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HYBRID MULTI-SCALE MATHEMATICAL MODELLING OF MALARIA INFECTION TRANSMISSION

By

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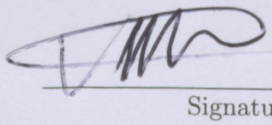

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I dedicate this work to my mother and my Grandmother

without them this work would not exist

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Abstract

Malaria is a life-threatening disease caused by a protozoan parasite called plasmodium, which lives part of its life in the humans and part in Anopheles mosquito. The development of malaria parasite in a human host commence in the liver cells where the malaria parasites undergo asexual multiplication to produce merozoites that are eventually released into the blood stream to invade red blood cells. The infected red blood cells burst after 2-3 days to release merozoites and gametocytes into the blood stream. This is associated with the clinical symptoms of the disease. Anopheles mosquito become infected when they feed and ingest human blood that contains mature gametocytes. The gametocytes develop into male and female gametes that fertilize to become zygotes in the mid-gut wall of the mosquito.

We model malaria using non-linear differential equations. We analyse the existence and stability of steady state solution, existence of equilibrium point without disease, local stability of disease free equilibrium, existence of endemic equilibrium state, local stability of endemic equilibrium, global stability of the disease free equilibrium. The key to our model analysis is to calculate the reproduction number.
We also perform the sensitive analysis using the reproduction number R_0 with respect to the parameter. This sensitive analysis allow us to compare the effectiveness of different control strategies.

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Chapter 1

Introduction

1.1 Background

Malaria is one of the most fatal diseases in the word and continuous to be one of the leading causes of mortality and morbidity in the world especially in sub-sahara Africa. According to the latest global estimation release in 2010, there were about 219 million cases of malaria reported and estimated death was about 1.24 million [58, 63]. The most vulnerable group is children less than five years old and pregnant women, with at least one child dying every minute from malaria in Africa [43, 63]. Though substantial gains have been made in reducing malaria transmission, the death toll from this disease still remains unacceptably high, and as such there is a renewed effort to reduce the disease burden further and move towards malaria eradication [4].

This disease are transmitted from mosquito vectors to human host. The disease is caused by a *protozoan* parasite called *plasmodium*(P), which lives part of its life in human and part in *Anopheles mosquito*. The development of malaria parasite in human commence in the liver cells where the malaria parasites undergo asexual multiplication to produce *merozoite* that are eventually released into the blood stream to

invade red blood cells. The infected red blood cells burst after $2-3$ days to release merozoite and gametocytes into the blood stream. This is associated with the clinical symptoms of the disease [15]. Anopheles mosquito become infected when they feed and ingest human blood that contains mature gametocytes [33, 51]. The gametocytes develop into male and female gametes that fertilize to become zygotes in the mid-gut wall of the mosquito. The zygote elongates to become ookinete and penetrates the mid-gut epithelium that later develops and ultimately produces sporozoite which become infective when they migrate to the salivary gland Tumwiine et al. [78]. The disease is endemic in tropical and subtropical regions, including Africa, Asia, Latin America, the Middle East and some part of Europe. There are more than 100 different species of plasmodium parasites, but only four species of parasite can cause infections in humans, namely *plasmodium falciparum*, *plasmodium vivax*, *plasmodium malariae* and *plasmodium ovale* (understanding malaria, Fighting an Ancient Scourge, February 2007, www.niaid.nih.gov). Most serious and fatal infections are caused by P.falcipurum and P.vivax.

Various control measures have been made to control this disease. These include chemotherapy, development of malaria vaccines and vector-population control. The use of artemisinin-based combination therapy (ACT) is advocated in treatment of clinical cases, but this approach is threatened by recent discovery emergence of resistant strains of the plasmodium parasite to artemisinin [60, 64]. The efforts have been made to the development of a malaria vaccine, which is viewed as a potent tool to reduce and eventually eliminate malaria. However, the development of an effective vaccine has been hampered by the complexity of the parasite and its life cycle

extensive antigenic variation and poor understanding of the interaction between plasmodium falciparum and the human immune system [25, 35, 37, 60, 61, 71] Some of the vector control tools that have been used widely with considerable success include long-lasting insecticide-treated nets (LLINs) and indoor residual sprays (IRs) [65, 66]. However, the future of vector control based on the use of LLINs or spring insecticides indoors is uncertain and is worsened by shortage of funds, poor bed-net coverage in some communities, as well as the development of insecticide-resistant mosquito [32, 34]. Outdoor biting among populations of An.gambinae is particularly of a serious concern, as they are not susceptible to current indoor control tools and are thus responsible for sustained malaria transmission [1]. This has prompted the need for new and more environmentally robust methods that can supplement the existing vector methods. New scientific knowledge about the ecology and behavior of mosquitoes and their natural predators and pathogens may lead to the development of new tools that can be incorporated into integrated vector management (IVM) programs.

In this dissertation, we model the average number of humans that are infected by gametocytes in the community and average number of mosquito vectors that are infected by the sporozoites.

1.2 The life-cycle of malaria

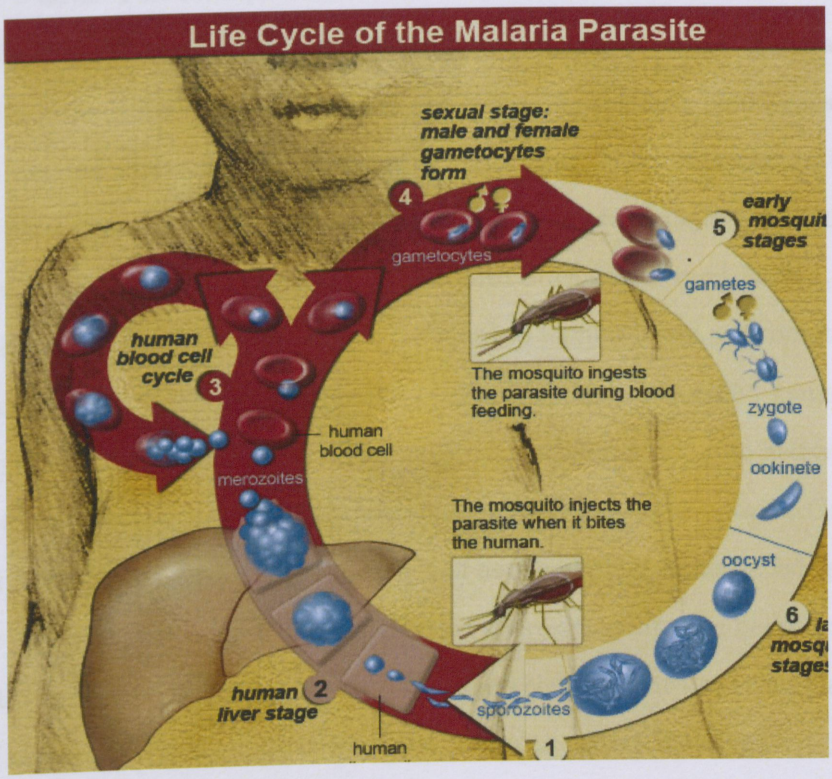

Figure 1.1: The life-cycle of malaria parasite (National Institute of Allergy and Infectious Diseases)

A female Anopheles mosquito carrying malaria-causing parasites feeds on a human blood and injects the parasites in the form of sporozoite into the bloodstream. The sporozoites travel to the liver and invade liver cells. Over $5-16$ days, the sporozoites grow, divide, and produce tens of thousands of haploid forms, called merozoites, per liver cell. Some malaria parasite species remain dormant for extended periods in the liver, causing relapses weeks or months later. The merozoites exit the liver cells and re-enter the bloodstream, beginning a cycle of invasion of red blood cells, asexual

replication, and release of newly formed merozoites from the red blood cells repeatedly over $1-3$ days. This multiplication can result in thousands of parasite-infected cells in the host bloodstream, leading to illness and complications of malaria that can last for months if not treated. Some of the merozoite-infected blood cells leave the cycle of asexual multiplication. Instead of replicating, the merozoites in these cells develop into sexual forms of the parasite, called male and female gametocytes, that circulate in the bloodstream. When a mosquito bites an infected human, it ingests the gametocytes. In the mosquito gut, the infected human blood cells burst, releasing the gametocytes, which develop further into mature sex cells called gametes. Male and female gametes fuse to form diploid zygotes, which develop into actively moving ookinete that burrow into the mosquito midgut wall and form oocyst. Growth and division of each oocyst produces thousands of active haploid forms called sporozoites. After $8-15$ days, the oocyst bursts, releasing sporozoites into the body cavity of the mosquito, from which they travel to and invade the mosquito salivary glands. The cycle of human infection re-starts when the mosquito takes a blood meal, injecting the sporozoites from its salivary glands into the human bloodstream [National Institution of Allergy and Infectious Diseases] .

1.3 Overview of the problem

Malaria is a serious health problem in South Africa and is responsible for up to 40 percent of daily out patient consultations at hospitals and clinics, and is responsible for 23 percent of deaths in children under five years of age [13] which means there is more work to be done if the country wants to achieve the goals set by RBM Initiative [14]. The disease also affects the majority of the labour force members especially the

poor and as a result, the cost of treatment is indirectly transferred to the government, because they cannot afford it. So apart from the health consequences; malaria puts a heavy burden on productivity and hence economic development. Although, a lot of Malaria Control programs are going on in the country, the disease seems to be still raging on. Hence, it is time we introduced mathematical models in the fight against malaria in the country and that is the goal of this dissertation. It has become necessary for the decision makers in Malaria Control programs to understand the main parameters in the transmission of the disease in order to be able to develop effective solution strategies for its prevention and control. We intend to use existing malaria data from South Africa Health Service to develop a mathematical model to understand the disease dynamics in South Africa and assist decision makers to formulate the best ideas to prevent, control and eradicate the disease. In this project, we intend constituting a model based on non-linear ODEs that describe the process of the spread of the disease, based on epidemiological compartment modelling.

1.3.1 Objectives

The objectives of this dissertation are as follows

- To develop a mathematical model to gain insight of malaria transmission from Anopheles mosquito vectors to human hosts, in South Africa.
- To test the model stability.
- To perform numerical simulations corresponding to various possible scenarios.
- To administer the transmission of gametocytes in human community.

1.3.2 Methodology

We intend to use differential equations to model the dynamics of the spread of malaria where humans and mosquito interact and infect each other. The model will take into account the important intervention strategies we have in the country such as clinical treatment and the death of the female Anopheles mosquito which is caused by natural death rate, indoor residual spraying (IRS) and insecticide for human population. The simulations will be conducted using python.

1.3.3 Organization of the dissertation

This dissertation is made up of 5 chapters. The first chapter introduces the topic of the study. It contains the background to the study, overview of the problem and objectives. Chapter two present modelling background of this work (work done by other researchers in mathematical modelling of malaria and the methods applied). The third chapter provides the method the researchers follow in modelling the problem. That is formulation of the model, analysis of the model, simulation and discussion of the results. In chapter four we extend the model of chapter three by putting the life-cycle of mosquito vector. Finally, chapter five provides conclusion of both models in chapter three and chapter four and the findings of the study. It also gives recommendation for further research.

Chapter 2

Modelling background

2.1 Introduction

In this dissertation, we present a new modelling framework for malaria transmission dynamics. Modelling framework is based on formulating equations which describe changes in community pathogen load at the infective stages of the pathogen, a new public health measure which is an aggregate biomarker of a community pathogen burden over a specific time period. In this case, the infective stages for malaria are the gametocytes and the sporozoites. The overall outcome of this modelling framework is a predictive multi-scale model which can be used as a model-based pathogen surveillance tool. Currently model-based pathogen surveillance is not feasible because existing single scale models for population surveillance of infectious disease systems based on compartmentalizing hosts into susceptible, exposed, infected, recovered (SEIR), and variations of this paradigm (e.g. SI, SIS, SIR etc.) which are either age-structured or sex structured do not explicitly incorporate a measure of pathogen load except in limited cases. The concept of community pathogen has its origins in the modelling of environmentally transmitted infectious disease systems.

Environmentally transmitted infectious disease systems are those disease which are transmitted through contact with a contaminated environment (water, soil, food, air, objects and some contact surfaces) which is contaminated with infectious pathogen (virus, bacteria, protozoan, fungi or prion). Modelling such infections involves modelling explicitly the dynamics of the pathogen population in the environment. The term community pathogen load was first introduced in mathematical epidemiology literature by Garira (2016) in the context of modelling directly transmitted infectious disease systems. The concept is based on the assumption that the risk of transmission of an infectious disease system is related to pathogen load in the community. The community pathogen load variable is then determined by up-scaling individual infectiousness (since each infected individual in the community is a reservoir of infectious pathogen) to average population infectiousness. This average population infectiousness in a particular community can then be used to determine the probability that a random physical contact (through ordinary contact, or sexual activity or contact through a bite) with an infected host (human, animal or vector) in a particular community will infect the host (human, animal or vector) in that community. The concept of community pathogen load therefore uses the idea of community pathogen pool as a population level metric of disease transmission. In this chapter, we illustrate the utility of using the idea of community pathogen load in modelling the transmission of directly transmitted infectious disease systems using African trypnosomiasis transmission [38]. We also review some of the work done on the malaria disease. A good number of researchers have invested their skills in understanding the dynamics of malaria transmission and control.

2.2 Malaria models

The first attempt of mathematical modelling was begun in 1911 by Ross [70], who was the first person to model the dynamics of malaria transmission. His work was extended by MacDonald in (1957), in a study called Ross-MacDonald work [61]. The model of Ross-MacDonald involved an interaction between infected human host and the infected mosquito vector. The model consisted of two non-linear differential equations with one variable representing humans and other variable representing mosquitos. The model of Ross-MacDonald was made up of two populations, that is human host and mosquitoes vector given by a system of differential equations:

$$\begin{cases} \frac{dx}{dt} = \frac{abM}{N} y(1-x) - rx, \\ \\ \frac{dy}{dt} = ax(1-y) - \mu y, \end{cases} \tag{2.2.1}$$

where x is the proportion of infected humans and y is the proportion of infected female anopheles mosquitoes. The number of bites of humans by a single mosquito per day is a, r is the recovery rate of humans, b is the probability of transmission of infection by an infected mosquito to a susceptible person per bite and μ is the mosquito death rate. N is the total size of human population and M is the total size of the mosquito population.

More work was done by Aron and May as cited by Chitnis [8] who described the properties of the model including the determination of the basic reproduction, number R_0 as

$$R_0 = \frac{Ma^2b}{N\mu r} \tag{2.2.2}$$

The basic reproduction number is a product of the number of humans that one infectious mosquito infects throughout its infectious period and the number of mosquitoes that one infectious human infects throughout his infectious period [8]. This was used as a measure of the transmission of prevalence or incidence of the diseases. From this work, they came to concrete conclusion that in order to counteract malaria anywhere, we need to reduce the number of infections up to below a certain value (reproduction) [29, 40]

Since the work of Ross-MacDonald, there has been various modifications, improvements and advancements in mathematical modeling of transmission of malaria. Additional work of mathematical modelling proposed by Dietz in(1993) which acquired immunity [29, 69]. The extension of this work conducted by Aron and Bailey [7] which also have the immunity. Anderson and may considered the effect of age structure on the basic Ross-MacDonald model [5]. Koella [1991] reviewed some work on the use of mathematical models of malaria transmission [55] and Nedelman[1989] have written some good previous on the mathematical modelling of spreading of malaria.

The model for Ngwa and Shu (2000) allows humans immune system to be temporarily to the disease, while still transmitting malaria to mosquito vectors. Chitnis (2008) in his PhD thesis developed a compartment model for malaria transmission based on a model of Ngwa and Shu. He defined a reproduction number R_0 for the expected number of secondary cases that one infected individual would cause during the infection period and showed the existence and stability of disease free equilibrium points and endemic equilibrium point [23]. He computed the sensitivity indices for R_0 and the parameters in the model. Chitnis et al (2006) presented a similar bifurcation analysis of an extension to the model in chitnis (2006) defining R_0 and

showing the existence and stability[21]. Abadi Abay Gebremeskel (2015) developed a mathematical modelling of endemic malaria transmission by giving an insight into the intersection between the host and vector population. Numerous other papers are devoted to the calculation of R_0 for different models of various diseases, including malaria [28, 30, 46, 47, 48, 57, 68, 72, 79] Furthermore, programmes that integrate vector eradication, drug treatment and personal protection were more likely to succeed than the use of only one intervention. They noted that temporary interventions could be the ones that lead to temporary reduction in prevalence of the disease. The model also predicted that when the basic reproductive number become very large, then virtually everyone in the population would be infected and no one is susceptible [26].

