). We assume that all the parameters are non-negative.

We solve for the equilibrium points by setting the right-hand sides of (1.1) to zero and the system takes the form

$$\begin{aligned} f_1(\overline{z}_1, \overline{z}_2, \ldots, \overline{z}_n) &= 0, \\ f_2(\overline{z}_1, \overline{z}_2, \ldots, \overline{z}_n) &= 0, \\ &\vdots \\ f_n(\overline{z}_1, \overline{z}_2, \ldots, \overline{z}_n) &= 0 \end{aligned} \tag{1.3}$$

A set of values that satisfy (1.3.) represent a system state such that if the system is in this state at some time $t_{1,}$ it remains in that state for all $t \geq t_{1,}$ in the absence of external disturbance.

Definition 1.3. *A stable node or focus of system* (1.3) *is called a sink of the linear system and an unstable node or focus of system* (1.3) *is called a source of linear system.*

Definition 1.4. *An equilibrium state $z(t) = 0$ is said to be locally stable if for every $\varepsilon > 0$ and $t_0 \in \mathbb{R}$, there exists $\delta(\varepsilon, t_0) > 0$ such that if $|z(t)| < \delta$ then $|z(t)| < \varepsilon$ for all $t > t_0$. If the equilibrium is locally stable and if for every t_0 there exists $\delta(t_0) > 0$ such that if $|z(t_0)| < \delta$ then $|z(t)| \to 0$ as $t \to \infty$, then the equilibrium point is locally asymptotically stable.*

Definition 1.5. *If asymptotic stability holds for any initial state then the equilibrium point is said to be globally asymptotically stable.*

In epidemiology there are equilibrium points (states), which are disease free equilibrium E_0 and endemic equilibrium point E^e. These disease free equilibrium points are points corresponding to the case when there is no infection (infected population) that is the absence of parasite and infected population. E_0 is obtained by setting infected I and recovered R compartments to zero ($I = R = 0$) in the case of the SIR model. But an endemic equilibrium point E^e corresponds to the presence of disease and infected population in a defined region such as $I > 0$.

The stability of the equilibrium points of (1.1) are obtained by using equilibrium points, this explanation cover all the systems that we come across through in this thesis. In short, the stability of system (1.1) is obtained by substituting equilibrium points obtained in equation (1.3).

If $(z_1(t), z_2(t), \ldots, z_n(t))$ is a solution of this system for $t \geq 0$ such that $(z_1(0), z_2(0), \ldots, z_n(0))$ is near an equilibrium $(\overline{z}_1, \overline{z}_2, \ldots, \overline{z}_n)$, we define

$$y_1(t) = z_1(t) - \overline{z}_1, y_2(t) = z_2(t) - \overline{z}_{2,} \ldots, y_n(t) = z_n(t) - \overline{z}_n.$$

Then

$$\begin{aligned}
\frac{dy_1(t)}{dt} &= f_1(\overline{z}_1 + y_1(t), \overline{z}_2 + y_2(t), \ldots, \overline{z}_n + y_n(t)),\\
\frac{dy_2(t)}{dt} &= f_2(\overline{z}_1 + y_1(t), \overline{z}_2 + y_2(t), \ldots, \overline{z}_{1n} + y_n(t)),\\
&\vdots\\
\frac{dy_n(t)}{dt} &= f_n(\overline{z}_1 + y_1(t), \overline{z}_2 + y_2(t), \ldots, \overline{z}_{1n} + y_n(t)).
\end{aligned} \tag{1.4}$$

Assume that the functions $f_1, f_2, \ldots, f_n$ are sufficiently differentiable, then expression (1.4) can be expressed in Taylor series. Since $y_{1,}y_2, \ldots, y_n$ are assumed to be small disturbances from the equilibrium, we drop terms of degree two or higher and consider linear parts of the equations.

The Jacobian matrix of a system of smooth $ODEs$ (1.1) is the matrix of the partial derivatives of the right-hand side with respect to state variable

$$J = D_z f = f_z = \left(\frac{\partial f_i}{\partial z_i}\right)$$

where all derivatives are evaluated at the equilibrium point $z = \overline{z}$. Its eigenvalues determine the stability properties of the equilibrium point.

We note that since $(\overline{z}_1, \overline{z}_2, \ldots, \overline{z}_n)$ is an equilibrium state,

$$\begin{aligned}
\frac{dy_1}{dt} &= a_{11}y_1 + a_{12}y_2 +, \ldots, a_{1n}y_n,\\
\frac{dy_2}{dt} &= a_{21}y_1 + a_{22}y_2 +, \ldots, a_{2n}y_n,\\
&\vdots\\
\frac{dy_n}{dt} &= a_{n1}y_1 + a_{n2}y_2 +, \ldots, a_{nn}y_n,
\end{aligned} \tag{1.5}$$

where $a_{11}, a_{12}, a_{21}, a_{22}, \ldots a_{nn}$, are the partial derivatives of the f_i evaluated at $(\overline{z}_1, \overline{z}_2, \ldots, \overline{z}_n)$. After linearisation we get the same system of form (1.2). System (1.5) can be written in a more compact form as

$$\frac{d\mathbf{Y}}{dt} = J\mathbf{Y} \tag{1.6}$$

where $\mathbf{Y} = (y_1, y_2, \ldots, y_n)$ and

$$\mathbf{J} = \begin{pmatrix} \frac{\partial f_1(\bar{z}_1,\bar{z}_{2,\ldots,}\bar{z}_n)}{z_1} & \frac{\partial f_1(\bar{z}_1,\bar{z}_{2,\ldots,}\bar{z}_{1n})}{z_2} & \cdots & \frac{\partial f_1(\bar{z}_1,\bar{z}_{2,\ldots,}\bar{z}_n)}{z_n} \\ \frac{\partial f_2(\bar{z}_1,\bar{z}_{2,\ldots,}\bar{z}_n)}{z_1} & \frac{\partial f_2(\bar{z}_1,\bar{z}_{2,\ldots,}\bar{z}_n)}{z_2} & \cdots & \frac{\partial f_2(\bar{z}_1,\bar{z}_{2,\ldots,}\bar{z}_n)}{z_n} \\ \vdots & \vdots & & \vdots \\ \frac{\partial f_n(\bar{z}_1,\bar{z}_{2,\ldots,}\bar{z}_{1n})}{z_1} & \frac{\partial f_n(\bar{z}_1,\bar{z}_{2,\ldots,}\bar{z}_n)}{z_2} & \cdots & \frac{\partial f_n(\bar{z}_1,\bar{z}_{2,\ldots,}\bar{z}_n)}{z_n} \end{pmatrix},$$

$$= \begin{pmatrix} a_{11} & a_{12} & \cdots & a_{1n} \\ a_{21} & a_{22} & \cdots & a_{2n} \\ \vdots & \vdots & \cdots & \vdots \\ a_{n1} & a_{n2} & & a_{nn} \end{pmatrix}. \tag{1.7}$$

is the Jacobian matrix of system (1.1) evaluated at $(\bar{z}_1, \bar{z}_2, \ldots, \bar{z}_n)$. System (1.5) is called the linearisation of (1.1) near $(\bar{z}_1, \bar{z}_2, \ldots, \bar{z}_n)$. The behaviour of the solution of (1.4) is determined by the eigenvalues of J, which are roots λ of the equation

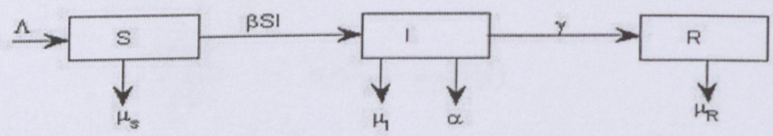
$$\det(J - \lambda I) = 0. \tag{1.8}$$

Every solution of (1.5) has the property that $y_1(t) \to 0, y_2(t) \to 0$ and $y_n(t) \to 0$ as $t \to +\infty$ if all the roots of (1.8) are negative or are complex with negative real parts. Then $(\bar{z}_1, \bar{z}_2, \ldots, \bar{z}_n)$ is said to be a locally asymptotically stable equilibrium of (1.4). If one or both eigenvalues are positive or have positive real parts, most solutions of (1.5) becomes unboundedly large as $t \to +\infty$ and consequently most solutions of (1.1) do not remain near $(\bar{z}_1, \bar{z}_2, \ldots, \bar{z}_n)$, even if they start very close and in this case, $(\bar{z}_1, \bar{z}_2, \ldots, \bar{z}_n)$ is said to be unstable.

In general, the local stability of a steady state is determined by studying the eigenvalues of the Jacobian matrix evaluated at that steady state. If all real parts of the eigenvalues are negative then the equilibrium state is locally asymptotically stable. For every Jacobian matrix whose eigenvalues can not be readily determined, the Routh Hurwitz criteria is applied on the coefficients of the characteristic equation of the respective Jacobian matrix.

An ordinary differential system (1.1) can be presented as a model of epidemics, in which the total population $N(t)$ is subdivided into mutually exclusive compartments namely susceptible $z_1 = S$, infectious $z_2 = I$ and recovered $z_3 = R$ at time t. Epidemics may rise from the introduction of a pathogen or strain to a previously unexposed population or as a result of the re-growth of susceptible numbers sometimes after a previous epidemic due to the same infectious agent (Switon, 2003). Since 1927, when Kermack-McKendrick developed a SIR model for the spread of cholera epidemic, differential equations have been widely used in mathematical epidemiology. Various epidemiological models have been formulated using differential equations which are SI, SIS and SIR in which $S(t)$ is the number of susceptibles at time $t, I(t)$ is the number of infectious individuals at time t and $R(t)$ is the removed or recovered group who may have gained temporary or permanent immunity, have died or have been isolated depending on the disease modelled. These models have been widely used and applied in modelling parasitic diseases, host-vector-host type of disease (e.g. malaria and sleeping sickness) and sexually transmitted disease (e.g. gonorrhoea, HIV/AIDS)(Genik *et al.*, 1991; Hyman and Li, 1997).

Figure 1.2. Schematic illustration of the SIR epidemiological model.



This type of epidemics model is well interpreted and other models in Table 1.2. and 1.3. An SIR model for a disease has three sub-populations namely: the susceptible $S(t)$, infected $I(t)$and recovered $R(t)$, so that

$$N(t) = S(t) + I(t) + R(t) \tag{1.9}$$

The model we present includes the recruitment of individuals in the susceptible population at a constant rate Λ. There is an infection rate of population in the susceptible population who become infected which is proportional to the contacts between the two compartments S and I given by $\beta S(t)\dfrac{I(t)}{N(t)}$. There is a recovery of $\gamma I(t)$ from the infected population into the recovered population. All subpopulations suffer natural death at a rate μ which is assumed to be proportional to the population number in each class and acts equally on all classes. The infected population suffers additional death caused due to the presence of the parasite in their body at rate $\alpha I(t)$.

This model can be represented as an ordinary differential equation system

$$\begin{aligned}\frac{dS(t)}{dt} &= \Lambda - \beta S(t)\frac{I(t)}{N(t)} - \mu_s S(t),\\ \frac{dI(t)}{dt} &= \beta S(t)\frac{I(t)}{N(t)} - (\mu_I + \alpha + \gamma)I(t), \qquad (1.10)\\ \frac{dR(t)}{dt} &= \gamma I(t) - \mu_R R(t)\end{aligned}$$

where $\Lambda, \alpha, \beta, \gamma, \mu_S, \mu_R, \mu_I \in \mathbb{R}^+$ and the initial conditions $S(0) = S_0 \geq 0, I(0) = I_0 \geq 0, R(0) = R_0 \geq 0$. The model is called an SIR model and this types of model was developed by several authors (Anderson et al., 1989; Bernoulli, 1760; Bailey, 1975; Gurarie *et al.,* 2006; Mason and Mckenzie, 1999; Macdonald, 1760). The SIR models are a particular class of deterministic systems distinguished by an explicitly dependence of the dynamics of the past events. Since most of the models in this thesis are deterministic, our attention is restricted to the equation of that type.

We now illustrate the basic reproductive number as the most important threshold parameter in modelling of infectious disease. It is defined as the average number of secondary cases produced by a typical infected individual in a population that is almost fully susceptible (May and Anderson, 1998) and mathematically as the spectral radius of the next generation matrix (van den Driessche and Watmough, 2002; Diekmann *et al.,* 1990). The basic reproductive number denoted by R_0, summarizes the infectiousness of a pathogen in a given population. Several key pieces of information relevant to the spread and control of an infection are contained in R_0.

Generally if an infection has a value of R_0 less than 1, it cannot have sustained transmission in the population and eventually goes extinct, though there may be isolated episodes and even brief chains of transmission.

If R_0 exceeds 1, the infection spreads in the population, because each case is expected to cause more than one additional case, leading to an initially exponential growth in the number of cases.

We show that model system (1.10) is dissipative, that is, all feasible solutions are uniformly bounded.

Theorem 1.1. All solutions of system (1.10) initiating in $\mathbb{R}^3_+$ are bounded and eventually enter the attracting set

$$\Omega = \{(S(t), I(t), R(t)) \in \mathbb{R}^3_+ : S, I, R < Q\}. \tag{1.11}$$

Proof: Since

$$\frac{dS(t)}{dt} < \Lambda - \mu_S S, \tag{1.12}$$

We see that $S(t) < \frac{\Lambda}{\mu_S + 1}$, for all large t,say $t > t_0$.

We note that $\frac{\Lambda}{\mu_S} = \max_{S \geq 0}(\Lambda - \mu_S)$. Adding the first two equations of (1.10) gives

$$\frac{dS(t)}{dt} + \frac{dI(t)}{dt} = \Lambda - \mu_S S(t) - (\mu_I + \gamma + \alpha)I(t) \leq \frac{\Lambda}{\mu_S} - (\mu_I + \gamma + \alpha)I(t) \tag{1.13}$$

Let $\Psi > 0$ be such that $\mu_I \Psi > \frac{\Lambda}{\mu_S + 1}$. Then so long as

$$S(t) + I(t) \geq \Psi + \frac{\Lambda}{\mu_S + 1},$$

and $t > t_0$, we have

$$\frac{dS(t)}{dt} + \frac{dI(t)}{dt} < -1.$$

Clearly, there must exist $t_1 > t_0$ such that $S(t) + I(t) < \Psi + \frac{\Lambda}{\mu_S + 1}, \forall t > t_1$. The asymptotic bound for $I(t)$, namely,

$$I \leq \Psi + \frac{\Lambda}{\mu_S + 1},$$

together with the differential inequality

$$R(t) \leq -\mu_R R(t) + \gamma(\Psi + \frac{\Lambda}{\mu_S + 1}) \tag{1.14}$$

which holds for large t, leads immediately to the asymptotic bound

$$R(t) \leq \mu_R^{-1} \gamma(\Psi + \frac{\Lambda}{\mu_S + 1}).$$

Therefore, all feasible solutions of system (1.10) enter the region Ω.

A steady state or an equilibrium point is a stationary point of the dynamical system which does not change in time. For a system of differential equations, equilibrium states are calculated by setting all the time derivatives equal to zero. We now apply the method used in equation (1.3) to find the equilibrium points of our example or (equation (1.10)),

$$\frac{dS(t)}{dt} = \frac{dI(t)}{dt} = \frac{dR(t)}{dt} = 0. \tag{1.15}$$

The equilibrium points (disease free and endemic) obtained for the model system (1.9) are

$$(\frac{\Lambda}{\mu_S}, 0, 0) \text{ and } \left(\frac{(\mu_I + \gamma + \alpha)}{\beta}, \frac{1}{(\mu_I + \gamma + \alpha)} \left(\Lambda - \frac{\mu_S}{\beta} \right), \frac{\gamma \mu_R}{(\mu_I + \gamma + \alpha)} \left(\Lambda - \frac{\mu_S}{\beta} \right) \right).$$

The equilibrium point $(\frac{\Lambda}{\mu_S}, 0, 0)$ is called the disease-free equilibrium and

$$\left(\frac{(\mu_I + \gamma + \alpha)}{\beta}, \frac{1}{(\mu_I + \gamma + \alpha)} \left(\Lambda - \frac{\mu_S}{\beta} \right), \frac{\gamma \mu_R}{(\mu_I + \gamma + \alpha)} \left(\Lambda - \frac{\mu_S}{\beta} \right) \right) \tag{1.16}$$

is the endemic equilibrium point.

The disease-free equilibrium point and endemic equilibrium point will be denoted by

$$E^0 = (S^0(t), I^0(t)) \text{ and } E^e = (S^e(t), I^e(t))$$

respectively. The disease-free equilibrium point E^0, correspond to the case when there is no infection (infected population) that is the absence of infected population. The endemic equilibrium point E^e, corresponds to the presence of the disease and infected population.

We have several methods of determining the important threshold parameter in modeling of infectious disease (basic reproductive number R_0). We now follow the next generation matrix method (Van den Driessche and Watmough, 2002) to the model (1.10). Using the vector notation to rewrite the equations of the system (1.10) in which the infections appear in terms of the difference between the rate of transfer into and out of compartment by all other processes, we have

$$\frac{d}{dt}\begin{pmatrix} I(t) \\ \\ S(t) \end{pmatrix} = \begin{pmatrix} \beta S(t)\dfrac{1}{N(t)} \\ \\ 0 \end{pmatrix} - \begin{pmatrix} (\mu_I+\gamma+\alpha)I(t) \\ \\ \Lambda - \beta S(t)\frac{1}{N(t)} - \mu_s S(t) \end{pmatrix} \tag{1.17}$$

We note from the next generation matrix method that F and V, are given as,

$$F = \begin{pmatrix} \beta & 0 \\ \\ 0 & 0 \end{pmatrix}, V = \begin{pmatrix} (\mu_I+\gamma+\alpha) & 0 \\ \\ \beta & \mu_S \end{pmatrix}, \tag{1.18}$$

and the basic reproductive number, R_0, is given as the spectral radius of the dominant eigenvalue of FV^{-1}(Van den Driessche and Watmough, 2002). Therefore,

$$R_0 = \rho(FV^{-1}) = \frac{\beta}{\mu_I+\gamma+\alpha}$$

gives the number of secondary infectious cases produced by an infectious individual who has been introduced into a population of susceptible during the individual's period of infectiousness.

To bring the infection under control we seek conditions on the parameters of the transmission process that will guarantee the existence of a stable disease free equilibrium state.

By using the Routh-Hurwitz criterion, it can be shown that E_0 is locally stable. Local stability of the disease free equilibrium of the model (1.10) can follow from van den Driessche and Watmough (2002).

The Jacobian matrix at a general point is

$$J(S(t), I(t)) = \begin{pmatrix} -\beta\dfrac{I(t)}{N(t)} - \mu_S & -\beta S(t)\dfrac{1}{N(t)} \\ \\ \beta\dfrac{I(t)}{N(t)} & \beta S(t)\dfrac{1}{N(t)} - (\mu_I+\gamma+\alpha) \end{pmatrix}. \tag{1.19}$$

At the disease-free equilibrium point,

$$E^0 = (S^0(t), I^0(t)) = \left(\frac{\Lambda}{\mu_S}, 0, 0\right).$$

Evaluating the Jacobian at this point gives

$$J(E^0) = \begin{pmatrix} -\mu_S & -\beta \\ 0 & \beta - (\mu_I + \gamma + \alpha) \end{pmatrix}. \quad (1.20)$$

The characteristic equation for the Jacobian matrix evaluated at the disease free equilibrium point given by ordinary differential equation (1.10), is

$$\lambda^2 + b_1\lambda + b_0 = 0 \quad (1.21)$$

where

$$b_1 = (\beta - (\mu_I + \gamma + \alpha)) - \mu_S,$$

$$b_0 = -\mu_S (\beta - (\mu_I + \gamma + \alpha)).$$

By using Routh criteria, each equilibrium point is locally stable if the following conditions are satisfied,

(i) $b_1 > 0$

(ii) $b_0 > 0$

We can see that b_1 is always positive.

$$b_0 = -\mu_S (\beta - (\mu_I + \gamma + \alpha))$$

is positive for

$$-\mu_S\beta < (\mu_I + \gamma + \alpha)$$

So, E^0 is locally stable.

Finding the eigenvalues of the Jacobian matrix gives

$$\lambda_1 = -\mu_S \text{ and } \lambda_2 = \beta - (\mu_I + \gamma + \alpha).$$

In order for the equilibrium point to be asymptotically stable, λ_1 and λ_2 should be both negative. We have $\lambda_1 < 0$ and $\lambda_2 < 0$ (if $\beta < (\mu_I + \gamma + \alpha)$) then the equilibrium point E^0 is asymptotically stable. This means that a small population of infectives introduced into the system would not cause a persistent infection. If $\lambda_2 > 0$, then the equilibrium point becomes unstable and an introduction of infective will result in a persistent infection (*endemic infection*).

We now show other method for determining the basic reproductive number R_0. The basic reproductive number R_0 can also obtained from the dominant eigenvalue of the Jacobian matrix which in this case is $\lambda_2 = \beta - (\mu_I + \gamma + \alpha)$. This gives R_0 as

$$R_0 = \frac{\beta}{\mu_I + \gamma + \alpha}.$$

Thus if $R_0 > 1$ then an endemic infection occurs and if $R_0 < 1$ there is no endemic infection.

Evaluating the Jacobian matrix at endemic equilibrium point

$$J(S^e, I^e) = \begin{pmatrix} -R_0\left(\Lambda - \dfrac{\mu_S}{\beta}\right) - \mu_S & \dfrac{-\beta}{R_0} \\ R_0\left(\Lambda - \dfrac{\mu_S}{\beta}\right) & \dfrac{\beta}{R_0} - (\mu_I + \gamma + \alpha) \end{pmatrix}. \tag{1.22}$$

The characteristics equation resulting form the Jacobian matrix is

$$\lambda^2 + \lambda\left\{\left(R_0(\Lambda - \frac{\mu_S}{\beta}) - \mu_S\right) - \left(\frac{\beta}{R_0} - (\mu_I + \gamma + \alpha)\right)\right\}$$

$$+\left(R_0\left(\Lambda - \frac{\mu_S}{\beta}\right) - \mu_S\right)\left(\frac{\beta}{R_0} - (\mu_I + \gamma + \alpha)\right) + \beta\left(\Lambda - \frac{\mu_S}{\beta}\right) = 0.$$

For this equilibrium, $R_0 > 1$ which implies that $\lambda_1 > 0$ and $\lambda_2 > 0$. From the characteristics equation the real part of both eigenvalues is negative when

$$\left(R_0\left(\Lambda - \frac{\mu_S}{\beta}\right) - \mu_S\right)\left(\frac{\beta}{R_0} - (\mu_I + \gamma + \alpha)\right) + \beta\left(\Lambda - \frac{\mu_S}{\beta}\right) > 0.$$

This holds using the fact that $\mu_S > 0$ and $R_0 > 0$. Hence the endemic equilibrium

$$(S^e(t), I^e(t)) = \left(\frac{1}{R_0}, \frac{R_0}{\beta}\left(\Lambda - \frac{\mu_S}{\beta}\right)\right)$$

is asymptotically stable.

Note that this equilibrium invariant in the first quadrant. All initial points are in the first quadrant because $S(t)$ and $I(t)$ represents population proportion and are therefore nonnegative. It can be concluded that if $R_0 < 1$, then the only equilibrium in the first quadrant is at the disease-free equilibrium and is asymptotically stable and if $R_0 > 1$ then the are two equilibrium points in the first quadrant which are disease free (unstable) and endemic equilibrium (stable) points.

1.9. Structure of the Thesis

Chapter 1 comprises of the introduction and general perception on the mode and transmission of malaria. In Chapter 2, we propose a transgenic malaria model by considering a simple mathematical model for interacting wild and modified mosquito populations as the proposed alternative for malaria disease control measure. Our model in chapter 3 assesses the dynamics of mosquito vector population, developed in order to inform the malaria control policy to consider immature mosquitoes as the only origin of Anopheles mosquito. The adult mosquito population is increasing every day in the environment due to higher number of immature mosquitoes developing into adult mosquitoes which causes the malaria infection to increase worldwide. In Chapter 4 of our work, we formulate and analyse a realistic mathematical modelling of host-pathogen interacting in malaria infection. This is done by considering plasmodium sporozoites into human host liver cells and the effect on red blood cells due to the presence of the merozoites load into human host body. Actually, when a female mosquito is infected with plasmodium falciparum and feeds on human host, parasites in the sporozoites stage enter the blood stream and are carried to the liver and infect liver cells. The infected liver cells rupture and merozoites are released into blood stream. These merozoites invade red blood cells to produce more merozoites, the immune reactions such as cytotoxic T cells which react in the liver cells and antibodies in the red blood cells fight against the parasites.

We also rap up our thesis by giving a conclusion and remarks in Chapter 5. The three models developed in chapters 2, 3 and 4 are analysed, with the following being carried out:

(*a*) The determination of equilibrium states and their classification as either the disease free or endemic equilibrium state.

(*b*) Establishing and analytically analysing expressions for the endemic equilibrium.

(*c*) Determining the reproduction number, R_0.

(*d*) Local asymptotic stability analysis of the disease-free state.

(*e*) Numerical solutions of the non-linear systems of ordinary differential equations were obtained using Matlab built-in function of *ode*45, which implement a version of Runge-Kuta Scheme.

In the final chapter, Chapter 5, we compare the results from preceding three chapters with the aim of drawing conclusions. We conclude the thesis by giving recommendations for future research work, with the full support to the idea of Macdonald (1957) that to fight malaria disease we should deal with mosquito.

Chapter 2

A Transgenic Mathematical Model of Malaria Transmission

2.1. Introduction

Malaria is a life threatening parasitic disease transmitted by mosquito and remains one of the major impediments to health and development in Africa (Lungu *et al.*, 2003). Worldwide, morbidity and mortality from mosquito-borne viral diseases are substantial and on the rise (Glubler, 2002). No licensed vaccine exists for the most important of these fatal diseases. Malaria is caused by protozoan parasites of the genus plasmodium. Only four types of the plasmodium parasite can infect humans; the most serious forms of the disease are caused by *plasmodium falciparum* and *plasmodium vivax*, but other related species (*plasmodium ovale* and *plasmodium malariae*) can also affect humans. Usually, people get malaria by being bitten by an infective female *Anopheles mosquito*. Only *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, which contains microscopic malaria parasites. About one week later, when the mosquito takes its next blood meal, these parasites mix with the mosquitoes saliva and are injected into the person being bitten. The parasites multiply within red blood cells, causing symptoms that include anaemia (light-headedness, shortness of breath, tachycardia, *etc.*), as well as other general symptoms such as fever, chills, nausea, flu-like illness, coma, and possibly death. One way to prevent the malaria epidemic is to control the growth of the mosquito population. Given the failure of current methods to control the spread of this disease, considerable effort has gone into novel mosquito population-suppression strategies. One alternative way that originates from advanced research is to block transmission by use of genetically modified mosquitoes that would resist infection by malaria parasites (Aultman, 2005). The sterile insects technique, which release sterile male insects that mate with wild females, resulting in no offspring, has been used successfully for more than 50 years for control and eradication of several pests and disease vectors (Dyck *et al.*, 1956; Krafsur, 1956). However, irradiated mosquitoes have difficulty competing with wild males for wild females and there are no large-scale mosquito programs currently in operation.

A proposed alternative approach that is also environmentally friendly is the release of male modified mosquitoes loaded with the gene that integrate the malaria resistant directly into the mosquitoes DNA. That gene makes it impossible for those mosquitoes to transmit the parasites that cause malaria. The transmitting of the beneficial gene to the entire female population will be done through interbreeding, by releasing male modified mosquitoes to mate with wild female mosquitoes. The application of this technique is not yet realised, but advances have been made and mathematical modelling can shed more light on the potential of this approach.

2.2. Model formulation and analysis

This section describes an epidemiological model for the transmission of malaria considering mosquitoe vector including wild and genetically modified mosquito and humans host populations given by $N_m(t)$ and $N_h(t)$, respectively. This model considers human hosts as SIR and vector mosquitoes sex structured as SI. The vector components of the model does not include immune class (Ngwa and Shu, 2008), as mosquitoes never recover from infection, that is, their infection period end with death due to their relatively short life-span.