Anderson and May also studied the effect of adding age to the basic Ross-MacDonald model. Finally, they looked at different control strategies, discussing the effect of a vaccine and the reduction of transmission rates on the malaria infection. Other reviews on mathematical modelling in malaria include Nedelman [15] and Koella [56]. Nedelman surveyed various data sets to statistically approximate parameters such as inoculation rates, rates of recovery and loss of immunity in the humans, human-biting rates of mosquitoes and infectivity and susceptibility of humans and mosquito. Koella also began with the Ross-Macdonald model which includes latent stage for the mosquito. He then studied the effect of variability of the parameters and added an infection-rate dependent period of immunity. Using this model with immunity, he studied the effects of vaccines, comparing those that act on asexual blood stages and those that block transmission, to show that the asexual blood stage vaccines are more effective. An important advance for the mathematical modelling of malaria was

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the inclusion of acquired immunity in the model proposed by Dietz, Molineaux and Thomas in 1974 [16]. Dietz et al. proposed a model with two different classes of humans: one without immunity to malaria and one class with some immunity. As the nonimmunity class falls sick, some people recover with immunity. The immune class can get infected, but does not fall clinically ill and cannot be infectious. The model by Dietz et al. Also included superinfection, a phenomenon usually associated with macro-parasites. As also described by Aron and May [17] and Anderson and May [22], superinfection is a significant increase of the parasite load, when an infected person is reinfected from the outside. This is usually modelled by making the recovery rate function of the inoculation rate. Another recent model has included the speed of drug-resistant plasmodium and of the evolution of immunity. Koella and Antia [56] discussed a model where, starting with the Ross-MacDonald model (1.1) and moving to more complicated models, they included a strain of disease that is resistance to treatment. Their results show that in their simple models, there is a threshold value of fraction of infectious humans treated, below which there is no resistance to drugs, and above which, resistance treatment spreads. In the more complicated models, this kind of resistance is usually not fixed, but there is a level of sensitivity to a drug that is maintained in the population. Koell and Bo te [studied a host-parasite evolution model of malaria where the host invests in its immune system over time and the parasite invests in its ability to evade the hosts immune response. In a second paper [76], Ngwa rewrote the reproduction number in terms of the original (with dimension) parameters. He also included a small disease induced death rate, using perturbation analysis to evaluate a first order approximation to the endemic equilibrium with disease induced death. Finally, he conducted some numerical simulations on a stochastic

expansion of the model. This profusion of model has been driven by the need to understand different aspects of the complexity of malaria epidemiology. Some of the important factors that we include are the presence of an exposed state in mosquito populations, including human immigration and disease-induce death. The model for malaria transmission that we analyse, is the extension of the equations introduced by Ngwa and Shu [45]. In the Ngwa and Shu model, humans follow an -like pattern and mosquitoes follow a pattern similar to that described by Yang but with only one immune class for humans [81]. Humans move from the susceptible to the exposed class at some probability when they come into contact with an infectious mosquito, and then to the infected class, as in conventional models. However, infectious people can then recover with, or without, a gain in immunity, or move to the recovered class. A new feature of this model is that although individuals in the recovered class are assumed to be immune, in the sense that they do not suffer from serious illnesses and do not contract clinical malaria, they still have low levels of plasmodium in their blood stream and can pass the infection to susceptible mosquitoes. After some period of time, these recovered individuals return to the susceptible class. Susceptible mosquitoes get infected and move to the exposed class, at some probability when they come into contact with either infectious humans or recovered humans (albeit at a much lower probability). They then pass on to the infection class. Both humans and mosquitoes leave the population through a density dependent natural death rate. This allows the model to account for changing human and mosquito populations. Variations in mosquito population models do not account for this. The model also includes human disease-induced death as mortality for malaria in areas of high transmission can be high, especially in infants. Ngwa and Shu [45] analysed this model

assuming a linear per capita death rate. They converted the system to dimensionless quantities and in these new variables, define a reproduction number. They showed that there exists an endemic equilibrium state (non-negative solution distinct from the diseases-free equilibrium), with no disease-induced death which is unique. Using linear analysis, they also showed that the disease-free equilibrium is locally asymptotically stable when the unique endemic equilibrium (for no diseases-induced death) is locally asymptotically stable. They concluded by using numerical simulations to support their proposition that the endemic equilibrium is stable for . In a second Papers, Ngwa rewrite the reproduction numbers in terms of the original (with dimension) parameters. He also includes a small disease induced death rate, using perturbation analysis to evaluate a first order approximation to the endemic equilibrium with disease induced death. Finally, he conducts some numerical simulations on a stochastic expansion of the model. This profusion of models has been driven by the need to understand different aspects of the complex malaria epidemiology. In our model we analyse, we aim to capture some of the more important aspects of this epidemiology while still keeping it mathematically tractable. Some of the important factors that we include are the presence of an exposed state in mosquitoes and dynamically changing human and mosquito populations, including human immigration and disease-induce death.

In 1766, Bernoulli modelled the effects of smallpox variolation (a precursor of vaccination) on life expectancy [11]. In the beginning of that century, there was much discussion about why an epidemic ended before all susceptible were infected with hypotheses about changing virulence of the pathogen during the epidemic. Kermack and McKerndrick described the dynamics of diseases transmission in terms of a system

of a system of differential equations [52, 53]. They were the first to use the so-called basic reproduction number, a threshold that determine if a disease dies out or spreads in a susceptible population. Literature review in [50, 54] show the raping growth of epidemiology modelling towards the end of the twentieth century as mathematical modeling became more popular to aid in public health policy making.

Many mathematical models describing the dynamics of Acquired immunodeficiency syndrome (AIDS) pandemic have been used to predict the course of the epidemic and identifying the most effective prevention strategies. The need for evaluating intervention strategies for newly emerging and re-emerging pathogen has revealed real impact of mathematical modeling on public health.

Some of the studied models have been classified as deterministic and stochastic. The deterministic models are transmission models which use continuous analogy of the disease by using ordinary differential equations to described the process, whereas stochastic models use statistical mechanism to describe the transmission of infection between two individuals. Rigorous mathematical analyses of the processes contribute to the understanding of disease transmission in much detail. Therefore, developing a mathematical model helps to address the essential processes involved in studying the epidemiology of an infectious disease and reveals the parameters that are most important and crucial for control and data collection mechanism.
Mathematical modeling is integrative in nature since it combines knowledge from from various disciplines like microbiology, social sciences and clinical science.

Chapter 3

A new basic multi-scale model of malaria infection

3.1 Introduction

Malaria is one of the most dangerous human infections caused by one of the four protozoan parasites of the genus *plasmodium*. There are four species that cause human malaria: *P. falciparum*, *P. vivax*, *P. malaries* and *P. ovale*. Most serious and fatal complication are caused by *P. falcipurum* and *P. vivax*. The disease is endemic in tropical and subtropical regions, including Africa, Asia, Latin America, Middle East and some parts of Europe. Each year, $2-3$ million children and pregnant women die from plasmodium falcipurum malaria and up to 500 million people throughout the word suffer from malaria clinical disease (Engers and Godal, 1998). Unlike other acute diseases for which people develop life-long resistance to reinfection, malaria only elicits partial immunity after several years of continuous exposure during which time recurring infections and illnesses occur which could be fatal especially to children and pregnant women. Malaria is transmitted to human host by the female anopheles

mosquitoes. According to Aron and May (1982), the biology of four species of plasmodium is generally the same and consists of two distinct phases called sexual and asexual stages. The asexual phase consists of *sporozoites* and sexual phase consists of gametocytes. When infectious female anopheles mosquito bite human beings they inject sporozoites and when infected anopheles mosquito bite infected humans they take the gametocytes. The sporozoites enter the liver through blood vessels.

This form of gametocytes in the liver goes asexual division and approximately 48 hours depending on species, the infected erythrocytes ruptures releasing about $8 - 32$ merozoites (Hellriegel 1992) which invade other erythrocytes (erythrocytic cycle). This process is responsible for the clinical symptoms of the disease. The erythrocytes cycle usually continues until controlled by the immune system response or chemotherapy or until the patient dies. Some merozoites disintegrate into sexual forms of the parasites called gametocytes (microgamete and macrogamete). Gametocytes are transmitted to a mosquito during the blood meal of an infected person. The female gametes are fertilized and develop into oocyst on the walls of the mosquitoes gut. Each oocyst gives rise to about 1000 immature sporozoites which migrate to the mosquitoes salivary grand and mature to repeat the cycle [49].

3.2 Model description

The model we formulate traces the life cycle of malaria parasite from Anopheles mosquito vectors to human host. The model is based on monitoring of the dynamics of the populations at time t of susceptible humans host $S_H(t)$, infected humans $I_H(t)$, community population of gametocytes $G_H(t)$, Susceptible mosquito vector $S_V(t)$, infected mosquito vector $I_V(t)$ and community population of Sporozoite $P_V(t)$. In particulars the model taking into account changes in community pathogen load at infective stages of the pathogen. In this model we make the following assumptions

- There is no vertical transmission of the disease in humans
- There is also no vertical transmission of the disease in the mosquito vectors
- The population of susceptible humans become infected with the contact of Anopheles mosquito vectors (sporozoites).
- The population of susceptible mosquito become infected due to contact with the population of gametocytes in the community.
- There is no migration of infectious humans.
- There is no immune response in humans.

The vector population does not include immune class as mosquito never recover from infection; that is their infection period ends with their death according to life-cycle [78, 74]. When mosquito vectors bite infected humans, $I_H(t)$, they take gametocytes, $G_H(t)$, and when they bite susceptible humans they release sporozoites, $P_V(t)$. At any time, new recruits enter the humans and mosquitoes populations

through birth at constant rates Λ_H and Λ_V, respectively. There is a natural death rate μ_H *and* μ_V in the human and mosquito vectors, respectively. Infected human hosts have an additional mortality rate of δ_H. There is also natural death rate of gametocytes and sporozoites in the community population of humans and mosquito vectors respectively. Similarly, infected mosquitoes have an additional mortality rate δ_V. $N_H(t)$ is the total human population and is given by

$$N_H(t) = S_H(t) + I_H(t). \tag{3.2.1}$$

Susceptible humans acquire sporozoites infection from mosquito vectors in the physical environment at rate $\lambda_V(t)$ given as

$$\lambda_V(t) = \frac{\beta_V P_V(t)}{P_0 + \in P_V(t)}, \tag{3.2.2}$$

where β_V is the maximum rate of exposure, $\in$ is the limitation of growth velocity of sporozoites with the increase of cases, P_V is the population of community sporozoites from infected mosquitoes and P_0 is half saturation constant. From the functional response, we notice that at low parasite densities, contacts are directly proportional to the host densities. $N_V(t)$ is the total mosquito vectors population and is given by

$$N_V(t) = S_V(t) + I_V(t). \tag{3.2.3}$$

Similarly, susceptible mosquito vectors acquire infection by gametocytes from infected humans in the physical environment at rate $\lambda_H(t)$ given by

$$\lambda_H(t) = \frac{\beta_H G_H}{G_0 + \in G_H}, \tag{3.2.4}$$

where β_H is the maximum rate of exposure, $\in$ is the limitation of growth velocity of gametocytes with increase of cases, G_0 is the half saturation constant.

The table below describes the variables of the model (3.2.5) with initial data estimates

Variable	Description	Initial value	Sources
$S_H(t)$	Number of susceptible humans host at time t	1000	Estimated
$I_H(t)$	Number of infected humans host at time t	70	Estimated
$G_H(t)$	Community population of gametocytes inside the infected human at time t	40	Estimated
$S_V(t)$	Number of susceptible mosquito vectors at time t	60	Estimated
$I_V(t)$	Number of infected mosquito vectors at time t	30	Estimated
$P_V(t)$	Community population of sporozoites inside the infected mosquito vectors at time t	15	Estimated

Table 3.1: List of Variables and their descriptions

The schematic diagram of the transmission of malaria in humans according to our model is shown below

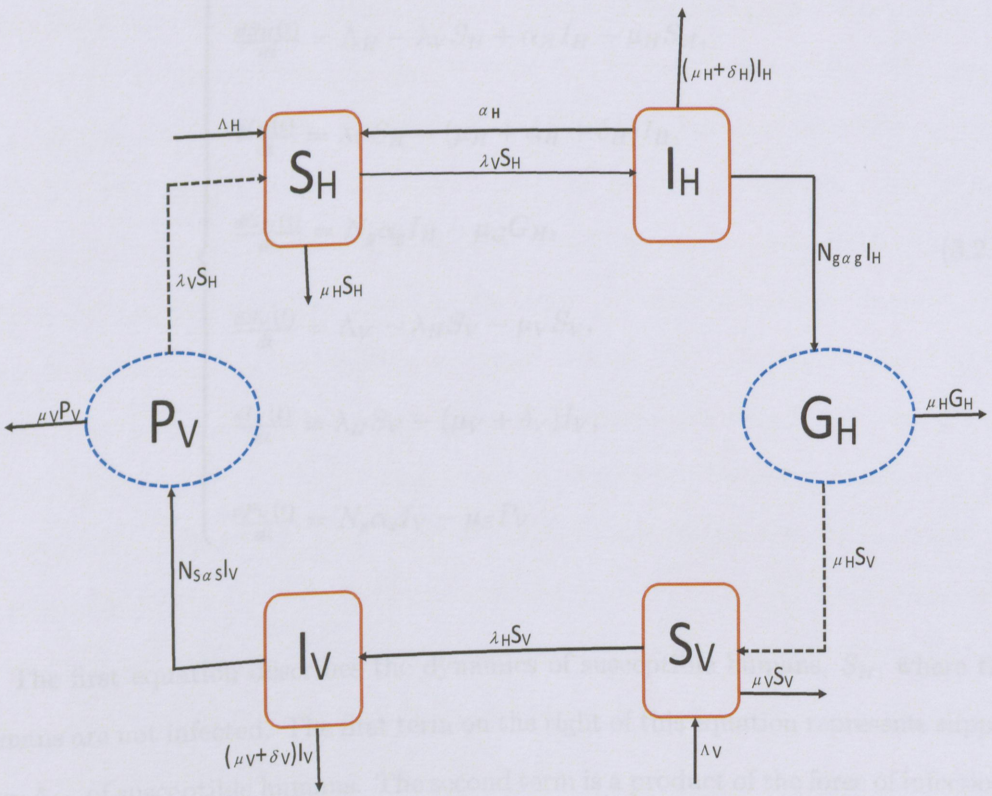

Figure 3.1: The compartmental model of human host and mosquito vectors. The population of susceptible humans infected by the sporozoite and the population of susceptible mosquito vectors infected by gametocytes when they interact. The dashed circle represents infectious of mosquito vectors and human. Dashed line represents force of infection. In this case we ignore vertical infections.

From the assumptions and inter-relations between the variables and parameters, we can describe the dynamics of the disease using the set of coupled equations.

$$\begin{cases} \frac{dS_H(t)}{dt} = \Lambda_H - \lambda_V S_H + \alpha_H I_H - \mu_H S_H, \\ \frac{dI_H(t)}{dt} = \lambda_V S_H - (\mu_H + \alpha_H + \delta_H) I_H, \\ \frac{dG_H(t)}{dt} = N_g \alpha_g I_H - \mu_G G_H, \\ \frac{dS_V(t)}{dt} = \Lambda_V - \lambda_H S_V - \mu_V S_V, \\ \frac{dI_V(t)}{dt} = \lambda_H S_V - (\mu_V + \delta_V) I_V, \\ \frac{dP_V(t)}{dt} = N_s \alpha_s I_V - \mu_S P_V. \end{cases} \tag{3.2.5}$$

The first equation describes the dynamics of susceptible humans, S_H, where the humans are not infected. The first term on the right of this equation represents supply rate, Λ_H, of susceptible humans. The second term is a product of the force of infection, λ_V, by the susceptible humans, S_H. The third term is the product of human recovery, α_H, by the infected humans, I_H. The last term of this equation is a product of natural death rate of humans, μ_H, by susceptible humans, S_H. The second equation models the dynamics of infected humans, I_H. The first term of this equation is the product of force infection, λ_V, by susceptible humans. The second term of the equation is the sum of the product of μ_H, α_H and δ_H, by infected humans I_H, where δ_H represent death by disease. The third equation models the dynamics of gametocytes inside the

infected humans. The first term of this equation represents population of humans infected by gametocytes, $N_g\alpha_g I_H$. The second term of this equation is the product of natural death rate of gametocytes, α_g, by gametocytes inside the infected humans. The fourth equation models the dynamics of susceptible mosquito vectors. The first term of the equation represents supply rate, Λ_V, of mosquito vectors. The second term of this equation is the product of force infection, λ_H, by susceptible mosquito vectors. The third term of this equation is the product of natural death rate of mosquito vectors, λ_V, by mosquito vectors. The fifth equation models the dynamics of infected mosquito vectors, I_V. The first terms of this equation is the product of force infection, λ_H, by susceptible mosquito vectors S_H. The second term of the equation is the product of the sum of natural death rate of mosquito vectors, μ_V, and death rate by disease, δ_V, by infected mosquito vectors I_V. The sixth equation models the dynamics of sporozoites P_V. The first term of this equation represents population of mosquito vectors, S_V, infected by sporozoites $N_S\alpha_S I_V$, where N_S is the community sporozoites inside the infected vector, α_S represents recovery of sporozoites in humans. The second term of this equation is the product of natural death rate of sporozoites inside the infected humans, μ_V, by sporozoite P_V.

3.3 Analysis of the model

We analyze the model to check whether the intervention strategies have any impact on the eradicated disease. The threshold parameters, which determine persistence or elimination of malaria will be determined and assessed. We start by determining the invariant region to check whether the model is biological meaningful and showing

that all solutions of (3.2.5) are positive for $\forall t \geq 0$ and are attracted in to the invariant region.

3.3.1 Feasible region of equilibria of model

Let Ω_H be the set of susceptible humans, infected humans and gametocytes. Ω_V is the set comprising susceptible mosquito vectors, infected mosquito vectors and sporozoites. Then Ω is the set comprising Ω_H and Ω_V.

Theorem: *The solution of the system* (3.2.5) *is feasible for* $\forall t \geq 0$ *provided that it is in* Ω.

Proof: Let $\Omega = (S_H, I_H, G_H, S_V, I_V, P_V) \in \mathbb{R}^6$ be any solution of the system (3.2.5) with non-negative initial conditions. Adding first and second equations of model system (3.2.5) in the absence of the disease (malaria), that is, $I_H = 0$ and letting $N_H = S_H + I_H$, we obtain the following inequality

$$\frac{dN_H(t)}{dt} \leq \Lambda_H - \mu_H N_H. \tag{3.3.1}$$

This implies that

$$\limsup_{t \to 0}(N_H(t)) \leq \frac{\Lambda_H}{\mu_H}, \tag{3.3.2}$$

that is, N_H is bounded from above by $\frac{\Lambda_H}{\mu_H}$.