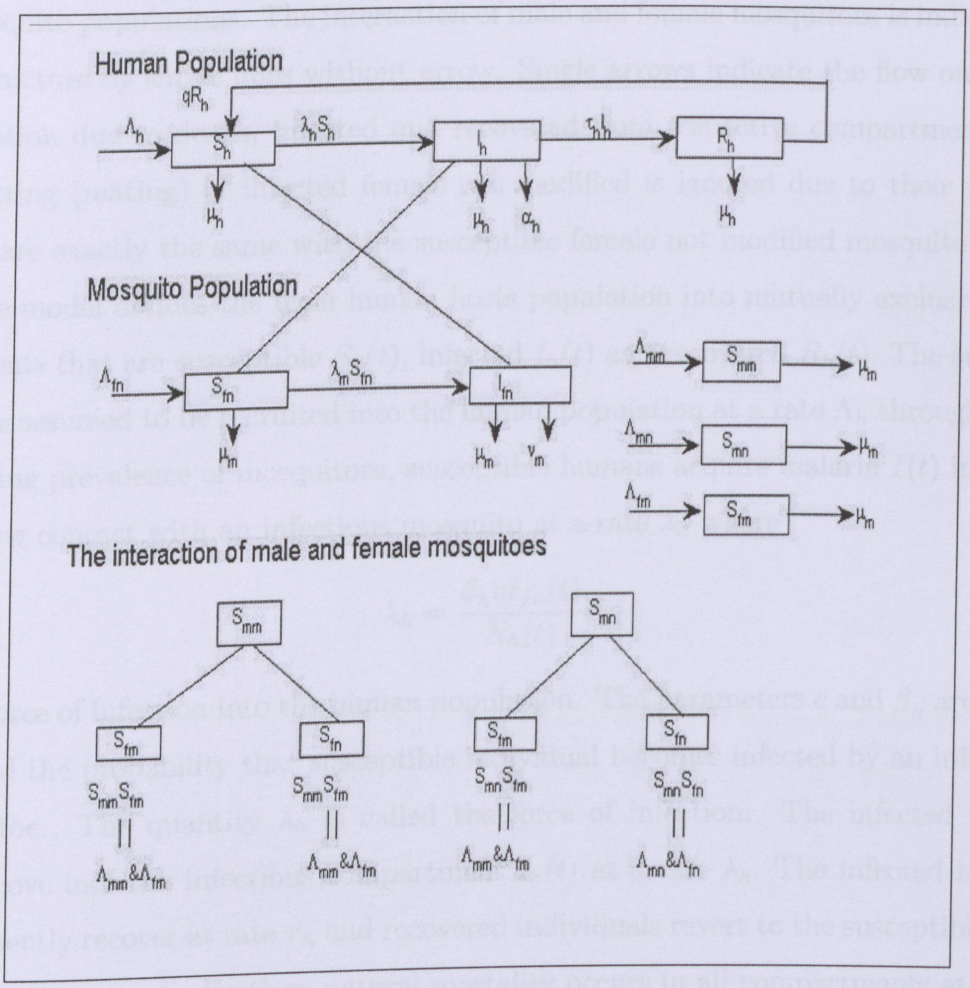


Figure 2.1: Schematic illustration of the basic transgenic mathematical model.

The male modified and male not modified susceptible mosquito vector population are denoted by $S_{mm}(t)$ and $S_{mn}(t)$ respectively. The susceptible female modified mosquito and susceptible female not modified mosquito vector population are denoted by $S_{fm}(t)$ and $S_{fn}(t)$ respectively. The supply rates of susceptible male modified mosquito and susceptible male not modified mosquito are assumed to be at constant rates denoted by Λ_{mm} and Λ_{mn} respectively. The supply rate of female modified mosquitoes and female not modified mosquitoes are also assumed to be at constant rates denoted by Λ_{fm} and Λ_{fn} respectively.

We assume that the male vector populations $S_{mm}(t), S_{mn}(t)$, mate with the female vectors $S_{fn}(t)$ and $S_{fm}(t)$ resulting in constant rate of supply to various compartments of mosquito populations. The interaction of male and female mosquitoes is indicated in the structure by single lines without arrow. Single arrows indicate the flow out of the population due to death, infected and recovered from respective compartment. The interacting (mating) of infected female not modified is ignored due to their progeny which are exactly the same with the susceptible female not modified mosquitoes.

The model divides the total human hosts population into mutually exclusive compartments that are susceptible $S_h(t)$, infected $I_h(t)$ and recovered $R_h(t)$. The susceptibles are assumed to be recruited into the human population at a rate Λ_h through birth. Assuming prevalence of mosquitoes, susceptible humans acquire malaria $I(t)$ infection following contact with an infectious mosquito at a rate λ_h where

$$\lambda_h = \frac{\beta_h c I_{fn}(t)}{N_h(t)}, \tag{2.1}$$

is the force of infection into the human population. The parameters c and β_h are biting rate and the probability that susceptible individual becomes infected by an infectious mosquitoe. The quantity λ_h is called the force of infection. The infected human hosts move into the infectious compartment $I_h(t)$ at a rate λ_h. The infected humans subsequently recover at rate τ_h and recovered individuals revert to the susceptible class at rate q $(0 < q < 1)$. Further, natural mortality occurs in all compartments at a rate μ_h and infectious humans suffer an additional death at rate α_h due to the presence of malaria parasites in their bodies.

The model also divides the total mosquito vector population into mutually exclusive compartments that are susceptible male modified $S_{mm}(t)$, susceptible male not modified $S_{mn}(t)$, susceptible female not modified $S_{fn}(t)$ and susceptible female modified $S_{fm}(t)$ and infected female not modified $I_{fn}(t)$. The recruitment rate of mosquito vectors into the susceptible compartments is through the interaction (mating) of modified and wild mosquitoes. The susceptible male modified and female modified are recruited at a rate Λ_{mm} and Λ_{fm}, respectively. The susceptible recruitment rate of male not modified and female not modified mosquito vector are given by Λ_{mn} and Λ_{fn} respectively. The susceptible female not modified mosquitoes become infected by biting infected humans at a rate λ_m where

$$\lambda_m = \frac{\beta_{fn} c I_h(t)}{N_h(t)}, \tag{2.2}$$

is the force of infection into the unmodified female mosquito population. The parameter β_{fn} is the probability that a bite results in transmission of the parasite from an infectious human to the susceptible female not modified mosquito. Further, natural mortality occurs in all compartments at rate μ_m with respect to the compartment in each class and infectious mosquitoes suffer an additional death at a rate ϑ_m due to the presence of infectious parasites in their bodies. The total human and mosquito populations is given by

$$\begin{aligned} N_h(t) &= S_h(t) + I_h(t) + R_h(t) \\ N_m(t) &= S_{mm}(t) + S_{mn}(t) + S_{fm}(t) + S_{fn}(t) + I_{fn}(t) \end{aligned} \tag{2.3}$$

Taking into account the assumptions made above, the interaction between human hosts and mosquito vectors population is described by the following system of equations:

$$
\begin{aligned}
\frac{dS_h(t)}{dt} &= \Lambda_h + qR_h(t) - \mu_h S_h(t) - \lambda_h S_h(t), \\
\frac{dI_h(t)}{dt} &= \lambda_h S_h(t) - (\mu_h + \tau_h + \alpha_h) I_h(t), \\
\frac{dR_h(t)}{dt} &= \tau_h I_h(t) - \mu_h R_h(t) - qR_h(t), \\
\frac{dS_{mm}(t)}{dt} &= \Lambda_{mm} - \mu_m S_{mm}(t), \\
\frac{dS_{mn}(t)}{dt} &= \Lambda_{mn} - \mu_m S_{mn}(t), \qquad (2.4) \\
\frac{dS_{fm}(t)}{dt} &= \Lambda_{fm} - \mu_m S_{fm}(t), \\
\frac{dS_{fn}(t)}{dt} &= \Lambda_{fn} - \mu_m S_{fn}(t) - \lambda_m S_{fn}(t), \\
\frac{dI_{fn}(t)}{dt} &= \lambda_m S_{fn}(t) - (\mu_m + \vartheta_m) I_{fn}(t),
\end{aligned}
$$

The initial conditions of the system (2.4) are given as

$$
\begin{aligned}
I_h^*(0) &= I_{fn}^*(0) = S_{fm}^*(0) = 0, S_h^*(0) = S_h^0, \qquad (2.5) \\
S_{mm}^*(0) &= S_{mm}^0, S_{mn}^*(0) = S_{mn}^0, S_{fn}^* = S_{fn}^0,
\end{aligned}
$$

where $N_h^0, S_h^0, N_m^0, S_{mm}^0, S_{mn}^0$ and S_{fn}^0 are non zero, some fixed positive number.

The recruitment rates of susceptible male modified and female modified are recruited at a rate Λ_{mm} and Λ_{fm}, respectively. The recruitment rates of susceptible recruitment rate of male not modified and female not modified mosquito vector are given by Λ_{mn} and Λ_{fn} respectively. These recruitments rates $(\Lambda_{mm}, \Lambda_{mn}, \Lambda_{fm}, \Lambda_{fn})$ are combined and have special name called recruitment rate of mosquito vector population

$$\Lambda_m = \Lambda_{mm} + \Lambda_{mn} + \Lambda_{fm} + \Lambda_{fn}. \tag{2.6}$$

The rate of change of the total populations of humans and mosquitoes in terms of variables are given by

$$\frac{dN_h(t)}{dt} = \Lambda_h - \mu_h S_h(t) - (\mu_h + \alpha_h) I_h(t) - \mu_h R_h(t),$$

by adding, substracting and grouping the like terms we obtain

$$\frac{dN_h(t)}{dt} = \Lambda_h - (\mu_h)(S_h(t) + I_h(t) + R_h(t)) - \alpha_h I_h(t)$$

which implies

$$\frac{dN_h(t)}{dt} \leq \Lambda_h - \mu_h N_h(t) - \alpha_h I_h(t). \tag{2.7}$$

Similarly the equation for the total mosquito population is given by

$$\frac{dN_m(t)}{dt} = \Lambda_{mm} - \mu_m S_{mm}(t) + \Lambda_{mn} - \mu_m S_{mn}(t) + \Lambda_{fm} - \mu_m S_{fm}(t) + \Lambda_{fn} - \mu_m S_{fn}(t) - (\mu_m + \vartheta_m) I_{fn}(t)$$

and by using equations (2.3) and (2.6) we get

$$\frac{dN_m(t)}{dt} \leq \Lambda_m - \mu_m N_m(t) - \vartheta_m I_{fn}(t) \tag{2.8}$$

Throughout this chapter we will analyse the equivalent system to (2.4) which is

$$
\begin{aligned}
\frac{dS_h(t)}{dt} &= \Lambda_h + qR_h(t) - \mu_h S_h(t) - \beta_h c I_{fn}(t)\frac{S_h(t)}{N_h(t)}, \\
\frac{dI_h(t)}{dt} &= \beta_h c I_{fn}(t)\frac{S_h(t)}{N_h(t)} - (\mu_h + \tau_h + \alpha_h) I_h(t), \\
\frac{dR_h(t)}{dt} &= \tau_h I_h(t) - \mu_h R_h(t) - qR_h(t), \\
\frac{dS_{mm}(t)}{dt} &= \Lambda_{mm} - \mu_m S_{mm}(t), \\
\frac{dS_{mn}(t)}{dt} &= \Lambda_{mn} - \mu_m S_{mn}(t), \\
\frac{dS_{fm}(t)}{dt} &= \Lambda_{fm} - \mu_m S_{fm}(t), \\
\frac{dS_{fn}(t)}{dt} &= \Lambda_{fn} - \mu_m S_{fn}(t) - \beta_{fn} c S_{fn}(t)\frac{I_h(t)}{N_h(t)}, \\
\frac{dI_{fn}(t)}{dt} &= \beta_{fn} c S_{fn}(t)\frac{I_h(t)}{N_h(t)} - (\mu_m + \vartheta_m) I_{fn}(t),
\end{aligned}
\tag{2.9}
$$

2.3. Analysis of the model

The mathematical model (2.9) is analysed in a feasible region as follows. We first show that for system (2.9) all feasible solutions of the model are uniformly bounded in a subset $\Omega \subset \mathbb{R}^3_+ \times \mathbb{R}^5_+$. This model consists of two different populations namely the human hosts and mosquito vectors population whose sizes are given in (2.7) and (2.8) respectively. We let

$$
\begin{aligned}
(S_h(t), I_h(t), R_h(t)) &\in \mathbb{R}^3_+, \\
(S_{mm}(t), S_{mn}(t), S_{fm}(t), S_{fn}(t), I_{fn}(t)) &\in \mathbb{R}^5_+,
\end{aligned}
\tag{2.10}
$$

be any solution of the system with initial conditions (2.5). Taking the time derivative of $N_h(t)$ along a solution path of the human system gives

$$\begin{aligned}\frac{dN_h(t)}{dt} &= \Lambda_h - \mu_h N_h(t) - \alpha_h I_h(t), \\ \frac{dN_m(t)}{dt} &= \Lambda_m - \mu_m N_m(t) - \vartheta_m I_{fn}(t).\end{aligned} \tag{2.11}$$

It is important to note that our model is of varying population sizes, that is

$$\frac{dN_h(t)}{dt} \neq 0, \frac{dN_m(t)}{dt} \neq 0,$$

and consequently, the trivial (extinction) equilibrium (where all variable of the model are zero at steady-state) is not feasible. From (2.11), we have

$$\begin{aligned}\frac{dN_h(t)}{dt} &= \Lambda_h - \mu_h N_h(t) - \alpha_h I_h(t) \\ &\leq \Lambda_h - (\mu_h + \alpha_h) N_h(t),\end{aligned}$$

and

$$\begin{aligned}\frac{dN_m(t)}{dt} &= \Lambda_m - \mu_m N_m(t) - \vartheta_m I_{fn}(t) \\ &\leq \Lambda_m - (\mu_m + \vartheta_m) N_m(t).\end{aligned}$$

By applying Rota and Birkhoff's theorem on differential inequality (Birkhoff and Rota, 1982) results in

$$\frac{dN_h(t)}{N_h(t)} \leq \Lambda_h - (\mu_h + \alpha_h)dt,$$

and

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

Similarly

$$\frac{dN_m(t)}{N_m(t)} \leq \Lambda_m - (\mu_m + \vartheta_m)dt,$$

and

$$0 \leq N_m(t) \leq \frac{\Lambda_m}{(\mu_m + \vartheta_m)} + N_m(0)e^{-\alpha_h t},$$

where $N_h(0)$ and $N_m(0)$ represent the values of the first and second equation in (2.3) evaluated at the initial values of the respective variables. Thus, as $t \to \infty$,

$$0 \leq N_h(t) \leq \frac{\Lambda_h}{\mu_h - \alpha_h},$$

and

$$0 \leq N_m(t) \leq \frac{\Lambda_m}{(\mu_m + \vartheta_m)}.$$

Finally we assume that

$$0 \leq N_h(t) \leq \frac{\Lambda_h}{\mu_h - \alpha_h},$$

and

$$0 \leq N_m(t) \leq \frac{\Lambda_m}{(\mu_m + \vartheta_m)}.$$

Therefore, all feasible solutions of the human components of the system (2.7) enter the region

$$\Omega_h = \{(S_h(t), I_h(t), R_h(t)) \in \mathbb{R}^3_+ \mid N_h(t) \leq \frac{\Lambda_h}{\mu_h - \alpha_h} + \zeta, \forall > 0\}. \tag{2.12}$$

A similar reasoning on the second equation in (2.3) yields that all feasible solutions of the mosquito component of system (2.9) will enter the region

$$\Omega_m = \{(S_{mm}(t), S_{mn}(t), S_{fm}(t), S_{fn}(t), I_{fn}(t)) \in \mathbb{R}^5_+ \mid N_m(t) \leq \frac{\Lambda_m}{(\mu_m + \vartheta_m)} + \zeta, \forall \zeta > 0\}. \tag{2.13}$$

Choosing $N = \min\{N_h(t), N_m(t)\}$, it is therefore evident that all possible solutions of the system (2.9) will enter the region

$$\Omega = \{\Omega_h \cup \Omega_m \subset \mathbb{R}^3_+ \times \mathbb{R}^5_+\}.$$

Hence, the region Ω of biological interest is positively invariant under the flow induced by system (2.9).

2.4. Basic properties

Theorem 1 *:Let the initial data be* $S_h(0) = S_h^0(0) > 0, I_h(0) = I_h^0(0) \geq 0, R_h(0) = R_h^0(0) > 0, N_h(0) = N_h^0(0) > 0, S_{mm}(0) = S_{mm}^0(0) > 0,$

$S_{mn}(0) = S_{mn}^0(0) \geq 0, S_{fm}(0) = S_{fm}^0(0) \geq 0, I_{fn}(0) = I_{fn}^0(0) > 0, N_m(0) = N_h(0) > 0.$

Then solutions $(S_h(t), I_h(t), N_h(t), S_{mm}(t), S_{mn}(t), S_{fm}(t), S_{fn}(t), I_{fn}(t))$ of system (2.9) remains positive for all time $t > 0$.

Proof: Assume that there exists some time $t_0 = 0$ such that $I_h(t_0) = 0$. Define

$$k = \text{minimum}_{t_0 \leq t \leq t_1} \left\{ \beta_h I_{fn}(t) \frac{S_h(t)}{I_h(t) N_h(t)} - (\mu_h + \tau_h + \alpha_h) \right\}.$$

Then, for $t \in [t_0; t_1], I_h'(t) \geq k I_h(t)$. Solving we get $I_h(t) = I_h(t_0)e^{kt}$. For $t = t_1$, we get $I_h(t_1) = I_h(0)e^{kt_1} > 0$, which is a contradiction. Thus, $I_h(t) > 0$ for all $t > 0$.

From the first equation of system (2.9), we can prove that $S_h(t)$ is positive. Let t_0 be the first time when $I_{fn}(t)S_h(t) = 0$. Assume that $S_h(t_0) = 0$. Then $I_{fn}(t) \geq 0$ for all $t \in [t_0, t_1]$, and we have

$$S_h'(t) \mid_{t=t_1} = \Lambda_h - \beta_h(t_1) I_{fn}(t_1) \frac{S_h(t_1)}{N_h(t_1)} - \mu_h S_h(t_1).$$

Since $S_h(t_0) > 0$ and $S_h(t_1) = 0$, we must have $S_h'(t) \mid_{t=t_1} \leq 0$ which is a contradiction.

By the same argument it can be proved that S_{fn} is positive. Suppose not. Let t_1 be the first time when $I_{fn}(t)S_{fn}(t) = 0$. Assume that $S_{fn}(t_1) = 0$. Then $I_{fn} \geq 0$ for all $t \in [t_0, t_1]$. From the seventh equation of the system (2.9), we have :

$$S_{fn}'(t) \mid_{t=t_1} = \Lambda_{mn} - \beta_{fn} S_{fn}(t_1) \frac{I_h(t_1)}{N_h(t_1)} - \mu_m S_{fn}(t_1).$$

Since $S_{fn}(t_0) \geq 0$, for $S_{fn}(t_1) = 0$ we must have $S_{fn}'(t) \mid_{t=t_1} \leq 0$ which is a contradiction.

Suppose that for some time t_1, $I_{fn}(t_1) = 0$. We have already shown that $S_{fn}, I_h > 0$ for $t > 0$. Then

$$I_{fn}'(t) \mid_{t=t_1} = \beta_{fn} S_{fn}(t_1) \frac{I_h(t_1)}{N_h(t_1)} - (\mu_m + \vartheta_m) I_{fn}(t_1).$$

But $I_{fn}(t_0) > 0$, for $I_{fn}(t_1) = 0$ to hold we must have $I'_{fn}(t) \mid_{t=t_1} \leq 0$ which is a contradiction.

If the initial conditions are positive, then the solution of the system (2.9) stay positive for $t > 0$.

The proof is complete.

2.5. Steady state Solutions

By calculating the zeros of the model (2.9), two equilibrium points are obtained. These are, the disease free and endemic equilibrium points which will be denoted by E_0 and E_e respectively.

The disease free equilibrium (DFE) of the system (2.9) is

$$\begin{aligned} E_0 &= (S_h^*, I_h^*, R_h^*, S_{mm}^*, S_{mn}^*, S_{fm}^*, S_{fn}^*, I_{fn}^*), \\ &= \left(\frac{\lambda_h}{\mu_h}, 0, 0, \frac{\Lambda_{mm}}{\mu_m}, \frac{\Lambda_{mn}}{\mu_m}, \frac{\Lambda_{fm}}{\mu_m}, \frac{\Lambda_{fn}}{\mu_m}, 0\right). \end{aligned}$$

The determination of the endemic equilibrium E_e will be discussed later. The two steady states have strong influence on the behaviour of the disease transmission in a community. Even though there could be infinitely many different initial distributions of malaria in a community, these equilibrium points are the final reachable states.

2.6. The basic reproductive number

We now calculate the basic reproductive number R_0, by using Diekman method (1990) and it is evaluated at disease free equilibrium state E_0.

The method involves arranging the system of the differential equations starting with the infective classes. The reproduction number provides an invasion criterion for the initial spread of the malaria parasites in a susceptible population, then decomposition of the model into components F and V yields;

$$\begin{aligned}
\frac{dI_h(t)}{dt} &= \beta_h c I_{fn}(t)\frac{S_h(t)}{N_h(t)} - (\mu_h + \tau_h + \alpha_h) I_h(t), \\
\frac{dS_h(t)}{dt} &= \Lambda_h + qR_h(t) - \mu_h S_h(t) - \beta_h c I_{fn}(t)\frac{S_h(t)}{N_h(t)}, \\
\frac{dI_{fn}(t)}{dt} &= \beta_{fn} c S_{fn}(t)\frac{I_h(t)}{N_h(t)} - (\mu_m + \vartheta_m) I_{fn}(t), \qquad (2.14) \\
\frac{dS_{fn}(t)}{dt} &= \Lambda_{fn} - \mu_m S_{fn}(t) - \beta_{fn} c S_{fn}(t)\frac{I_h(t)}{N_h(t)}.
\end{aligned}$$

To obtain the basic reproductive number we define the matrix of rate of new infectious:

$$F_i = \begin{pmatrix} \beta_h c I_{fn}(t)\dfrac{S_h(t)}{N_h(t)} \\ \\ \beta_{fn} c S_{fn}(t)\dfrac{I_h(t)}{N_h(t)} \end{pmatrix}.$$

Then we compute the partial derivatives of the matrix evaluated at the disease free equilibrium points, $F_i(x_i) = \dfrac{\partial F(I_h, I_{fn})}{\partial I_h}$ and $\dfrac{\partial F(I_h, I_{fn})}{\partial I_{fn}}$,where x_i is the disease free equilibrium.

Lemma 2 *If F is non-negative, V is a non-singular $M-$matrix and all eigenvalues of J_4 have positive real part.*

$$F = \begin{pmatrix} 0 & \beta_h c \\ \\ \dfrac{\beta_{fn} c \Lambda_{fn} \mu_h}{\mu_m \Lambda_h} & 0 \end{pmatrix}. \qquad (2.15)$$

We then define a matrix $V_i = V_i^- - V_i^+$, which is the difference between the inflows and outflows of the infective groups,

$$\begin{aligned} V_i &= \begin{pmatrix} MI_h \\ KI_{fn} \end{pmatrix} - \begin{pmatrix} 0 \\ 0 \end{pmatrix}. \\ &= \begin{pmatrix} MI_h \\ KI_{fn} \end{pmatrix}. \end{aligned}$$

The infectious compartments are $I_h(t)$ and $I_{fn}(t)$, giving 2−dimension matrix,

$$\begin{aligned} V_i(x_i) &= \left(\frac{\partial V}{\partial(I_h^*, I_{fn}^*)} \right), \\ V &= \begin{pmatrix} M & 0 \\ 0 & K \end{pmatrix}. \end{aligned}$$

Assuming that F_i and V_i meet the conditions outlined by Diekmann *et al., (*1990) and van den Driessche & Watmough (2002), we can compute the next generation matrix and find the dominant eigenvalue of $G = FV^{-1}$. Since V is non-singular we can determine V^{-1}. Thus,

$$V^{-1} = \frac{1}{\det V} Adj(V),$$

$$\begin{pmatrix} \frac{1}{M} & 0 \\ 0 & \frac{1}{K} \end{pmatrix},$$

where

$$M = (\mu_h + \tau_h + \alpha_h)$$

is the outflow rate from the human infectious compartment, $I_h(t)$,

$$K = (\mu_m + \vartheta_m)$$

is the outflow rate from the infectious female not modified compartment, $I_{fn}(t)$.

The dominant eigenvalue is

$$G = \begin{pmatrix} 0 & \dfrac{\beta_h c}{(\mu_m + \vartheta_m)} \\ \dfrac{\beta_{fn} c \Lambda_{fn} \mu_h}{\Lambda_h \mu_m M} & 0 \end{pmatrix}.$$

The reproductive number $R_{0,}$ is given by the spectral radius of matrix FV^{-1}(Diekman *et al.*,1990), and thus $\rho(G) = R_0$.

Thus our basic reproductive number is given by

$$R_0 = \sqrt{\frac{\beta_{fn}\beta_h c^2 \Lambda_{fn} \mu_h}{\Lambda_h(\mu_h + \tau_h + \alpha_h)(\mu_m + \vartheta_m)(\mu_m)}}. \tag{2.16}$$

The basic reproductive number denoted by R_0, is defined as the mean number of secondary infections arising from a single individual during his or her entire infectious period, in a population of susceptibles (Heesterbeek and Dietz., 1996). If $R_0 < 1$, then on average an infected individual over the course of the infectious period produces less than one infected person and the infection will die out in the long run. If however $R_0 > 1$, then each infected individual on average produces more than one new infection and the disease can invade the population.

In some literature (Chitins *et al.*, 2006) the reproductive number is equivalent to the square root of R_0 which is approximated the number of secondary infections due to one infected individual and is consistent with the definition given by the next generation operator approach (Diekman *et al.*,1990).

Near disease free equilibrium, each infected host produces

$$R_h = \frac{\beta_h c \mu_h}{\Lambda_h(\mu_h + \tau_h + \alpha_h)}$$

new infected vectors over its expected infectious period. In the DFE, each infected vector produces

$$R_m = \frac{\beta_{fn} c \Lambda_{fn}}{(\mu_m + \vartheta_m)(\mu_m)}$$

new infected hosts over its expected infectious period.

Therefore R_h and R_m are the partial disease reproductive number in humans and mosquitoes respectively. The product of R_h and R_m gives the disease reproductive number from host to vector. Hence R_0 is proportional to both transmission rates $\beta_h c$ and $\beta_m c$. The contact rate c, is therefore a squared term. If contact rate between female not modified mosquitoes and humans is made almost impossible, then the disease transmission is greatly reduced. From the formula R_m, an increase in mortality $(\mu_m + \vartheta_m)$ has two effects. First, susceptible female not modified mosquito density $\dfrac{\Lambda_{fn}}{(\mu_m + \vartheta_m)}$, is reduced and second, the infectious period of mosquitoes $\dfrac{1}{(\mu_m + \vartheta_m)}$ is also reduced. Reduction of wild mosquito has linearly proportional effects on transmission of malaria disease.

To bring the infection under control, we seek conditions of the parameters of the transmission and modified process that will guarantee the existence of a stable disease free state.

2.7. Existence and stability of equilibrium points

2.7.1. Local stability of the disease-free equilibrium E_0

In the absence of infection, the model has a steady state, E_0 called the disease-free equilibrium, where $E_0 = \left(\dfrac{\Lambda_h}{\mu_h}, 0, 0, \dfrac{\Lambda_{mm}}{\mu_m}, \dfrac{\Lambda_{mn}}{\mu_m}, \dfrac{\Lambda_{fm}}{\mu_m}, \dfrac{\Lambda_{fn}}{\mu_m}, 0\right)$. The stability of the disease free-equilibrium point state can be obtained from studying the eigenvalues of the Jacobian matrix evaluated at the equilibrium point. If all the eigenvalues have negative real parts, then the equilibrium point is stable. At the disease free equilibrium E_0, $I_h = R_h = I_{fn} = 0$ and the population $S_h(t), N_h(t), S_{mm}(t), S_{mn}(t), S_{fn}(t), S_{fm}(t), N_m(t)$ are non-zero. From the equations of the system (2.7), we consider the matrix

$$F_{(S_h(t),I_h(t),I_{fn}(t))} = \begin{pmatrix} X_1(S_h(t), I_h(t), I_{fn}(y)) \\ X_2(S_h(t), I_h(t), I_{fn}(t)) \\ X_3(S_h(t), I_h(t), I_{fn}(t)) \end{pmatrix}.$$

$$0 = \begin{pmatrix} \Lambda_h + qR_h(t) - \mu_h S_h(t) - \lambda_h S_h(t), \\ \lambda_h S_h(t) - (\mu_h + \tau_h + \alpha_h) I_h(t), \\ \lambda_m S_{fn}(t) - (\mu_m + \vartheta_m) I_{fn}(t). \end{pmatrix} \tag{2.17}$$

where X_1 is the susceptible hosts population differential equation compartment, X_2 is the infectious host population differential equation compartment, X_3 is the infectious female not modified vectors population differential equation compartment.

The partial derivatives of the matrix of the host and vector populations are given by

$$D_{F(S_h(t),I_h,(t)I_{fn}(t))} = \begin{pmatrix} \dfrac{\partial X_{1(S_h,I_h,S_{fn},I_{fn})}}{\partial S_h} & \dfrac{\partial X_{1(S_h,I_h,S_{fn},I_{fn})}}{\partial I_h} & \dfrac{\partial X_{1(S_h,I_h,S_{fn},I_{fn})}}{\partial I_{fn}} \\ \\ \dfrac{\partial X_{2(S_h,I_h,S_{fn},I_{fn})}}{\partial S_h} & \dfrac{\partial X_{2(S_h,I_h,S_{fn},I_{fn})}}{\partial I_h} & \dfrac{\partial X_{2(S_h,I_h,S_{fn},I_{fn})}}{\partial I_{fn}} \\ \\ \dfrac{\partial X_{3(S_h,I_h,S_{fn},I_{fn})}}{\partial S_h} & \dfrac{\partial X_{3(S_h,I_h,S_{fn},I_{fn})}}{\partial I_h} & \dfrac{\partial X_{3(S_h,I_h,S_{fn},I_{fn})}}{\partial I_{fn}} \end{pmatrix}$$

The general Jacobian matrix of the model system (1.7) is given by

$$J_{E^*} = \begin{pmatrix} -\left(\mu_h + \beta_h I_{fn} \dfrac{1}{N_h}\right) & 0 & -\beta_h c \dfrac{S_h}{N_h} \\ \\ \beta_h c I_{fn} \dfrac{1}{N_h} & -(\mu_h + \tau_h + \alpha_h) & \beta_h c \dfrac{S_h}{N_h} \\ \\ 0 & \beta_{fn} c S_{fn} \dfrac{1}{N_h} & -(\mu_m + \vartheta_m) \end{pmatrix}$$

We evaluate the Jacobian matrix at equilibrium free disease point to get

$$J_{E_0^*} = \begin{pmatrix} -\mu_h & 0 & -\beta_h c \\ 0 & -(\mu_h+\tau_h+\alpha_h) & \beta_h c \\ 0 & \dfrac{\beta_{fn} c \Lambda_{fn}\mu_h}{\mu_m \Lambda_h} & -(\mu_m+\vartheta_m) \end{pmatrix}. \tag{2.18}$$

Linearizing system (2.9) at equilibrium $E_0 = \left(\frac{\Lambda_h}{\mu_h}, 0, 0, \frac{\Lambda_{mm}}{\mu_m}, \frac{\Lambda_{mn}}{\mu_m}, \frac{\Lambda_{fm}}{\mu_m}, \frac{\Lambda_{fn}}{\mu_m}, 0\right)$, we obtain the characteristic equation about E_0

$$(\lambda+\mu_h)\left(\lambda^2+b_1\lambda+b_0\right)=0,$$

where

$$\begin{aligned} b_1 &= (\mu_h+\tau_h+\alpha_h)+(\mu_m+\vartheta_m), \\ b_0 &= (\mu_h+\tau_h+\alpha_h)(\mu_m+\vartheta_m) - \frac{\beta_{fn}\beta_h c^2 \Lambda_{fn}\mu_h}{(\mu_m+\delta_m)\Lambda_h}. \end{aligned}$$

Clearly, one root of the characteristic equation (2.16) is $\lambda_1 = -\mu_h$. The other two roots are

$$\lambda_{2,3} = \frac{-\left(M+(\mu_m+\vartheta_m)\right) \pm \sqrt{\left(M+(\mu_m+\vartheta_m)\right)^2 - 4\left((\mu_h+\tau_h+\alpha_h)(\mu_m+\vartheta_m) - \dfrac{\beta_{fn}\beta_h c^2\Lambda_{fn}\mu_h}{\mu_m\Lambda_h}\right)}}{2}, \tag{2.19}$$

are determined by the quadratic equation $\lambda^2+b_1\lambda+b_0=0$.

By using Routh-Hurwitz criteria, each equilibrium point is locally stable if the following conditions are satisfied,

(i) $b_1 > 0$

(ii) $b_0 > 0$

We can see that b_1 is always positive.

$$b_0 = (\mu_h + \tau_h + \alpha_h)(\mu_m + \vartheta_m) - \frac{\beta_{fn}\beta_h c^2 \Lambda_{fn}\mu_h}{\mu_m \Lambda_h},$$

is positive for

$$(\mu_h + \tau_h + \alpha_h)(\mu_m + \vartheta_m) > \frac{\beta_{fn}\beta_h c^2 \Lambda_{fn}\mu_h}{\mu_m \Lambda_h}.$$

Thus, from (2.17) we have $b_0 > 0$. It follows from

$$(\mu_h + \tau_h + \alpha_h)(\mu_m + \vartheta_m)\mu_m\Lambda_h > (\mu_h + \tau_h + \alpha_h)(\mu_m + \vartheta_m) > \frac{\beta_{fn}\beta_h c^2 \Lambda_{fn}\mu_h}{(\mu_m + \delta_m)\Lambda_h}$$

that

$$(\mu_h + \tau_h + \alpha_h)(\mu_m + \vartheta_m) > \frac{\beta_{fn}\beta_h c^2 \Lambda_{fn}\mu_h}{(\mu_m + \delta_m)\Lambda_h}. \tag{2.20}$$

Thus $b_1 > 0$ and all roots of the equation (2.19) have real parts if and only if $R_0 < 1$. We then conclude that the disease free equilibrium of system (2.9) is locally asymptotically stable if $R_0 < 1$.

If $R_0 = 1$, one eigenvalue of (2.17) is 0 and it is simple. If $R_0 > 1$, the characteristic equation (2.19) has positive eigenvalue. So, E_0 is thus unstable.

Theorem 2 *The disease-free equilibrium $I_h = R_h = I_{fn} = 0$ of the system* (2.19) *is locally asymptotically stable if and only if*

$$R_0 \equiv \sqrt{\frac{\beta_{fn}\beta_h c^2 \Lambda_{fn}\mu_h}{\Lambda_h\mu_m(\mu_h + \tau_h + \alpha_h)(\mu_m + \vartheta_m)}} < 1. \tag{2.21}$$

2.7.2. Existence and stability of the endemic equilibrium E_e.

We have shown in the previous section that when $R_0 < 1$, the disease free state is asymptotically stable and an endemic equilibrium is not feasible. When the condition is violated then the system (2.12) has an endemic equilibrium $E_e = (S_h^*(t), I_h^*(t), S_{fn}^*(t), I_{fn}^*(t))$. The expression for endemic equilibrium is long if expressed explicitly. We shall show the existence of endemic equilibrium and analyse the stability. We solve for equilibrium points by setting the right hand sides of model (2.9) to zero and thus the system takes the form

$$
\begin{aligned}
\Lambda_h + qR_h(t) - \mu_h S_h(t) - \beta_h c I_{fn}(t)\frac{S_h(t)}{N_h(t)} &= 0,\\
\Lambda_h - \mu_h N_h(t) - \alpha_h I_h(t) &= 0\\
\tau_h I_h(t) - \mu_h R_h(t) - qR_h(t) &= 0, \qquad (2.22)\\
\Lambda_{fn} - \mu_m S_{fn}(t) - \beta_{fn} c S_{fn}(t)\frac{I_h(t)}{N_h(t)} &= 0,\\
\beta_{fn} c S_{fn}(t)\frac{I_h(t)}{N_h(t)} - (\mu_m + \vartheta_m) I_{fn}(t) &= 0.
\end{aligned}
$$

The expression for recovered $R_h(t)$ in terms of $I_h(t)$, is given by

$$
\begin{aligned}
\tau_h I_h(t) - \mu_h R_h(t) - qR_h(t) &= 0,\\
R_h^*(t) &= \frac{\tau_h I_h^*(t)}{H}, \qquad (2.23)
\end{aligned}
$$

where

$$H = (\mu_h + q),$$

The expression of $S_h^*(t)$ in terms of $I_{fn}^*(t)$ and $I_h^*(t)$, from equations (2.22) and (2.23), is given as follows:

$$
\begin{aligned}
\Lambda_h + qR_h(t) - \mu_h S_h(t) - \beta_h c I_{fn}(t)\frac{S_h(t)}{N_h(t)} &= 0,\\
S_h^*(t) &= \frac{\Lambda_h H - \tau_h q I_h^*(t)}{\mu_h H + \dfrac{\beta_h c H I_{fn}^*(t)}{N_h^*(t)}}, \qquad (2.24)
\end{aligned}
$$

where

$$M = (\mu_h + \tau_h + \alpha_h).$$

The algebraic expression for $I_{fn}^*(t)$ and $S_{fn}^*(t)$ in terms of $I_h^*(t)$ from equation (2.22), is given by

$$\begin{aligned}\Lambda_{fn} - \mu_m S_{fn}^*(t) - \beta_{fn} c S_{fn}^* \frac{I_h^*(t)}{N_h(t)} &= 0,\\ S_{fn}^*(t) &= \frac{\Lambda_{fn}}{(\mu_m + \vartheta_m) + \beta_{fn} c I_h^*(t)},\end{aligned} \tag{2.25}$$

and

$$\begin{aligned}I_{fn}^*(t) &= \frac{\beta_{fn} c S_{fn}^*(t) \dfrac{I_h^*(t)}{N_h(t)}}{(\mu_m + \vartheta_m)},\\ I_{fn}^*(t) &= \frac{\beta_{fn} c \Lambda_{fn} \mu_h I_h^*(t)}{\Lambda_h \mu_m (\mu_m + \vartheta_m) - (\alpha_h \mu_m (\mu_m + \vartheta_m) - \beta_{fn} c \mu_m) I_h^*(t)},\end{aligned} \tag{2.26}$$

The algebraic expression of $N_h(t)$ in terms of $I_h^*(t)$ is given as

$$\begin{aligned}\Lambda_h - \mu_h N_h(t) - \alpha_h I_h^*(t) &= 0,\\ N_h^*(t) &= \frac{\Lambda_h - \alpha_h I_h^*(t)}{H},\end{aligned} \tag{2.27}$$

Expressing endemic equilibrium points in terms of $I_h^*(t)$ from the equations in system (2.9), we get

$$E_e = \begin{cases} S_h^*(I_h^*(t)) = \dfrac{\Lambda_h H - \tau_h q I_h^*(t)}{\mu_h H + \dfrac{\beta_h H I_{fn}^*}{N_h^*}}. \\[2ex] R_h^*(I_h^*(t)) = \dfrac{\tau_h I_h^*(t)}{H}, \\[2ex] N_h^*(I_h^*(t)) = \dfrac{\Lambda_h - \alpha_h I_h^*(t)}{H}, \\[2ex] S_{fn}^*(I_h^*(t)) = \dfrac{\Lambda_{fw}}{(\mu_m + \vartheta_m) + \beta_{fn} c I_h^*(t)}, \\[2ex] I_{fn}^*(I_h^*(t)) = \dfrac{\beta_{fn} c \Lambda_{fn} \mu_h I_h^*(t)}{\Lambda_h \mu_m (\mu_m + \vartheta_m) - (\alpha_h \mu_m (\mu_m + \vartheta_m) - \beta_{fn} c \mu_m) I_h^*(t)}, \end{cases} \tag{2.28}$$

After substituting the expressions for $S_h^*(t), R_h^*(t), N_h^*(t), S_{fn}^*(t), I_{fn}^*(t)$ in second equation of (2.9) and equating to zero we get

$$I_h^*(t)(I_h^{*2}(t) + b_1 I_h^*(t) + b_0) = 0. \tag{2.29}$$

where

$$b_1 = \frac{R_0\Lambda_h(\mu_m + \vartheta_m)(\tau_h q + HM) + R_0\Lambda_h^2\alpha_h(\mu_m + \vartheta_m)(1-\mu_h) + \beta_{fn}c\Lambda_h\mu_h}{\alpha_h^2(\mu_m + \vartheta_m) - \beta_{fn}c\alpha_h},$$

$$b_0 = \frac{\Lambda_{fn}\mu_h(\mu_m + \vartheta_m) - R_0\Lambda_h^2 H(\mu_m + \vartheta_m)}{\alpha_h^2(\mu_m + \vartheta_m) - \beta_{fn}c\alpha_h}.$$

By solving the equation in (2.29), we get the solutions of $I_h^*(t)$. $I_h^*(t) = 0$ gives the disease free equilibrium while the remaining quadratic equation can be analysed for the possible existence of endemic equilibria. By inspection of the coefficients of b_0 and b_1 of the quadratic equation in (2.29), the following cases $(a), (b)$ and (c) gives the scenarios where existence of endemic equilibria for the model is possible.

(a) If $\alpha_h^2(\mu_m + \vartheta_m) - \beta_{fn}c\alpha_h > 0$, then the model has

(i) an endemic equilibrium if $R_0 < 1 \Longleftrightarrow b_0 < 0$;

(ii) two endemic equilibria if $R_0 > 1, b_1 < 0$ and $b_1^2 - 4b_0 > 0$;

(iii) no endemic equilibria otherwise.

(b) If $\alpha_h^2(\mu_m + \vartheta_m) - \beta_{fn}c\alpha_h < 0$, then the model has

(i) an endemic equilibrium if $R_0 > 1 \Longleftrightarrow b_0 > 0$;

(ii) two endemic equilibria if $R_0 < 1, b_1 < 0$ and $b^2 - 4b_0 > 0$;

(iii) no endemic equilibrium otherwise

(c) An endemic equilibrium exists if $b_1 < 0$ and either $b_0 = 0$ or $b_1^2 - 4b_0 = 0$.

2.8. Numerical simulation

In this section we solve the dynamics of the model (2.9) over time t numerically using a Matlab programme built-in function of $ode45$, which we use to implement a version of the Runge-Kuta Scheme. For computer runs, we stimulate the initial and long term behaviour.

Table 2.2: Numerical values of parameters used in the simulations performed.

Definition	**Symbol**	**Estimate(range)(day^{-1})**	**Source**
Humans recruitment rate	Λ_h	0.005	Estimate
Humans natural death	μ_h	0.003	Estimate
Probability of transmission of			
infection to humans	$\beta_h c$	0.56	Estimate
Probability of transmission of			
infection to mosquitoes	$\beta_{fn} c$	0.631	Estimate
Recovered rate of humans			
being susceptibles	q	0.04	Chayaka *et al.*, 2006
Recovered rate	τ_h	0.05	Estimate
Hosts mortality due to disease	α_h	0.014	Estimate
Female vectors not modified			
recruitment rate	Λ_{fn}	0.046	Estimated
Vectors natural mortality rate	μ_m	0.3429	Estimated
Male modified mosquitoes			
recruitment rate	Λ_{mm}	0.7	Estimate
Additional death rate of mosquitoes	ϑ_m	0.0103	Chayaka *et al.*, 2006

of susceptible humans $S_h(t)$, infectious humans $I_h(t)$, recovered humans $R_h(t)$, susceptible male modified mosquitoes $S_{mm}(t)$, susceptible female not modified mosquitoes

$S_{fn}(t)$, infectious female not modified mosquitoes $I_{fn}(t)$. The parameters in our model as shown in Table 2.2 are reasonable estimates however, which is the basis for an infection to persist or to be eradicated. Figure 2.3 shows the initial and long-terms behaviour of the human and mosquito populations.

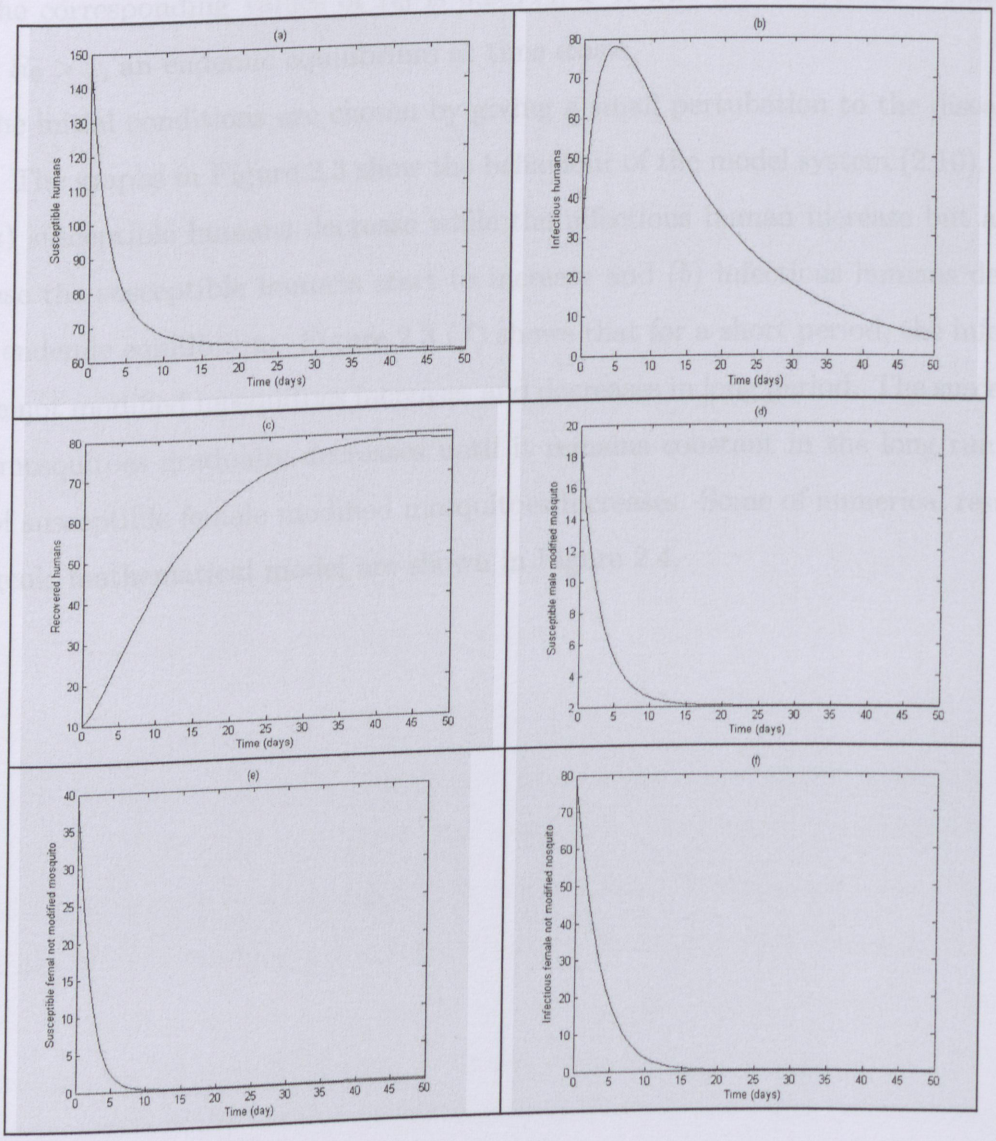


Figure 2.3: Graphs showing the behaviour of the transgenic mathematical model using parameters in Table 2.2. The graph panels $(a) - (f)$ show the dynamics of (a) susceptible humans, (b) infectious humans, (c) recovered humans, (d) susceptible male

modified mosquitoes $S_{mm}(t)$, (e) susceptible female not modified mosquitoes $S_{fn}(t)$ and (f) infectious female not modified mosquitoes $I_{fn}(t)$.

Figurer 2.3 shows the behaviour of model (2.4). The initial conditions used were, $S_h(0) = 150, I_h(0) = 30, R_h(0) = 10, S_{mm}(0) = 19, S_{fn} = 40, I_{fn}(0) = 80, S_{mn}(0) = 45$.

The corresponding values of R_0 is $0.26714 < 1$. The model system is stable and when $R_0 > 1$, an endemic equilibrium at time exists.

The initial conditions are chosen by giving a small pertubation to the disease free state. The graphs in Figure 2.3 show the behaviour of the model system (2.10). Figure 2.3 (a) susceptible humans decrease while the infectious human increase but as time increase the susceptible humans start to increase and (b) infectious humans decrease to an endemic equilibrium. Figure 2.3 (f) shows that for a short period, the infectious female not modified mosquitoes increases and decreases in long period. The susceptible male mosquitoes gradually decreases until it remains constant in the long run while that of susceptible female modified mosquitoes increases. Some of numerical results of transgenic mathematical model are shown in Figure 2.4.

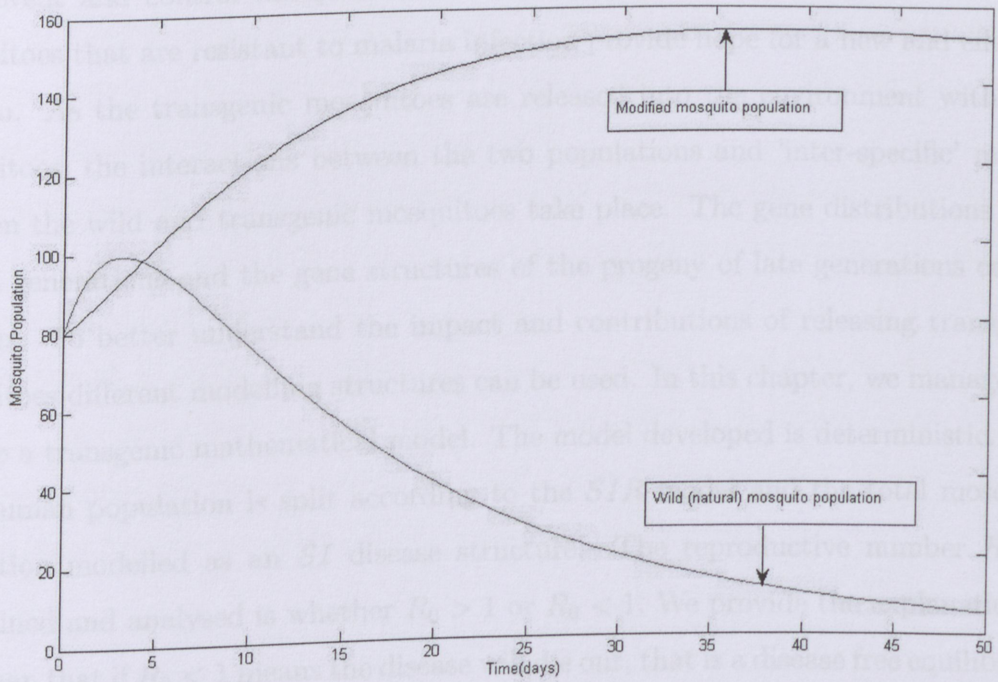


Figure 2.4: Graph comparing the dynamics of modified and wild (Natural) mosquito population.

Figure 2.4 shows that wild (natural) mosquitoes are getting diminished from the environment. This gives us a hope that modified mosquitoes population are growing and are dominating every day in the environment. When the modified mosquito population is dominating, we end up with a new type of mosquito population which does not transmit malaria. The cases of infected human population will be decreasing because the infected mosquitoes are no longer existing in the environment. Those who are already infected will recover or suffer a natural death only. Even though the modified mosquito bites infected human, it will not transmit malaria parasite to the next person.

2.9. Discussion

To prevent and control mosquito-borne diseases in particular, malaria - transgenic mosquitoes that are resistant to malaria infection provide hope for a new and effective weapon. As the transgenic mosquitoes are released into the environment with wild mosquitoes, the interactions between the two populations and 'inter-specific' mating between the wild and transgenic mosquitoes take place. The gene distributions after several generations and the gene structures of the progeny of late generations can be complex. To better understand the impact and contributions of releasing transgenic mosquitoes different modelling structures can be used. In this chapter, we managed to develop a transgenic mathematical model. The model developed is deterministic. The total human population is split according to the SIR model and the total mosquito population modelled as an SI disease structure. The reproductive number R_0, is determined and analysed is whether $R_0 > 1$ or $R_0 < 1$. We provide the explanation of it to mean that if $R_0 < 1$ means the disease will die out, that is a disease free equilibrium is attained and if the $R_0 > 1$, the disease will persist, leading to an endemic equilibrium. The stability of disease free and endemic disease equilibrium were analysed in the local region. The study shows that the model has a disease free equilibrium which is locally asymptotically stable whenever the reproductive number R_0, is less than 1.

In the mosquito population, the moment we introduce the modified male mosquitoes, some of the wild mosquitoes lose their naturality. As these modified male mosquitoes mate with wild mosquito, the resulting offspring is a modified mosquitoe. These modified mosquitoes reduce the infection rate because they do not transmit malaria. The decreasing wild mosquito vector population shown in Figures 2.3 (e) and (f) shows that susceptible female not modified mosquitoes and infectious female not modified mosquito are not sustained in the environment. The more wild Anopheles mosquitoes are lost the lower the infection, and we also end up with a modified mosquito population which does not cause malaria to the people. These results give hope in the fight against malaria disease because the more modified mosquitoes, the more wild (natural) mosquito lost their naturality and at the end we will have new species of anopheles which do not transmit malaria. Since adult mosquitoes fly long distances, modified mosquitoes can be spread every where in the continent (Smith and Mckenzie, 2004). In this model we have grouped all transgenic mosquitoes into a single population without distinguishing their zygosity.

Even though the intervention methods are not applied in this study we can guess that the combination of transgenic mosquitoes and control measures can curb the spread of malaria significantly.

Including all possible details would lead to a very complicated system. At this point however, the most serious limitation is clearly not the lack of model complexity but the lack of parameter values needed for quantitative outcome. Once better estimates of parameters become available, more detailed studies can be done.

Chapter 3

A Mathematical Model for the Dynamics of Vector Population and Malaria Transmission

3.1. Introduction

When *Anopheles mosquitoes* obtain blood meal by bitting human host population, they leave for aquatic environment to lay their *eggs*, after about 2-3 days the eggs hatch into *larval*.

In this chapter, we give the dynamics of vector mosquito population to understand how this species develop from *egg* stage to adult mosquito. This immature stage of vector population is seen as the origin of malaria vector born disease. The mosquito goes through four separate and distinct stages of its life cycle and they are as follows: egg, larval, pupa and adult. Each of these stages can be easily recognised by their special appearance. All species of female *Anopheles* mosquitoe lay their *eggs* in a variety of water surfaces (aquatic environment). She can either lay her *eggs* one at a time or in groups called a raft every 10 to 14 days. Most *eggs* can survive the winter and hatch in the spring. Within two days of being laid, the mosquito *eggs* hatch into *larvae*. The *larvae* live at the surface of the water and breathe through an air tube called a *siphon*. As they grow and develop, the *larvae* shed their skin several times. If disturbed, the *larvae* can swim and dive away from the surface of the water. In the final underwater stage of development, the *larvae* develop into *pupae*, this process lasts anywhere between four and fourteen days. They float to the surface of the water and breathe through two small tubes called trumpets. At the end of this stage, the *pupae* encase themselves within a pupal case where they transform into *adult* mosquitoes. The fully developed mosquito then crawls to a protected area and rests while its external skeleton hardens. Once dry, the *adult* mosquito flies away to feed and seek a mate. While males feed on plant juices with their shorter mouth parts, females feed on human and animal blood with their longer mouth parts (*proboscis*). After feeding, the females lay their *eggs*. The cycle will continue for as long as the female lives. The adult mosquito most especially *Anopheles mosquito* can not survive in the absence of human and vertebrate host. These two populations, when they interact cause malaria which leads to serious sickness and death to the human host population.

To the best of our knowledge, none of the previous work considered the immature and mature stages of mosquito populations in the control of malaria transmission. These aspects differentiate our model from other malaria models and make it realistic by describing the growth of vectors population form aquatic environment. In the model, we introduce a three water body stages of immature mosquito, two compartments of matured vector mosquito population and three compartment of human hosts population.

3.2. Model formulation and analysis

This section describes a mathematical dynamic model for the mosquito vector population, where its life cycle is divided into two stages. The immature mosquito, is divided into three subpopulation: eggs $E_w(t)$, larval $L_w(t)$ and pupal $P_w(t)$, and the adult mosquito, is subdivided into two subpopulations: susceptible mosquito $S_v(t)$ and infectious mosquito $I_v(t)$ at a time t.