Similarly, letting $N_V = S_V + I_V$ and adding equation fourth and fifth of the model system (3.2.5) we obtain

$$\frac{dN_V(t)}{dt} \leq \Lambda_V - \mu_V N_V. \tag{3.3.3}$$

This implies that

$$\limsup_{t\to 0}(N_V(t)) \leq \frac{\Lambda_V}{\mu_V}, \tag{3.3.4}$$

that is N_V is bounded from above by $\frac{\Lambda_V}{\mu_V}$.

Similar inequality can be derived from third and sixth equations of the model system (3.2.5).

Hence, all solutions of the system (3.2.5) enter the invariant attracting region

$$\begin{aligned}\Omega = \{(S_H, I_H, G_H, S_V, I_V, P_V); 0 \leq S_H + I_H \leq M_1, 0 \leq S_V + I_V \leq M_2, \\ 0 \leq G_H \leq M_3, 0 \leq P_V \leq M_4\}\end{aligned} \tag{3.3.5}$$

where

$$\begin{cases} M_1 = \frac{\Lambda_H}{\mu_H}, \\ M_2 = \frac{\Lambda_V}{\mu_V}, \\ M_3 = \frac{N_G \alpha_G \Lambda_H}{\mu_G \mu_H}, \\ M_4 = \frac{N_S \alpha_S \Lambda_V}{\mu_S \mu_V}. \end{cases} \tag{3.3.6}$$

Therefore the solution of model (3.2.5) enter the invariant region Ω. The model (3.2.5) is biologically meaningful and mathematical well-posed in the domain Ω.

3.3.2 Positivity of solution

In order to show that the solution is positive we need to show that

$$(S_H(t), S_V(t), I_H(t), I_V(t), G_H(t), P_V(t)) \in \Omega, \tag{3.3.7}$$

where $S_H(t), S_V(t) > 0$ and $I_H(t), I_V(t), G_H(t), P_V(t) \geq 0 \ \ \forall t > 0$.

From the first equation of model system (3.2.5), we assume that $\Lambda_H > 0$ and $I_H = 0$. On the basis of this assumption we obtain

$$\frac{dS_H(t)}{dt} > -(\mu_H + \lambda_V(t))S_H(t), \tag{3.3.8}$$

Separating the variables and then integrating the differential inequality we obtain that

$$S_H(t) \geq S_H(0) \exp\left(-\int_0^t (\mu_H + \lambda_V(\tau)))d\tau > 0. \tag{3.3.9}$$

Since $S_H > 0$, from second equation of model system (3.2.5) we obtain

$$\frac{dI_H(t)}{dt} > -(\mu_H + \alpha_H + \delta_H(t))I_H(t), \tag{3.3.10}$$

Again separating the variables and then integrating the differential inequality we obtain that

$$I_H(t) \geq I_H(0) \exp -(\mu_H + \lambda_H + \delta_H) > 0. \tag{3.3.11}$$

Also, since $I_H > 0$, from the third equation of model system (3.2.5 we obtain

$$\frac{dG_H(t)}{dt} > -\mu_G G_H(t), \tag{3.3.12}$$

After separating the variables and then integrating the differential inequality we obtain that

$$G_H(t) > G_H(0) \exp -\mu_G(t) > 0. \tag{3.3.13}$$

From the fourth equation of the model system (3.2.5), we assume that $\Lambda_V > 0$, from this assumption we obtain

$$\frac{dS_V(t)}{dt} > -(\lambda_V + \mu_V)S_V(t), \tag{3.3.14}$$

In the same way as above we separate the differential inequality to obtain that

$$S_V(t) \geq S_V(0) \exp\left(-\int_0^t (\mu_V + \lambda_H(\tau))d\tau > 0. \right. \tag{3.3.15}$$

For $S_V > 0$, in the fifth equation of model system (3.2.5), we obtain

$$\frac{dI_V(t)}{dt} > -(\mu_V + \delta_V)I_V(t), \tag{3.3.16}$$

From above inequality separate the variables and then integrating the differential inequality we obtain that

$$I_V(t) \geq I_V(0) \exp -(\mu_V + \lambda_V) > 0. \tag{3.3.17}$$

Now for $I_V > 0$, in the sixth equation of the model system (3.2.5) we obtain that

$$\frac{dP_V(t)}{dt} > -\mu_S P_V(t), \tag{3.3.18}$$

So that

$$P_V(t) \geq P_V(0) \exp -\mu_S(t) > 0. \tag{3.3.19}$$

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This shows that the solutions of the model system (3.2.5) are positive for all $t > 0$, because $\exp(-\mu_H t) > 0$ for all $\mu_H \in \mathbb{R}$. Now that it has been established that our model has both the invariant and positive of solutions, we can move on to determine the existence of the equilibrium point which will assist in calculation of the reproduction number by the next generation methods.

3.3.3 Existence of steady-state solution

The infection-free equilibrium state is represented by the solution of the system of equation (3.2.5) with the right-hand side of the equations set equal to zero. Such solutions are also called steady state solutions. Let $E^*(S_H^*, I_H^*, G_H^*, S_V^*, I_V^*, P_V^*)$ be the steady state solution obtained after setting $\frac{dS_H}{dt} = \frac{dI_H}{dt} = \frac{dG_H}{dt} = \frac{dS_V}{dt} = \frac{dI_V}{dt} = \frac{dP_V}{dt} = 0$ in system (3.2.5). The steady state solution is obtained by solving the system below

$$\begin{cases} \Lambda_H - \lambda_V S_H + \alpha_H I_H - \mu_H S_H = 0, \\ \lambda_V S_H - (\mu_H + \alpha_H + \delta_H) I_H = 0, \\ N_g \alpha_g I_H - \mu_g G_H = 0, \\ \Lambda_V - \lambda_H S_V - \mu_V S_V = 0, \\ \lambda_H S_V - (\mu_V + \delta_V) I_V = 0, \\ N_S \alpha_S I_V - \mu_S P_V = 0. \end{cases} \tag{3.3.20}$$

3.3.4 Disease-free Equilibrium (DFE)

Disease-free equilibrium point is a point at which a steady state solution is achieved, that is there is no malaria parasite in the human population or plasmodium parasite in the mosquito population. Let us define the disease classes as human or mosquito populations that are infected or infectious, that is, I_H, G_H, I_V and P_V . In the absence of the disease, we have $I_H^* = G_H^* = I_V^* = P_V^* = 0$.

Therefore system (3.3.20) becomes

$$\begin{cases} \Lambda_H - \mu_H S_H = 0, \\ \Lambda_V - \mu_V S_V = 0, \end{cases} \tag{3.3.21}$$

which implies that

$$\begin{cases} S_H = \frac{\Lambda_H}{\mu_H}, \\ S_V = \frac{\Lambda_V}{\mu_V}. \end{cases} \tag{3.3.22}$$

Therefore, the disease-free equilibrium point of malaria model of equation (3.2.5) is given by

$$E_0 = (S_H^*, I_H^*, G_H^*, S_V^*, I_V^*, P_V^*) = (\frac{\Lambda_H}{\mu_H}, 0, 0, \frac{\Lambda_V}{\mu_V}, 0, 0). \tag{3.3.23}$$

The above equation represents the state in which there is no malaria infection in the society.

3.3.5 Basic reproduction number

The basic reproduction number, R_0, is a threshold value that is often used in mathematical models to measure the rate of spread of a disease. It is defined as the number of new infections in humans that arise as a result of a single infected individual being introduced into a fully susceptible population. When $R_0 < 1$, it implies that on average an infectious individual infects less than one person throughout his /her infectious period and in this case the disease is wiped out. On the other hand, when $R_0 > 1$, then on average every infectious individual infects more than one individual during his/ her infectious period and the disease persists in the population. P.van den Driessche and J. Watmough described the next generation method used to compute the basic reproduction number [79]. Given a system, where the rate at which new infection appears in each comportment, R_0 is the rate of transfer into each compartment as well as the rate of transfer out of each compartment. The model (3.2.5) can then be written in the form

$$\begin{cases} \frac{dX}{dt} = f(X, Y, Z), \\ \frac{dY}{dt} = g(X, Y, Z), \\ \frac{dZ}{dt} = h(X, Y, Z), \end{cases} \tag{3.3.24}$$

where

$$\begin{cases} X = (S_H, S_V), \\ Y = (I_H, I_V), \\ Z = (G_H, P_V), \end{cases} \tag{3.3.25}$$

The component X denotes the number of susceptibles, while the component Y represents the number of infected individuals that do not transmit the disease. Component Z represent the number of individuals capable of transmitting the disease.

Following [18] we define $\tilde{g}(X^*, Z)$, by

$$\tilde{g}(X^*, Z) = (\tilde{g_1}(X^*, Z), \tilde{g_2}(X^*, Z)), \tag{3.3.26}$$

with

$$\begin{cases} \tilde{g_1}(X^*, Z) = \frac{\beta_V P_V \Lambda_H}{\mu_H(P_0+\epsilon P_V)(\mu_H+\alpha_H+\delta_H)}, \\ \tilde{g_2}(X^*, Z) = \frac{\beta_H G_H \Lambda_V}{\mu_V(G_0+\epsilon G_H)(\mu_V+\delta_V)}, \end{cases} \tag{3.3.27}$$

where $X^* = (S_H^*, S_V^*)$. Substituting the value of $\tilde{g_1}$ and $\tilde{g_2}$ into the second and fifth equations of model system (3.2.5) and letting $h_1 = \frac{dP_V}{dt}$, $h_2 = \frac{dG_H}{dt}$ we obtain

$$\begin{cases} h_1 = \frac{N_G \alpha_G \beta_V P_V \Lambda_H}{\mu_H(P_0+\epsilon P_V)(\mu_H+\alpha_H+\delta_V)} - \mu_G G_H, \\ h_2 = \frac{N_S \alpha_S \beta_H G_H \Lambda_V}{(G_0+\epsilon G_H)(\mu_V+\delta_V)} - \mu_S P_V. \end{cases} \tag{3.3.28}$$

Let $A = D_z h(X^*, \tilde{g}(X^*, 0), 0)$ and further assume that A can be written in the form $A = M - D$, where $M \geq 0$ and $D > 0$, is a diagonal matrix.

The partial derivatives of h_1 and h_2 with respect to G_H and P_V at disease free state respectively are

$$\begin{cases} \frac{\partial h_1}{\partial G_H} = -\mu_G, \\ \frac{\partial h_1}{\partial G_H} = \frac{N_G \alpha_G \beta_V \Lambda_H}{\mu_H P_0 (\mu_H + \alpha_H + \delta_H)}, \\ \frac{\partial h_2}{\partial P_V} = \frac{N_S \alpha_S \beta_H \Lambda_V}{\mu_V G_0 (\mu_V + \delta_V)}, \\ \frac{\partial h_2}{\partial G_H} = -\mu_S. \end{cases} \tag{3.3.29}$$

Then A becomes

$$A = \begin{pmatrix} -\mu_G & \frac{N_G \alpha_G \beta_V \Lambda_H}{\mu_H P_0 (\mu_H + \alpha_H + \delta_H)} \\ \frac{N_S \alpha_S \beta_H \Lambda_V}{\mu_V G_0 (\mu_V + \delta_V)} & -\mu_S \end{pmatrix} \tag{3.3.30}$$

Since $A = M - D$, we deduce matrices M and D to be

$$M = \begin{pmatrix} 0 & \frac{N_G \alpha_G \beta_V \Lambda_H}{\mu_H P_0 (\mu_H + \alpha_H + \delta_H)} \\ \frac{N_S \alpha_S \beta_H \Lambda_V}{\mu_V G_0 (\mu_V + \delta_V)} & 0 \end{pmatrix} \tag{3.3.31}$$

$$D = \begin{pmatrix} \mu_G & 0 \\ 0 & \mu_S \end{pmatrix} \tag{3.3.32}$$

$$\Rightarrow D^{-1} = \begin{pmatrix} \frac{1}{\mu_G} & 0 \\ 0 & \frac{1}{\mu_S} \end{pmatrix} \tag{3.3.33}$$

Multiplying M by D^{-1} we have that,

$$MD^{-1} = \begin{pmatrix} 0 & \frac{N_G \alpha_G \beta_V \Lambda_H}{\mu_H \mu_S P_0 (\mu_H + \alpha_H + \delta_H)} \\ \frac{N_S \alpha_S \beta_H \Lambda_V}{\mu_V \mu_G G_0 (\mu_V + \delta_V)} & 0 \end{pmatrix} \tag{3.3.34}$$

Now we determine the eigenvalue of the above matrix,

$$\left| MD^{-1} - \lambda I \right| = \begin{vmatrix} -\lambda & \frac{N_G \alpha_G \beta_V \Lambda_H}{\mu_H \mu_S P_0 (\mu_H + \alpha_H + \delta_H)} \\ \frac{N_S \alpha_S \beta_H \Lambda_V}{\mu_V \mu_G G_0 (\mu_V + \delta_V)} & -\lambda \end{vmatrix} = 0 \tag{3.3.35}$$

The basic reproductive numbers for human and mosquito vectors are given by,

$$\lambda^2 - R_{0H} R_{0V} = 0 \tag{3.3.36}$$

$$R_{0H} = \frac{N_g \alpha_g \beta_H \Lambda_H}{\mu_H \mu_g G_0 (\mu_H + \alpha_H + \delta_H)} \quad and \quad R_{0V} = \frac{N_S \alpha_S \beta_V \Lambda_V}{\mu_V \mu_S P_0 (\mu_V + \delta_V)}, \tag{3.3.37}$$

where R_{0H} describes the number of humans that one infectious mosquito infects over its expected infection period in completely susceptible humans population, while R_{OV} is the number of mosquitoes infectious human during the period of infectiousness in a completely susceptible mosquitoes population.

The overall basic reproduction number $R_0 = \rho(MD^-1)$ is given by

$$R_0 = \sqrt{R_{0H} R_{0V}} = \sqrt{\frac{N_g \alpha_g \beta_H \Lambda_H N_S \alpha_S \beta_V \Lambda_V}{\mu_H \mu_g \mu_V \mu_S P_0 G_0 (\mu_V + \delta_V)(\mu_H + \alpha_H + \delta_H)}}. \tag{3.3.38}$$

3.3.6 Local stability of the disease free equilibrium

The local stability of the disease-free equilibrium can be analyzed using the Jacobin matrix of the malaria model at the disease free equilibrium point. Referring to the result of van den Driessche and Watmough (2002), the following theorem holds [79].

Theorem: *The disease-free equilibrium state is locally asymptotically stable if* $R_0 < 1$ *and is unstable if* $R_0 > 1$ [78, 79]

Proof:

The Jacobian matrix J of malaria model (3.2.5) is given by

$$\mathrm{J}=\begin{pmatrix} -b_1 & b_2 & 0 & 0 \\ b_3 & -b_4 & 0 & 0 \\ 0 & 0 & -b_5 & b_6 \\ 0 & 0 & 0 & -b_7 \end{pmatrix},$$

where

$$\begin{cases} b_1 = (\mu_H + \alpha_H + \delta_H), \\ b_2 = \frac{\beta_H \Lambda_H}{\mu_H G_0}, \\ b_3 = N_g \alpha_g, \\ b_4 = \mu_g, \\ b_5 = (\mu_V + \delta_V), \\ b_6 = \frac{\beta_V \Lambda_V}{\mu_V P_0}, \\ b_7 = \mu_S. \end{cases} \tag{3.3.39}$$

The eigenvalues of the Jacobian matrix are the sclutions of the characteristic equation $\left|J - \lambda I\right|$=0, that is,

$$\begin{vmatrix} b_1 - \lambda & b_2 & 0 & 0 \\ b_3 & -b_4 - \lambda & 0 & 0 \\ 0 & 0 & -b_5 - \lambda & b_6 \\ 0 & 0 & 0 & -b_7 - \lambda \end{vmatrix} = 0 \tag{3.3.40}$$

From (3.3.40) we obtain

$$\lambda^4 + \gamma_1\lambda^3 + \gamma_2\lambda^2 + \gamma_3\lambda + \gamma_0 = 0, \tag{3.3.41}$$

where

$$\begin{cases} \gamma_1 = b_1 + b_4 + b_5 + b_7, \\ \gamma_2 = b_1b_4 + b_1b_5 + b_1b_7 + b_4b_7 + b_5b_7 - b_2b_3, \\ \gamma_3 = b_1b_4b_5 + b_1b_4b_7 + b_1b_5b_7 + b_4b_5b_7 - b_2b_3b_5 - b_2b_3b_7, \\ \gamma_4 = b_1b_4b_5b_7 + b_2b_3b_5b_7. \end{cases} \tag{3.3.42}$$

Here we use Routh-Hurwitz stability criterion to determine the stability of disease free state. The steady state associated with the characteristic equation (polynomial) (3.3.41) is stable if and only if the determinates of all Hurwitz matrices are positive

[41]. The Hurwitz determints of the characteristic equation (3.3.41) are given by

$$\begin{cases} G_0 = 1, \\ G_1 = \gamma_1, \\ G_2 = \begin{vmatrix} \gamma_1 & 1 \\ \gamma_3 & \gamma_2 \end{vmatrix}, \\ G_3 = \begin{vmatrix} \gamma_1 & 1 & 0 \\ \gamma_3 & \gamma_2 & \gamma_1 \\ \gamma_5 & \gamma_4 & \gamma_3 \end{vmatrix}, \\ G_4 = \begin{vmatrix} \gamma_1 & 1 & 0 & 0 \\ \gamma_3 & \gamma_2 & \gamma_1 & 1 \\ \gamma_5 & \gamma_4 & \gamma_3 & \gamma_1 \end{vmatrix}. \end{cases} \tag{3.3.43}$$

where $\gamma_i = 0$ if $i > n$. All of the roots of the polynomial $P(\lambda)$ are negative or negative real parts if and only if determinants of all Hurwitz matrices are positive: det $G_j > 0$, j=1,2,...,n. We show that when $R_0 < 1$, all the coefficients, γ_i, of the characteristics equation and G_j are positive. From the characteristic equation, with $n = 4$, the Routh-Hurwitz criteria are

$\gamma_1 > 0$, $\gamma_2 > 0$, $\gamma_3 > 0$,$\gamma_4 > 0$ and $det(G_1) = \gamma_1 > 0$.