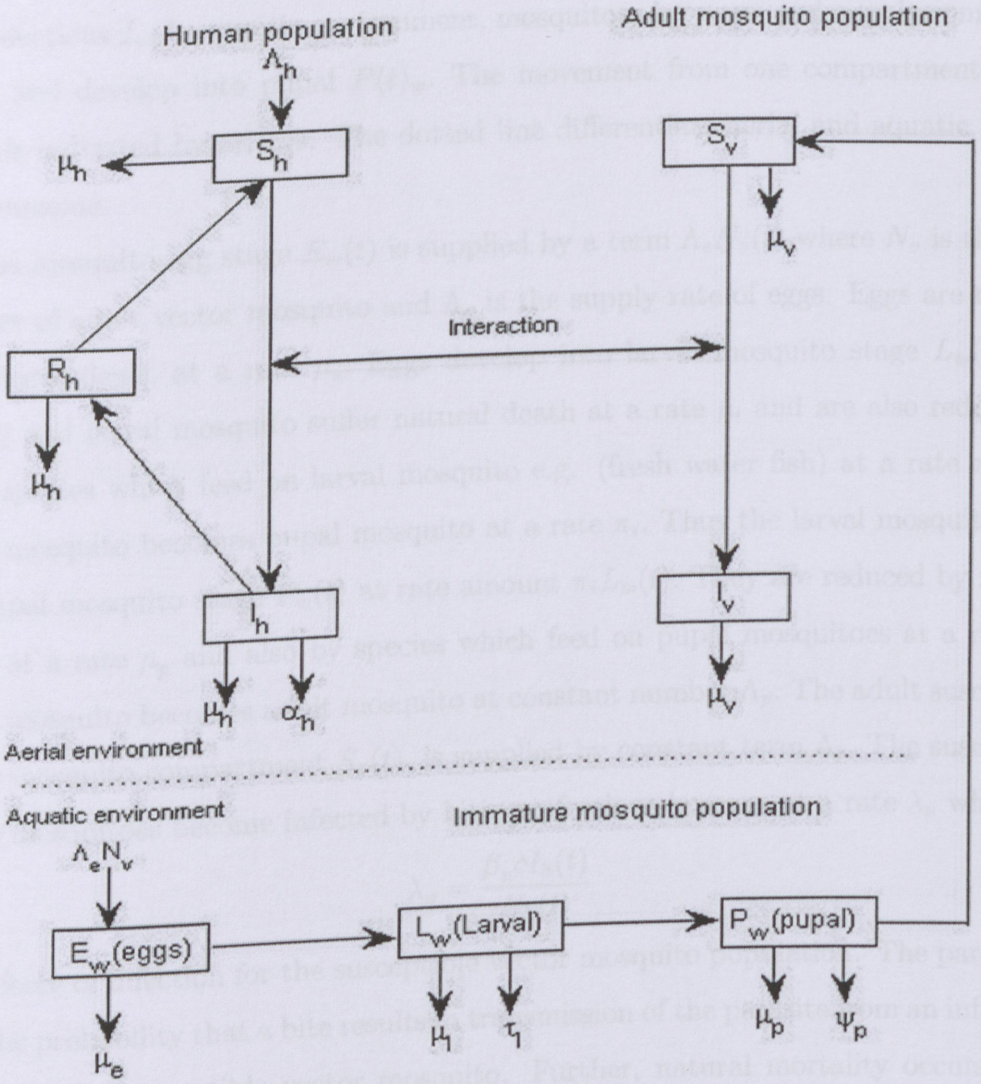


Figure 3.1: Schematic structure of malaria vector population

The above structure divides the human population into three populations namely: susceptible human host, S_h, Infectious human host, I_h, Recovered human host, $R_h(t)$. These subpopulations give an SIR disease model which has been explained well in table 1.1 and 1.2 of Chapter 1. The mosquito population lifecycle progresses through aerial and aquatic environments and follow a SI disease structure model. In aerial environment we divide the adult mosquito into two compartments: Susceptible $S_v(t)$ and infectious I_v. In aquatic environment, mosquitoes lay eggs, and eggs become larval $L_w(t)$ and develop into pupal $P(t)_w$. The movement from one compartment to another is indicated by arrows. The dotted line differentiate aerial and aquatic (water) environments.

The mosquito egg stage $E_w(t)$ is supplied by a term $\Lambda_e N_v(t)$ where N_v is the total number of adult vector mosquito and Λ_e is the supply rate of eggs. Eggs are reduced by natural death at a rate μ_e. Eggs develop into larval mosquito stage $L_w(t)$ at a rate θ_e and larval mosquito suffer natural death at a rate μ_l and are also reduced by other species which feed on larval mosquito e.g. (fresh water fish) at a rate τ_l. The larval mosquito becomes pupal mosquito at a rate π_i. Thus the larval mosquito enter the pupal mosquito stage $P_w(t)$ at rate amount $\pi_i L_w(t)$. They are reduced by natural death at a rate μ_p and also by species which feed on pupal mosquitoes at a rate ψ_p. Pupal mosquito becomes adult mosquito at constant number Λ_p. The adult susceptible vector mosquito compartment $S_v(t)$, is supplied by constant term Λ_p. The susceptible vector mosquitoes become infected by biting infectious humans at a rate λ_v where

$$\lambda_v = \frac{\beta_v c I_h(t)}{N_h(t)} \tag{3.1}$$

is the force of infection for the susceptible vector mosquito population. The parameter β_v is the probability that a bite results in transmission of the parasite from an infectious human to the susceptible vector mosquito. Further, natural mortality occurs in all compartments at a rate μ_v with respect to the compartment in each class

The model divides, the total human hosts population into mutually exclusive compartments as susceptible $S_h(t)$, infected $I_h(t)$ and recovery $R_h(t)$. The susceptibles are assumed to be recruited into the human population at a rate Λ_h through birth. Assuming prevalence of mosquitoes, susceptible humans acquire malaria $I(t)$ infection after contact with an infectious mosquito at a rate λ_h where

$$\lambda_h = \frac{\beta_h c I_v(t)}{N_h(t)} \tag{3.2}$$

is the force of infection into the human population. The parameters c and β_h are biting rate and the probability that susceptible individual becomes infected by an infectious mosquito. The infected human hosts move into the infectious compartment $I_h(t)$ at a rate λ_h and they recovered at rate α_h into susceptible $S_h(t)$. Those who survive from malaria move into recovered compartment $R_h(t)$ and recovered individuals revert to the susceptible class at rate q $(0 < q < 1)$. Further, natural mortality occurs in all compartments at a rate μ_h and infectious humans suffer an additional death at rate α_h due to the presence of malaria parasites in their bodies.

In developing the model, we also make the following assumptions:

(a) The model assumes that the mosquito lay their eggs into water.

(b) As male mosquito do not transmit the disease, the vector population sub-model considered only the female Anopheles mosquito.

(c) The model also assume that adult mosquitoes suffer only natural death, they do not suffer death caused by disease.

(d) We assume that female mosquito vectors feed on human blood only.

The total human ,immature mosquito and adult mosquito population is given by

$$\begin{aligned} N_h(t) &= S_h(t) + I_h(t) + R_h(t), \\ N_v(t) &= S_v(t) + I_v(t). \end{aligned} \tag{3.3}$$

Taking into account the assumptions made above, the interaction between human and mosquito populations, is described by the following system of equations:

$$\begin{aligned}
\frac{dE_w(t)}{dt} &= \Lambda_e N_v(t) - (\mu_e + \theta_e)E_w(t), \\
\frac{dL_w(t)}{dt} &= \theta_e E(t) - (\mu_l + \tau_l + \pi_l)L(t), \\
\frac{dP_w(t)}{dt} &= \pi_l L_w(t) - (\mu_p + \psi_p)P_w(t) - \Lambda_p, \\
\frac{dS_v(t)}{dt} &= \Lambda_p - \lambda_v S_v(t) - \mu_v S_v(t), \\
\frac{dI_v(t)}{dt} &= \lambda_v S_v(t) - \mu_v I_v(t), \\
\frac{dS_h(t)}{dt} &= \Lambda_h + qR_h(t) - \mu_h S_h(t) - \lambda_h S_h(t), \\
\frac{dI_h(t)}{dt} &= \lambda_h S_h(t) - (\mu_h + \tau_h + \alpha_h)I_h(t), \\
\frac{dR_h(t)}{dt} &= \tau_h I_h(t) - \mu_h R_h(t) - qR_h(t).
\end{aligned} \tag{3.4}$$

Since the model (3.4) monitors human and mosquito lifecycle populations, it is assumed that all the parameters of the model are non-negative.

The initial condition of the system (3.4) is given as

$E(0) = E^0, L(0) = 0, P(0) = 0, S_v(0) = S_v^0, I_v(0) = 0, S_h(0) = S_h^0, I_h(0) = 0, R_h(0) = 0,$

where N_h^0, N_v^0, S_h^0, and E^0 are non zero, some fixed positive numbers.

The differential equations of the susceptibles humans hosts $S_h(t)$ and mosquito vectors $S_v(t)$ populations are modelled as

$$\begin{aligned}\frac{dS_h(t)}{dt} &= \Lambda_h + qR_h(t) - \mu_h S_h(t) - \lambda_h S_h(t),\\ \frac{dS_v(t)}{dt} &= \Lambda_p - \lambda_v S_v(t) - \mu_v S_v(t).\end{aligned}$$

Using the fact that $S_h(t) = N_h(t) - I_h(t) - R_h(t)$ and $S_v(t) = N_v(t) - I_v(t)$ we analyse the following equivalent system to (3.4) of differential equation by letting

$$m = (N_h(t), I_h(t), R_h(t), E_w(t), L_w(t), N_v(t), I_v(t))^T,$$

then a function differential equation for the system can be written as

$$\frac{dm(t)}{dt} = \begin{cases} \dfrac{dN_h(t)}{dt} = \Lambda_h - (\mu_h + \alpha_h)N_h(t). \\ \dfrac{dI_h(t)}{dt} = \lambda_h(N_h(t) - I_h(t) - R_h(t)) - (\mu_h + \tau_h + \alpha_h)I_h(t), \\ \dfrac{dR_h(t)}{dt} = \tau_h I_h(t) - \mu_h R_h(t) - qR_h(t), \\ \dfrac{dE(t)}{dt} = \Lambda_e N_v(t) - (\mu_e + \theta_e)E_w(t), \\ \dfrac{dL_w(t)}{dt} = \theta_e E_w(t) - (\mu_l + \tau_l + \pi_l)L_w(t), \\ \dfrac{dP_w(t)}{dt} = \pi_l L_w(t) - (\mu_p + \psi_p)P_w(t) - \Lambda_p, \\ \dfrac{dN_v(t)}{dt} = \Lambda_p - \mu_v N_v(t), \\ \dfrac{dI_v(t)}{dt} = \lambda_v(N_v(t) - I_v(t)) - \mu_v I_v(t), \end{cases} \tag{3.5}$$

With $N_h(t) > 0$ and $N_v(t) > 0$, the initial conditions can be written as $m_0 \geq 0$.

3.2.1. Invariant regions

The model (3.4) will be analysed in a feasible region as follows. We first show that system (3.5) is bounded, that is, all feasible solutions are uniformly bounded in a proper subset of $\Omega \subset \mathbb{R}^3_+ \times \mathbb{R}^2_+$. The system (3.5) consists of two different populations namely the human and the mosquito population whose size are given in (3.3). Let

$$(S_h(t), I_h(t), R_h(t)) \in \mathbb{R}^3_+,$$

be any solution of the system with initial condition (3.5).

Taking the time derivative of $N_h(t)$ along a solution path of the human system gives

$$\frac{dN_h(t)}{dt} = \Lambda_h - (\mu_h + \alpha_h)N_h,$$

and also the time derivative of $N_v(t)$ along the adult mosquito system gives

$$\frac{dN_v(t)}{dt} = \Lambda_p - \mu_v N_v(t).$$

The immature mosquito population time derivative feasible solutions is done unlike in human and adult mosquito system, we do them separately to avoid counting them twice

$$\begin{aligned}
\frac{dE_w(t)}{dt} &= \frac{\Lambda_e\Lambda_p}{\mu_v} - (\mu_e - \theta_e)E_w(t),\\
\frac{dL_w(t)}{dt} &= \frac{\theta_e\Lambda_e\Lambda_p}{\mu_v(\mu_e+\theta_e)} - (\mu_l + \tau_l + \pi_l)L_w(t),\\
\frac{dP_w(t)}{dt} &= \frac{\pi_l\theta_e\Lambda_e\Lambda_p}{\mu_v(\mu_e+\theta_e)(\mu_l+\tau_l+\pi_l)} - \Lambda_p - (\mu_p + \psi_p)P_w(t).
\end{aligned}$$

The time derivative of immature mosquito total population is given by

$$\frac{dE_w(t)}{dt} + \frac{dL_w(t)}{dt} + \frac{dP_w(t)}{dt} > 0.$$

It is important to note that our model is of varying population sizes, that is

$$\frac{dN_h(t)}{dt} \neq 0 \text{ and } \frac{dN_v(t)}{dt} \neq 0,$$

and consequently, the trivial solution is not feasible.

Applying Rota and Birkhoff's theorem on differential inequality (Birkhoff and Rota, 1992) results in

$$0 \leq N_h(t) \leq \frac{\Lambda_h}{\mu_h + \alpha_h}$$

Therefore, all feasible solutions of the human component of system (3.5) enter the region

$$\Omega_h = \{\{S_h(t), I_h(t), R_h(t)\} \in \mathbb{R}^3_+ \mid N_h(t) \leq \frac{\Lambda_h}{\mu_h + \alpha_h}, \forall \varsigma > 0\}.$$

A similar reasoning on the second last equation in (3.3), yield the result that a feasible solution of the vector population component of system (3.5) enter the region

$$\Omega_v = \{\{S_v(t), I_v(t)\} \in \mathbb{R}^2_+ \mid N_v(t) \leq \frac{\Lambda_p}{\mu_v}, \forall \varsigma > 0\}.$$

All feasible region solution of the vector component equation for E_w, L_w and P_w of system (3.5) enter the region

$$\Omega_v = \left\{\{E(t), P(t), L(t)\} \in \mathbb{R}^1_+ \times \mathbb{R}^1_+ \times \mathbb{R}^1_+ / N_v(t) \leq \frac{\pi_l \theta_e \Lambda_e \Lambda_p}{\mu_v \Lambda_p(\mu_e + \theta_e)(\mu_l + \tau_l + \pi_l)(\mu_p + \psi_p)} \forall \varsigma > 0\right.$$

If we take any population $N = \min\{N_h(t), N_v(t)\}$, it is therefore evident that all possible solution of system (3.5) will enter the region.

$$\Omega = \Omega_h \cup \Omega_v \in \mathbb{R}^3_+ \times \mathbb{R}^2_+ \times \mathbb{R}^1_+ \times \mathbb{R}^1_+ \times \mathbb{R}^1_+$$

Hence, the region Ω, of biological interest, is positively invariant under the flow induced by system (3.4).We note from the total population size (3.3) that $N_h(t)$ and $N_v(t)$ can be uniquely determined

3.2.2. Basic properties

Theorem 3 *Let the initial data be* $S_h(0) = S^0_h \geq 0, I_h(0) = I^0_h(0) \geq 0, R_h(0) = R^0_h(0) > 0, E_w(0) = E^0 > 0,$

$$L_w(0) = 0, P_w(0) = 0, S_v(0) = S_v(0) > 0, I_v(0) = I^0_v(0) > 0.$$

Then solutions $(N_h(t), I_h(t), N_v(t), I_v(t))$ of system (3.4) remains positive for all time $t > 0$.

Proof: Assume that there exists some time $t_0 = 0$ such that $I_h(t_0) = 0$. Define:

$$k = \text{minimum}_{t_0 \leq t \leq t_1} \left\{ \beta_h I_v(t) \frac{S_h(t)}{I_h(t) N_h(t)} - (\mu_h + \tau_h + \alpha_h) \right\}.$$

Then, for $t \in [t_0; t_1]$, $I_h'(t) \geq k I_h(t)$. Solving we get $I_h(t) = I_h(t_0)e^{kt}$. For $t = t_1$, we get $I_h(t_1) = I_h(0)e^{kt_1} > 0$, which is contradiction. Thus, $I_h(t) > 0$ for all $t > 0$.

From the sixth equation of system (3.4), we can prove that $S_h(t)$ is positive. Let t_0 be the first time when $I_v(t)S_h(t) = 0$. Assume that $S_h(t_0) = 0$. Then $I_v(t) \geq 0$ for all $t \in [t_0, t_1]$, we have

$$S_h'(t) \mid_{t=t_1} = \Lambda_h - \beta_h(t_1) I_v(t_1) \frac{S_h(t_1)}{N_h(t_1)} - \mu_h S_h(t_1).$$

Since $S_h(t_0) > 0$ and $S_h(t_1) = 0$, we must have $S_h'(t) \mid_{t=t_1} \leq 0$ which is a contradiction.

By the same argument it can be proved that $S_v(t_1)$ is positive. Let t_1 be the first time when $I_v(t_1)S_v(t_1) = 0$. Assume that $S_v(t_1) = 0$. Then $I_v \geq 0$ for all $t \in [t_0, t_1]$. From the fourth equation of the system (3.4), we have :

$$S_v'(t) \mid_{t=t_1} = \Lambda_l P(t) - \beta_v S_v(t_1) \frac{I_h(t_1)}{N_h(t_1)} - \mu_v S_v(t_1).$$

Since $S_v(t_0) \geq 0$, for $S_v(t_1) = 0$ we must have $S_v'(t)/_{t=t_1} \leq 0$ which is a contradiction.

Suppose that for some time t_1, $I_v(t_1) = 0$. We have already shown that $S_v, I_h > 0$ for $t > 0$. Then

$$I_v'(t)/_{t=t_1} = \beta_v S_v(t_1) \frac{I_h(t_1)}{N_h(t_1)} - \mu_v I_v(t_1).$$

But $I_v(t_0) > 0$ for $I_v(t_1) = 0$ to hold we must have $I_v'(t)/_{t=t_1} \leq 0$ which is a contradiction.

If the initial conditions are positive, then the solution of the system (3.4) stay positive for $t > 0$.

The proof is complete.

3.2.3. Steady state solutions

As $t \to \infty$ and if the system goes to an equilibrium point, then the time changes in population proportions will become zero. These are, the disease free and endemic equilibrium points which will be denoted by E_0 and E^e respectively. The disease free equilibrium state is given by

$$\begin{aligned} E_0 &= \{N_h^*, I_h^*, R_h^*, N_v^*, I_v^*, E_w^*, L_v^*, P_w^*\}, \\ &= \left\{\frac{\Lambda_h}{\mu_h + \alpha_h}, 0, 0, \frac{\Lambda_p}{\mu_v}, 0, \frac{\Lambda_e \Lambda_p}{(\mu_e + \theta_e)\mu_v}, 0, 0\right\}, \end{aligned}$$

and the endemic equilibrium state

$$E^e = \{N_h^e, I_h^e, R_h^e, N_v^e, I_v^e, E_w^e, L_w^e, P_w^e\}.$$

The determination of the endemic equilibrium E^e will be discussed later. These two steady states determine the behaviour of the disease transmission in the community. Even though the disease can be distributed in many different ways in a community, these two equilibrium points are the final reachable states.

3.2.4. The basic reproductive number

The higher the growth of the mosquito population, the more human population gets infected. To calculate the basic reproductive number R_0 for model (3.5), we follow the same method used in Chapters 2 and 3 due to Diekman method (1990). The reproductive number R_0 will be evaluated at the disease free equilibrium state E_0.

The newly infectious rate of human hosts and mosquito vectors populations is defined as

$$F_i = \begin{pmatrix} \lambda_h(N_h(t) - I_h(t) - R_h(t)) \\ \\ \lambda_v(N_v(t) - I_v(t)) \end{pmatrix}.$$

The partial derivatives of the newly infectious population evaluated at the disease free equilibrium points,

$F_i(x_i) = \dfrac{\partial F(I_h(t), I_v(t))}{\partial I_h(t)}$ and $\dfrac{\partial F(I_h(t), I_v(t))}{\partial I_v(t)}$.

The rate at which the disease transfers into free disease population is given by F

$$F = \begin{pmatrix} 0 & \beta_h c \\ \dfrac{\beta_v c \Lambda_p(\mu_h + \alpha_h)}{\mu_v \Lambda_h} & 0 \end{pmatrix}.$$

The rate at which infected mosquito and human populations leave the compartments (class) due to the cause of natural death, death caused by disease and recovered due to the course of the strongness of their immune system, is given by

$$V_i = \begin{pmatrix} (\mu_h + \tau_h + \alpha_h) I_h(t) \\ \mu_v I_v(t) \end{pmatrix}.$$

The evaluation of V at disease free equilibrium state is given by

$$V = \begin{pmatrix} (\mu_h + \tau_h + \alpha_h) & 0 \\ 0 & \mu_v \end{pmatrix}$$

Since F_i and V_i meet the conditions outlined by Diekman *et al.*, (1990), we can find the next generation matrix. As V is non-singular, we determine the inverse of V

$$V^{-1} = \begin{pmatrix} \dfrac{1}{(\mu_h + \tau_h + \alpha_h)} & 0 \\ 0 & \dfrac{1}{\mu_v} \end{pmatrix}.$$

According to van den Drieche and Wat mough (2002), the generation of the disease into the populations is determined by the product of the followings matrices F and V^{-1} where

$$F = \begin{pmatrix} 0 & \beta_h c \\ \dfrac{\beta_v c \Lambda_p(\mu_h + \alpha_h)}{\mu_v \Lambda_h} & 0 \end{pmatrix},$$

and
$$V^{-1} = \begin{pmatrix} \dfrac{1}{(\mu_h + \tau_h + \alpha_h)} & 0 \\ 0 & \dfrac{1}{\mu_v} \end{pmatrix}.$$

The product of FV^{-1} is called the reproductive number R_0 by Diekmann *et al* (1990). Thus our reproductive number

$$R_0 = \rho\left(FV^{-1}\right) = \frac{\beta_v \beta_h c^2 \Lambda_p (\mu_h + \alpha_h)}{\mu_v^2 \Lambda_h (\mu_h + \tau_h + \alpha_h)}$$

or

$$R_0 = \sqrt{\frac{\beta_v \beta_h c^2 \Lambda_p (\mu_h + \alpha_h)}{\mu_v^2 \Lambda_h (\mu_h + \tau_h + \alpha_h)}}. \tag{3.6}$$

The total number of human who become infectious due to this mosquito bite during its entire infectious period is approximately

$$R_{mh} = \frac{\beta_h c (\mu_h + \alpha_h)}{\mu_v^2}.$$

Consider again a single infectious human entering the disease free population at equilibrium. Therefore the total number of mosquitoes which become infectious because of its human is approximately

$$R_{hm} = \frac{\beta_v c \Lambda_p}{\Lambda_h (\mu_h + \tau_h + \alpha_h)}.$$

Therefore R_{mh} and R_{hm} are disease reproductive number form mosquitoes to humans and from humans to mosquitoes respectively. The product $R_{mh} R_{hm} = R_0$ gives the disease reproductive number from host to host and from vector to vector. The quantity R_0 measures the expected number of new secondary cases produced from a single infected individual in a population where the large number of immature mosquitoes become adult mosquitoes.

To bring the disease under control we prove that the transmission system (3.4) will guarantee the existence of a stable disease free state, by assuming that $I_h(t) = I_v(t) = 0$.

3.2.5. Stability of the disease free equilibrium

The stability of the disease free equilibrium can be obtained from studying the eigenvalues of the Jacobian matrix evaluated at the disease free equilibrium. If all eigenvalues have negative real parts, then the equilibrium is stable. At the disease free equilibrium E_0, $I_h^0(t_0) = I_v^0(t_0) = R_h^0(t_0) = 0$ and the populations $N_h(t)$, $S_h(t)$, $S_v(t)$ and $N_v(t)$ are non zero.

The general Jacobian matrix of the system (3.5) is given by

$$J_{E^*} = \begin{pmatrix} -(\mu_h + \alpha_h) & 0 & 0 \\ \dfrac{\beta_h c I_v}{N_h^2} + \dfrac{\beta_h c I_v R_h}{N_h^2} & -\dfrac{\beta_h c I_v}{N_h} - (\mu_h + \tau_h + \alpha_h) & \beta_h c - \dfrac{\beta_h c I_h}{N_h} - \dfrac{R_h \beta_h c}{N_h} \\ -\dfrac{\beta_v c I_h N_v}{N_h^2} + \dfrac{\beta_v c I_h I_v}{N_h^2} & \dfrac{\beta_v c N_v}{N_h} - \dfrac{\beta_v c I_v}{N_h} & -\dfrac{\beta_v c I_h}{N_h} - \mu_v \end{pmatrix}. \tag{3.7}$$

By evaluating the general Jacobian matrix at disease free equilibrium we get

$$J_{E_0^*} = \begin{pmatrix} -(\mu_h + \alpha_h) & 0 & 0 \\ 0 & -(\mu_h + \tau_h + \alpha_h) & \beta_h c \\ 0 & \dfrac{\beta_v c \mu_v}{(\mu_h + \alpha_h)\Lambda_p} & -\mu_v \end{pmatrix}. \tag{3.8}$$

Using the reduced system of equation (3.5), we linearize system at equilibrium

$$E_0 = \left\{ \frac{\Lambda_h}{\mu_h + \alpha_h}, 0, 0, \frac{\Lambda_p}{\mu_v}, 0, \frac{\Lambda_e \Lambda_p}{(\mu_e + \theta_e)\mu_v}, 0, 0 \right\},$$

we obtain the characteristic equation about E_0.

$$-(\mu_h + \alpha_h)(\lambda^2 + b_1 \lambda + b_0) = 0, \tag{3.9}$$

where

$$b_1 = (\mu_h + \tau_h + \alpha_h) + \mu_v,$$

$$b_0 = (\mu_h + \tau_h + \alpha_h)\mu_v - \frac{\beta_h \beta_v c^2 \mu_v}{(\mu_h + \alpha_h)\Lambda_p}.$$

Clearly, one root of the characteristic equation (3.9) is $\lambda_1 = -(\mu_h + \alpha_h)$ which is clearly negative. The other two roots

$$\lambda_{2,3} = \frac{-b_1 \pm \sqrt{b_1^2 - 4(((\mu_h + \tau_h + \alpha_h) + \mu_v))(1 - R_0)}}{2}, \tag{3.10}$$

are determined by the quadratic equation

$$(\lambda^2 + b_1\lambda + b_0) = 0$$

If $R_0 < 1$, then

$$(\mu_h + \tau_h + \alpha_h)\mu_v - \frac{\beta_h \beta_v c^2 \mu_v}{(\mu_h + \alpha_h)\Lambda_p} > 0.$$

Thus, from (3.10) we have $b_0 > 0$. It follows from

$$(\mu_h + \tau_h + \alpha_h)\mu_v(\mu_h + \alpha_h) > (\mu_h + \tau_h + \alpha_h)\mu_v > \frac{\beta_h \beta_v c^2 \mu_v}{(\mu_h + \alpha_h)\Lambda_p},$$

that is

$$(\mu_h + \tau_h + \alpha_h)\mu_v > \frac{\beta_h \beta_v c^2 \mu_v}{(\mu_h + \alpha_h)\Lambda_p}. \tag{3.11}$$

Thus $b_1 > 0$ and all roots of the equation, (3.10) have real parts if and only if $R_0 < 1$. So, E_0 is locally stable for $R_0 < 1$. If $R_0 = 1$, one eigenvalue of (3.10) is 0 and it is simple. If $R_0 > 1$, the characteristics equation (3.10) has positive eigenvalue so, E_0 is thus unstable.

The disease-free equilibrium $I_h(t_0) = R_h(t_0) = I_v(t_0) = 0$ of the system (3.5) is locally asymptotically stable if and only if

$$R_0 \equiv \sqrt{\frac{\beta_h \beta_v c^2 \mu_v}{\Lambda_p \mu_v (\mu_h + \alpha_h)(\mu_h + \tau_h + \alpha_h)(\mu_h + \alpha_h)}} < 1.$$

3.2.6. The endemic equilibrium and its stability

Endemic equilibrium of the model (3.5) correspond to the case where the disease may persist in the population, that is when $I_h(t), I_v(t) \neq 0$. Since the expression for the endemic equilibrium is too long to be clearly expressed in closed form, we shall show existence based on some conditions on the model parameters.

To do this, let $\{N_h^e(t), I_h^e(t), R_h^e(t), N_v^e(t), I_v^e(t), E^e(t), L^e(t), P^e(t)\}$ be endemic equilibrium in their interior of Ω and equate the right hand side of (3.5) to zero:

$$\begin{aligned}
&\Lambda_h - (\mu_h + \alpha_h)N_h(t) = 0,\\
&\lambda_h(N_h(t) - I_h(t) - R_h(t)) - (\mu_h + \tau_h + \alpha_h)I_h(t) = 0,\\
&\tau_h I_h(t) - \mu_h R_h(t) - qR_h(t) = 0,\\
&\Lambda_e N_v(t) - (\mu_e + \theta_e)E_w(t) = 0,\\
&\theta_e E_w(t) - (\mu_l + \tau_l + \pi_l)L_w(t) = 0,\\
&\pi_l L_w(t) - (\mu_p + \psi_p)P_w(t) - \Lambda_p = 0,\\
&\Lambda_p - \mu_v N_v(t) = 0,\\
&\lambda_v(N_v(t) - I_v(t)) - \mu_v I_v(t) = 0.
\end{aligned} \tag{3.12}$$

The expression for $R_h(t)$ in terms of $I_h(t)$, is given by

$$\begin{aligned}
R_h &= \frac{\tau_h I_h}{(\mu_h + q)},\\
&= \frac{\tau_h I_h}{R},
\end{aligned}$$

where $R = (\mu_h + q)$.