Also

$$det(G_2) = \begin{vmatrix} \gamma_1 & 1 \\ 0 & \gamma_2 \end{vmatrix} = \gamma_1\gamma_2 > 0, \tag{3.3.44}$$

$$det(G_3) = \begin{vmatrix} \gamma_1 & 1 & 0 \\ \gamma_3 & \gamma_2 & \gamma_1 \\ 0 & 0 & \gamma_3 \end{vmatrix} = \gamma_1\gamma_2\gamma_3 - \gamma_3^2 > 0, \tag{3.3.45}$$

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and

$$det(G_4) = \begin{vmatrix} \gamma_1 & 1 & 0 & 0 \\ \gamma_3 & \gamma_2 & \gamma_1 & 1 \\ 0 & 0 & 0 & \gamma_1 \end{vmatrix} = \gamma_1\gamma_2\gamma_3 - \gamma_1^2\gamma_4 - \gamma_3^2 > 0 \tag{3.3.46}$$

where

$\gamma_1\gamma_2\gamma_3$ is greater than $-(\gamma_1\gamma_2 + \gamma_3^2)$. Since all the determinants of the Hurwitz matrices are positive, we then deduce that all the eigenvalues of the Jacobian matrix have negative real part. Hence disease-free equilibrium point is asymptotically stable and $R_0 < 1$.

3.3.7 Global stability of the disease free equilibrium

By theorem in the previous sub-section 3.3.6 we deduce that the disease free equilibrium is locally asymptotically stable wherever $R_0 < 1$ and unstable when $R_0 > 1$. In this section, we list two conditions that if met, also guarantee the global asymptotic stability of the disease free state. We write equation (3.2.5) in the form

$$\begin{cases} \frac{dX}{dt} = F(X, Z), \\ \\ \frac{dZ}{dt} = G(X, Z), \qquad G(X, 0) = 0, \end{cases} \tag{3.3.47}$$

where $X = (S_H, S_V)$ comprises of the uninfected components and $Z = (I_H, I_V, G_H, P_V)$, comprises of infected and infectious components.

$$E_0 = (X^*, 0) = (\frac{\Lambda_H}{\mu_H}, 0, \frac{\Lambda_V}{\mu_V}, 0, 0, 0), \tag{3.3.48}$$

denotes the disease free equilibrium of the system. To guarantee global asymptotic stability, the conditions H_1 and H_2 below must be met [18].

H_1 : for $\frac{dX}{dt} = F(X,0)$, $\quad X^*$ is globally asymptotically stable (g.a.s),

$H_2 : G(X,Z) = AZ - G(X,Z) \geq 0.$ for $(X,Z) \in \mathbb{R}_{+6}$ where $A = D_Z G(X^*,0)$ is an M- matrix and $\mathbb{R}_6^+$ is the region where the model makes biological sense.

Now we determine F(X,0) at disease free from first and fourth equation respectively

$$F(X,0) = \begin{pmatrix} \Lambda_H - \mu_H S_H \\ \Lambda_V - \mu_V S_V \end{pmatrix} \tag{3.3.49}$$

and

$$A = \begin{pmatrix} b_1 & 0 & 0 & \frac{\beta_V \Lambda_H}{P_0 \mu_H} \\ N_G \alpha_G & b_2 & 0 & 0 \\ 0 & \frac{\beta_H \Lambda_V}{G_0 \mu_V} & b_3 & 0 \\ 0 & 0 & N_S \alpha_S & b_4 \end{pmatrix} \tag{3.3.50}$$

where

$$\begin{cases} b_1 = -(\mu_H + \alpha_H + \delta_H), \\ b_2 = -\mu_G, \\ b_3 = -(\mu_V + \delta_V), \\ b_4 = -\mu_S. \end{cases} \tag{3.3.51}$$

$$G(X,Z) = \begin{pmatrix} (\frac{\Lambda_H}{P_0\mu_H} - \frac{S_H}{(P_0+\epsilon P_V)})\beta_V P_V \\ 0 \\ (\frac{\Lambda_V}{G_0\mu_V} - \frac{S_V}{(G_0+\epsilon G_H)})\beta_H G_H \\ 0 \end{pmatrix} \tag{3.3.52}$$

Since $\frac{\Lambda_H}{P_0\mu_H} \geq \frac{S_H}{P_0+\epsilon P_V}$ and $\frac{\Lambda_V}{G_0\mu_V} \geq \frac{S_V}{G_0+\epsilon G_H}$, then $\hat{G}(X,Z) \geq 0$ for all $(X,Z) \in \mathbb{R}_6^+$. It is also clear that matrix A is an M-matrix since the off diagonal elements of A are non-negative. We state a theorem which summarises this in sub-section 3.3.6.

Also by theorem in the previous sub-section 3.3.6, the fixed point $E_0 = (X^*, 0) = (\frac{\Lambda_H}{\mu_H}, 0, \frac{\Lambda_V}{\mu_V}, 0, 0, 0)$ is a globally asymptotically stable (g.a.s) equilibrium of system (3.2.5) if $R_0 < 1$ and the assumptions on H_1 and H_2 are satisfied.

3.3.8 The endemic equilibrium point (EEP)

The endemic equilibrium point is the steady state solution, where the disease cannot be totally eradicated in the population of humans, (i.e disease persists in the population). Let $E^*(S_H^*, I_H^*, G_H^*, S_V^*, I_V^*, P_V^*)$ be the endemic state, then $E^*(S_H^*, I_H^*, G_H^*, S_V^*, I_V^*, P_V^*) \neq (0,0,0,0,0,0)$ and at the endemic equilibrium both human and mosquito vectors are infected by sporozoites and Gametocytes respectively. Expressions of endemic equilibrium point are given below. The endemic value of infected human is given by

$$I_H^* = \frac{\lambda_V^* S_H}{(\mu_H + \alpha_H + \delta_H)} = \frac{\lambda_V^* \Lambda_V}{\mu_H(\mu_H + \alpha_H + \delta_H) + \lambda_V^*(\mu_H + \delta_H)} \tag{3.3.53}$$

We deduce from above equation that the infected population is proportional to five quantities, force of infection, λ_H^*, recovery of humans, α_H, death rate of infected

humans, δ_H and supply rate of susceptible humans, Λ_H. The endemic value of susceptible human is given by

$$S_H^* = \frac{\Lambda_H + \alpha_H I_H^*}{(\mu_H + \lambda_V^*)} = \frac{\Lambda_H}{(\mu_H + \lambda_V^*)} + \frac{\alpha_H \lambda_V^* \Lambda_H}{(\mu_H + \lambda_V^*)[\mu_H(\mu_H + \alpha_H + \delta_H) + \lambda_V^*(\mu_H + \delta_H)]} \tag{3.3.54}$$

susceptible human is proportional to five quantity, recovery of human, α_H, force of infection from infected mosquito vectors, λ_V^*, supply rate of human, Λ_H, natural death rate of human, μ_H, and death rate by disease, δ_H. The gametocytes taken by the mosquito vectors from infected human is given by

$$G_H^* = \frac{N_g \alpha_g I_H^*}{\mu_g} = \frac{N_g \alpha_g \lambda_V^* \Lambda_H}{\mu_H(\mu_H + \alpha_H + \delta_H) + \lambda_V^*(\mu_H + \delta_H)} \tag{3.3.55}$$

The above equation represents the total population of the infected human by gametocytes. It proportional to the seventh quantities, average number of human host who are infected by gametocytes at time t, $N_g(t)$, recovery of human from gametocytes, α_g, force of infection from mosquito vectors, λ_V^*, supply rate of humans, Λ_H, natural death rate of humans, μ_H, recovery of human, α_H, death rate by disease, δ_H . The infected mosquito vectors is given by

$$I_V^* = \frac{\lambda_H^* S_H}{(\mu_V + \delta_V)} = \frac{\lambda_H^* \Lambda_V}{(\mu_V + \lambda_H^*)(\mu_V + \delta_V)} \tag{3.3.56}$$

from the above equation the infected mosquito vectors is proportional to four quantities, λ_H^* which represent the force of infection, Λ_V represent recruitment of mosquito vectors, μ_V is the natural death of mosquito vectors and δ_V death rate of mosquito vector by disease. The susceptible mosquito's vector is given by

$$S_V^* = \frac{\Lambda_V}{(\lambda_H^* + \mu_V)}. \tag{3.3.57}$$

from the above equation susceptible mosquito vectors is proportional to three quantity, λ_H^* which represent the force of infection, supply rate of mosquito vectors,Λ_V, natural death rate of mosquito vectors, μ_V. The equation below represent sporozoites of mosquito vectors which is given by

$$P_V^* = \frac{N_S \alpha_S I_V^*}{\mu_S} = \frac{N_S \alpha_S \lambda_H^* \Lambda_V}{\mu_S(\mu_V + \lambda_H^*)(\mu_V + \delta_V)}. \tag{3.3.58}$$

from the above equation N_S represent the total population mosquito vectors who are infected by sporozoites in the community, λ_V^* is the force of the infection from mosquito vectors. Therefore the endemic equilibrium state is $E^*(S_H^*, I_H^*, G_H^*, S_V^*, I_V^*, P_V^*)$.

3.3.9 The existence of endemic equilibrium state

In this section we present some results concerning the existence of an endemic equilibrium or constant solution for model system (3.2.5). To do this we shall make use of a threshold parameter, which we have already denoted by R_0.

Theorem: *The model system* (3.2.5) *formulated in terms of proportion has at least one endemic equilibrium solution given by* $E^*=(S_H^*, I_H^*, G_H^*, I_V^*, P_V^*)$, *with* $S_H^*, I_H^*, G_H^*, I_V^*, P_V^*$ *all non-negative, whose existence and properties are determined by the threshold parameter* R_0.

Proof. Let

$E^*=(S_H, I_H, G_H, I_V, P_V)$ be a constant solution of the model system (3.2.5). We can easily express $(S_H^*, I_H^*, G_H^*, S_V^*, P_V^*)$ in terms of I_V in the form of

$$
\begin{cases}
I_H^*(I_V^*) = \frac{N_S\alpha_S\beta_V\Lambda_H I_V^*}{N_S\alpha_S\beta_V I_V^* + \mu_H(P_0 + N_S\alpha_S \in I_V^*) - N_S\alpha_S\beta_V\alpha_H I_V^*}, \\
S_H^*(I_V^*) = \frac{\Lambda_H(P_0\mu_S + N_S\alpha_S \in I_V^*}{N_S\alpha_S\beta_V I_+^*\mu_H(P_0\mu_S + N_S\alpha_S \in I_V^*)} + \frac{\alpha_H(P_0\mu_S + N_S\alpha_S \in I^*)I_H^*}{N_S\alpha_S\beta_V I_V^* + \mu_H(P_0\mu_S + N_S\alpha_S I_V^*)}, \\
G_H^*(I_V^*) = \frac{N_g\alpha_g N_S\alpha_S\beta_V\Lambda_H I_V^*}{\mu_g[N_S\alpha_S\beta_V I_V^* + \mu_H(P_0 + N_S\alpha_S \in I_V^*) - N_S\alpha_S\beta_V\alpha_V\alpha_H I_V^*]}, \\
S_V^*(I_V^*) = \frac{a_1 I_V^* + a_2 + a_3 I_V^* - a_4 I_V^* + a_5 I_V^*}{b_1 I_V^* + b_2 + b_3 I_V^* - b_4 I_V^* + b_5 I_V^* + b_6 I_V^*}, \\
P_V^*(I_V^*) = \frac{N_S\alpha_S I_V^*}{\mu_S}, \\
\lambda_V^*(I_V^*) = \frac{N_S\alpha_S\beta_V I_V^*}{\mu_S P_0 + N_S\alpha_S \in I_V^*)}, \\
\lambda_H^*(I_V^*) = \frac{\beta_H G_H}{G_0 + \in G_H}, \\
\lambda_H^*(I_V^*) = \frac{c_1 I_V^*}{c_2 I_V^* + c_3 + c_4 I_V^* - c_5 I_V^* + c_6 I_V^*}.
\end{cases}
\tag{3.3.59}
$$

where

$$
\begin{cases}
a_1 = G_0\mu_g\Lambda_V N_S\alpha_S\beta_V, \\
a_2 = G_0\mu_g\mu_H P_0, \\
a_3 = G_0\mu_g\Lambda_V N_S\alpha_S \in, \\
a_4 = G_0\mu_g\Lambda_V N_S\alpha_S\alpha_H, \\
a_5 = N_g\alpha_g N_S\alpha_S \in \beta_V\Lambda_V\Lambda_H.
\end{cases}
\tag{3.3.60}
$$

$$\begin{cases} b_1 = G_0\mu_g\mu_V N_S\alpha_S\beta_V, \\ b_2 = G_0\mu_g\mu_V\mu_H P_0, \\ b_3 = G_0\mu_g\mu_V N_S\alpha_S \in, \\ b_4 = N_S\alpha_S\beta_V\alpha_H G_0\mu_g\mu_V, \\ b_5 = N_S\alpha_S N_g\alpha_g \in \mu_V\beta_V\Lambda_H, \\ b_6 = N_g\alpha_g N_S\alpha_S\beta_H\beta_V\Lambda_H. \end{cases} \tag{3.3.61}$$

$$\begin{cases} c_1 = N_g\alpha_g N_S\alpha_S\beta_H\beta_V\Lambda_H, \\ c_2 = G_0\mu_g N_S\alpha_S\beta_V, \\ c_3 = G_0\mu_g\mu_H P_0, \\ c_4 = N_S\alpha_S G_0\mu_g \in, \\ c_5 = N_S\alpha_S G_0\mu_g\beta_V\alpha_H, \\ c_6 = N_g\alpha_g N_S\alpha_S \in \beta_V\Lambda_H. \end{cases} \tag{3.3.62}$$

substituting $\lambda_H(I_V^*)$ and $S_V(I_V^*)$ into the equation of I_V which is given by

$$\frac{dI_V(t)}{dt} = \lambda_H S_V - (\mu_V + \delta_V)I_V. \tag{3.3.63}$$

$$\frac{d_1 I_V^{*2} + d_2 I_V^*}{(d_3 I_V^* + c_3)(d_4 I_V^* + b_2)} - d_5 I_V^* = 0. \tag{3.3.64}$$

where

$$\begin{cases} d_1 = c_1a_1 + c_1a_3 - c_1a_4 + c_1a_5, \\ d_2 = c_1a_2, \\ d_3 = c_2 + c_4 - c_5 + c_6, \\ d_4 = b_1 + b_3 - b_4 + b_5 + b_6, \\ d_5 = (\mu_V + \delta_V). \end{cases} \tag{3.3.65}$$

$$I_V^*(e_1 I_V^{2*} - c_2 I_V^* - e_3) = 0 \tag{3.3.66}$$

$$I_V^* = \frac{e_2 \pm \sqrt{e_2^2 - 4e_1e_3}}{2e_1}, \tag{3.3.67}$$

where

$$\begin{cases} e_1 = d_3 d_4 d_5, \\ e_2 = d_1 - d_2 d_3 d_5 - c_3 d_4 d_5, \\ e_3 = d_2 - b_2 c_3 d_3, \end{cases} \tag{3.3.68}$$

for the endemic equilibrium. Since $e_1 e_3 < 0$ for $R_0 > 1$, we can easily deduce from (3.3.66) that only one positive endemic equilibrium exist expression for $R_0 > 1$. Consequently, there exists one unique endemic equilibrium for model system (3.2.5) whenever $R_0 > 1$.

3.3.10 Local stability of the endemic equilibrium

The stability of the endemic equilibrium of the model (3.2.5) can be analyzed using the centre manifold Theory described by ***Castillo-Chavez and song*** 2004 [19]. To apply centre of manifold Theory we make the change of variables in the model system (3.2.5). Let $x_1 = S_H$, $x_2 = I_H$, $x_3 = G_H$, $x_4 = S_V$, $x_5 = I_V$, $x_6 = P_V$.

The model system (3.2.5) can be written in vector form as

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

$$H(X) = (h_1, h_2, h_3, h_4, h_5, h_6), \tag{3.3.69}$$

where

$X_i = (x_1, x_2, ..., x_6)^T$ and $H = (h_1, h_2 ... h_6)$ are transpose matrices. The model system

(3.2.5) becomes

$$\begin{cases} \frac{dx_1(t)}{dt} = \Lambda_H - \frac{\beta_H \Lambda_H x_3}{\mu_H(G_0 + \in x_3)} + \alpha_H x_2 - \mu_H x_1 = h_1 \\ \frac{dx_2(t)}{dt} = \frac{\beta_H \Lambda_H x_3}{\mu_H(G_0 + \in x_3)} - (\mu_H + \alpha_H + \delta_H)x_2 = h_2 \\ \frac{dx_3(t)}{dt} = N_g \alpha_g x_2 - \mu_g x_3 = h_3 \\ \frac{dx_4(t)}{dt} = \Lambda_V - \frac{\beta_V \Lambda_V x_6}{\mu_V(P_0 + \in x_6)} - \mu_V x_4 = h_4 \\ \frac{dx_5(t)}{dt} = \frac{\beta_V \Lambda_V x_6}{\mu_V(P_0 + \in x_6)} - (\mu_V + \delta_V)x_5 = h_5 \\ \frac{dx_6(t)}{dt} = N_S \alpha_S x_5 - \mu_S x_6 = h_6 \end{cases} \tag{3.3.70}$$

where

$$\lambda_V(t) = \frac{\beta_V x_6(t)}{p_0 + \in x_6(t)}, \quad \lambda_H(t) = \frac{\beta_H x_3}{x_0 + \in x_3}, \tag{3.3.71}$$

and $N_H = x_1 + x_2 + x_3$ and $N_V = x_4 + x_5 + x_6$ with $\beta^* = \beta_H$. Let β^* be bifurcation parameter of the system is linearized at disease free equilibrium point when with when $\beta^* = \beta$ with $R_0 = 1$. Thus β^* can be solved from reproductive number when $R_0 = 1$ as

$$\sqrt{\frac{N_g \alpha_g \beta_H \Lambda_H N_S \alpha_S \beta_V \Lambda_V}{\mu_H \mu_g \mu_V \mu_S P_0 G_0 (\mu_V + \delta_V)(\mu_H + \alpha_H + \delta_H)}} = 1$$

By squaring both side we have that

$$\frac{N_g \alpha_g N_S \alpha_S \beta_H \Lambda_H \beta_V \Lambda_V}{\mu_H \mu_g \mu_V \mu_S G_0 P_0 (\mu_V + \delta_V)(\mu_H + \alpha_H + \delta_H)} = 1$$

$$\beta^* = \frac{\mu_H \mu_g \mu_V \mu_S G_0 P_0 (\mu_V + \delta_V)(\mu_H + \alpha_H + \delta_H)}{N_g \alpha_g N_S \alpha_S \Lambda_H \beta_V \Lambda_V}$$

Then zero is a simple eigenvalue of the following Jacobian matrix, with the application of the bifurcation parameters. The Jacobian matrix associated with equation

system (3.3.68) at is E_0 given by

$$J(E_0) = \begin{pmatrix} b_1 & \alpha_H & \frac{-\beta_H \Lambda_H}{\mu_H G_0} & 0 & 0 & 0 \\ 0 & b_2 & \frac{\beta_H \Lambda_H}{\mu_H G_0} & 0 & 0 & 0 \\ 0 & N_g \alpha_g & b_3 & 0 & 0 & 0 \\ 0 & 0 & 0 & b_4 & 0 & \frac{-\beta_V \Lambda_V}{\mu_V P_0} \\ 0 & 0 & 0 & 0 & b_5 & \frac{\beta_V \Lambda_V}{\mu_V P_0} \\ 0 & 0 & 0 & 0 & N_S \alpha_S & b_6 \end{pmatrix}$$

where

$$\begin{cases} b_1 = -\mu_H \\ b_2 = -(\mu_H + \alpha_H + \delta_H) \\ b_3 = -\mu_g \\ b_4 = -\mu_V \\ b_5 = -(\mu_V + \delta_V) \\ b_6 = -\mu_S \end{cases} \tag{3.3.72}$$

we have the following system

$$\begin{cases} -\mu_H v_1 = 0 \\ \alpha_H v_1 - (\mu_H + \alpha_H + \delta_H) v_2 + N_g \alpha_g v_3 = 0 \\ \frac{-\beta_H \Lambda_H}{\mu_H G_0} v_1 + \frac{\beta_H \Lambda_H}{\mu_H G_0} v_2 - \mu_g v_3 = 0 \\ -\mu_V v_4 = 0 \\ -(\mu_V + \delta_V) v_5 + N_S \alpha_S v_6 = 0 \\ \frac{\beta_V \Lambda_V}{\mu_V P_0} v_4 + \frac{\beta_V \Lambda_V}{\mu_V P_0} v_5 - \mu_S v_6 = 0 \end{cases} \tag{3.3.73}$$

From the left hand side of equation system (3.3.73), we get the following eigenvectors

$$\begin{cases} v_1 = 0, \\ v_2 = v_2 free, \\ v_3 = \frac{(\mu_H + \alpha_H + \delta_H}{N_g \alpha_g} v_2, \\ v_4 = 0, \\ v_5 = v_5, \\ v_6 = \frac{\beta_V \Lambda_V}{\mu_V P_0 \mu_S} v_5. \end{cases} \tag{3.3.74}$$

We now compute the sign of a and b using manifold Theory

$$\begin{cases} a = \sum_{k,i,j=2}^{3} v_k w_i w_j \frac{\partial^2 h_k}{\partial x_i \partial x_j}(0,0) + \sum_{k,i,j=2}^{6} v_k w_i w_j \frac{\partial^2 h_k}{\partial x_i \partial x_j}(0,0) \\ b = \sum_{k,i=2}^{3} v_k w_i \frac{\partial^2 h_k}{\partial x \partial \beta}(0,0) + \sum_{k,i=1=2}^{6} v_k w_i \frac{\partial^2 h_k}{\partial x \partial \beta}(0,0) \end{cases} \tag{3.3.75}$$

Since $v_1 = v_4 = 0$ for $k = 1, 4$ and then $k = 2, 3, 5, 7$ should be considered. That is, the following function will be used to compute a and b from the system (3.3.68)

$$\begin{cases} h_2 = \frac{\beta_H x_3 x_1}{G_0} - (\mu_H + \alpha_H + \delta_H)x_2 = \frac{\beta_H x_3}{G_0}(N_H - x_2 - x_3) - (\mu_H + \alpha_H + \delta_H)x_2 \\ \quad = \frac{\beta_H x_3 N_H}{G_0} - \frac{\beta_H x_3 x_2}{G_0} - \frac{\beta_H x_3^2}{G_0} - (\mu_H + \alpha_H + \delta_H) \\ \\ h_5 = \frac{\beta_V x_6 x_4}{P_0} - (\mu_V + \delta_V)x_5 = \frac{\mu_V x_6}{P_0}(N_V - x_5 - x_6) - (\mu_V + \delta_V)x_5 \\ \quad = \frac{\beta_V x_6 N_V}{P_0} - \frac{\beta_V x_6 x_5}{P_0} - \frac{\beta_V x_6^2}{P_0} - (\mu_V + \delta_V)x_5 \end{cases} \tag{3.3.76}$$

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

$$\begin{cases} \frac{\partial^2 h_2}{\partial x_2 \partial x_3} = \frac{\partial^2 h_2}{\partial x_3 \partial x_2} = \frac{-\beta_H}{G_0} \\ \\ \frac{\partial^2 h_5}{\partial x_5 \partial x_6} = \frac{\partial^2 h_5}{\partial x_6 \partial x_5} = \frac{-\beta_V}{P_0} \end{cases} \tag{3.3.77}$$

Hence

$$\begin{cases} a = v_2 w_2 w_3 \frac{\partial^2 h_2}{\partial x_2 \partial x_3} + v_5 w_5 w_6 \frac{\partial^2 h_5}{\partial x_5 \partial x_6} \\ \quad = v_2 w_2 w_3 (\frac{-\beta_H}{G_0}) + v_5 w_5 w_6 (\frac{-\beta_V}{P_0}) \\ \quad = -(v_2 w_2 w_3 \frac{\beta_H}{G_0} + v_5 w_5 w_6 \frac{\beta_V}{P_0}) < 0 \end{cases} \tag{3.3.78}$$

Similarly partial derivatives that are not zero when calculating b are

$$\begin{cases} \frac{\partial h_2}{\partial \beta_H} = \frac{x_3 N_H}{G_0} \Rightarrow \frac{\partial^2 h_2}{\partial \beta_H \partial x_3} = \frac{N_H}{G_0} \\ \\ \frac{\partial h_5}{\partial \beta_V} = \frac{x_6 N_V}{G_0} \Rightarrow \frac{\partial^2 h_5}{\partial \beta_V \partial x_6} = \frac{N_V}{P_0} \end{cases} \tag{3.3.79}$$

Hence

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$$\begin{cases} b = v_2 w_3 \frac{\partial^2 h_2}{\partial \beta_H} \partial x_3 + v_2 w_6 \frac{\partial^2 h_5}{\partial \beta_V \partial x_6} \\ \quad = v_2 w_3 (\frac{N_H}{G_0}) + v_2 w_6 (\frac{N_V}{P_0}) \\ \quad = v_2 w_3 \frac{N_H}{G_0} + v_2 w_6 \frac{N_V}{P_0} > 0 \end{cases} \tag{3.3.80}$$

Hence $a < 0$ and $b > 0$. Therefore the centre manifold Theory holds.

3.3.11 Sensitivity Analysis

To determine the relative importance of parameters to the initial transmission of the disease, we perform a sensitivity analysis of the basic reproduction number with respect to the parameter of the model.

$$R_0 = \sqrt{R_{0H} R_{0V}} = \sqrt{\frac{N_g \alpha_g \beta_H \Lambda_H N_S \alpha_S \beta_V \Lambda_V}{\mu_H \mu_g \mu_V \mu_S P_0 G_0 (\mu_V + \delta_V)(\mu_H + \alpha_H + \delta_H)}}$$

We evaluate the sensitive analysis of reproductive number with all parameter described in the table(3.3) and (3.4) as

$$\Upsilon_u^{R_0} = \frac{\partial R_0}{\partial u} \times \frac{u}{R_0} \tag{3.3.81}$$

where $\frac{u}{R_0}$ normalise the coefficient by removing the effect of units(Njagarah and Nyabadza, 2013)

R_0 to α_g

Let

$$a_0 = \frac{N_g \beta_H \Lambda_H N_S \alpha_S \beta_V \Lambda_V}{\mu_H \mu_V \mu_S P_0 G_0 (\mu_V + \delta_V)(\mu_H + \alpha_H + \delta_H)} \tag{3.3.82}$$

$$R_0 = \sqrt{a_0 \alpha_g} \tag{3.3.83}$$

$$\begin{cases} \Upsilon_{\alpha_g}^{R_0} = \frac{\partial R_0}{\partial \alpha_g} \times \frac{\alpha_g}{R_0} \\ \\ = \frac{1}{2}(a_0\alpha_g)^{\frac{-1}{2}} \times a_0 \times \frac{\alpha_g}{R_0} \\ = \frac{a_0}{2\sqrt{a_0\alpha_g}} \times \frac{\alpha_g}{\sqrt{a_0\alpha_g}} \\ \\ = \frac{1}{2} \end{cases} \tag{3.3.84}$$

R_0 to β_H

Let

$$a_0 = \frac{N_g \Lambda_H N_S \alpha_S \alpha_g \beta_V \Lambda_V}{\mu_H \mu_g \mu_V \mu_S P_0 G_0 (\mu_V + \delta_V)(\mu_H + \alpha_H + \delta_H)} \tag{3.3.85}$$

$$R_0 = \sqrt{a_0 \beta_H} \tag{3.3.86}$$

$$\begin{cases} \Upsilon_{\beta_H}^{R_0} = \frac{\partial R_0}{\partial \beta_H} \times \frac{\beta_H}{R_0} \\ \\ = \frac{1}{2}(a_0\beta_H)^{\frac{-1}{2}} \times a_0 \times \frac{\beta_H}{R_0} \\ = \frac{a_0}{2\sqrt{a_0\beta_H}} \times \frac{\beta_H}{\sqrt{a_0\beta_H}} \\ \\ = \frac{1}{2} \end{cases} \tag{3.3.87}$$

R_0 to Λ_H

Let

$$a_0 = \frac{N_g \beta_H N_S \alpha_S \alpha_g \beta_V \Lambda_V}{\mu_H \mu_g \mu_V \mu_S P_0 G_0 (\mu_V + \delta_V)(\mu_H + \alpha_H + \delta_H)} \tag{3.3.88}$$

$$R_0 = \sqrt{a_0 \Lambda_H} \tag{3.3.89}$$

$$\begin{cases} \Upsilon_{\Lambda_H}^{R_0} = \frac{\partial R_0}{\partial \Lambda_H} \times \frac{\Lambda_H}{R_0} \\ \\ = \frac{1}{2}(a_0\Lambda_H)^{\frac{-1}{2}} \times a_0 \times \frac{\Lambda_H}{R_0} \\ = \frac{a_0}{2\sqrt{a_0\Lambda_H}} \times \frac{\Lambda_H}{\sqrt{a_0\Lambda_H}} \\ \\ = \frac{1}{2} \end{cases} \tag{3.3.90}$$

R_0 to N_S

Let

$$a_0 = \frac{N_g\Lambda_H\alpha_g\beta_H\alpha_S\beta_V\Lambda_V}{\mu_H\mu_g\mu_V\mu_S P_0 G_0(\mu_V+\delta_V)(\mu_H+\alpha_H+\delta_H)} \tag{3.3.91}$$

$$R_0 = \sqrt{a_0 N_S} \tag{3.3.92}$$

$$\begin{cases} \Upsilon_{N_S}^{R_0} = \frac{\partial R_0}{\partial N_S} \times \frac{N_S}{R_0} \\ \\ = \frac{1}{2}(a_0 N_S)^{\frac{-1}{2}} \times a_0 \times \frac{N_S}{R_0} \\ = \frac{a_0}{2\sqrt{a_0 N_S}} \times \frac{N_S}{\sqrt{a_0 N_S}} \\ \\ = \frac{1}{2} \end{cases} \tag{3.3.93}$$

R_0 to β_V

Let

$$a_0 = \frac{N_g\Lambda_H N_S\alpha_g\beta_H\alpha_S\Lambda_V}{\mu_H\mu_g\mu_V\mu_S P_0 G_0(\mu_V+\delta_V)(\mu_H+\alpha_H+\delta_H)} \tag{3.3.94}$$

$$R_0 = \sqrt{a_0\beta_V} \tag{3.3.95}$$

$$\begin{cases} \Upsilon_{\beta_V}^{R_0} = \frac{\partial R_0}{\partial \beta_V} \times \frac{\beta_V}{R_0} \\ \\ = \frac{1}{2}(a_0\beta_V)^{\frac{-1}{2}} \times a_0 \times \frac{\beta_V}{R_0} \\ = \frac{a_0}{2\sqrt{a_0\beta_V}} \times \frac{\beta_V}{\sqrt{a_0\beta_V}} \\ \\ = \frac{1}{2} \end{cases} \tag{3.3.96}$$

By the same argument we get the other parameter as shown in the table

Parameter	Description	Sign	Value
α_g	Gametocytes recovery in human	+	0.5
α_S	Sporozoite recovery in human	+	0.5
α_H	Human recovery	-	0.0025
δ_H	Infected death rate of human	-	0.5
δ_V	Infected death rate of mosquito vector	-	0.5
N_g	Population of gametocytes inside the infected human	+	0.5
N_S	Community population of sporozoites inside the infected mosquito vectors	+	0.5
β_H	Human infected rate	+	0.5
β_V	Mosquito infected rate	+	0.5
Λ_H	Human birth rate	+	0.5
Λ_V	Mosquito birth rate	+	0.5
μ_H	Human natural death rate	-	0.504
μ_g	Gametocytes natural death rate	-	0.5
μ_V	Mosquito vector natural death rate	-	0.82
μ_S	Sporozoites natural death rate	-	0.5
G_0	Gametocytes saturated constant	-	0.5
P_0	Sporozoites saturated constant	-	0.5

Table 3.2: The sensitivity indices, $\frac{\partial R_0}{\partial \partial u} \times \frac{u}{R_0}$ of the variable of the variable of the human host and mosquito vector in table 3 and table 4, measure the relative change in the solution to the changes in the parameters.

3.4 Numerical simulation

In this section, we present the numerical analysis of the model. A numerical simulation of the model system (3.2.5) is conducted to find out the dynamics of the disease in the human population. The simulation were conducted using python and MATLAB ode45.