The expression for $I_h(t)$ in terms of $I_v(t)$, is given by

$$\begin{aligned} I_h(t) &= \frac{\lambda_h(N_h(t)-R_h(t))}{(\mu_h+\tau_h+\alpha_h)+\lambda_h}, \\ &= \frac{\beta_h c N_h(t) I_v(t) R}{RDN_h(t)+\beta_h c I_v(t) R+\tau_h N_h(t)}, \end{aligned}$$

where $D = (\mu_h + \tau_h + \alpha_h)$.

The algebraic expression for $I_v(t)$ in terms of $I_h(t)$ from equation (3.12),We express the endemic equilibrium points in terms of variables from the equation (3.12), as

$$N_h^e(t) = \frac{\Lambda_h}{(\mu_h + \alpha_h)},$$

$$I_h^e(t) = \frac{\beta_h\beta_v c^2 \Lambda_p RH - RD\mu_v^2\Lambda_p - \mu_v^2\tau_h\Lambda_h}{\beta_v c\mu_v RDH + \beta_h\beta_v c^2\Lambda_h\Lambda_p R + \beta_h c\tau_h\mu_v H},$$

$$R_h^e(t) = \frac{\beta_h\beta_v c^2 \Lambda_p \tau_h RH - RD\mu_v^2\Lambda_p\tau_h - \mu_v^2\tau_h^2\Lambda_h}{\beta_v c\mu_v R^2 DH + \beta_h\beta_v c^2\Lambda_h\Lambda_p R^2 + \beta_h c\tau_h\mu_v HR},$$

$$E_w^e(t) = \frac{\Lambda_e\Lambda_p}{(\mu_e + \theta_e)\mu_v},$$

$$L_w^e(t) = \frac{\theta_e\Lambda_e\Lambda_p}{\mu_v(\mu_e + \theta_e)(\mu_l + \tau_l + \pi_l)},$$

$$P_w^e(t) = \frac{\pi_l\theta_e\Lambda_e\Lambda_p - \Lambda_p\mu_v(\mu_e + \theta_e)(\mu_l + \tau_l + \pi_l)}{\mu_v(\mu_p + \psi_p)(\mu_e + \theta_e)(\mu_l + \tau_l + \pi_l)},$$

$$N_v^e(t) = \frac{\Lambda_p}{\mu_p},$$

$$I_v^e(t) = \frac{\beta_v c\Lambda_p(\beta_h\beta_v c^2\Lambda_p RH - RD\mu_v^2\Lambda_p - \mu_v^2\tau_h\Lambda_h)}{\beta_v c\mu_v(\beta_h\beta_v c^2\Lambda_p RH - RD\mu_v^2\Lambda_p - \mu_v^2\tau_h\Lambda_h) + \Lambda_p\mu_v(\beta_v c\mu_v RDH + \beta_h\beta_v c^2\Lambda_h\Lambda_p R + \beta_h c\tau_h\mu_v H)}.$$

In order to analyse the stability of the endemic equilibrium, we substitute the endemic equilibrium point into Jacobian matrix $J_{E^*(N_h, I_h, I_v)}$ of (3.7) and its coordinates should satisfy the conditions $N_h^e(t) > 0, I_h^*(t) > 0$ and $I_v^*(t) > 0$. After some algebraic manipulation we produce the quadratic equation where the roots are expressed as follows

$$\lambda(x_2\lambda^2 + \lambda x_1 + x_0) = 0$$

where the first eigenvalue is $\lambda_1 = -(\mu_h + \alpha_h)$, which is exactly similar to the one obtained in the disease free equilibrium state. The interest is on the other two eigenvalues that will be determined by the constant terms x_2, x_1 and x_0, where

$$
\begin{aligned}
x_2 &= 1, \\
x_1 &= I_h^e(t)\left(\left(\frac{\beta_h c(\mu_h+\alpha_h)+\beta_v c(\mu_h+\alpha_h)}{\Lambda_h}\right)+(\mu_h+\tau_h+\alpha_h)+\mu_v\right), \\
x_0 &= I_v^e(t)\left(\frac{\beta_h c\mu_v(\mu_h+\alpha_h)+\beta_h\beta_v c^2(\mu_h+\alpha_h)}{\Lambda_h}\right)+I_h^e(t)\left(\frac{\beta_v c(\mu_h+\tau_h+\alpha_h)+\beta_h\beta_v c^2}{\Lambda_p}\right) \\
&\quad +R_h^e(t)\left(\frac{\beta_h\beta_v c^2\Lambda_p(\mu_h+\alpha_h)^2}{\Lambda_h^2\mu_v}-\frac{\beta_h\beta_v c^2\Lambda_p(\mu_h+\alpha_h)^2}{\Lambda_h^2}I_v^e(t)\right).
\end{aligned}
$$

The other eigenvalues are determined by the following quadratic equation

$$\lambda_{2,3}=\frac{-x_1\pm\sqrt{x_1^2-4x_2x_0}}{2}.$$

From analyses of the coefficient of the quadratic equation we have the following lemma

Lemma 4 *The model system* (3.5) *has*

(a) a unique endemic equilibrium if $x_0<0 \Leftrightarrow R_0>1$

(b) a unique endemic equilibrium if $x_1<0$, and $x_0=0$ or $x_1^2-4x_1x_0=0$

(c) a unique endemic equilibrium if $x_0>0, x_1<0$ and $x^2-4x_2x_0$

(b) no endemic equilibrium otherwise

3.3. Numerical Simulation

In this section we carry out numerical simulation for model system using Matlab built-in function of $ode45$, which implements the version of Runge-kuta scheme. The parameter values that we use for numerical simulations are in **Table 3.2.**

Table 3.1. showing numerical values of parameters used in the numerical simulations with subscripts (h) and (v) denoting human hosts and mosquito vectors populations respectively.

Parameter	Symbol	Estimate day^{-1}	Source
Hosts recruitment rate	Λ_h	0.55	Chayaka *et al.*, 2006
Rate of immature mosquito to adult (susceptibles)	Λ_p	0.65	Chayaka *et al.*, 2006
Hosts natural mortality rate	μ_h	0.0031	Estimated
Vectors natural mortality rate	μ_v	0.06	Chayaka *et al.*, 2006
Hosts mortality due to disease	α_h	0.20	Chayaka *et al.*, 2006
Recovered rate	τ_h	0.05	Chayaka *et al.*, 2006
Rate of recovered being susceptibles	q	0.04	Chayaka *et al.*, 2006
Probability transmission of infection to human	$\beta_h c$	0.40	Estimated
Probability transmission of infection to mosquito	$\beta_v c$	0.80	Estimated
The supply rate of eggs	Λ_e	0.89	Estimated
Eggs natural death rate	μ_e	0.04	Estimated
The rate of eggs to becomes larval	θ_e	0.92	Estimated
The larval natural death rate	μ_l	0.06	Estimated
The rate at which larval reduced by other species	τ_l	0.08	Estimated
The purpal natural death	μ_p	0.073	Estimated
The rate at which purpall reduced by other species	ψ_p	0.08	Estimated
The constant rate of adult mosquito from pupal stage	Λ_p	0.85	Estimated

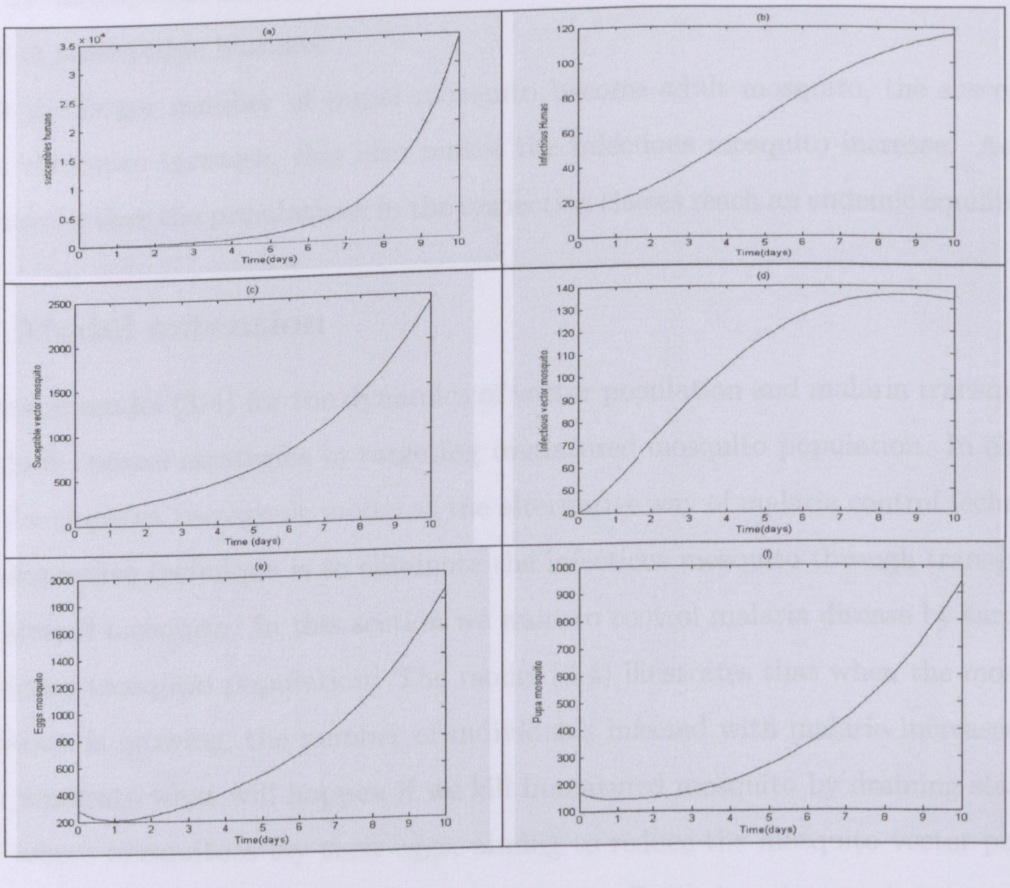


Figure 3.2: Graphs show the behaviour of the system (3.4) and (3.5) for human host population and the dynamics of mosquito vector populations.

The dynamics of (a) susceptible humans, (b) infectious humans, (c) susceptible vector mosquito, (d) infectious vector mosquito, (e) eggs mosquito stage and (f) pupal mosquito stage. Initial conditions used are $S_h(0) = 50, I_h(0) = 17, S_v(0) = 60, I_v(0) = 40, E_w(0) = 280, P_w(0) = 250$.

Figure 3.2 shows the initial and long term behaviour of the populations in the following compartment: Susceptible humans S_h, infectious humans I_h, Susceptible vector mosquito $S_v(t)$, infectious vector mosquito $I_v(t)$, eggs mosquito stage $E_w(t)$ and pupal mosquito stage $P_w(t)$. The initial conditions are chosen by giving a small perturbation to the disease free state.

Susceptible humans initially decrease while the infectious humans increase, but with time the susceptible humans start to increase and infectious humans increase slowly unlike in susceptible humans.

As the larger number of pupal mosquito become adult mosquito, the susceptible vector mosquito increase, this also makes the infectious mosquito increase. As time increases further the populations in the respective classes reach an endemic equilibrium.

3.4. Model extension

We extend model (3.4) for the dynamics of vector population and malaria transmission to include control strategies in targeting immatured mosquito population. In chapter 2, we developed a transgenic model as the alternative way of malaria control technique. The alternative technique is to eliminate the infectious mosquito through transgenetically altered mosquito. In this section we want to control malaria disease by targeting immatured mosquito population. The model (3.4) illustrates that when the mosquito population is growing, the number of individuals infected with malaria increases. We try to illustrate what will happen if we kill immatured mosquito by draining standing water where mosquitoes lay their eggs, aiming to reduce the mosquito vector population. This strategy targets the mosquito egg stage $E_w(t)$, larval mosquito stage $L_w(t)$ and pupal mosquito stage $P_w(t)$ which includes methods such as the destruction of mosquito breeding sites by applying control measures aiming to kill larval mosquito, which leads to reduction in the number of immatured mosquito reducing the number of pupal developing into adult mosquitoes. This effect is modelled by parameters r_e, r_l and r_p which is the death caused by intervention (destroying their breeding sites) at eggs, larval and pupa stages. The mosquito egg stage $E(t)$ is supplied by a term $\Lambda_e N_v(t)$ where $N_v(t)$ is the total number of adult vector mosquito and Λ_e is the supply rate of eggs. Eggs are reduced by natural death at a rate μ_e. Eggs develop into larval mosquito stage $L(t)$ at a rate θ_e and larval mosquito suffer natural death at a rate μ_l and are also reduced by other species which feed on larval mosquito e.g. (fresh water fish) at a rate τ_l. The larval mosquito becomes pupal mosquito at a rate π_i. The larval mosquito enter pupal mosquito stage $P(t)$ at this amount $\pi_i L(t)$, they are reduced by natural death at a rate μ_p and also by species which feed on pupa mosquitoes at a rate ψ_p. Pupal mosquito becomes adult at constant number Λ_p. All immatured mosquito population suffer additional death due to the destructing of their breeding sites at a rate r which is assumed to be proportional to the population in each stage and acts equally on all stages of immature mosquito population. The extended model then becomes

$$
\begin{aligned}
\frac{dE_w(t)}{dt} &= \Lambda_e N_v(t) - (\mu_e + \theta_e)E_w(t) - r_e E_w(t),\\
\frac{dL_w(t)}{dt} &= \theta_e E_w(t) - (\mu_l + \tau_l + \pi_l)L_w(t) - r_l L_w(t),\\
\frac{dP_w(t)}{dt} &= \pi_l L_w(t) - (\mu_p + \psi_p)P_w(t) - \Lambda_p - r_p P_w(t),\\
\frac{dS_v(t)}{dt} &= \Lambda_p - \lambda_v S_v(t) - \mu_v S_v(t),\\
\frac{dI_v(t)}{dt} &= \lambda_v S_v(t) - \mu_v I_v(t),\\
\frac{dS_h(t)}{dt} &= \Lambda_h + qR_h(t) - \mu_h S_h(t) - \lambda_h S_h(t),\\
\frac{dI_h(t)}{dt} &= \lambda_h S_h(t) - (\mu_h + \tau_h + \alpha_h)I_h(t),\\
\frac{dR_h(t)}{dt} &= \tau_h I_h(t) - \mu_h R_h(t) - qR_h(t).
\end{aligned}
\tag{3.13}
$$

3.5. The comparison of equilibrium points and reproductive number R_0 of model (3.5) and (3.13)

In this section we compare the endemic equilibrium points of the first model (3.5) and the second model (3.13) based on the immatured mosquitoes population of both models.

The disease free equilibrium of the second model (3.13) is

$$
\begin{aligned}
E_0 &= \{N_h^*, I_h^*, R_h^*, N_v^*, I_v^*, E_w^*, L_w^*, P_w^*\}, \\
&= \left\{\frac{\Lambda_h}{\mu_h+\alpha_h}, 0, 0, \frac{\Lambda_p}{\mu_v}, 0, \frac{\Lambda_e\Lambda_p}{[(\mu_e+\theta_e)+r_e]\mu_v}, 0, 0\right\},
\end{aligned}
$$

where $I_h^0(t_0) = R_h^0 = I_v^0 = L_w^0 = P_w^0(t_0) = 0$ and the explicit form of the endemic equilibrium point of the model (3.13),

$$N_h^{ee}(t), I_h^{ee}(t), R_h^{ee}(t), E_w^{ee}(t), L_w^{ee}(t), P_w^{ee}(t), N_v^{ee}(t), I_v^{ee}(t)$$

is expressed in terms of variables from equation (3.13) as:

$$N_h^{ee}(t) = \frac{\Lambda_h}{(\mu_h + \alpha_h)},$$

$$I_h^{ee}(t) = \frac{\beta_h\beta_v c^2\Lambda_p RH - RD\mu_v^2\Lambda_p - \mu_v^2\tau_h\Lambda_h}{\beta_v c\mu_v RDH + \beta_h\beta_v c^2\Lambda_h\Lambda_p R + \beta_h c\tau_h\mu_v H},$$

$$R_h^{ee}(t) = \frac{\beta_h\beta_v c^2\Lambda_p\tau_h RH - RD\mu_v^2\Lambda_p\tau_h - \mu_v^2\tau_h^2\Lambda_h}{\beta_v c\mu_v R^2 DH + \beta_h\beta_v c^2\Lambda_h\Lambda_p R^2 + \beta_h c\tau_h\mu_v HR},$$

$$E_w^{ee}(t) = \frac{\Lambda_e\Lambda_p}{[(\mu_e + \theta_e) + r_e]\mu_v}, \tag{3.14}$$

$$L_w^{ee}(t) = \frac{\theta_e\Lambda_e\Lambda_p}{\mu_v[(\mu_e + \theta_e) + r_e][(\mu_l + \tau_l + \pi_l) + r_l]},$$

$$P_w^{ee}(t) = \frac{\pi_l\theta_e\Lambda_e\Lambda_p - \Lambda_p\mu_v[(\mu_e + \theta_e) + r_e][(\mu_l + \tau_l + \pi_l) + r_l]}{\mu_v[(\mu_p + \psi_p) + r_p][(\mu_e + \theta_e) + r_e][(\mu_l + \tau_l + \pi_l) + r_l]},$$

$$N_v^{ee}(t) = \frac{\Lambda_p}{\mu_p},$$

$$I_v^{ee}(t) = \frac{\beta_v c\Lambda_p(\beta_h\beta_v c^2\Lambda_p RH - RD\mu_v^2\Lambda_p - \mu_v^2\tau_h\Lambda_h)}{\beta_v c\mu_v(\beta_h\beta_v c^2\Lambda_p RH - RD\mu_v^2\Lambda_p - \mu_v^2\tau_h\Lambda_h) + \Lambda_p\mu_v(\beta_v c\mu_v RDH + \beta_h\beta_v c^2\Lambda_h\Lambda_p R + \beta_h c\tau_h\mu_v H)}.$$

The reproductive number R_0 of the first model system (3.13) and of the second model system (3.5) are denoted by R_0^f and R_0^s respectively. These two reproductive numbers are identical,

$$R_0^f = \sqrt{\frac{\beta_v\beta_h c^2\Lambda_p(\mu_h + \alpha_h)}{\mu_v^2\Lambda_h(\mu_h + \tau_h + \alpha_h)}}.$$

The model systems (3.5) and (3.13) differ in their endemic equilibrium points due to control measures being applied in the second model (3.13) which target the immature mosquito population $E_w(t), L_w(t), P_w(t)$, the control measures killed the immature mosquitoes at rates r_e, r_l and r_p with respect to their classes. The endemic equilibrium points E^e and E^{ee} of immature mosquito population in the aquatic environment are given as,

Endemic equilibrium point for the first model, E^e

$$E_w^e(t) = \frac{\Lambda_e \Lambda_p}{(\mu_e + \theta_e)\mu_v}$$

$$L_w^e(t) = \frac{\theta_e \Lambda_e \Lambda_p}{\mu_v(\mu_e + \theta_e)(\mu_l + \tau_l + \pi_l)},$$

$$P_w^e(t) = \frac{\dfrac{\pi_l \theta_e \Lambda_e \Lambda_p - \Lambda_p \mu_v(\mu_e + \theta_e)}{(\mu_l + \tau_l + \pi_l)}}{\dfrac{\mu_v(\mu_p + \psi_p)}{(\mu_e + \theta_e)(\mu_l + \tau_l + \pi_l)}},$$

Endemic equilibrium point for the second model, E^{ee}

$$E_w^{ee}(t) = \frac{\Lambda_e \Lambda_p}{[(\mu_e + \theta_e) + r_e]\mu_v},$$

$$L_w^{ee}(t) = \frac{\theta_e \Lambda_e \Lambda_p}{\dfrac{\mu_v[(\mu_e + \theta_e) + r_e]}{[(\mu_l + \tau_l + \pi_l) + r_l]}},$$

$$P_w^{ee}(t) = \frac{\dfrac{\pi_l \theta_e \Lambda_e \Lambda_p - \Lambda_p \mu_v}{[(\mu_e + \theta_e) + r_e][(\mu_l + \tau_l + \pi_l) + r_l]}}{\dfrac{\mu_v[(\mu_p + \psi_p) + r_p][(\mu_e + \theta_e) + r_e]}{[(\mu_l + \tau_l + \pi_l) + r_l]}}. \tag{3.15}$$

We can rewrite the endemic equilibrium of the second model in terms of $E_w^e(t)$, $L_w^e(t)$ and $P_w^e(t)$ as

$$E_w^{ee}(t) = \frac{E_w^e(t)\mu_v(\mu_e + \theta_e)}{(\mu_e + \theta_e)\mu_v + r_e\mu_v}, \tag{3.16}$$

$$L_w^{ee}(t) = \frac{L_w^e(t)\mu_v(\mu_e + \theta_e)(\mu_l + \tau_l + \pi_l)}{[\mu_v(\mu_e + \theta_e) + r_e\mu_v][(\mu_l + \tau_l + \pi_l) + r_l]} \tag{3.17}$$

and

$$P_w^{ee}(t) = \frac{L_w^e(t)\pi_l\mu_v(\mu_e + \theta_e)(\mu_l + \tau_l + \pi_l) - \Lambda_p\mu_v[(\mu_e + \theta_e) + r_e][(\mu_l + \tau_l + \pi_l) + r_l]}{\mu_v[(\mu_p + \psi_p) + r_p][(\mu_e + \theta_e) + r_e][(\mu_l + \tau_l + \pi_l) + r_l]}, \tag{3.18}$$

where $E_w^e(t)$, $L_w^e(t)$ and $P_w^e(t)$ are respectively, mosquito egg, larval and pupal endemic equilibrium points.

The equations (3.16), (3.17) and (3.18) expresses the endemic equilibrium point of the immature mosquito population of the second model (3,14) in terms of endemic equilibrium point of the first model (3.5). These expression are not that convincing like endemic expressions in equation (3.15). The endemic equations $E_w^e(t)$ and $E_w^{ee}(t)$ in equation (3.15) differ only by rates r_e, r_l and r_p, which reduces the number of immature mosquitoes in mosquito eggs $E_w(t)$, larval mosquitoes $P_w(t)$ and Pupal mosquitoes $P_w(t)$. These two equilibrium points are not the same, so we can mathematically use the following inequality

$$E_w^{ee}(t) < E_w^e, L_w^{ee}(t) < L_w^e(t) \text{ and } P_w^{ee}(t) < P_w^e(t). \tag{3.19}$$

Equation (3.19) confirms that the endemic equilibrium point E^e of the immature mosquito population of the model system (3.5) is greater the endemic equilibrium point E^{ee} of the model system (3.13) of the immature mosquito population. This means that the disease is still endemic as it is expressed by endemic equilibrium E^e and E^{ee}. The endemic equilibrium point E^{ee} shows that malaria disease can also be controlled by targeting the immature mosquito population in the territorial environment. The control measures being applied in immature mosquito population do not eradicate malaria disease, it reduces the number of vectors in the aerial environment which reduces the number of malaria cases in the community.

If immature mosquitoes and adult mosquitoes are controlled, the malaria disease can be eradicated completely. Because control of mosquito population in one environment is not sufficient to eradicate malaria disease. Control of malaria disease by targeting mosquito in aerial and aquatic environments can control malaria disease.

The disease free and endemic equilibrium points of the system (3.13) are analysed. The behaviour of the model (3.13) was studied by numerical simulations built in using matlab function *ode*45, which implements the version of Runge-kuta scheme. The parameter values that we used for numerical simulations are estimated as follow $r_e = 0.089$, $r_l = 0.06$ and $r_p = 0.07$. In our model we chose to add small extra death rate caused by intervention in immatured mosquito population to asses what would happen to the infectious human population when a small number of immature mosquitoes become adult mosquito population size.

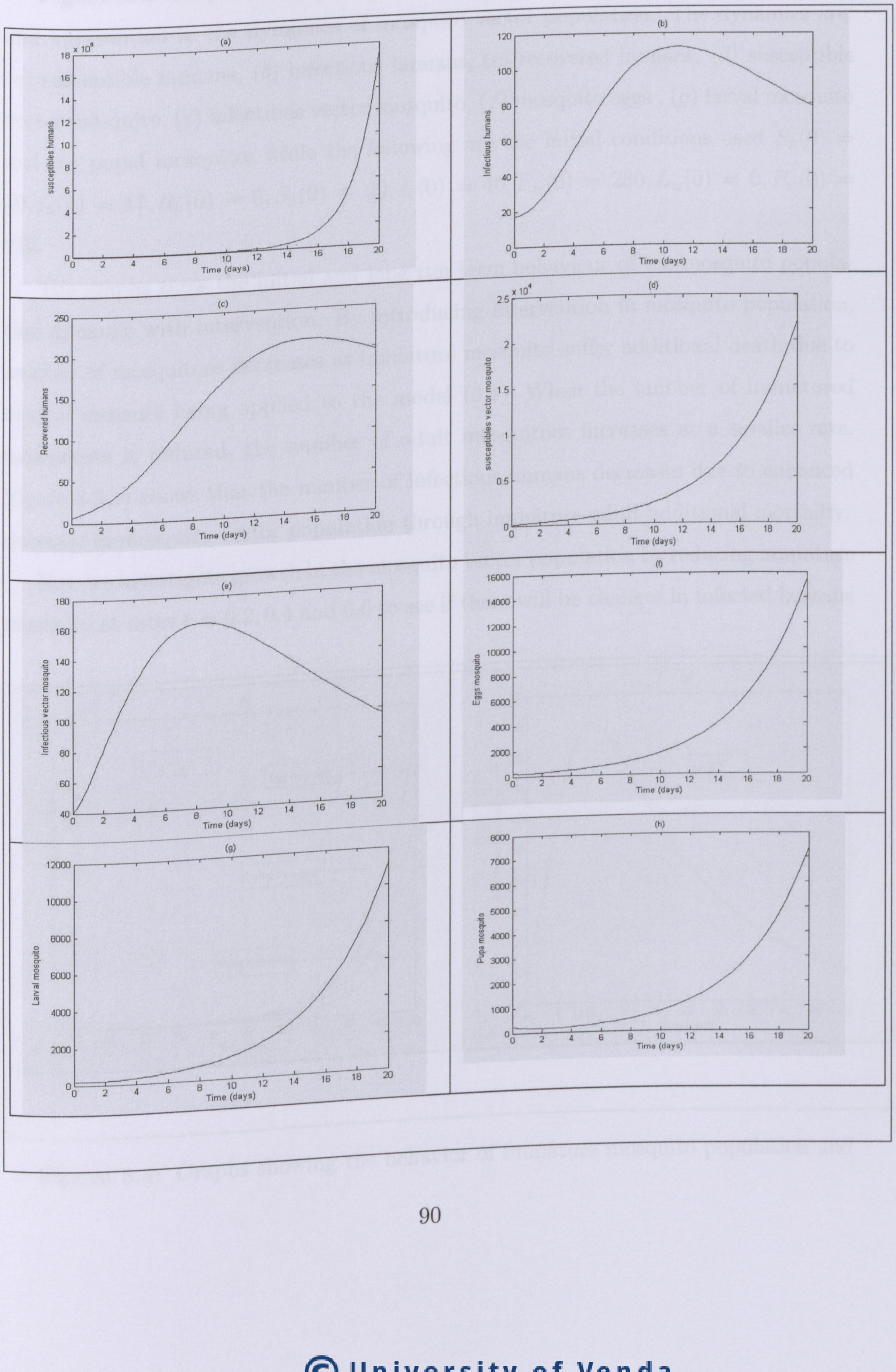

(a)
susceptibles humans
Time (days)
(b)
Infectious humans
Time (days)
(c)
Recovered humans
Time (days)
(d)
susceptibles vector mosquito
Time (days)
(e)
Infectious vector mosquito
Time (days)
(f)
Eggs mosquito
Time (days)
(g)
Larval mosquito
Time (days)
(h)
Pupa mosquito
Time (days)

Figure 3.3: Graphs showing the behaviour of system (3.13) for human population and intervention in the dynamics of mosquito vector population. The dynamics are: (a) susceptible humans, (b) infectious humans, (c) recovered humans, (d) susceptible vector mosquito, (e) infectious vector mosquito, (f) mosquito eggs , (g) larval mosquito and (h) pupal mosquito; while the following are the initial conditions used $S_h(0) = 50, I_h(0) = 17, R_h(0) = 6, S_v(0) = 60, I_v(0) = 40, E_w(0) = 280, L_w(0) = 0, P_w(0) = 250$.