3.4.1 Table of simulation

Parameter	Meaning	Baseline value	Range explored	Units	Source or Rational
Λ_H	Supply rate of susceptible humans	0.00011	0.00011-0.00016	day^{-1}	Estimated
β_H	Maximum exposure rate of humans	0.5	0.5000-0.8000	day^{-1}	[73]
α_H	Natural recovery rate of humans	$\frac{1}{200}$	$\frac{1}{200}$	day^{-1}	[6]
μ_H	Natural death rate of humans	0.0000391	0.00004899	day^{-1}	[3, 31]
δ_H	Disease induced death rate of humans	0.00000426	0.00000426-0.000005333	day^{-1}	[2]
α_G	Natural recovery of human to Gametocytes	0.002	0.002-0.005	day^{-1}	Estimated
N_G	Community of gametocytes inside the infected human	0.089	0.089-0.099	day^{-1}	Estimated
μ_G	Natural death rate of Gametocytes	0.002	0.002-0.005	day^{-1}	Estimated

Table 3.3: Between-human host parameter values for model system

Parameter	Meaning	Baseline value	Range explored	Units	Source or Rational
Λ_V	Supply rate of susceptible mosquitoes	0.071	0.071-0.083	day^{-1}	[5]
β_V	Maximum exposure rate of mosquitoes	0.83	0.830000-0.9300	day^{-1}	[45]
μ_V	Natural death rate of mosquito	0.071	0.071-0.093	day^{-1}	[36, 77]
N_S	Community population of sporozoites inside the infected vectors	0.2	0.2-0.9	day^{-1}	Estimated
P_0	Saturation constant of sporozoites	0.02	0.02-0.08	day^{-1}	Estimated
δ_V	Infection induce death rate of mosquito	0.04	0.04-0.08	day^{-1}	Estimated
μ_S	Natural death rate of sporozoites	0.01	0.01-0.09	day^{-1}	Estimated

Table 3.4: Between mosquito vectors, parameter values for model system

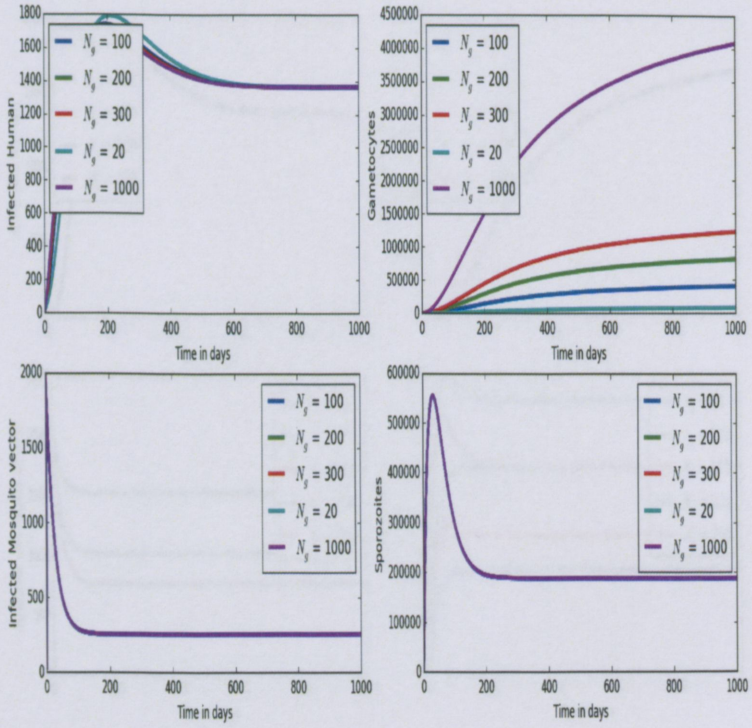

Figure 3.2: A numerical simulation of the malaria model system (3.2.5) with the values of the parameters given in tables 3.3 and 3.4. These parameters correspond to the reproductive number. The behavior of infected human and Gametocytes, differ for different value of N_g. Infected mosquito vector and sporozoite are the some for different value of N_g. The initial condition is: $S_H = 4000$, $I_H = 5$, $G_H = 100$, $S_V = 2000$, $I_V = 30$, $P_V = 10$; which correspond to $\Lambda_H = 0.8600$, $\Lambda_V = 5$, $\mu_1 = 0.003$, $\mu_2 = 0.0021$, $\mu_3 = 0.0324$, $\mu_4 = 0.0045$, $\delta_l = 0.0039$, $\delta_2 = 0.059$, $\alpha_l = 0.003$, $\alpha_2 = 0.007$, $\alpha_3 = 0.08$, $\beta_H = 0.0003457$, $\beta_V = 0.4432$, $P_0 = 40$, $N_1 = 0.089$, $N_2 = 0.0789$, $G_0 = 20$, $\in = 0.05$. The simulation were conducted using python

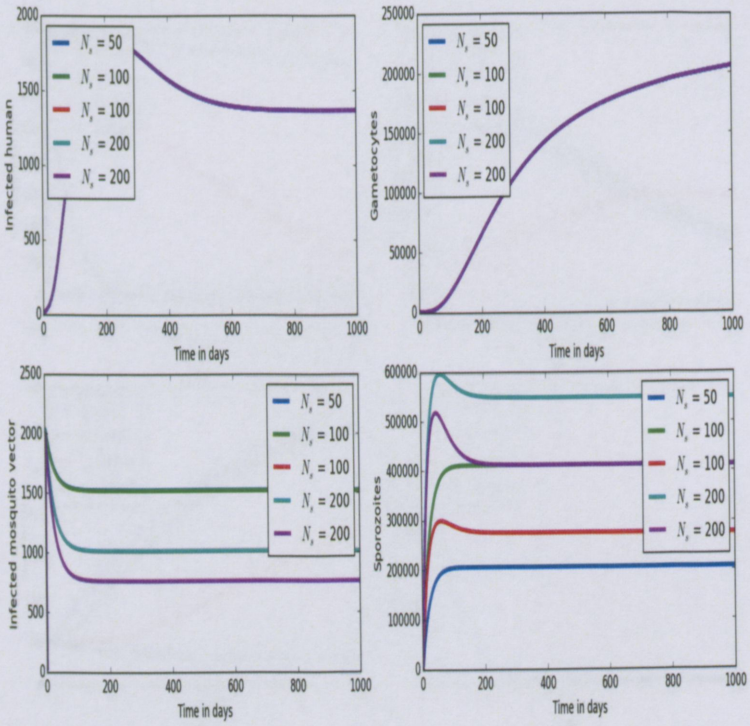

Figure 3.3: A numerical simulation of the malaria model system (3.2.5) with the values of the parameters given in table 3.3 and 3.4. These parameters correspond to the reproductive number. The behavior of sporozoite and infected mosquito vectors differ for different value of N_s. Infected human and Gametocytes remain the some for different value of N_s. The initial condition is: $S_H = 4000$, $I_H = 5$, $G_H = 100$, $S_V = 2000$, $I_V = 30$, $P_V = 10$; which correspond to $\Lambda_H = 0.8600$, $\Lambda_V = 5$, $\mu_1 = 0.003$, $\mu_2 = 0.0021$, $\mu_3 = 0.0324$, $\mu_4 = 0.0045$, $\delta_l = 0.0039$, $\delta_2 = 0.059$, $\alpha_l = 0.003$, $\alpha_2 = 0.007$, $\alpha_3 = 0.08$, $\beta_H = 0.0003457$, $\beta_V = 0.4432$, $P_0 = 40$, $N_1 = 0.089$, $N_2 = 0.0789$, $G_0 = 20$, $\in = 0.05$. The simulation were conducted using python

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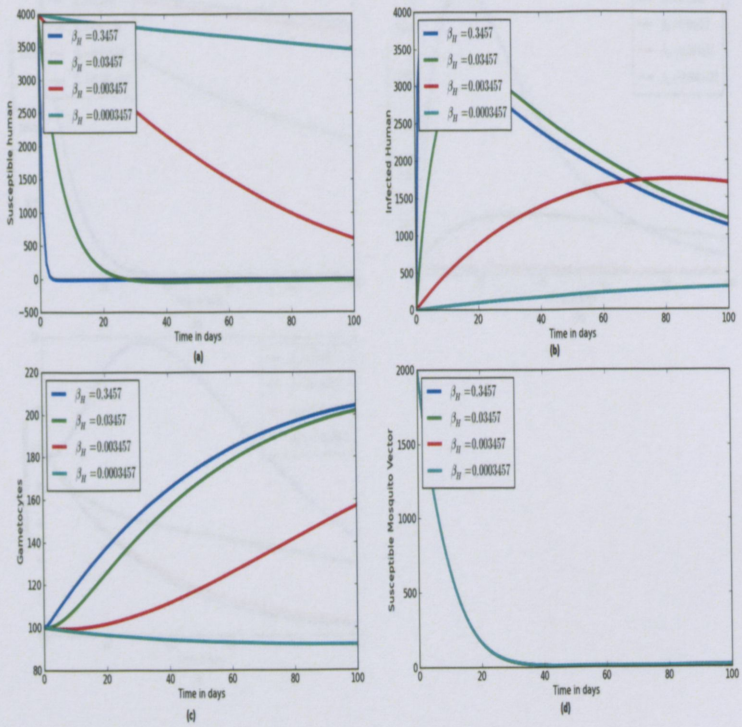

Figure 3.4: A numerical simulation of the malaria model system (3.2.5) with the values of the parameters given in the table 3.3 and. These parameters correspond to the reproductive number. The initial condition is $S_H = 4000$, $I_H = 5$, $G_H = 100$, $S_V = 2000$, $I_V = 30$, $P_V = 10$; which correspond to $\Lambda_H = 0.8600$, $\Lambda_V = 5$, $\mu_1 = 0.003$, $\mu_2 = 0.0021$, $\mu_3 = 0.0324$, $\mu_4 = 0.0045$, $\delta_l = 0.0039$, $\delta_2 = 0.059$, $\alpha_l = 0.003$, $\alpha_2 = 0.007$, $\alpha_3 = 0.08$, $\beta_H = 0.0003457$, $\beta_V = 0.4432$, $P_0 = 40$, $N_1 = 0.089$, $N_2 = 0.0789$, $G_0 = 20$, $\in = 0.05$. The simulation were conducted using python, for different values of the infection rate of humans β_H: $\beta_H = 0.3457$, $\beta_H = 0.03457$, $\beta_H = 0.003457$ $\beta_H = 0.0003457$. The simulation were conducted using python.

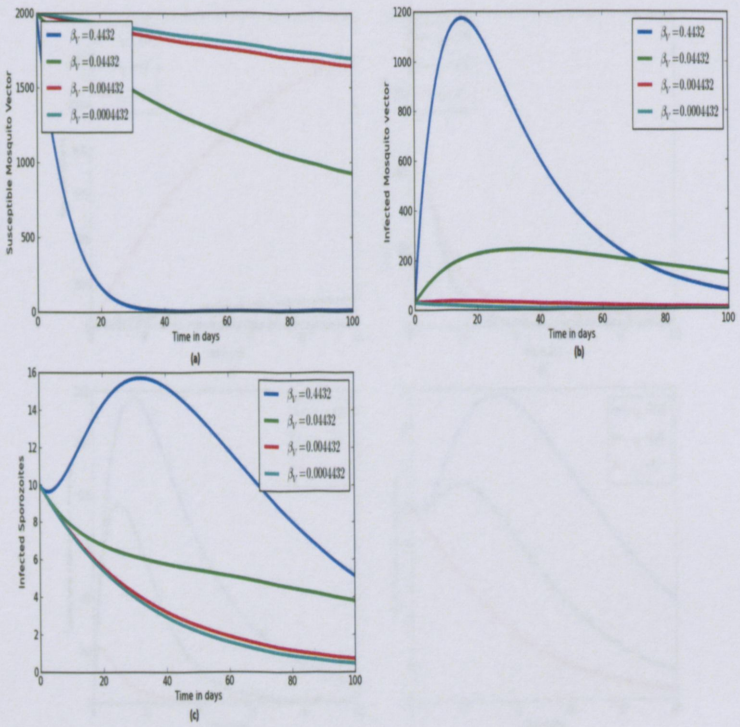

Figure 3.5: A numerical simulation of the malaria model system (3.2.5) with the values of the parameters given in the table 3.3 and 3.4. These parameters correspond to the reproductive number. The behavior of susceptible mosquito vectors, infected mosquito vectors and Sporozoite differ for different value of β_V. The initial condition is: $S_H = 4000$, $I_H = 5$, $G_H = 100$, $S_V = 2000$, $I_V = 30$, $P_V = 10$; which correspond to $\Lambda_H = 0.8600$, $\Lambda_V = 5$, $\mu_1 = 0.003$, $\mu_2 = 0.0021$, $\mu_3 = 0.0324$, $\mu_4 = 0.0045$, $\delta_l = 0.0039$, $\delta_2 = 0.059$, $\alpha_l = 0.003$, $\alpha_2 = 0.007$, $\alpha_3 = 0.08$, $\beta_H = 0.0003457$, $\beta_V = 0.4432$, $P_0 = 40$, $N_1 = 0.089$, $N_2 = 0.0789$, $G_0 = 20$, $\in = 0.05$. The simulation were conducted using python, for different values of the infection rate of mosquitoes vector β_V: $\beta_V = 0.4432$, $\beta_V = 0.04432$, $\beta_V = 0.004432$ $\beta_V = 0.0004432$. The simulation were conducted using python.

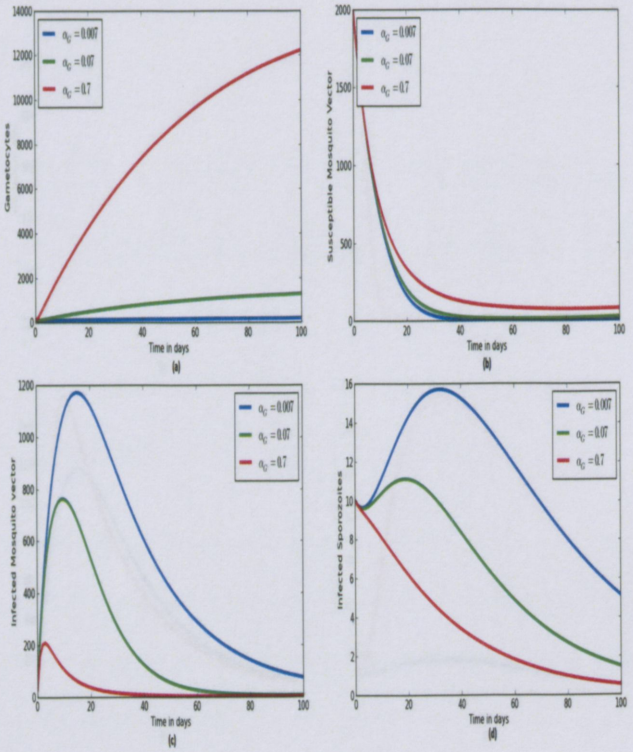

Figure 3.6: A numerical simulation of the malaria model system (3.2.5) with the values of the parameters given in table 3.3 and 3.4. These parameters correspond to the reproductive number. The behaviour of Gametocytes, Susceptible mosquito vectors, Infected mosquito vector and infected sporozoites differ for different value of α_g. The initial condition is: $S_H = 4000,\ I_H = 5,\ G_H = 100,\ \ S_V = 2000,\ I_V = 30,\ P_V = 10$; which correspond to $\Lambda_H = 0.8600,\ \ \Lambda_V = 5,\ \mu_1 = 0.003,\ \mu_2 = 0.0021,\ \mu_3 = 0.0324,\ \mu_4 = 0.0045,\ \delta_l = 0.0039,\ \delta_2 = 0.059,\ \alpha_l = 0.003,\ \ \alpha_2 = 0.007,\ \alpha_3 = 0.08,\ \beta_H = 0.0003457,\ \beta_V = 0.4432,\ \ P_0 = 40,\ N_1 = 0.089,\ N_2 = 0.0789,\ G_0 = 20,\ \in = 0.05$. The simulation were conducted using python, for different values of α_g: $\alpha_g = 0.007,\ \alpha_g = 0.07,\ \ \alpha_g = 0.7$. The simulation were conducted using python.

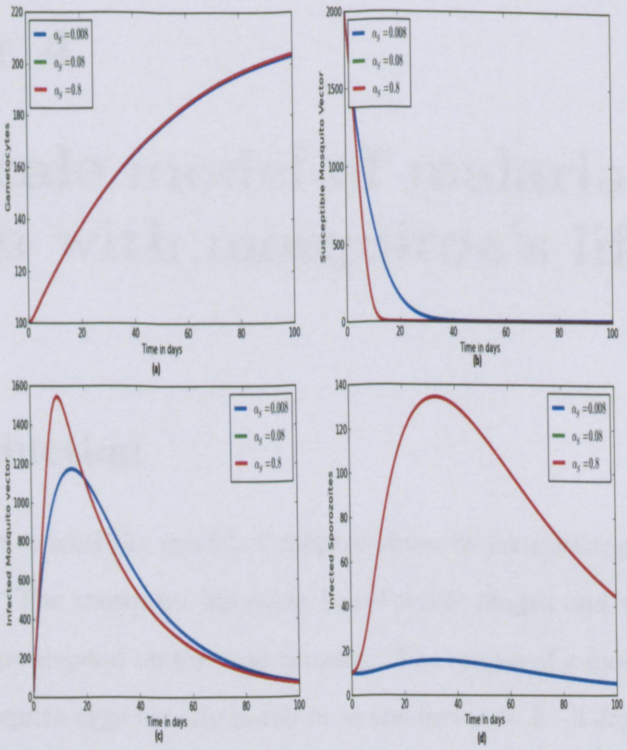

Figure 3.7: A numerical simulation of the malaria model system (3.2.5) with the values of the parameters given in table 3.3 and 3.4. These parameters correspond to the reproductive number. The behavior of gametocytes, susceptible mosquito vectors, infected mosquito vectors and Sporozoites differ for different value of αS. The initial condition is: $S_H = 4000$, $I_H = 5$, $G_H = 100$, $S_V = 2000$, $I_V = 30$, $P_V = 10$; which correspond to $\Lambda_H = 0.8600$, $\Lambda_V = 5$, $\mu_1 = 0.003$, $\mu_2 = 0.0021$, $\mu_3 = 0.0324$, $\mu_4 = 0.0045$, $\delta_l = 0.0039$, $\delta_2 = 0.059$, $\alpha_l = 0.003$, $\alpha_2 = 0.007$, $\alpha_3 = 0.08$, $\beta_H = 0.0003457$, $\beta_V = 0.4432$, $P_0 = 40$, $N_1 = 0.089$, $N_2 = 0.0789$, $G_0 = 20$, $\in = 0.05$. The simulation were conducted using python, for different values of α_S: $\alpha_S = 0.008$, $\alpha_S = 0.08$, $\alpha_S = 0.8$. The simulation were conducted using python.

Chapter 4

Multi-scale model of malaria infection with mosquitoe's life cycle

4.1 Introduction

In this chapter, we extend the model of chapter three by introducing the life cycle of mosquito vectors. The mosquito life cycle has discrete stages and the development time for these stages depend on the environment. The stages of a mosquito start with the eggs. The mosquito eggs usually hatch in to the larvae in $2-3$ days, although this process depends on the temperature and can take up to $2-3$ weeks in cold weather. The eggs are not resistant to drying, so they require water for successful hatching. The eggs develop to the larva which also require water and prefer clean unpolluted water [27]. The have to frequently rise to the water surface to breathe. They feed on algae, bacteria and other microorganisms. The larva develops into a pupa and the pupa also require water and need to resurface frequently to breathe [20]. The pupa develop into the adult mosquito vectors. The newly emerged adult rests on the surface of the water for a short time to allow itself to dry and all its body parts to harden. The wings have to spread out and dry properly before it can fly. Blood

feeding and mating do not occur for a couple of days after the adults emerge. Anopheles mosquito feeding on infected hosts ingest sexual forms developing in red blood cells. The female macrogametocyte mature in the mosquito stomach and combine forming a zygote that undergoes mitosis. The products of mitosis are ookinete, which force themselves between the epithelial cells to the outer surface of the stomach, and form into small spheres called oocysts.The oocysts enlarge as the nucleus divides, eventually rupturing and releasing thousands of motile sporozoites into the body cavity. The sporozoites migrate to the salivary glands, making the female mosquito infective. The vector phase of the life cycle, called sporogony, is completed in 8 to 35 days depending on species and environmental conditions. How long each stage lasts depends on both temperature and species characteristics.

The life cycle of malaria is complex with development stage and corresponding symptoms differing according to the plasmodium species involved [59, 75]. Sporozoites the infective stage of plasmodia are injected from the salivary glands of infected mosquitoes during feeding. The sporozoites disappear from the blood within 30 minutes. Many are destroyed by white blood cells, but some enter liver cells.

All infections due to P.falciparum and P.malariae is the primary type develop cause liver cell rupture and releases merozoites just as described for P.falciparum and P.malariae. The other form, which develops concurrently, is known as the hypnozoites. The sporozoites that enter liver cells differentiate into hypnozoites that remain dormant [9] for weeks, months, or years. At some future time, the hypnozoites become active and undergo exoerythrocytic schizogony, forming a wave of merozoites that

invade the blood and cause a delayed case or a clinical relapse.

The erythrocytic released merozoites invade red blood cells (erythrocytes), where they develop into trophozoite [42, 62, 67, 80].

After a period of growth, the trophozoites divide and develop, eventually forming $(8 - 24)$ merozoites in each red blood cell. When this process is complete, the host red blood cells rupture, releasing mature merozoites. The symptoms associated with malaria occur at this point. The merozoites then invade fresh erythrocytes and another generation of parasites develop in the same manner. This process occurs repeatedly during the course of infection and is called erythrocytic schizogony. The length of this development cycle differs according to the species of parasite, varying from 48 hours in vivax, ovale, and falciparum malaria, to 72 hours in P.malariae infections. In the early stages of infection there is no characteristic periodicity as groups of parasite develop at different times. The febrile episodes caused are inconsistent. Later, the erythrocytic schizogony development cycle becomes synchronized, and the febrile paroxysms become more consistent. Some merozoites differentiate into sexual forms (female macrogametocyte, male micro-gametocytes) and develop in invaded red blood cells.

Anopheles mosquitoes are essential for development, multiplication, and spread of plasmodia. Therefore, any area harboring Anopheles mosquitoes may be at risk for malaria transmission. Specific environmental conditions optimal for anopheline mosquito vector and parasite development include temperature between 20^0 and 30^0

and a mean relative humidity of 60 [10, 20]. The sporogony phase requires temperature between 16^0 and 33^0c [44]. High relative humidity increase mosquito life-span, thereby increasing the probability of mosquitoes becoming infective. Areas with high rainfall have increased malaria incidence because of an increase in breeding sites. The accompanying high humidity increase survival rates of female anopheline mosquitoes. Elevation, along with cooler temperatures and lower humidity, is also a factor as transmission rarely occurs above $2000 - 2500$ meters. When an infectious mosquito bites a human, the parasite in the form of sporozoite in the silava of mosquito enter the human. The sporozoites then migrate to the liver, invading the hepatic cells. In $5 - 15$ days, the sporozoites develop into schizonts. The schizonts contain thousand of daughter merozoites cells.

4.2 Model description formulation

The model is based on monitoring the dynamics of the population at any time t of eggs of mosquito vectors E(t), larva of mosquito vectors L(t), pupa of mosquito vectors P(t), adult of mosquito vectors $S_V(t)$, infected mosquito vectors $I_V(t)$, Sporozoite $P_V(t)$, susceptible humans $S_H(t)$, infected humans $I_H(t)$ and Gametocytes G_H. The model has nine non-linear differential equations which describe the spread of malaria,where six state variables are associated with mosquito vectors and three state variables with human hosts. The vector population does not include immune class as mosquito never recover from infection, that is their infection period ends with their death due to the relatively life-cycle [24, 39, 74, 78].

The model that we formulate traces explicitly the life-cycle of malaria parasite

from mosquito vectors to human host. The table below describes the variables of the model (4.2.1) with estimated initial data

Variable	Description	Initial value	Sources
E(t)	Eggs of mosquito vectors	1000	Estimated
L(t)	Larva of mosquito vectors	70	Estimated
P(t)	Pupa of mosquito vectors	70	Estimated
$S_V(t)$	Number of mosquito vector to malaria infection at time t	4000	Estimated
$I_V(t)$	Number of mosquito vector to malaria infection at time t	5	Estimated
$P_V(t)$	Community population of sporozoites inside the infected mosquito vectors at time t	100	Estimated
$S_H(t)$	Number of host human susceptible to malaria infection at time t	2000	Estimated
$I_H(t)$	Number of infections host humans at time t	30	Estimated
$G_H(t)$	Community population of gametocytes inside the infected human at time t	20	Estimated

Table 4.1: List of Variables and their descriptions

The schematic diagram of the transmission of malaria in humans according to our model is shown below

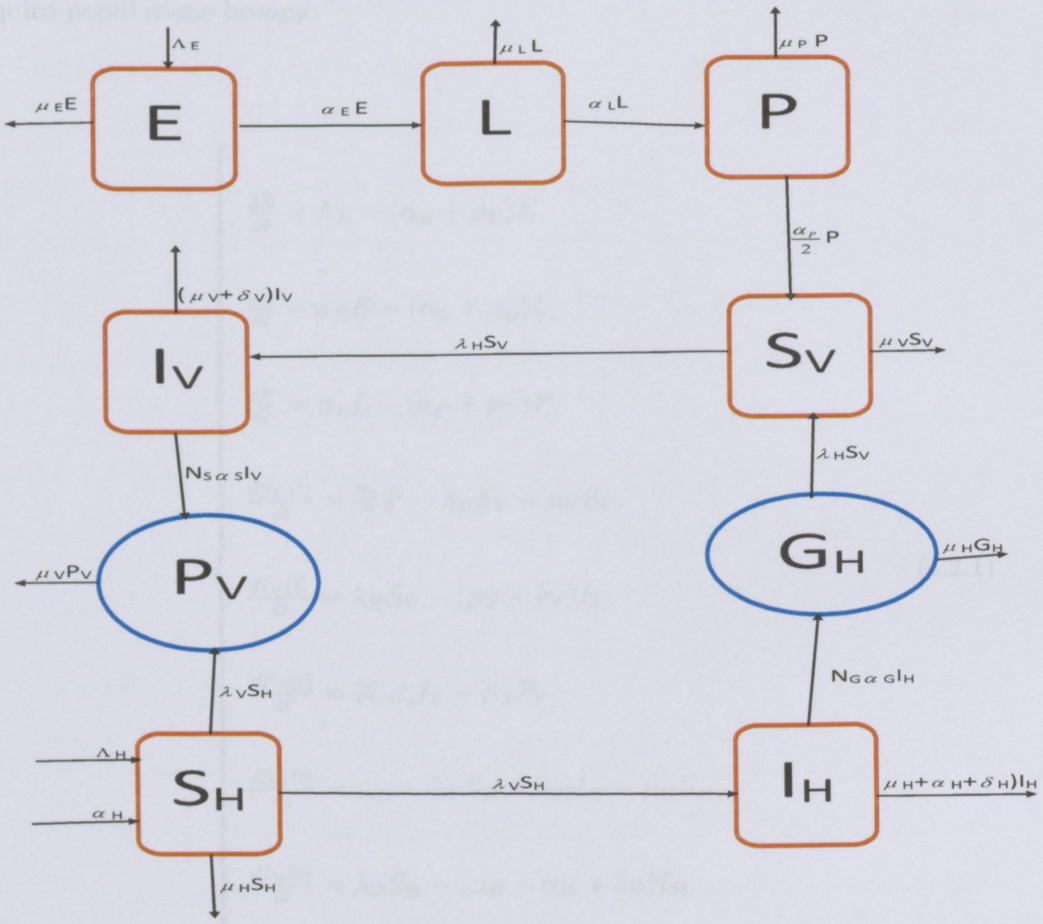

Figure 4.1: The compartmental model of human host with life cycle of mosquito vectors

By considering the above assumptions, notation of variables and parameters, the ordinary differential equations which describe the dynamics of malaria in human and mosquito populations become

$$
\begin{cases}
\frac{dE}{dt} = \Lambda_E - (\alpha_E + \mu_E)E, \\
\frac{dL}{dt} = \alpha_E E - (\alpha_L + \mu_L)L, \\
\frac{dP}{dt} = \alpha_L L - (\alpha_P + \mu_P)P, \\
\frac{dS_V(t)}{dt} = \frac{\alpha_P}{2} P - \lambda_H S_V - \mu_V S_V, \\
\frac{dI_V(t)}{dt} = \lambda_H S_V - (\mu_V + \delta_V)I_V, \\
\frac{dP_V(t)}{dt} = N_s \alpha_s I_V - \mu_S P_V, \\
\frac{dS_H(t)}{dt} = \Lambda_H - \lambda_V S_H + \alpha_H I_H - \mu_H S_H, \\
\frac{dI_H(t)}{dt} = \lambda_V S_H - (\mu_H + \alpha_H + \delta_H)I_H, \\
\frac{dG_H(t)}{dt} = N_g \alpha_g I_H - \mu_G G_H.
\end{cases}
\tag{4.2.1}
$$

The first equation describes the dynamics of mosquito eggs, $E(t)$, first term on the right of this equation, Λ_E, represents the supply rate of the mosquito eggs. The second term is the sum of the product of natural death rate of mosquito eggs μ_E. Since the eggs do not recover,α_E, the term $\alpha_E E$ disappear. The second equation

represents the dynamics of Larva at a time t. The first term on the right of this equation is the product of α_E, by mosquito vectors eggs E, since the eggs do not recover this term disappear. The second term of this equation represent natural death rate of Larva, μ_L, since the larva do not recover, the term $\alpha_L L$ disappear. The third equation represents the dynamics pupa $P(t)$ and μ_p represent natural death rate of the pupa. Since the pupa do not recover, then the term $\alpha_P P$ disappear. The fourth equation represents the dynamics of Susceptible mosquito S_V. The second term of this equation is the product of force infection, λ_H, by susceptible mosquito vectors. The third term of this equation is the product of natural death rate of mosquito vectors, λ_V, by mosquito vectors. The third term of this equation is the product of natural death rate of mosquito vectors, λ_V, by mosquito vectors S_V. Since the model in chapter 4 is the extension of chapter 3, the other remaining equation was explained in chapter 3.

4.3 Analysis of the model

We analyze the model to check if the intervention strategies have any impact on the disease, that is whether the disease be eradicated or not. The threshold parameters which determine persistence or elimination of malaria will be determined and studied. Therefore, we start by determining the invariant region to check whether the model is biological meaningful and showing that all solution of (4.2.1) are positive for $\forall\ t \geq 0$ and are attracted in the region.

4.3.1 Feasible region of equilibria of model

Let Ω_H be the set of susceptible humans, infected humans and gametocytes. Ω_V is the set comprising susceptible mosquito vectors, Infected mosquito vectors and sporozoites. Ω is the set comprising Ω_H and Ω_V.

Theorem: *The solution of the system* (4.2.1) *is feasible for all* $t \geq 0$ *if the solution belong to the* $\Omega = \Omega_H + \Omega_V$.

Proof: Let $\Omega = (E, L, P, S_V, I_V, P_V, S_H, I_H, G_H) \in \mathbb{R}^9$ be any solution of the system (4.2.1) with non-negative initial conditions. By adding seventh and eighth equations of model system (4.2.1) in the absence of the disease (malaria), that is, $I_H = 0$ and letting $N_H = S_H + I_H$, then equation (4.2.1) becomes

$$\frac{dN_H(t)}{dt} \leq \Lambda_H - \mu_H N_H. \tag{4.3.1}$$

This implies that

$$\limsup_{t \to 0}(N_H(t)) \leq \frac{\Lambda_H}{\mu_H}. \tag{4.3.2}$$

that is N_H is bounded from above by $\frac{\Lambda_H}{\mu_H}$.

Similarly, letting $N_V = S_V + I_V$ and adding fourth and fifth equations of model system equation (4.2.1) we obtain

$$\frac{dN_V(t)}{dt} \leq \Lambda_V - \mu_V N_V, \tag{4.3.3}$$

This implies that

$$\limsup_{t \to 0}(N_V(t)) \leq \frac{\Lambda_V}{\mu_V}. \tag{4.3.4}$$

that is N_V is bounded from above by $\frac{\Lambda_H}{\mu_V}$.

Similar inequality can be derived for third and sixth equations of model system (4.2.1). Hence, all solutions of the system (4.2.1) enter the invariant attracting region

$$\begin{cases} \Omega\{(E, L, P, S_V, I_V, P_V, S_H, I_H, G_H); 0 \leq E \leq M_1, 0 \leq L \leq M_2, \\ 0 \leq P \leq M_3, 0 \leq S_V + I_V \leq M_4, 0 \leq P_V \leq M_5 \\ 0 \leq S_H + I_H \leq M_6, 0 \leq G_H \leq M_7\}, \end{cases} \tag{4.3.5}$$

where

$$\begin{cases} M_1 = \frac{\Lambda_E}{(\alpha_E+\mu_E)}, \\ M_2 = \frac{\alpha_E}{(\alpha_l+\mu_l)} \frac{\Lambda_E}{(\alpha_E+\mu_E)}, \\ M_3 = \frac{\alpha_l}{(\alpha_P+\mu_P)} \frac{\alpha_E}{(\alpha_l+\mu_l)} \frac{\Lambda_E}{(\alpha_E+\mu_E)}, \\ M_4 = \frac{\alpha_p}{2\mu_V} \frac{\alpha_l}{(\alpha_P+\mu_P)} \frac{\alpha_E}{(\alpha_l+\mu_l)} \frac{\Lambda_E}{(\alpha_E+\mu_E)}, \\ M_5 = \frac{N_S\alpha_S}{\mu_S} \frac{\alpha_p}{2\mu_V} \frac{\alpha_l}{(\alpha_P+\mu_P)} \frac{\alpha_E}{(\alpha_l+\mu_l)} \frac{\Lambda_E}{(\alpha_E+\mu_E)}, \\ M_6 = \frac{\Lambda_H}{\mu_H}, \\ M_7 = \frac{N_G\alpha_G\Lambda_H}{\mu_G\mu_H}. \end{cases} \tag{4.3.6}$$

Therefore the solution of model (4.2.1) enter the invariant region Ω. The model (4.2.1) is biologically meaningful and mathematical well-posed in the domain Ω.

4.3.2 Positivity of solution

In order to show that the solution is positive we need to show that

$$\{E(t), L(t), P(t), S_V(t), I_V(t), P_V(t), S_H(t), I_H(t), G_H(t)\} \in \Omega \tag{4.3.7}$$

where $E(t), L(t), P(t)) > 0$,$S_V(t), S_H, > 0$,$P_V(t), I_V(t), I_H(t), G_H(t) \geq 0 \ \ \forall t > 0$.
From the first equation in the model system (4.2.1), $\Lambda_E >$, we have

$$\frac{E(t)}{dt} > -(\alpha_E + \mu_E)E(t), \tag{4.3.8}$$

Separating the variables and then integrating the differential inequality we obtain that

$$E(t) \geq E(0) \exp -(\alpha_E + \mu_E)t > 0. \tag{4.3.9}$$

Since $E > 0$, from second equation of the model system (4.2.1) we obtain

$$\frac{dL(t)}{dt} > -(\alpha_l + \mu_l)L(t), \tag{4.3.10}$$

Separating the variables and then integrating the differential inequality we obtain that

$$L(t) \geq L(0) \exp -(\alpha_l + \mu_l)t > 0. \tag{4.3.11}$$

since $L > 0$, from third equation of model system (4.2.1) we obtain

$$\frac{dP}{dt} > -(\alpha_P + \mu_P)P(t), \tag{4.3.12}$$

Separating the variables and then integrating the differential inequality we obtain that

$$P(t) \geq P(0) \exp -(\alpha_p + \mu_p)t > 0. \tag{4.3.13}$$

Since $P > 0$, from the fourth equation of model system (4.2.1) we obtain

$$\frac{dS_V(t)}{dt} > -(\mu_V + \lambda_H(t))S_V(t), \tag{4.3.14}$$

Separating the variables and then integrating the differential inequality we obtain that

$$S_V(t) \geq S_V(0)\exp\left(-\int_0^t (\mu_V + \lambda_H(\tau))d\tau > 0. \right. \tag{4.3.15}$$

Since $S_V > 0$, from the fifth equation of model system (4.2.1), we obtain:

$$\frac{dI_V(t)}{dt} = -(\mu_V + \delta_V)I_V(t), \tag{4.3.16}$$

Separating the variables and then integrating the differential inequality we obtain that

$$I_V(t) \geq I_V(0)\exp -(\mu_V + \lambda_V) > 0. \tag{4.3.17}$$

since $I_V > 0$, from the sixth equation of model system (4.2.1) we obtain:

$$\frac{dP_V(t)}{dt} > -\mu_S P_V(t), \tag{4.3.18}$$

Separating the variables and then integrating the differential inequality we obtain that

$$P_V(t) \geq P_V(0)\exp -\mu_S(t) > 0. \tag{4.3.19}$$

From the seventh equation of model system (4.2.1), we assume that $\Lambda_H > 0$ and $I_H = 0$, from this assumption we obtain

$$\frac{dS_H(t)}{dt} > -(\mu_H + \lambda_V(t))S_H(t), \tag{4.3.20}$$

Separating the variables and then integrating the differential inequality we obtain that

$$S_H(t) \geq S_H(0) \exp\left(-\int_0^t (\mu_H + \lambda_V(\tau))d\tau > 0. \right. \tag{4.3.21}$$

Since $S_H > 0$, from eighth equation of model system (4.2.1) we obtain

$$\frac{dI_H(t)}{dt} > -(\mu_H + \alpha_H + \delta_H(t))I_H(t), \tag{4.3.22}$$

Separating the variables and then integrating the differential inequality we obtain that

$$I_H(t) \geq I_H(0) \exp -(\mu_H + \lambda_H + \delta_H) > 0. \tag{4.3.23}$$

Since $I_H > 0$, from the ninth equation of model system (4.2.1) we obtain

$$\frac{dG_H(t)}{dt} > -\mu_G G_H(t), \tag{4.3.24}$$

Separating the variables and then integrating the differential inequality we obtain that

$$G_H(t) > G_H(0) \exp -\mu_G(t) > 0. \tag{4.3.25}$$

This shows that the solutions of the model system (4.2.1) are positive for all $t > 0$, because $\exp \mu_H t > 0$ for all $\mu_H \in \mathbb{R}$. Now that it has been established that our model has both the invariant and positive of solutions, we can move on to determine the existence of the equilibrium point which will assist in calculation of the reproductive number by the next generation methods.