The graphs show the initial and long run term behaviour of the mosquito population dynamic with intervention. By introducing intervention in mosquito population, number of mosquitoes decreases as immature mosquito suffer additional death due to control measure being applied to the model (3.4). When the number of immatured mosquitoes is reduced, the number of adult mosquitoes increases at a smaller rate. Figure 3.3(c) shows that the number of infectious humans decreases due to enhanced decrease in mosquito vector population through immature adult additional mortality.

Now we investigate growth in the mosquito vector population by reducing immature mosquito at rates $r = 0.2, 0.4$ and 0.6 to see if there will be changes in infected humans

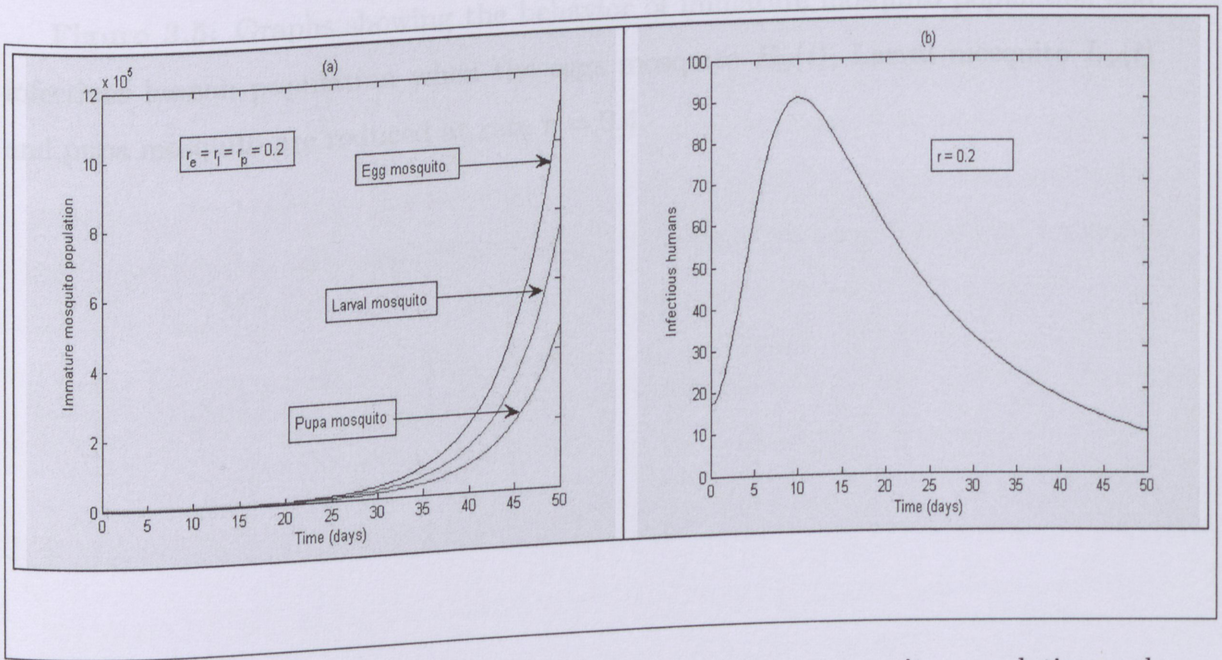


Figure 3.4: Graphs showing the behavior of immature mosquito population and

infectious human population when the eggs mosquito $E_w(t)$, Larval mosquito $L_w(t)$ and pupa mosquito are reduced at rate $r = 0.2$.

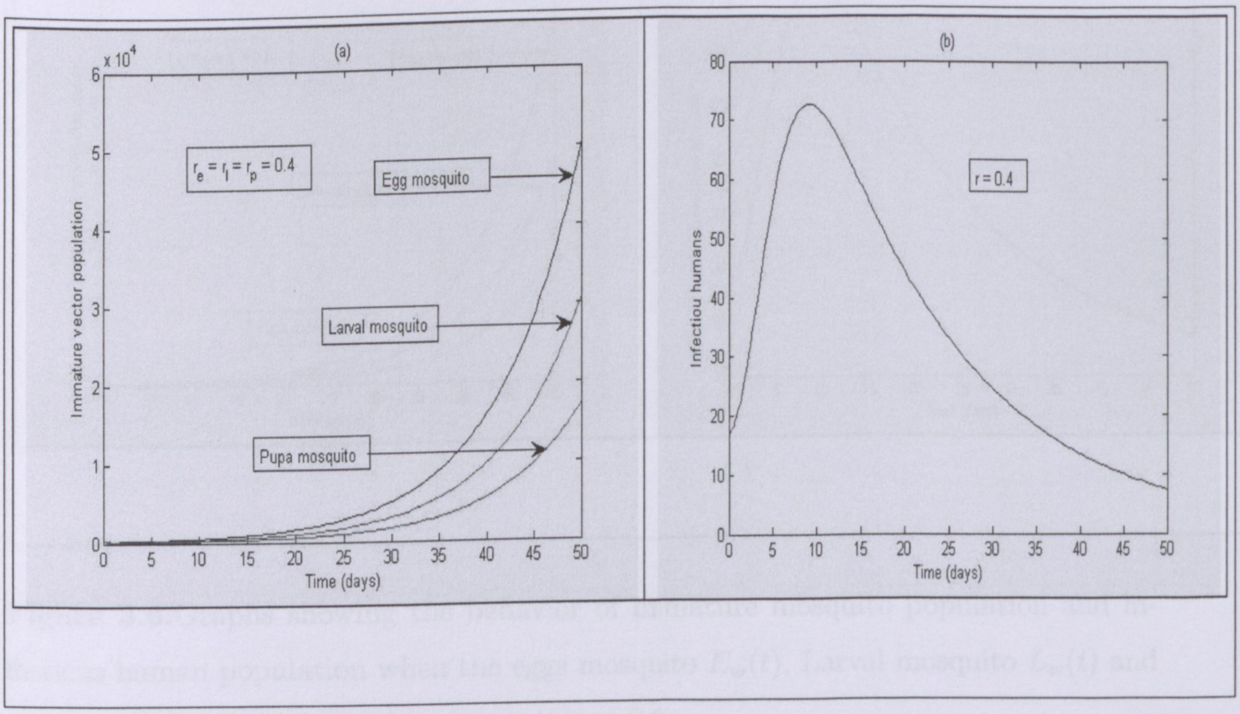


Figure 3.5: Graphs showing the behavior of immature mosquito population and infectious human population when the eggs mosquito $E_w(t)$, Larval mosquito $L_w(t)$ and pupa mosquito are reduced at rate $r = 0.4$.

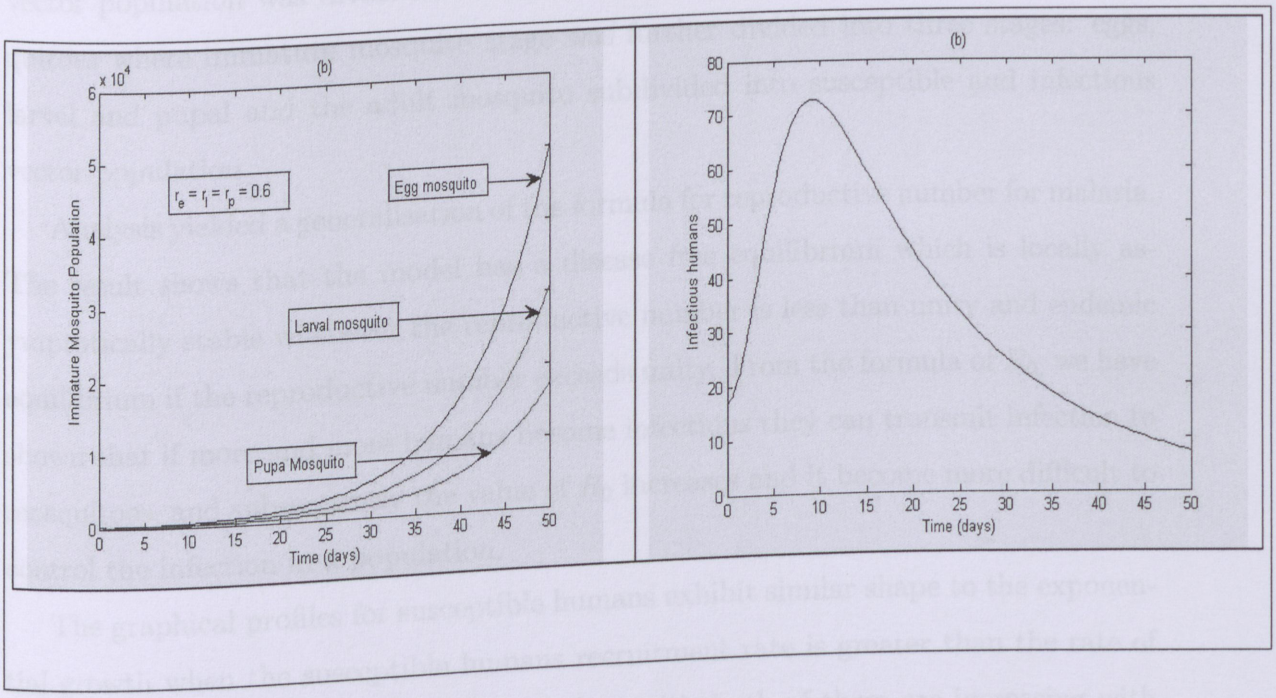


Figure 3.6: Graphs showing the behavior of immature mosquito population and infectious human population when the eggs mosquito $E_w(t)$, Larval mosquito $L_w(t)$ and pupa mosquito $P_w(t)$ are reduced at rate $r = 0.6$.

These figures show that when the number of immature mosquito population are reduced at rates $r = 0.2, 0.4$ and 0.6,the number of infected human population is decreasing because fewer immatured mosquitoes become adult. The infectious human population shown in figure 3.4 (a), figure 3.5 (b) and figure 3.6 (c) is always decreasing with the reduction in the number of immature mosquitoes due to intervention which gives hope that in the long run, malaria disease can eventually be controlled. The infectious human graph ultimately reaches a steady state. The infectious humans graph seen not differ for $r = 0.3, 0.4$ and 0.6.

3.6. Concluding Remarks

A mathematical model for the dynamics of malaria vector population was developed by taking into account human host population and mosquito vector lifecycle. Mosquito vector population was divided into two subpopulations as immature and adult mosquitoes where immature mosquito stage was further divided into three stages: eggs, larval and pupal and the adult mosquito subdivided into susceptible and infectious vector population.

Analysis yielded a generalisation of the formula for reproductive number for malaria. The result shows that the model has a disease free equilibrium which is locally asymptotically stable whenever the reproductive number is less than unity and endemic equilibrium if the reproductive number exceeds unity. From the formula of R_0, we have shown that if more and more humans become infectious they can transmit infection to mosquitoes, and subsequently the value of R_0 increases and it become more difficult to control the infection in a population.

The graphical profiles for susceptible humans exhibit similar shape to the exponential growth when the susceptible humans recruitment rate is greater than the rate of infection. This is confirmed by graphs (a) and (b), both of them are increasing with graphs (b) growing slower than (a). The increase in susceptible humans happens in first few days but with time the susceptible start to decrease and the infectious humans start to gradually increase. This leads to increase the infectious mosquito vector.

Some time we find that the susceptible humans grow simultaneously with susceptible mosquito population. In this case the susceptible mosquito population interacts with susceptible humans and these two populations do not cause malaria. The favours the mosquito like cycle because female Anopheles will get blood so that they successful lay more eggs resulting to an increase in susceptible mosquitoes. When the susceptible and infectious mosquito vector increase they will be abundant and once an individual is infected this leads to more infection to susceptible mosquito around. Again from graphs (b) and (c) these graph behave similar when the infectious humans increases also the infectious mosquito increase, at that level the community they in danger of being infected.

According to the results of this study, recommended control strategies to fight malaria should include destroying mosquito breeding sites combined with the use of recommend drugs in addition to using mosquito treated nets in houses. In addition insecticides can be used to induced mortality to adult mosquitoes.

Chapter 4

Modelling Host-Pathogen Interacting in Malaria Infection

4.1. Introduction

In this chapter, we introduce a new intra-host model of malaria infection to understand the immune system response that is elicited by the malaria parasite and the progression of the infection in the host at cell level.

Plasmodium falciparum malaria is a major cause of death in the tropics. The disease is transmitted through the bite of an infected mosquito which introduces *plasmodium* sporozoites rapidly into the liver of the host. These develop and replicate into merozoites which in the parasitic stage infects erythrocytes and causes the pathology of the disease. It is unclear why natural infections do not induce protection against the initial liver stage of plasmodium. Instead it only generates low cytotoxic CD8$^+$ T cell responses (Doolan *et al.*,1993; Aidoo *et al.*, 2000 and Plebanski *et al.*, 1997). In endemic areas, this lack of protection against liver infection results in constant malaria reinfection throughout life (Aidoo et al, 2000). Protective immuninty against malaria infection takes many years to develop, despite repeated exposure to the parasite in malaria-endemic areas of the world (Snow *et al*, 1999). Within minutes from an infectious mosquito bite, sporozoites that have not been blocked by cytotoxic T cells will infect host liver cells during the pre-erythrocytic stage. Parasites differentiate and replicate inside hepatocytes for approximately a week before lysing them (Nardin *et al.*, 1993). The liver stage is also called the pre-erythrocytic stage. Six to seven days after infection (contingent on the species), the schizont ruptures releasing merozoites into the blood stream. These merozoites released into blood stream invade neighbouring or circulating erythrocytes and become first trophozoites and then erythrocytes schizonts (by a phase of asexual reproduction).

Normally the human immune system wages an internecine war against the malaria parasites as it tries to eradicate an infection. Having identified parasites, the system ramps up production of antibodies that ain to kill the parasite themselves. In turn the parasites response is to change its proteins in the liver stages. The process through which cell mediated immune response develops involves the detection of the antigen, instruction by helper cells for the production of cytotoxic T cells specific to the antigen, differentiation and the proliferation of active cytotoxic T cells. Human immune system is a remarkably sophisticated defender of the body. It has immune reaction cells that can be mobilized to destruct an invader, with cells of the innate immune system forming the first line of defense and those of the adaptive immune system arriving later but extremely specific weaponry. The rapid increase in the parasite biomass then activates innate immune mechanism (Good *et al*, 2005). When the infected erythrocytes burst, the foreign materials also activate monocytes and macrophages, releasing cytokines that stimulate other cells of the immune system (Kwiakowski, 1995; Clark *et al.*, 1981). The blood stage of malaria parasites cannot induce the cluster differentiation ($CD8^+$) T cell response even though the response is induced by other infected tissue such as the liver, are probably not vulnerable to its cytotoxic action (Perlmann and Troye-Blomberg, 2002; Saul, 1998). The $CD8^+$ T cells have been implicated as critical effectors cells in protection against the pre-eryhrocytic (liver cells) stage of malaria.

Several authors have shown that in vivo depletion of $CD8^+$ T cells drastically reduced protective immunity against a challenge with liver sporozoites (Chen *et al.*, 1977; Schofield *et al.*, 1987; Weiss *et al.*, 1988).

Considerable work has been done on the mathematical modelling of *plasmodium falciparum* infection (Gurarie *et al.*, 2006; Gurarie and Dietz, 1999). These models do not incorporate the effect of the immune response and treatment explicitly, that is , they do not show the effect of immune effectors on merozoite invasion of erythrocytes and suppression of parasite production by antibody. Another drawback with these models, is that they do not take into account the accelerated rate of production of red blood cells during a malaria infection and the loss of uninfected red blood cells. Previous works have not considered explicitly the liver stage malaria infection which is the starting point where the parasites in the sporozoites stage enter the blood stream are carried to the liver and infect liver cells. We examine the liver stage in this thesis. From available evidence on the effect of the immune system on disease progression (Stevenson and Riley, 2004; Elloso *et al.*, 1994; Bate *et al.*, 1988) we formulate an intra-host model of malaria infection with immune response.

We start by introducing the basic intra-host model of malaria infection which has been formulated by Anderson *et al* (1989), which will be used as the foundation of our model.

We will also consider the extended basic intra-host model which was formulated by Garira and his Ph.D. student, Chiyaka, (2007). They extend the basic intra-host model by incorporating the effect of immune response. They derived the reproductive number and the stability analysis carried out. They also extended the model to include treatment with an antimalaria drug. They suggested that if there are mechanisms in the body that increase the death rate of immune cells, then there will be an increase in the severity of the infection. This shows that for a person infected by pathogens that kill some of the immune cells like the *human immunodeficiency virus* which kills the $CD4^+$cells (Shiri *et al.*, 2005) or *mycobacterium tuberculosis* which kills the macrophages, and the co-infected with plasmodium falciparum, the immune system will be greatly compromised and the person will suffer severe malaria if not treated in time.

In this chapter, we extend Chiyaka and Garira (2007) intra-host model to incorporate sporozoite parasites in the liver cells and merozoites in the red blood cells. In liver cells, cytotoxic T cells react against the sporozoite parasites and in red blood cells, immune system and antibodies react against merozoites parasites.

4.2. Intra-host model without immunity

Intra host models of malaria infection describe the dynamics of the blood stages of the parasites and their interaction with host cells which are uninfected red blood cells, infected red blood cells and immune effectors (Molineax and Dietz, 1999). One of the earliest models used to describe intra-host dynamics of malaria infection is that of Anderson et al (1989): They divide immunology of malaria into three populations namely, uninfected red blood cells $B(t)$, infected red blood cells $B^*(t)$ and merozoites cells $M(t)$. These quantities denote the concentrations of these cells in a given volume of blood or tissue. Uninfected red blood cells are recruited at a constant rate Λ_b from the bone marrow into the circulation, and have an average life expectancy of $\dfrac{1}{\mu_b}$. These uninfected red blood cells $B^*(t)$ are infected through invasion by merozoites at a rate β and become infected red blood cells $B^*(t)$. The infected red blood cells die at a rate μ_{b^*}. Merozoites parasite $M(t)$ are released when infected red blood cells burst, hence the number of merozoites produced depends on the death rate of the infected red blood cells. The average number of merozoites produced per each bursting infected red blood cells is r. Free merozoites are removed from the system through natural death at a rate μ_m or through infecting red blood cells.

The schematic illustration of the interaction of red blood cells and merozoites is as shown in figure 4.1.

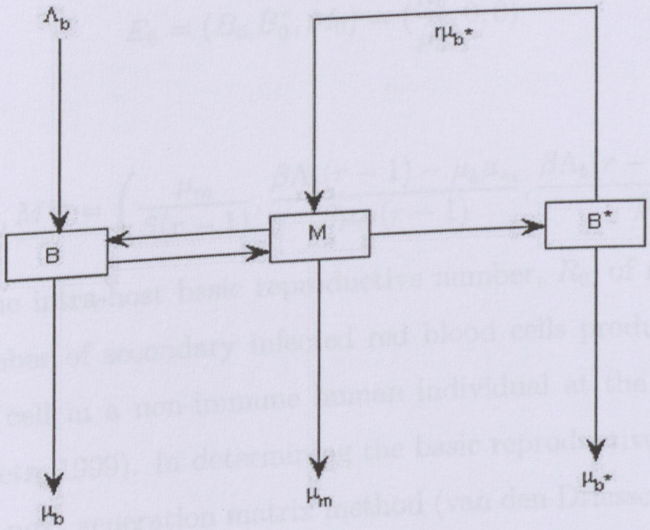


Figure 4.1: Schematic illustration of the basic inta-host model of malaria.

The above formulation leads us to the following system of differential equations (Anderson et al, 1989):

$$
\begin{aligned}
\frac{dB(t)}{dt} &= \Lambda_b - \beta B(t)M(t) - \mu_b B(t),\\
\frac{dB^*(t)}{dt} &= \beta B(t)M(t) - \mu_{b^*}B(t) \qquad (4.1)\\
\frac{dM(t)}{dt} &= r\mu_{b^*}B(t) - \mu_m M(t) - \beta B^*(t)M(t)
\end{aligned}
$$

where $\Lambda_b, \beta, r, \mu_b, \mu_{b^*}, \mu_m, \in \mathbb{R}^+$ and the initial conditions are $B(0) = B_0 \geq 0, B^*(0) = B_0^* \geq 0$ and $M(0) \geq 0$.

Solving (4.1), two steady states are obtained and these are the disease free equilibrium state denoted by E_0 and the endemic equilibrium state denoted by E^*.

$$E_0 = (B_0, B_0^*, M_0) = (\frac{\Lambda_b}{\mu_b}, 0, 0) \tag{4.2}$$

and

$$E^e = (B^e, B^{*e}, M^e) = \left(\frac{\mu_m}{\beta(r-1)}, \frac{\beta\Lambda_b(r-1) - \mu_b\mu_m}{\beta\mu_{b^*}(r-1)}, \frac{\beta\Lambda_b(r-1) - \mu_b\mu_m}{\beta\mu_m}\right).$$

For model (4.1), the intra-host basic reproductive number, R_0, of malaria parasite is defined as the number of secondary infected red blood cells produced per primarily infected red blood cell in a non-immune human individual at the onset of infection (Molineaux and Dietz, 1999). In determining the basic reproductive number of model (4.1), we follow the next generation matrix method (van den Driesscle and Watmough, 2002). We note from next generation matrix method that F and V, are given as,

$$F = \begin{pmatrix} 0 & \beta\frac{\Lambda_b}{\mu_b} & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, V = \begin{pmatrix} \mu_{b^*} & 0 & 0 \\ -r\mu_{b^*} & \mu_m + \beta\frac{\Lambda_b}{\mu_b} & 0 \\ 0 & \beta\frac{\Lambda_b}{\mu_b} & \mu_{b^*} \end{pmatrix}$$

and the intra-host basic reproduction number, R_0, is given as the spectral radius of the dominant eigenvalue of FV^{-1} (van den Driesscle and Watmough, 2002).

Therefore

$$R_0 = \rho(FV^{-1}) = \frac{r\beta\Lambda_b}{\mu_b\mu_m + \beta\Lambda_b}. \tag{4.3}$$

Our basic model in (4.1) which is an extension of a five differential equations model from Chayaka (2007). thesis. They build their model from model system (4.1) by including the response of the immune system. In developing the model, they assume five interacting populations at a given time t. These are the red blood cells $B(t)$, infected red blood cells $B^*(t)$, merozoites $M(t)$, immune cells $D(t)$ and antibodies $A(t)$. The

S-dimesional system in given by

$$
\begin{aligned}
\frac{dB(t)}{dt} &= \Lambda_b + \sigma B^*(t) - \frac{\beta B(t) M(t)}{1 + C_0 A(t)} - \mu_b B(t) - \omega B(t) M(t) D(t), \\
\frac{dB^*(t)}{dt} &= \frac{\beta B(t) M(t)}{1 + C_0 A(t)} - \mu_{b^*} B^*(t) - \mu_{b^*} B(t) - k_{b^*} D(t) B^*(t), \\
\frac{dM(t)}{dt} &= \frac{r\mu_{b^*} B^*(t)}{1 + c_1 D(t)} - \mu_m M(t) - k_m D(t) M(t) - \frac{\beta B(t) M(t)}{1 + c_0 A(t)}, \\
\frac{dD(t)}{dt} &= \Lambda_d + D(t) \left(\frac{\rho_{b^*} B^*(t)}{k_0 + B^*(t)} + \frac{\rho_m M(t)}{k_1 + M(t)} \right) - \mu_d D(t), \\
\frac{dA(t)}{dt} &= \eta D(t) \frac{M(t)}{k_1 + M(t)} - \mu_A A(t).
\end{aligned}
\tag{4.4}
$$

The intra host basic reproductive number R_0 of the malaria parasite is defined as the number of secondary infected red blood cells produced per primary infected red blood cells in a host, the onset of infection (Molineaux and Dietz, 1999). The free equilibrium state is given as

$$
E_0 = \left(\frac{\Lambda_b}{\mu_b}, 0, 0, \frac{\Lambda_d}{\mu_d}, 0 \right). \tag{4.5}
$$

The reproductive number R_0, is the dominant eigenvalue of the matrix FV^{-1}. For the model system (4.4), we get

$$
R_0 = \rho(FV^{-1}) = \frac{r\mu_{b^*} \beta \Lambda_b \mu_d^3}{(\mu_d + c_1 \Lambda_d)(\mu_d \mu_{b^*} + k_{b^*} \Lambda_d)(\mu_d \mu_m \mu_b + \mu_b k_m \Lambda_d + \mu_d \beta \Lambda_b)} \tag{4.6}
$$

4.3. Intra-host model with immune response in the liver and blood stages of malaria infections

We build up our final model from the model system (4.4) by considering the intervation of sporozoite parasites in liver cells and merozoites parasites in red blood cells with immune system. In developing the model, exo-erythrocytic stage was based on four compartments namely: sporozoites $P(t)$,uninfected liver cells $L(t)$, infected liver cells $L^*(t)$ and cytotoxic T cells $C(t)$. The erythrocytic stage has five compartments:

uninfected red blood cells $B(t)$, infected red blood cells $B^*(t)$, merozoites cells $M(t)$, immune cells $D(t)$ and antibodies. We also make the following assumptions:

(a) The sporozoites are injected into human body at a one-off time through the bite of an infected mosquito.

(b) Cytotoxic T cells are elicited by the presence of sporozoites into liver cells and reduce the rate of infection in the liver cells.

(c) Due to the many different immune cells elicited by the presence of merozoites malaria parasites, the model assumes them to be grouped together as one population for simplicity.

(d) The red blood cells are supplied from the bone marrow at a constant rate. We assume that the supply rate is accelerated by the presence of infected red blood cells. They are reduced through infection by merozoites and natural death at a constant rate.

(e) Infected red blood cells die at constant rate and are also killed by the presence of immune effectors. They produce merozoites by bursting.

(f) Production rate of merozoites is reduced by immune cells. These free parasites suffer a natural death, are eliminated from circulating by immune cells and are also reduced through infecting red blood cells.

(g) Immune cells are produced at a constant rate and their production is stimulated by the presence of infected red blood cells and merozoites. They are also reduced at a constant rate.

(h) Antibodies that block the invasion of red blood cells proliferate in the presence of merozoites. Antibodies decay at a constant rate.

(i) We further assume that CTL immunity is the major form of immune response in the liver stage while the blood stage has anti-body dependent immunity.

The assumptions lead to the following system of differential equations which describe the interactions among sporozoites, uninfected liver cells, infected liver cells, cytotoxic T cells, uninfected red blood cells, infected red blood cells, merozoites cells, immune system and antibodies.

$$\frac{dP(t)}{dt} = -\mu_p P(t) - \theta_p C(t)P(t), \tag{4.7}$$

$$\frac{dL(t)}{dt} = \Lambda_l - \frac{\beta_0 P(t)L(t)}{1+aC(t)} - \mu_l L(t), \tag{4.8}$$

$$\frac{dL^*(t)}{dt} = \frac{\beta_0 P(t)L(t)}{1+aC(t)} - \mu_{l^*} L^*(t) - \theta_{l^*} C(t)L^*(t), \tag{4.9}$$

$$\frac{dC(t)}{dt} = s_c + \varpi C(t)L(t)P(t) - \mu_c C(t), \tag{4.10}$$

$$\frac{dB(t)}{dt} = \Lambda_b - \frac{\beta_b M(t)B(t)}{1+\alpha_0 A(t)} - \mu_b B(t) - \theta_l M(t)D(t)B(t), \tag{4.11}$$

$$\frac{dB^*(t)}{dt} = \frac{\beta_b M(t)B(t)}{1+\alpha_0 A(t)} - \mu_{b^*} B^*(t) - \theta_{b^*} D(t)B^*(t), \tag{4.12}$$

$$\frac{dM(t)}{dt} = \frac{n\mu_{l^*} L^*(t)}{1+\alpha_2 D(t)} + \frac{r\mu_{b^*} B^*(t)}{1+\alpha_1 D(t)} - \mu_m M(t) - \theta_m D(t)M(t) \tag{4.13}$$

$$-\frac{\beta_b M(t)B(t)}{1+\alpha_0 A(t)},$$

$$\frac{dD(t)}{dt} = \Lambda_d + \frac{\rho_{b^*} B^*(t)D(t)}{f_0 + B^*(t)} + \frac{\rho_m M(t)D(t)}{f_1 + M(t)} - \mu_d D(t), \tag{4.14}$$

$$\frac{dA(t)}{dt} = \frac{\eta D(t)M(t)}{f_1 + M(t)} - \mu_A A(t). \tag{4.15}$$

An immune system response to the foreign antigen requires the presence of an antigen-presenting cell (APC), (usually either a macrophages or dendritic cell) in combination with B cell or T cell.

The dynamics of sporozoites parasites $P(t)$, is described by equation (4.7), sporozoites are injected by infected Anopheles mosquito at a constant rate P_0. The sporozoites are reduced by natural death at a rate μ_p and are also destroyed by cytotoxic T cells at a rate θ_p. Equation (4.8) models the dynamics of uninfected liver cells $L(t)$. The uninfected liver cells are supplied at a constant rate Λ_l, liver cells become infected by sporozoites at a constant rate β_0 and the rate of infection is reduced by $\frac{1}{1+aC(t)}$ where a is the rate at which $C(t)$ reduces the sporozoites into the liver cells. They are lost through natural death at rate μ_l.

Equation (4.9) models the dynamics of infected liver cells $L^*(t)$. The infected liver cells are supplied by the lost term form equation (4.8). The infected liver cells are reduced through natural death at a constant rate μ_{l^*} and also apoptosis at a rate θ_{l^*}. The dynamic of cytotoxic T cells $C(t)$ is described by equation (4.10). The cytotoxic T cells increase directly from thymus at rate s_c. They proliferate at a mass action rate $\varpi L(t)P(t)$ and they die at a constant rate μ_c. The dynamics of red blood cells $B(t)$ is described by equation (4.11). The uninfected red blood cells are supplied at rate Λ_b from the bone marrow (McQueen and Mckensie, 2004). Uninfected red blood cells are infected by merozoites. The term $\beta_b M(t)B(t)$ models the rate at which free merozoites infect red blood cells where β_b is the rate of infection. The term $\frac{1}{1+\alpha_0 A(t)}$ represents the role of antibodies in controlling parasitemia, where α_0 is the efficiency of antibodies in reducing erythrocytic invasion. This means that an increase in the number of antibodies reduces the rate of infection of red blood cells by merozoites. The red blood cells are reduced by natural death at rate μ_b, since their average life span is $\frac{1}{\mu_b}$ assuming exponential residence times. The equation (4.12) models the dynamics of infected red blood cells $B^*(t)$. The infected red blood cells are gained from the loss term in the equation (4.11). The infected red blood cells are lost through death at rate μ_{b^*} and killed directly by immune cells at rate θ_{b^*} (Stevenson and Riley, 2004; Fritche, 2001).

The rate of change of merozoites $M(t)$ is described by equation (4.13). Merozoites are supplied at rates r and n from the dead infected red blood cells μ_{b^*} and also from dead infected liver cells μ_{l^*}. The infected red blood cells and infected liver cells burst during death. Hence the number of merozoites produced depends on the death rate of infected red blood cells and infected liver cells. An average of r merozoites are released per bursting infected red blood cell and also an average of n merozoites are released per bursting infected liver cells. Rate of parasites production by infected cells are suppressed by immune cells with a factor $\dfrac{1}{1+\alpha_1 D(t)}$ and $\dfrac{1}{1+\alpha_2 D(t)}$ where α_1 and α_2 are the efficiency of immune cells in suppressing parasites production. The infected liver cells rupture and merozoites are released into uninfected red blood cells. Merozoites are lost through natural death at rate μ_m and are also removed by the immune system cells at rate θ_m. Equation (4.14) models the population of immune cells (e.g. macrophages, natural killer cells, CD4$^+$ T cells). The immune cells are supplied at rate Λ_d, which is the combined terms of different immune cells. These are stimulated through the terms $\dfrac{\rho_{b^*}B^*(t)D}{f_0+B^*(t)}+\dfrac{\rho_m M(t)}{f_1+M(t)}$ for immune cells in the presence of infected red blood cells $B^*(t)$ and merozoites $M(t)$, where ρ_{b^*} and ρ_m represent the immunogenicity of infected red blood cells and merozoites respectively (Molineaux and Dietz, 1999). The parameter f_0 is the density of infected red blood cells at which immune cells grow in the absence of merozoites and f_1 is the density of merozoites at which immune cells grow in the absence of infected red blood cells. Immune cells suffer a natural death, at a rate μ_d. The population of antibodies is described by equation (4.15). Antibodies are stimulated via the term $\dfrac{\eta D(t)M(t)}{f_1+M(t)}$ where η is the maximum rate of increase of antibodies. Antibodies is that inhibit invasion of red blood cells by merozoites are secreted by immune cells in the presence of merozoites. They decay at a constant rate μ_A.

4.4. Basic properties

Theorem 4.1. *Let the initial data be* $P(0) = P_0 \geq 0, L(0) = L_0 \geq 0, L^*(0) \geq 0,$ $C(0) = C_0 \geq 0, B(0) = B_0 \geq 0, B^*(0) = B_0^* \geq 0,$ $M(0) = M_0 \geq 0, D(0) = D_0 \geq 0$ *and* $A(0) = A_0 \geq 0$. *Then the solution* $(P(t), L(t), L^*(t), C(t), B(t), B^*(t), M(t), D(t), A(t))$ *are always positive for any time* $t \in [0, \nu]$ *for some* $\nu > 0$.

Proof: We will perform the proof of the following ideas by (Ma *et al.*, 2002). It is easy to see that $P(t) > 0$ for all $t \in [0, \nu]$. This follows from equation (4.7) that $\frac{dP(t)}{dt} = P_0 > 0$ for all $t \in [0, \nu]$ when $P(t) = 0$. We can also see $\frac{dL(t)}{dt} = \Lambda_l > 0 \forall t \in [0, \nu]$ when $L(t) = 0$, $\frac{dB(t)}{dt} = \Lambda_b > 0 \forall t \in [0, \nu]$ when $B(t) = 0$ and $\frac{dD(t)}{dt} = \Lambda_d > 0 \forall t \in [0, \nu]$ when $D(t) = 0$ from equations $(4.8), (4.11)$ and (4.14) respectively.

Therefore $P(t), L(t), B(t)$ and $D(t)$ are always positive.

We assume that there exists some time $t_1 \in (0, \nu)$ such that $L^*(t_1) = 0$, other variables are positive and $L^*(t) > 0$ for $t = [0, t_1)$. Integrating equation (4.9) and (4.12) from 0 to t_1 we have

$$L^*(t_1) = L_0^*(0) \exp\left\{-\int_0^{t_1} (\mu_{l^*} + \theta_{l^*} C(\tau))\, d\tau\right\}$$

$$+ \exp\left\{-\int_0^{t_1} (\mu_{l^*} + \theta_{l^*} C(\tau))\, d\tau\right\}$$

$$\times \int_0^{t_1} \frac{\beta_0 P(\tau) L(\tau)}{1 + aC(\tau)} \exp\left\{\int_0^{\tau} (\mu_{l^*} + \theta_{l^*} C(x))\, dx\right\} d\tau \geq 0,$$

and

$$B^*(t_1) = B^*(0)\exp\left\{-\int_0^{t_1}(\mu_{b^*} + \theta_{b^*}D(\tau))d(\tau)\right\}$$

$$+\exp\left\{-\int_0^{t_1}(\mu_{b^*} + \theta_{b^*}D(\tau))d\tau\right\}$$

$$\times\int_0^{t_1}\left(\frac{\beta_b M(\tau)B(\tau)}{1+\alpha_0 A(\tau)}\right)\left\{-\int_0^{t_1}(\mu_{b^*} + \theta_{b^*}D(\tau))d(\tau)\right\}$$

$$\exp\left\{-\int_0^{\tau}(\mu_{b^*} + \theta_{b^*}D(x))dx\right\}d\tau \geq 0,$$

which contradicts $L^*(t_1) = B^*(t_1) = 0$.

Assume there is some time $t_2 \in (0,\nu)$ such that $A(t_2) = 0$ and $A(t) > 0$. Then integrating equation (4.15) from 0 to t_2, we have

$$A(t_2) \ = \ A(0)e^{-\mu_A t_2} + e^{\mu_A t_2}\int_0^{t_2}\frac{\eta D(\tau)M(\tau)}{f_1 + M(\tau)}d\tau \geq 0,$$

which contradicts $A(t_2) = 0$.

Similarly for $M(t)$, assume that there is some time $t_3 \in (0,\nu)$ such that $M(t_3) = 0$ and $M(t) > 0$. Integrating (4.13) from 0 to t_3, we see that

$$M(t_3) = M(0)\exp\left\{-\int_0^{t_3}(\mu_m + \theta_m D(\tau))d\tau\right\}$$

$$+\exp\left\{-\int_0^{t_3}(\mu_m + \theta_m D(\tau))d\tau\right\}$$

$$\times \int_0^{t_3} \left(\frac{n\mu_{l^*} L^*(\tau)}{1+\alpha_2 D(\tau)} + \frac{r\mu_b B^*(\tau)}{1+\alpha_1 D(\tau)} \right) \exp\left\{ - \int_0^{t_3} (\mu_m + \theta_m D(x)) dx \right\} d\tau \geq 0,$$

which contradicts $M(t_3) = 0$.

This implies that the solution $(P(t), L(t), L^*(t), C(t), B(t), B^*(t), M(t), D(t), A(t))$ is always non-negative for $t \geq 0$.

4.5. Intra-host basic reproductive number

We now drive the basic reproductive number R_0, for the model system given by equations $(4.7 - 4.15)$ by using the Diekman (1990) method. The R_0 is evaluated at the disease free equilibrium state E_0.

The model system given by equation $(4.7) - (4.15)$ has two steady states, the disease free equilibrium state

$$\begin{aligned} E_0 &= (\overline{P}, \overline{L}, \overline{L^*}, \overline{C}, \overline{B}, \overline{B^*}, \overline{M}, \overline{D}, \overline{A}) \\ &= \left(0, \frac{\Lambda_l}{\mu_l}, 0, \frac{s_c}{\mu_c}, \frac{\Lambda_b}{\mu_b}, 0, 0, \frac{\Lambda_d}{\mu_d}, 0\right) \end{aligned}$$

and the endemic equilibrium state bounded by

$$E_e = (P_e, L_e, L_e^*, C_e, B_e, B_e^*, M_e, D_e, A_e).$$

The primary infectious rate of host by parasites is defined by

$$f_{(L^*, B^*)} = \begin{pmatrix} \dfrac{\beta_0 P(t) L(t)}{1+aC(t)} \\ \\ \dfrac{\beta_b M(t) B(t)}{1+\alpha_0 A(t)} \\ \\ \dfrac{n\mu_{l^*} L^*(t)}{1+\alpha_2 D(t)} + \dfrac{r\mu_{b^*} B^*(t)}{1+\alpha_1 D(t)} \end{pmatrix}$$

Following the method of the next generation matrix (Van den Driessche and Watmough, 2002), the matrix F is given by

$$F = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & \dfrac{\beta_b \Lambda_b}{\mu_b} \\ \dfrac{n\mu_{l^*}}{1+\alpha_2(\dfrac{\Lambda_d}{\mu_d})} & \dfrac{r\mu_{b^*}}{1+\alpha_1(\dfrac{\Lambda_d}{\mu_d})} & 0 \end{pmatrix}$$

and also matrix V^{-1} given by

$$V^{-1} = \begin{pmatrix} \mu_{l^*} + \theta_{l^*}\left(\dfrac{s_c}{\mu_c}\right) & 0 & 0 \\ 0 & \mu_{b^*} + \theta_{b^*}\left(\dfrac{\Lambda_d}{\mu_d}\right) & 0 \\ 0 & 0 & \dfrac{\beta_b \Lambda_b}{\mu_b} \end{pmatrix},$$

The product FV^{-1} is called the next generation matrix (Diekmann *et al.*, 1990). The reproductive number R_0, is the dominant eigenvalue of the matrix FV^{-1}.

Thus our reproductive number is

$$R_0 = \rho(FV^{-1}) = \frac{n\mu_{l^*} r\mu_{b^*}\Lambda_b}{(1+\alpha_2\dfrac{\Lambda_d}{\mu_d})(1+\alpha_1\dfrac{\Lambda_d}{\mu_d})(\mu_{l^*}+\theta_{l^*}\dfrac{\Lambda_c}{\mu_c})(\mu_{b^*}+\beta_{b^*}\dfrac{\Lambda_d}{\mu_d})}. \tag{4.16}$$

The intra-host reproductive number R_0 of the malaria parasite is defined as the number of secondary infected liver and red blood cells produced per primary infected liver and red blood cell in a host at onset of infection (Molineaux and Dietz, 1999). If $R_0 < 1$, then on average an infected liver and red blood cell produce less than one new infected live and red blood cells and the infection cannot grow. If however $R_0 > 1$, then on average each infected liver and red blood cell produce more than one new infected liver and red blood cell and infection is maintained.

To bring the infection (parasitemia) under control we seek conditions on the parameters of the infection that will guarantee the existence of stable disease free state.

4.6. Stability of the disease free equilibrium

Theorem 4.2. *If R_0, the disease free equilibrium E_0 of system (4.7)0 − (4.15) is locally asymptotically stable but, if $R_0 > 1$, then it is unstable.*

Proof: The proof follows from theorem 2 of van den Driessche and Watmough (2002).

Theorem 4.3. *If $R_0 < 1$, then the disease equilibrium* $\left(0, \frac{\Lambda_l}{\mu_l}, 0, \frac{s_c}{\mu_c}, \frac{\Lambda_b}{\mu_b}, 0, 0, \frac{\Lambda_d}{\mu_d}, 0\right)$

of system (4.7) − (4.15) is a global attractor, that is

$\lim_{t\to\infty}(P(t), L(t), L^*(t), C(t), B(t), B^*(t), M(t), D(t), A(t)) \to \left(0, \frac{\Lambda_l}{\mu_l}, 0, \frac{s_c}{\mu_c}, \frac{\Lambda_b}{\mu_b}, 0, 0, \frac{\Lambda_d}{\mu_d}, 0\right)$ *for any positive solution of the system.*

Proof: We first rewrite the infected compartments liver cells $L^*(t)$ and $B^*(t)$ as integral equations. The sporozoites $P(t)$ and merozoites cells $M(t)$ can be written as also integral equations.

Thus $L(t)$, $L^*(t)$, $B^*(t)$ and $M(t)$ are written as

$$P(t) = \int_{-\infty}^{t} P_0 \exp\left\{-(\mu_p + \theta_p C(s)\right\} ds,$$

and

$$L^*(t) = \int_{-\infty}^{t} \frac{\beta_0 P(s) L(s)}{1 + aC(s)} \exp\left\{-\left(\mu_{l^*} + \theta_{l^*} C(s)\right)\right\} ds.$$

Rewrite parasites as

$$B^*(t) = \int_{-\theta}^{t} \frac{\beta_0 M(s) B(s)}{1 + \alpha_0 A(s)} \exp\left\{-(\mu_{b^*} + \theta_{b^*} D(s)) ds\right\},$$

and

$$M(t) = \int_{-\infty}^{t} \left(\frac{r\mu_b B^*(s)}{1 + \alpha_1 D(s)} + \frac{n\mu_{l^*} L^*(\tau)}{1 + \alpha_2 D(\tau)}\right) \exp\left\{-\left(\mu_m + \theta_m D(s) + \frac{\beta_b B(s)}{1 + \alpha_0 A(s)}\right)\right\} ds.$$

Using the substitution in the liver stage by setting $u = s$, taking the limsup of both sides of the equations for $P(t)$, infected liver cells $L^*(t)$ and sporozoites cell $P(t)$ (parasites), and apply the fact that $\limsup \int f \leq \limsup f$, known as the Fatou's lemma (Royden, 1988; Bruckner, 1997).

$$
\begin{aligned}
\limsup_{t\to\infty} L^*(t) &= \limsup_{t\to\infty} \int_0^\infty \left(\frac{\beta_0 P(t-u)L(t-u)}{1+aC(t-u)}\right) \times \\
&\quad \exp\left\{-\left(\mu_{l^*} + \theta_{l^*} C(t-u)\right) u\right\} du, \\
&\leq \int_0^\infty \limsup_{t\to\infty} \left(\frac{\beta_0 L(t-u)}{1+aC(t-u)}\right) \limsup_{t\to\infty} P(t-u) \times \\
&\quad \exp\left\{-\left(\mu_{l^*} + \theta_{l^*} C(t-u)\right) u\right\} du, \\
&\leq \limsup_{t\to\infty} \frac{\beta_0 L(t)}{1+aC(t)} \limsup_{t\to\infty} P(t) \times \\
&\quad \int_0^\infty \exp\left\{-\left(\mu_{l^*} + \theta_{l^*}\frac{s_c}{\mu_c}\right)\right\} dx, \\
&\leq \frac{\beta_0 \Lambda_l}{\mu_l\left(\mu_{l^*} + \theta_{l^*}\frac{s_c}{\mu_c}\right)} \limsup_{t\to\infty} P(t).
\end{aligned}
\tag{4.17}
$$

Following the same arguments on the equation for $P(t)$, we get

$$
\limsup_{t\to\infty} P(t) \leq \frac{\Lambda_p}{\left(\mu_p + \theta_p \frac{s_c}{\mu_c}\right)}. \tag{4.18}
$$

Substituting (4.18) into (4.17), we get

$$
\limsup_{t\to\infty} L^*(t) \leq \frac{\beta_0 \Lambda_l \Lambda_p}{\mu_l\left(\mu_{l^*} + \theta_{l^*}\frac{s_c}{\mu_c}\right)\left(\mu_p + \theta_p\frac{s_c}{\mu_c}\right)}, \tag{4.19}
$$

We also use similar argument into infected red blood cells $B^*(t)$ and in merozoites $M(t)$, and the fact that $\limsup \int f \leq \limsup f$, known as the Fatou's lemma (Royden, 1988;

Bruckner, 1997).

$$\limsup_{t\to\infty} B^*(t) = \limsup_{t\to\infty} \int_0^\infty \frac{\beta_b M(t-u)B(t-u)}{1+\alpha_0 A(t-u)} \times$$

$$\exp\{-(\mu_{b^*}+\theta_{b^*}D(t-u))u\}\,du,$$

$$\leq \int_0^\infty \limsup_{t\to\infty} \frac{\beta_b B(t-u)}{(1+\alpha_0 A(t-u))}$$

$$\limsup_{t\to\infty} M(t-u) \times \exp\{-(\mu_{b^*}+\theta_{b^*}D(t-u))u\}\,du,$$

$$\leq \limsup_{t\to\infty} \frac{\beta_b B(t)}{(1+\alpha_0 A(t))} \limsup_{t\to\infty} M(t)$$

$$\int_0^\infty \exp\left\{-(\mu_{b^*}+\theta_{b^*}\frac{\Lambda_d}{\mu_d})\right\} dx,$$

$$\leq \frac{\beta_b \Lambda_b}{\mu_b(\mu_{b^*}+\theta_{b^*}\frac{\Lambda_d}{\mu_d})} \limsup_{t\to\infty} M(t). \tag{4.20}$$

Following the same arguments on the equation for $M(t)$, we get

$$\limsup_{t\to\infty} M(t) \leq \frac{\beta_0 \Lambda_l \Lambda_p (r\mu_{b^*}+n\mu_{l^*})}{\left(\begin{array}{c}\left(1+\alpha_1\frac{\Lambda_d}{\mu_d}\right)\left(1+\alpha_2\frac{\Lambda_d}{\mu_d}\right)\left(\mu_m+\theta_m\frac{\Lambda_d}{\mu_d}\right)\mu_l \\ \times\left(\mu_{l^*}+\theta_{l^*}\frac{s_c}{\mu_c}\right)\left(\mu_p+\theta_p\frac{s_c}{\mu_c}\right)\end{array}\right)} \limsup_{t\to\infty} B^*(t) \tag{4.21}$$

Substituting (4.21) into (4.20), we get

$$\limsup_{t\to\infty} B^*(t) \leq \frac{\beta_b\Lambda_b\beta_0\Lambda_l\Lambda_p(r\mu_{b^*}+n\mu_{l^*})}{\left(\begin{array}{c}\mu_b(\mu_{b^*}+\theta_{b^*}\frac{\Lambda_d}{\mu_d})\left(1+\alpha_1\frac{\Lambda_d}{\mu_d}\right)\left(1+\alpha_2\frac{\Lambda_d}{\mu_d}\right)\left(\mu_m+\theta_m\frac{\Lambda_d}{\mu_d}\right)\mu_l \\ \times\left(\mu_{l^*}+\theta_{l^*}\frac{s_c}{\mu_c}\right)\left(\mu_p+\theta_p\frac{s_c}{\mu_c}\right)\end{array}\right)}\limsup_{t\to\infty} B^*(t).$$

$$= \frac{R_0\beta_b\beta_0\Lambda_l\Lambda_p(r\mu_{b^*}+n\mu_{l^*})(\mu_{l^*}+\theta_{l^*}\frac{\Lambda_c}{\mu_c})(\mu_{b^*}+\beta_{b^*}\frac{\Lambda_d}{\mu_d})}{\left(\begin{array}{c}n\mu_{l^*}r\mu_{b^*}\mu_b\mu_l(\mu_{b^*}+\theta_{b^*}\frac{\Lambda_d}{\mu_d})\left(\mu_m+\theta_m\frac{\Lambda_d}{\mu_d}\right)\left(\mu_{l^*}+\theta_{l^*}\frac{s_c}{\mu_c}\right) \\ \times\left(\mu_p+\theta_p\frac{s_c}{\mu_c}\right)\end{array}\right)}\limsup_{t\to\infty} B^*(t).$$

Thus if $R_0 < 1$, we have a strict inequality (and contradiction) $\lim_{t\to\infty}\sup B^*(t) < \lim_{t\to\infty}\sup B^*(t)$, unless $\lim_{t\to\infty}\sup B^*(t) = 0$. we conclude that when $R < 1$,

$\lim_{t\to\infty}\sup(P(t), L(t), L^*(t), C(t), B(t), B^*(t), M(t), D(t), A(t)) \to \left(0, \frac{\Lambda_l}{\mu_l}, 0, \frac{s_c}{\mu_c}, \frac{\Lambda_b}{\mu_b}, 0, 0, \frac{\Lambda_d}{\mu_d}, 0\right)$ i.e. the disease free equilibrium is locally stable.

4.7. Analysis of endemic equilibrium

When $R_0 > 1$, the condition for the stability of the disease free equilibrium is violated and besides the disease free equilibrium, the system of equations (4.7) – (4.15) has an endemic equilibrium, $E_e = (P_e, L_e, L_e^*, C_e, B_e, B_e^*, M_e, D_e, A_e)$. The explicit derivative of the endemic equilibrium is not performed to be produced here, therefore we shall only state the expression for E_e and perform its stability analysis. From the system of equations (4.7) – (4.15), it can be shown that

$$
E_e = \begin{cases}
P_e = P_0 e^{-[\mu_p + \theta_p C_*]}, \text{ but} \\[2ex]
L_e = \dfrac{\Lambda_l[1 + aC_*]}{\beta_0 P_* + \mu_l[1 + aC_*]}, \\[2ex]
L_e^* = \dfrac{\beta_0 P_* L_*}{[\mu_{l^*} + \theta_{l^*} C_*][1 + aC_*]}, \\[2ex]
C_e = \dfrac{s_c}{\varpi L_* P_* + \mu_c}, \\[2ex]
B_e = \dfrac{\Lambda_b[1 + \alpha_0 A_*]}{\beta_b M_* + [\mu_b + \theta_l M_* D_*][1 + \alpha_0 A_*]}, \\[2ex]
B_{e*}^* = \dfrac{\beta_b M_* B_*}{[1 + \alpha_0 A_*][\mu_{b^*} + \theta_{b^*} D_*]}, \\[2ex]
M_e = \dfrac{[r\mu_{b^*} B_*^*[1 + \alpha_1 D_*] + n\mu_{l^*} L_*^*[1 + \alpha_2 D_*]][1 + \alpha_0 A_*]}{[1 + \alpha_1 D_*][1 + \alpha_2 D_*][[\mu_m + \theta_m D_*](1 + \alpha_0 A_*) + \beta_b B_*]}, \\[2ex]
D_e = \dfrac{\Lambda_d[f_0 + B_*^*)(f_1 + M_*)]}{\rho_{b^*} B_*^*[f_1 + M_*] + \rho_m M_*[f_0 + B_*^*)] + \mu_d[f_0 + B_*^*][f_1 + M_*]}, \\[2ex]
A_e = \dfrac{\eta D_* M_*}{[f_1 + M_*]\mu_A}.
\end{cases} \tag{4.22}
$$

The endemic equilibrium state is too long to be produced, it is cumbersome to prove its local stability analytically. We however expressed endemic equilibrium state as functions which depend on some compartments.

Once the sporozoites parasites invade the liver cells they die and burst and produce merozoites into the red blood cells and the remaining sporozoite parasites are destroyed by cytotoxic T cells. The sporozoite parasites are diminished and $(P_e, L_e) \rightarrow 0$ as time $t \rightarrow \infty$.

The first equation of (4.22), represents sporozoites endemic equilibrium number P_e, with the constant term P_0 as initial sporozoites injected by infected anopheles mosquito, the growth of this state is governed by natural death μ_p and cytotoxic T cells C_* at rate θ_p as time t is moves to the positive infinity. Thus $P_e \to 0$ as time $t \to \infty$.

The second equation of state (4.22) represents equilibrium number of uninfected liver cells L_e. This equilibrium number of uninfected liver cells is reduced by sporozoites at rate β_0 and natural death μ_l. While cytotoxic T cells at rate protect the uninfected liver cells and enable them to grow at rate a.

The third equation of the system (4.22) represents the equilibrium number of infected liver cells L_e^*. This equilibrium number L_e^* is reduced by natural death μ_{l^*}, cytotoxic T cells are also reduced by interaction with uninfected red blood cells B_e at rate β_1 and $L_e^* \to 0$ as time $t \to \infty$.

The fourth equation of state (4.22) represents equilibrium number of cytotoxic T cells C_*, a reaction of the cells which react in the liver cells. This equilibrium number depends on the interaction of compartments L_e and P_e , when they interact, which in turn stimulate cytotoxic T cells against them. Once C_e cells increase, the infected number of liver cells decrease. This number is reduced by natural death at a rate μ_c.

The fifth equation of the state (4.22) represents equilibrium number of uninfected red blood cells B_e, this is the expected number of red blood cells produced from the bone marrow at equilibrium. This is the number reduced by merozoites M_e at a rate β_b and natural death μ_b. The red blood cells when infected leads us to equilibrium number of infected red blood cells B_e^*, which is expressed by the sixth equation of (4.22). The equilibrium number here is determined by density of merozoites in red blood cells. The increase in the infectivity rate β_l complicates the life of human host. This infection slowed down by immune cells and by infection of the red blood cells and also by natural death at rate μ_m. But when they die they burst to produce merozoites, which circulate with into red blood cells. Considering the expression for equilibrium number of merozoites M_e, we see that their increase is determined by death of infected red blood cells B_e^*. This equilibrium number is decreased by the number of immune cells which react in the red blood cells.

The equilibrium of second to the last equation of (4.22) represents the number of immune cells D_e. The immune reaction formed against merozoites parasites increases with respect to the load of parasite deposited into red blood cells. The immune system is determined by density of merozoites $[f_0+M_e]$ in the red blood cell and also by density of infected red blood cells $[f_0 + B_e^*]$. When the density of merozoites and infected red blood cells increases, the immune system decreases. Immune cells like any living cells suffer a natural death at a rate μ_d, this lost of immune cells gives parasite chance to grow freely without any attack.

The last expression of (4.22) represents the equilibrium number of antibodies A_e. These cells are formed after immune cells D_e identify the antigen of the merozoites parasites M_e. The equilibrium number of antibodies cells is reduced by the density of merozoites cells $[f_1 + M_e]$ and natural death μ_d

We conclude that an increase in the immune response will save the health of human host while decrease the response of the immune cells leads to poor health of the human host. We can see here easily that once the cytotoxic fails to reduce the sporozoite parasites in the liver cells, the parasites will circulate to the red blood cells. But the increase of immune response lead to better health.

4.8. Numerical simulations

Parameter	Symbol	Estimated Value
Death rate of sporozoites	μ_p	3.0
Destruction rate of sporozoites	θ_p	0.09
Supply rate of unifected liver cells	Λ_l	3242
Infection rate of liver cells	β_0	0.07
Efficiency of cytotoxic T cells	a	0.5
Death rate of uninfected liver cells	μ_l	0.8
Death rate of infected liver cells	μ_{l^*}	0.9
Merozoites released per each bursting infected liver cells.	n	12
Supply rate of Cytotoxic T cells	s_c	5
Proliferate rate of cytotoxic T cells	ϖ	0.006
Death rate of cytotoxic T cells	μ_c	1.5
Supply rate of uninfected red blood cells	Λ_b	41664
Destruction of red blood cells rate through phagocytosis of erythrocytes bound to merozoites	θ_l	0.03
Efficiency of antibodies	α_0	0.6
Infection rate of red blood cells by merozoites	β_b	0.08
Death rate of uninfected red blood cells	μ_b	0.8
Death rate of infected red blood cells	μ_{b^*}	1.0
Destruction of merozoites into infected red blood cells	θ_{b^*}	0.03

Merozoites released per each bursting infected red blood cells	r	16
Death rate of merozoites	μ_m	3.0
Destruction of merozoites by immune cells	θ_m	0.04
Supply rate of immune cells	Λ_d	30
Immunosensitivity of infected red blood cells	ρ_{b^*}	0.05
Immunosensitivity of merozoites cells	ρ_m	0.05
Stimulation constant for immune cells due to		
infected red blood cells	f_0	2000
Stimulation constant for immune cells		
due to merozoites	f_1	1500
Death rate of immune cells	μ_d	1.53
Deterioration rate of antibodies	μ_A	0.4
Maximum rate of increase of antibodies	η	0.6

Table 4.1: shows numerical values of parameters used in the simulations performed.

To study the dynamics of the model over time, we solve the system of differential equations (4.7) and (4.15) numerically using a Matlab programme buit-in function of ode45, which implement the version of Runge-kuta Scheme. For computer runs, we use initial conditions $P(0) = 45, L(0) = 400, L^*(0) = 50,\ C(0) = 9, B(0) = 500, B^*(0) = 5,\ M(0) = 50, D(0) = 30$ and $A(0) = 10$.

The parameters in our model as shown in Table 4.1. However, our main thrust is on the overall effect they have on the basic reproductive number which is the basics for an infection to persist or to be eradicated.

Figure 4.2. shows the behaviour of the model system (4.7) – (4.15). It shows that the population of sporozoites, uninfected liver cells, infected liver cells, uninfected red blood cells, infected red blood cells and merozoites reach a steady endemic state since $R_0 > 1$.

Figure 4.2 (a) and 4.2 (c) show the behaviour of sporozoites and infected liver cells of the model system (4.7) – (4.15) respectively. These two graphs behave alike when the number of sporozoites in the liver cells increase, thus the number of infected liver cells increases with the number of merozoites in the red blood cells. If small quantity of parasite is injected into human host, the reaction of cytotoxic is more powerful that the chance of sporozoites to invade liver cells is too small and finally gives us the types of graphs in Figure 4.2(d). But the behaviour of Figure 4.2 (b) show that uninfected liver cells is decreasing because sporozoites parasites are many in the liver cells. This is usual because all infected graphs are decreasing as the parasites invade the cells in large quantity.

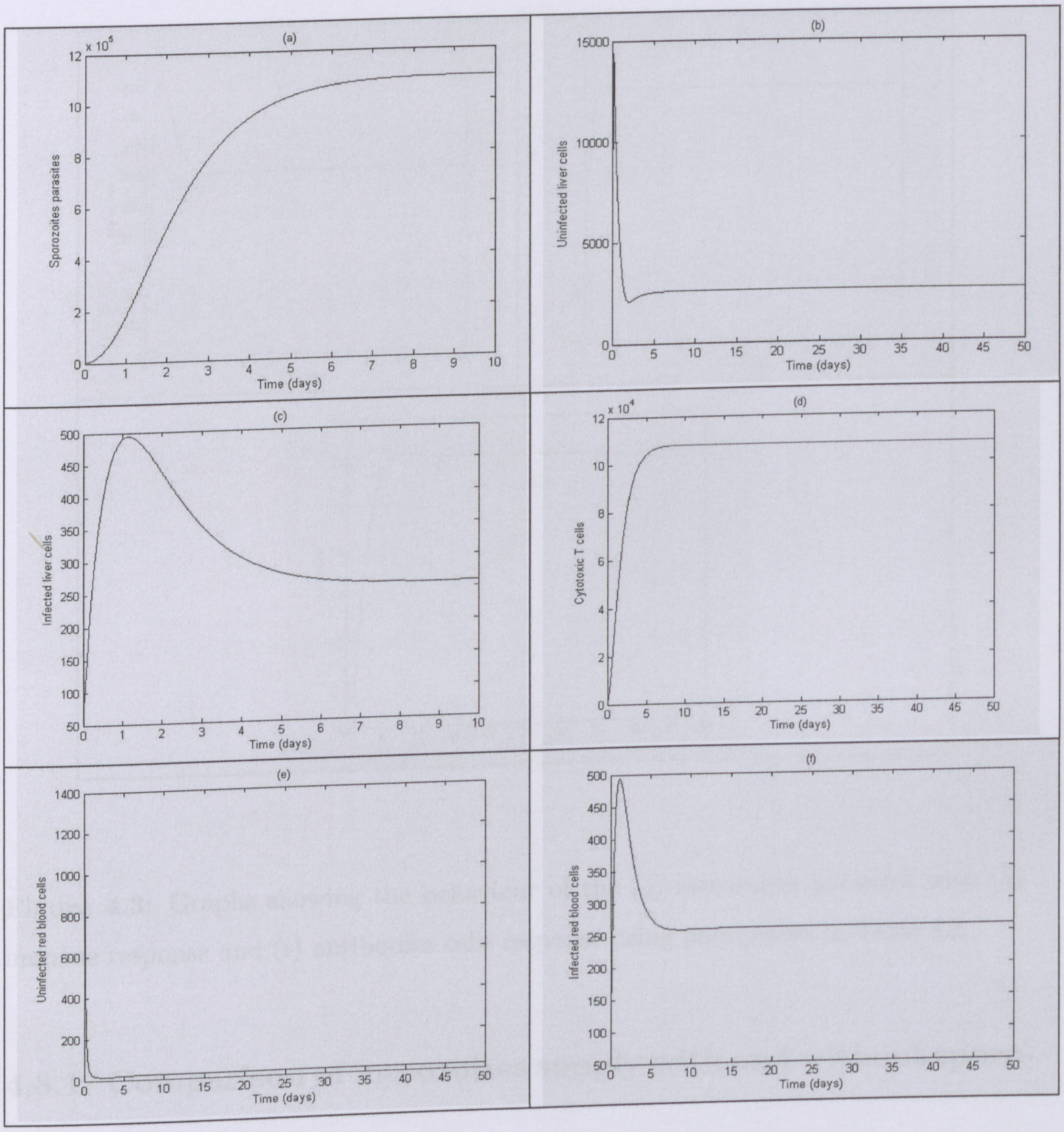


Figure 4.2 Graphs showing the behaviour of the model with immune response only using parameters in Table 3.2. The dynamics of (a) sporozoites, (b) uninfected liver cells, (c) infected liver cells, (d) cytotoxic T cells, (e) uninfected red blood cells and (f) infected red blood cells.

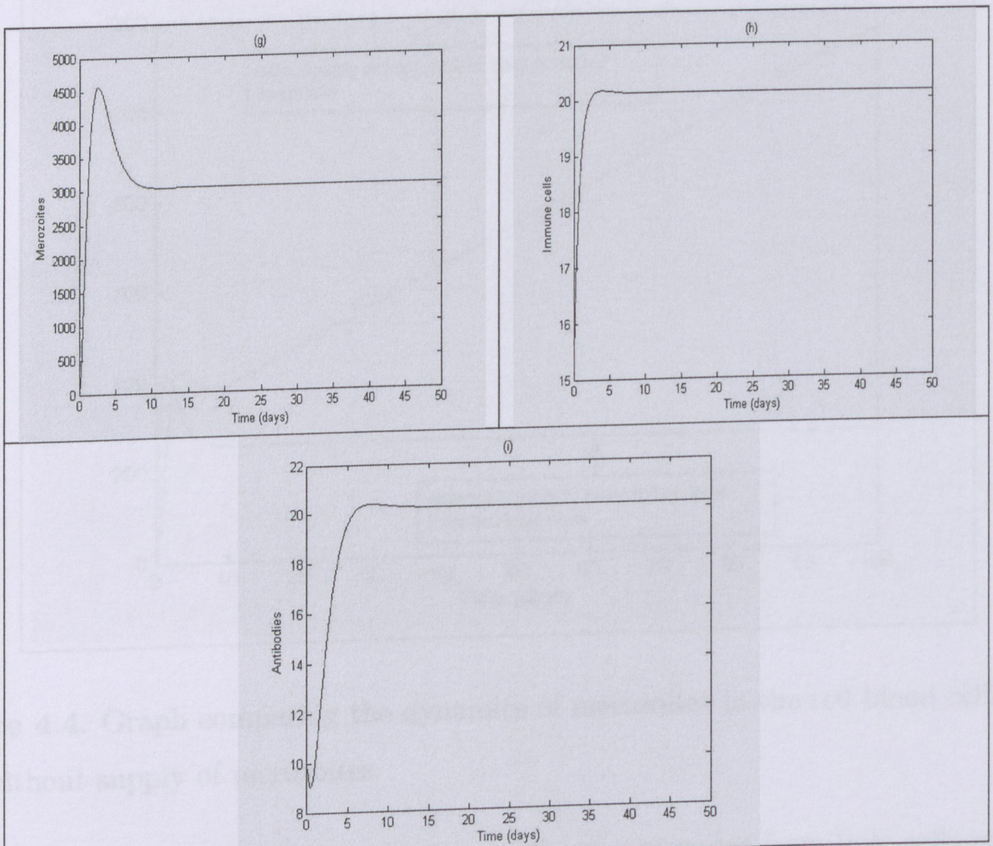


Figure 4.3: Graphs showing the behaviour of the (g) merozoites parasites with (h) immune response and (i) antibodies cells response using parameters in Table 4.2.

4.8.1. Comparison of merozoites supply with and without sporozoites

To illustrate numerically the dynamics of merozoites in the red blood cells with supply and without supply of merozoites from liver cells, we consider the work done by Chiyaka (2007) in her Ph.D thesis which has been restated as model (4.4) and our model system (4.7) – (4.15).

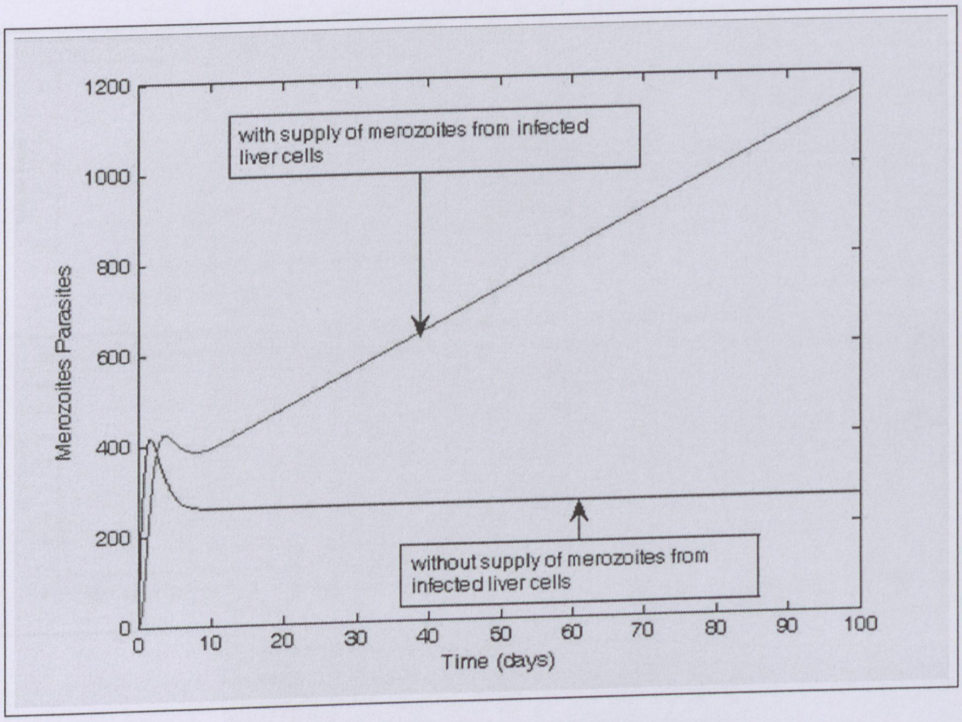


Figure 4.4. Graph comparing the dynamics of merozoites in the red blood cells with and without supply of merozoites.

Figure 4.4 shows that the curve with supply of merozoites from liver cells initially increases but after 5-7 days it reaches a steady state while the curve without supply of sporozoites initially increases but after 5-8 days reached steady state which is lower than the curve with supply of sporozoites from liver cells.

We show that the sporozoites parasites in the liver cells increase which the merozoites parasites in the red blood cells which complicate the control of malaria disease. Now we consider the reduction of the number of sporozoites in the liver cells by increasing rate of θ_p which the rate cytotoxic T cells destroy the sporozoites in the liver cells $L(t)$. By destroying sporozoites in the liver cells, we expect the number of infected liver cells and infected red blood cells to increase as the sporozoites are reduced.

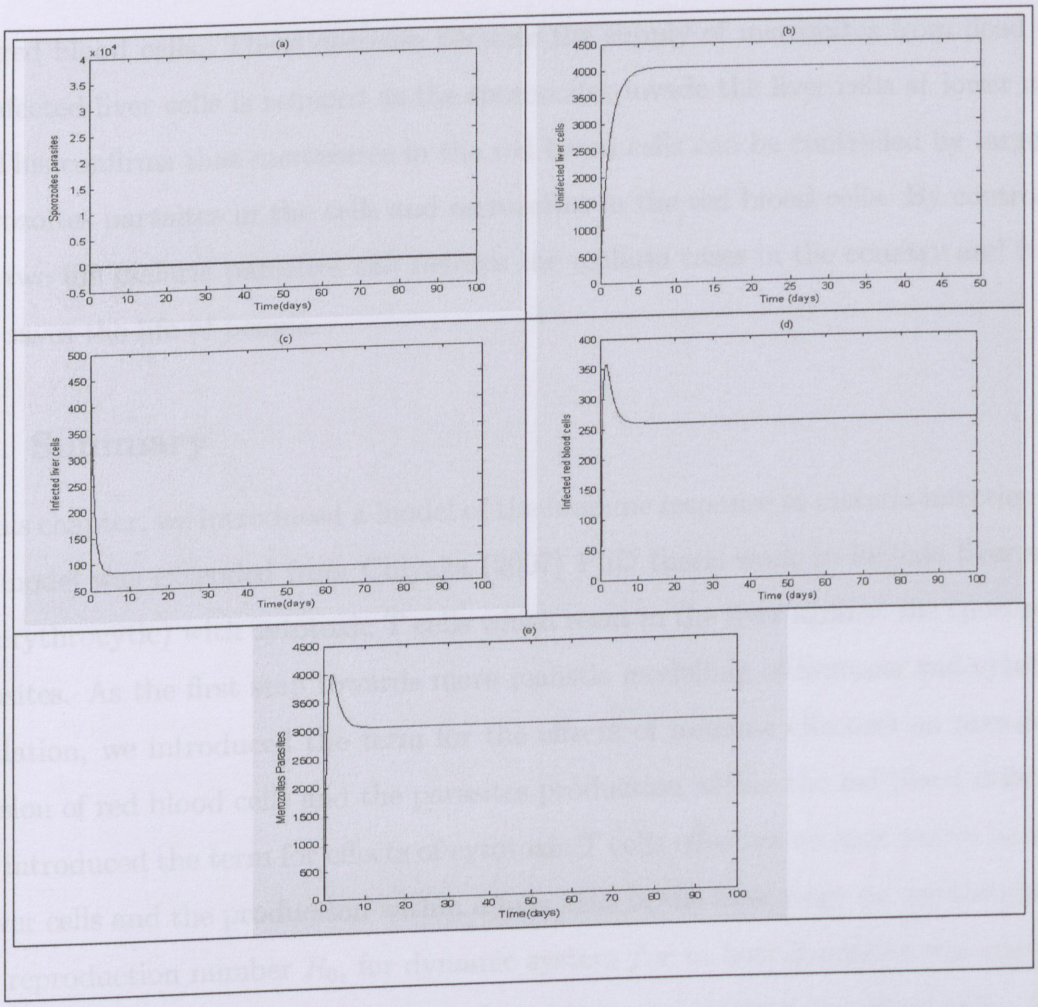


Figure 4.5: Graphs showing the dynamics of (a) sporozoites $P(t)$, (b) uninfected liver cells $L(t)$, (c) infected liver cells $L^*(t)$, (d) infected red blood cells $B^*(t)$ and merozoites parasites $M(t)$ when the number of sporozoites parasites are reduced by increasing the death rate.

Figure 4.5 shows that the number of merozoites decreases due to reduction in the number of sporozoites by increasing the strength of cytotoxic cell which kill the sporozoites in the liver cells. Figure 4.4 (b) shows the dynamic of uninfected liver cells $L(t)$. These increase when compared to figure 4.2(b) caused by reducing the number of parasites in the liver cells. Figure 4.4 (c) and (d) give the dynamics of infected liver cells and red blood cells. Both of them are decrease due to the high death rate of sporozoites parasites in the liver cells. Figure 4.5 (e), give the dynamics of merozoites parasite in the red blood cells. These decrease because the supply of merozoites from dead cells of infected liver cells is reduced as the sporozoites invade the liver cells at lower rate.

This confirms that merozoites in the red blood cells can be controlled by targeting sporozoites parasites in the cells and merozoites in the red blood cells. By controlling this two life malaria parasites can reduces the malaria cases in the country and it will also saves the life of people.

4.9. Summary

In this chapter, we introduced a model of the immune response to malaria infection and the model was extended from Chiyaka (2007) PhD thesis work to include liver stage (ex-erythrocytic) with cytotoxic T cells which react in the liver against the sporozoites parasites. As the first step towards more realistic modelling of immune and cytotoxic regulation, we introduced the term for the effects of immune effectors on merozoites invasion of red blood cells and the parasites production within the red blood cells. We also introduced the term for effects of cytotoxic T cells effectors on sporozoites invasion of liver cells and the production within a liver cells in the liver stage (ex-erythrocytes). The reproduction number R_0, for dynamic system for in host dynamics was analysed by looking at infector compartments infected liver and infected red blood cells. Even though the R_0 expression does not contain parasites terms, it consists of cytotoxic T cells and life span of uninfected red blood cells. Where the rate of infection is reduced by immune system and cytotoxic T cells.

Our results show that without any treatment the only effective way of the cytotoxic T cells response in its mission to clear parasites is its ability to inhibit parasites growth in ex-erythrocytes and also immune response to inhibit merozoites parasites growth in erythrocytic. It is also more effective to increase death rate of infected liver cells than death rate of sporozoites by cytotoxic T cells and also of infected red blood cells than death rate of merozoites by immune cells, as the results that were also obtained elsewhere (Anderson *et al.*, 1989). This is because one infected red blood cells is capable of producing sixteen merozoites, so killing it will prevent the survival of the sixteen merozoites.

Our results show that malaria disease in human body can be controlled by reducing the number of sporozoite parasites in the liver cells and merozoite parasites in the red blood cells. As sporozoites invade liver cells to release merozoites into red blood cells, infected red blood cells produce more merozoites which makes disease more difficult to control.

Most of the available malaria drugs act by retarding development of merozoites parasites only. But the liver will keep on depositing merozoites cells into red blood cells. Drugs that kill sporozoites directly together with those that retard the development of merozoites parasites should also be made available to make the treatment more effective.

Our model also suggests that if there are mechanisms in the body that increase the death rate of cytotoxic T cells and immune cells, then there will be an increase in the severity of the infection. This shows that for a person infected by pathogens that kill the $CD4^+$ T cells (Shiri *et al.*, 2005) or mycobacterium tuberculosis which kills the macrophages, If infected by Plasmodium falciparum parasites, the immune system is compromised and the person suffers severe malaria if not treated in time. People who suffer from disease such as acquired immunodeficiency syndrome or tuberculosis should be advised to seek early treatment when symptoms of malaria start to appear.

Our mathematical analysis is useful in explaining some of the observed patterns during a malaria infection. This gives our model the ability to provide a basic representation of the complex web that accompanies an intruding malaria parasites during the erythrocytic and ex-erythrocytic stages.

For people moving to endemic areas, prophylactic drugs should be taken a week before departure so that an adequate concentration is attained in the blood before exposure to parasites and continued a month after return to kill any parasites incubating in the liver can emerge.

The complexity of the parasites, the difference forms it assumes in the body and possibility of the patient being infected by several stains concurrently make model predictions more difficult.

Sporozoites are a target for vaccine development but are able to replace their coats, varying the antigens they present.

One function of modelling is to point out where further quantitative measurements can improve our understanding of the malaria disease process.

Chapter 5

Conclusion

5.1. Introduction

We have developed and analysed mathematical models of malaria infectious and transmission. The point of interest was to suggest mathematically how Anopheles mosquitoes can be controlled in the environment given a vaccine for malaria is not available. This idea was developed by Macdonald (1957) who suggested that malaria disease can be controlled internsively by reducing the number of mosquitoes. This work sought to develop a mathematical models involving transgenic male mosquitoes by considering the mating of male modified and wild mosquitoes. We also developed a mathematical model for the dynamics of malaria vector population, considering immature and adult mosquitoes in order to include the effect of intervention methods that target the breeding sites of mosquitoes. We have attempted to know how malaria parasites get into human host body, thus we ended up developing a new intra-host model of malaria infection. These models were then qualitatively analysed for the existence of equilibria and stability associated with these states through the use of extensive mathematical techniques. In addition to allowing the determination of various epidemiological thresholds (such as the reproductive numbers), analyses enable us to gain deeper insight into the stability and persistence of the various models. Comprehensive numerical techniques were employed to verify analytic results and illustrate possible behaviour of the models.

5.2. Summary and concluding remarks

A transgenic mathematical model of malaria that describes the interaction of wild and modified mosquitoes was proposed in Chapter 2. The model was developed by considering the mating of modified and wild mosquitoes. The modified mosquitoes was loaded with gene that integrate the malaria resistant directly into the mosquito DNA. The gene makes it impossible for those mosquitoes to transmit the parasites that cause malaria. Local stability of the disease free equilibrium were investigated. Conditions for existence and uniqueness of the endemic equilibrium were derived. A transgenic mathematical model reproductive number R_0 was identified. Where R_0 expression shows that the human infection is reduced by natural death of mosquitoes and also mosquitoes infection reduced by death of infected human host.

We also concluded that wild mosquitoes vacate the environment when the number of modified mosquitoes increases whereas the infection number of human host is going down. This was shown by numerical analyses where the female not modified mosquito graph increase for short period of time then decreases. This shows that wild mosquitoes were giving the modified mosquitoes room which was seen as the alternative way of reducing malaria by reducing the vector that are responsible for transmitting the disease in the community.

In Chapter 3, we presented and analysed a mathematical model for the dynamic of malaria vector population. Where the immatured mosquitoes are divided into three subpopulations, eggs, larval, pupal and the mature mosquitoes (adult) are divided into susceptible and infected mosquitoes. The adult mosquitoes interact with human host in the process of sucking blood from human host for eggs. The mathematical properties of the model were explored. Analysis of the reproductive number showed that the infection for both human host and mosquito vector are reduced by natural death for these two populations. The result shows that the model has a disease free equilibrium which is locally asymptotically stable whenever the reproductive number which is less than unity and endemic equilibrium if the reproductive number exceeds unity. From the formula of R_0, we have shown that if more and more humans become infectious the transmission of infection to mosquitoes increases and subsequently, the value of R_0 increases and it become more difficult to control the infection in a population. If however the immatured mosquitoes become adult, the number of anopheles mosquito increases and the infection to humans increases which subsequently means the number of immatured mosquitoes increases through birth.

In chapter 4, we presented and analysed a modelling host-pathogen interaction of malaria within a host infection which was done by considering sporozoites parasites in the liver cells and merozoites parasites in the red blood cells interacting with the immune system. The liver cell population was divided into uninfected liver cells, infected liver cells and cytotoxic T cells which react in the liver cells against the sporozoites parasites after being injected by infected *anopheles mosquito.* The red blood cells population was divided into three subpopulation namely uninfected, infected and merozoites cells with immune effectors and antibodies. The stability analysis of the disease free equilibrium state was carried out, where the stable disease free equilibrium coexist with a stable endemic equilibrium when the reproductive number is less than unity. We deduced that the model was persistent for values of the reproductive number greater than unity. The model was numerically analysed to assess the effect of the dynamics of the red blood and liver cells. We also concluded that the effect decreases the population of liver and red blood cells. The model showed that the parasites population decreases as the immune population increases. This gives the hope that malaria can be controlled by targeting sporozoites in the liver cells and merozoites in the red blood cells, if this is applied, infection can be eradicated within host. The study revealed that sporozoite parasites which infect liver cells increases the number of merozoites in the red blood cells, and subsequently these make it difficult for the disease to be controlled. Because most drugs are developed against the merozoites parasites while infected liver cells keep on supplying merozoites in the red blood cells.

While the health and welfare department are busy controlling adult mosquitoes, the immature mosquitoes are free developing to be adult mosquitoes.

Our results showed in Figure 3.2 that when the mosquito population increases the infection rate also increases. An increase in the number of immatured mosquitoes means adult mosquitoes also increase the Anopheles species which makes it for vector to interact with people because they will be found everywhere.

According to the results of this study, it is strongly recommended that the more the mosquitoes the more cases of malaria infection. To rescue the life of community, we might fight malaria by reducing the number of mosquito from breeding sites by destroying their eggs, using recommended chemicals for protection, using mosquito net in our house windows and also by using insecticides to control the adult mosquitoes.

In summary, the results obtained from the development and analysis of mathematical models are as follow:

(*a*) In a new intra-host model of malaria infection, we find that mechanisms that increase the death rate of immune cells in the body increases the severity of infection and drugs based on inhibiting parasite production are more effective than that those based on merozoites invasion of erythrocytes. The liver cells which are infected by sporozoites parasites always keep on releasing merozoites in the red blood cells.

(*b*) From the transgenic model we have seen that when the transgenic mosquitoes increase in the environment the wild (natural) mosquitoes get replaced in the environment which leads to new species of mosquitoes which do not transmit malaria disease.

(*c*) A mathematical model for the dynamics of malaria vector population proved that when more immatured mosquitoes become adult mosquito, the rate of infection increases and the malaria disease continues to infect disproportionately children and pregnant women.

Understanding of the invasion mechanisms of plasmodium is essential to develop effective strategies against malaria. Interfering with plasmodium induced suppression may lead to the establishment of effective protective immunity against the liver stage, opening new possibilities of treatment and prevention.

Blood stage induced immuno suppression should also be considered for vaccine design, as it reinforces the necessity of vaccinating against both liver and blood stages.

All proposed mathematical models in this thesis can be used as weapons of fighting the malaria disease. These have not yet fully employed in any development policy of malaria control.

Our mission and aim as stated in Chapter 1 is to develop mathematical models that can be used to inform policy about the frame work for control and implementation of successful malaria the control programmes in South Africa.

5.3. Future research direction

The results of this thesis leave room for possible future work. We propose the following future research directions.

(*a*) Studies have analysed the impact of the different levels of immune protection in preventing and controlling malaria using some published literature and reasonable parameter estimates. The knowledge gained from the theoretical study represents a basis for the implementation of practical projects, is based on fightings of this work for both endemic and non endemic areas.

(*b*) In the thesis, we have grouped all transgenic mosquitoes into a single population without distinguishing their zygosity. To have more complete understanding of the impact of implementing the new techniques and more accurate predictions of gene or genotype distributions or structure in all generations of the interacting mosquito populations, we open the line of research to formulate and investigate more realistic heterogeneous models with wild, homozygous and heterozygous transgenic mosquitoes.

(*c*) Studies showed that transgenic mosquitoes cannot transmit malaria in the model. But the mathematical model presented in this study do not include any factors effect modified mosquitoes. Some biological details are sacrificed in order to make a model mathematically tractable. Nevertheless, based on observations, one important point to consider is the immigration of females that have already had fertile matings and will lay fertile eggs nullifying the effect of male mosquito modification, which is left for a future work. Clarification of the role of immigrants in a population is important not only for the (sterile insect release method)SIT, but also for assessing whether local effort at larval control sites with insecticides together with environmental management could have impact on the adult population or whether they are likely to be swamped by immigration.

(*d*) Studies have shown that HIV/AIDS coinfection with malaria has its impact on disease presentation, with increased risk of complicated malaria and death. An important extension of this work would be to consider the coinfection of malaria and HIV/AIDS or Turberculosis and the effects of treatment and drug interaction.

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