4.3.3 Existence of steady-state solution

The infection-free equilibrium state is represented by the solution of the system of equation (4.2.1) with the right-hand side of the equations set equal to zero. Such solutions are also called steady state solutions. Let

$E(E^*, L^*, P^*, S_V^*, I_V^*, P_V^*, S_H^*, I_H^*, G_H^*)$ be the steady state solution obtained after setting

$\frac{dE}{dt} = \frac{dL}{dt} = \frac{dP}{dt} = \frac{dS_V}{dt} = \frac{dI_V}{dt} = \frac{dP_V}{dt} = \frac{dS_H}{dt} = \frac{dI_H}{dt} = \frac{dG_H}{dt} = 0$ in system (4.2.1). The steady state solution obtained by solving (4.3.26)

$$
\begin{cases}
\Lambda_E - (\alpha_E + \mu_E)E^* = 0, \\
\alpha_E E^* - (\alpha_l + \mu_l)L^* = 0, \\
\alpha_l L^* - (\alpha_p + \mu_p)P^* = 0, \\
\frac{\alpha_p}{2} P^* - \lambda_H^* S_V^* - \mu_V S_V^* = 0, \\
\lambda_H^* S_V^* - (\mu_V + \delta_V)I_V^* = 0, \\
N_S \alpha_S I_V^* - \mu_S P_V^* = 0, \\
\Lambda_H - \lambda_V^* S_H^* + \alpha_H I_H^* - \mu_H S_H^* = 0, \\
\lambda_V^* S_H^* - (\mu_H + \alpha_H + \delta_H)I_H^* = 0, \\
N_G \alpha_G I_H^* - \mu_G G_H^* = 0.
\end{cases}
\tag{4.3.26}
$$

4.3.4 Disease-free equilibrium (DFE)

Disease-free equilibrium point is point at which a steady state solution is achieved, that is there is no malaria parasite in the human population or plasmodium parasite in the mosquito population. Let us define the disease classes as human or mosquito populations that are infected or infectious, that is, I_H, G_H, I_V and P_V . In the absence of the disease, we have $I_H^* = G_H^* = I_V^* = P_V^* = 0$.

Therefore system (4.3.26) becomes

$$\begin{cases} \Lambda_E - (\alpha_E + \mu_E)E^* = 0, \\ \alpha_E E^* - (\alpha_L + \mu_L)L^* = 0, \\ \alpha_l L^* - (\alpha_p + \mu_p)P^* = 0, \\ \mu_V S_V^* - \frac{\alpha_p}{2} P^* = 0, \\ \Lambda_H - \mu_H S_H^* = 0, \end{cases} \tag{4.3.27}$$

which implies that

$$\begin{cases} E^* = \frac{\Lambda_E}{(\alpha_E+\mu_E)}, \\ L^* = \frac{\alpha_E}{(\alpha_l+\mu_l)}\frac{\Lambda_E}{(\alpha_E+\mu_E)}, \\ P^* = \frac{\alpha_l}{(\alpha_p+\mu_p)}\frac{\alpha_E}{(\alpha_l+\mu_l)}\frac{\Lambda_E}{(\alpha_E+\mu_E)}, \\ S_V^* = \frac{\alpha_p\alpha_l\alpha_E\Lambda_E}{2(\alpha_E+\mu_E)(\alpha_l+\mu_l)(\alpha_p+\mu_p)\mu_V}, \\ S_H^* = \frac{\Lambda_H}{\mu_H}. \end{cases} \tag{4.3.28}$$

Therefore, the disease-free equilibrium point of malaria model system (4.2.1) is given by

$$\begin{aligned} E_0 &= (E^*, L^*, P^*, S_V^*, I_V^*, P_V^*, S_H^*, I_H^*, G_H^*) \\ &= (\tfrac{\Lambda_E}{(\alpha_E+\mu_E)}, \tfrac{\alpha_E}{(\alpha_l+\mu_l)}\tfrac{\Lambda_E}{(\alpha_E+\mu_E)}, \\ &\tfrac{\alpha_l}{(\alpha_p+\mu_p)}\tfrac{\alpha_E}{(\alpha_l+\mu_l)}\tfrac{\Lambda_E}{(\alpha_E+\mu_E)}, \tfrac{\alpha_p\alpha_l\alpha_E\Lambda_E}{2(\alpha_E+\mu_E)(\alpha_l+\mu_l)(\alpha_p+\mu_p)\mu_V}, 0, 0, \tfrac{\Lambda_H}{\mu_H}, 0, 0) \end{aligned} \tag{4.3.29}$$

which represent the state in which there is no infection of malaria in the society.

4.3.5 Basic reproduction number

The basic reproduction number R_0, is a threshold value that is often used in Mathematical model to measure the spread of a disease. It is defined as the number of new infections in humans that arise as a result of a single infected individual being

introduced in a fully susceptible population. When $R_0 < 1$, it implies that on average an infectious individual infects less than one person throughout his /her infectious period and in this case the disease is wiped out. On the other hand, when $R_0 > 1$, then on average every infectious individual infects more than one individual during his/ her infectious period and the disease persist in the population. P.van den Dressage and J. Although [79] described the next generation method used to compute the basic reproduction number. Given as system, where is the rate at which new infection appear in each comportment, is the rate of transfer into each compartment and is the rate of transfer out of each compartment. The model (4.2.1) can be written in the form of

$$\begin{cases} \frac{dX}{dt} = f(X, Y, Z), \\ \frac{dY}{dt} = g(X, Y, Z), \\ \frac{dZ}{dt} = h(X, Y, Z). \end{cases} \tag{4.3.30}$$

where

$$\begin{cases} X = (S_V, S_H), \\ Y = (E, L, P, I_V, I_H), \\ Z = (P_V, G_H). \end{cases} \tag{4.3.31}$$

The component X denote the number of susceptibles, while the component Y represent the number of infected individuals that do not transmit the disease. Component of Z represent the number of individuals capable of transmitting the disease.
Following [18] we define by $\tilde{g}(X^*, Z)$ by

$$\tilde{g}(X^*, Z) = (\tilde{g_1}(X^*, Z), \tilde{g_2}(X^*, Z), \tilde{g_3}(X^*, Z), \tilde{g_4}(X^*, Z)\tilde{g_5}(X^*, Z)), \tag{4.3.32}$$

with

$$\begin{cases} \tilde{g_1}(X^*, Z) = \frac{\Lambda_E}{(\alpha_E+\mu_E)}, \\ \tilde{g_2}(X^*, Z) = \frac{\alpha_E}{(\alpha_l+\mu_l)} \frac{\Lambda_E}{(\alpha_E+\mu_E)}, \\ \tilde{g_3}(X^*, Z) = \frac{\alpha_l}{(\alpha_p+\mu_p)} \frac{\alpha_E}{(\alpha_l+\mu_l)} \frac{\Lambda_E}{(\alpha_E+\mu_E)}, \\ \tilde{g_4}(X^*, Z) = \frac{\beta_H G_H \alpha_p \alpha_l \alpha_E \Lambda_E}{(G_0+\epsilon G_H)\Phi_1}, \\ \tilde{g_5}(X^*, Z) = \frac{\beta_V P_V \Lambda_H}{(P_0+\epsilon P_V)\Phi_2}, \end{cases} \tag{4.3.33}$$

where

$$\begin{cases} \Phi_1 = 2\mu_V(\alpha_p + \mu_p)(\alpha_l + \mu_l)(\alpha_E + \mu_E)(\mu_V + \delta_V), \\ \Phi_2 = (\mu_H + \alpha_H + \delta_H)\mu_H. \end{cases} \tag{4.3.34}$$

Substituting the value of $\tilde{g_4}(X^*, Z)$ and $\tilde{g_5}(X^*, Z)$ into model system (4.2.1) of equation 6 and 9 we have that

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$$\begin{cases} h_1 = N_S\alpha_S\tilde{g}_4(X^*, Z) - \mu_S P_V, \\ \\ h_2 = N_G\alpha_G\tilde{g}_5(X^*, Z) - \mu_G G_H. \end{cases} \tag{4.3.35}$$

$$h = \begin{cases} h_1 = \frac{N_S\alpha_S G_H\beta_H\alpha_p\alpha_l\alpha_E\Lambda_E}{2(G_0+\epsilon G_H)\Phi_1} - \mu_S P_V, \\ \\ h_2 = \frac{N_G\alpha_G\beta_V P_V\Lambda_H}{(P_0+\epsilon P_V)\Phi_2} - \mu_G G_H. \end{cases} \tag{4.3.36}$$

Let $A = D_z h(X^*, \tilde{g}(X^*, 0), 0)$ and further assume that A can be written in the form $A = M - D$, where $M \geq 0$ and $D > 0$, a diagonal matrix.

The partial derivatives of h_1 and h_2 with respect to P_V and G_H at disease free state, respectively, are

$$\begin{cases} \frac{\partial h_1}{\partial P_V} = -\mu_S, \\ \\ \frac{\partial h_1}{\partial G_H} = \frac{N_S\alpha_S\beta_H\alpha_p\alpha_L\alpha_E\Lambda_E}{\Phi_1 G_0}, \\ \\ \frac{\partial h_2}{\partial P_V} = \frac{N_G\alpha_G\beta_V\Lambda_H}{P_0\mu_H\Phi_2}, \\ \\ \frac{\partial h_2}{\partial G_H} = -\mu_G. \end{cases} \tag{4.3.37}$$

Then A becomes

$$A = \begin{pmatrix} -\mu_S & \frac{N_S\alpha_S\beta_H\alpha_p\alpha_l\Lambda_E}{\Phi_1\mu_G G_0} \\ \frac{N_G\alpha_G\beta_V\Lambda_H}{P_0\mu_S\Phi_2} & -\mu_G \end{pmatrix} \tag{4.3.38}$$

Since $A = M - D$, we deduce matrices M and D to be

$$M = \begin{pmatrix} 0 & \frac{N_S \alpha_S \beta_H \alpha_p \alpha_l \Lambda_E}{\Phi_1 \mu_G G_0} \\ \frac{N_G \alpha_G \beta_V \Lambda_H}{P_0 \mu_S \Phi_2} & 0 \end{pmatrix}. \tag{4.3.39}$$

$$D = \begin{pmatrix} \mu_S & 0 \\ 0 & \mu_G \end{pmatrix} \tag{4.3.40}$$

$$\Rightarrow D^{-1} = \begin{pmatrix} \frac{1}{\mu_S} & 0 \\ 0 & \frac{1}{\mu_G} \end{pmatrix} \tag{4.3.41}$$

$$\left| MD^{-1} - \lambda I \right| = \begin{vmatrix} -\lambda & \frac{N_S \alpha_S \beta_H \alpha_p \alpha_l \alpha_E \Lambda_E}{\Phi_1 G_0 \mu_G} \\ \frac{N_G \alpha_G \beta_V \Lambda_H}{P_0 \Phi_2 \mu_S} & -\lambda \end{vmatrix} = 0 \tag{4.3.42}$$

The basic reproduction numbers for human and mosquito life cycle vectors are given by, respectively.

$$R_{0H} = \frac{N_g \alpha_g \beta_H \Lambda_H}{\mu_H \mu_g G_0 (\mu_H + \alpha_H + \delta_H)} \quad and \quad R_{0V} = \frac{N_S \alpha_S \beta_V \alpha_p \alpha_l \alpha_E \Lambda_E}{2\mu_V \mu_S P_0 (\alpha_p + \mu_p)(\alpha_l + \mu_l)(\alpha_E + \mu_E)(\mu_V + \delta_V)} \tag{4.3.43}$$

where R_{0H} describes the number of human that one infectious mosquito infects over its expected infection period in completely susceptible humans population, while R_{OV} is the number of mosquitoes infectious human during the period of infectiousness in a completely susceptible mosquitoes population.

The basic reproduction number is the spectral radius (dominate eigenvalue) of the matrix MD^{-1}, that is,

$$R_0 = \sqrt{R_{0H}R_{0V}} = \sqrt{\frac{N_S\alpha_S\beta_H\alpha_p\alpha_l\alpha_E\Lambda_E N_G\alpha_G\beta_V\Lambda_H}{2P_0G_0\mu_G\mu_H\mu_S\mu_V(\alpha_p+\mu_p)(\alpha_l+\mu_l)(\alpha_E+\mu_E)(\mu_V+\delta_V)(\mu_H+\alpha_H+\delta_H)}} \tag{4.3.44}$$

4.3.6 Local stability of the disease free equilibrium

Theorem: 4.3.6.1. *The disease-free equilibrium point is locally asymptotically stable if $R_0 < 1$ and is unstable if $R_0 > 1$* [79].

Proof:

The matrix of system of equation is

$$\text{J}=\begin{pmatrix} -b_1 & b_2 & 0 & 0 \\ b_3 & -b_4 & 0 & 0 \\ 0 & 0 & -b_5 & b_6 \\ 0 & 0 & 0 & -b_7 \end{pmatrix},$$

where

$$\begin{cases} b_1 = (\mu_H + \alpha_H + \delta_H), \\ b_2 = \frac{\beta_H\Lambda_H}{\mu_H G_0}, \\ b_3 = N_g\alpha_g, \\ b_4 = \mu_g, \\ b_5 = (\mu_V + \delta_V), \\ b_6 = \frac{\beta_V\Lambda_V}{\mu_V P_0}, \\ b_7 = \mu_S. \end{cases} \tag{4.3.45}$$

The eigenvalue of the Jacobian matrix are the solution of the characteristic equation $\left|J - \lambda I\right| = 0$, that is

$$\begin{vmatrix} b_1 - \lambda & b_2 & 0 & 0 \\ b_3 & -b_4 - \lambda & 0 & 0 \\ 0 & 0 & -b_5 - \lambda & b_6 \\ 0 & 0 & 0 & -b_7 - \lambda \end{vmatrix} = 0 \tag{4.3.46}$$

which forms the characteristics equation

$$\lambda^4 + \gamma_1\lambda^3 + \gamma_2\lambda^2 + \gamma_3\lambda + \gamma_0 = 0, \tag{4.3.47}$$

where

$$\begin{cases} \gamma_1 = b_1 + b_4 + b_5 + b_7, \\ \gamma_2 = b_1b_4 + b_1b_5 + b_1b_7 + b_4b_7 + b_5b_7 - b_2b_3, \\ \gamma_3 = b_1b_4b_5 + b_1b_4b_7 + b_1b_5b_7 + b_4b_5b_7 - b_2b_3b_5 - b_2b_3b_7, \\ \gamma_4 = b_1b_4b_5b_7 + b_2b_3b_5b_7. \end{cases} \tag{4.3.48}$$

We use Routh-Hurwitz stability criterion to determine stability conditions, the steady state solution associated with the characteristic equation (polynomial) (4.3.47) is stable if and only if the determinate of all Hurwitz matrices are positive [41]. Hurwitz

determinate of the characteristic equation (4.3.47) are given by

$$\begin{cases} G_0 = 1, \\ G_1 = \gamma_1, \\ G_2 = \begin{vmatrix} \gamma_1 & 1 \\ \gamma_3 & \gamma_2 \end{vmatrix}, \\ G_3 = \begin{vmatrix} \gamma_1 & 1 & 0 \\ \gamma_3 & \gamma_2 & \gamma_1 \\ \gamma_5 & \gamma_4 & \gamma_3 \end{vmatrix}, \\ G_4 = \begin{vmatrix} \gamma_1 & 1 & 0 & 0 \\ \gamma_3 & \gamma_2 & \gamma_1 & 1 \\ \gamma_5 & \gamma_4 & \gamma_3 & \gamma_1 \end{vmatrix}. \end{cases} \tag{4.3.49}$$

where $\gamma_i = 0$ if $i > n$. All of the roots of the polynomial $P(\lambda)$ are negatives or negative real parts if and only if determinants of all Hurwitz matrices are positive: det $G_j > 0$, j=1,2,...,n. We show that when $R_0 < 1$, all the coefficients, γ_i, of the characteristics equation and G_j are positive. From the characteristic equation, with $n = 4$, the Routh-Hurwitz criteria are:

$\gamma_1 > 0$, $\gamma_2 > 0$, $\gamma_3 > 0$,$\gamma_4 > 0$ and $det(G_j) = \gamma_1 > 0$,

$$det(G_2) = \begin{vmatrix} \gamma_1 & 1 \\ 0 & \gamma_2 \end{vmatrix} = \gamma_1\gamma_2 > 0, \tag{4.3.50}$$

$$det(G_3) = \begin{vmatrix} \gamma_1 & 1 & 0 \\ \gamma_3 & \gamma_2 & \gamma_1 \\ 0 & 0 & \gamma_3 \end{vmatrix} = \gamma_1\gamma_2\gamma_3 - \gamma_3^2 > 0, \tag{4.3.51}$$

$$det(G_4) = \begin{vmatrix} \gamma_1 & 1 & 0 & 0 \\ \gamma_3 & \gamma_2 & \gamma_1 & 1 \\ 0 & 0 & 0 & \gamma_1 \end{vmatrix} = \gamma_1\gamma_2\gamma_3 - \gamma_1^2\gamma_4 - \gamma_3^2 > 0 \tag{4.3.52}$$

Since all the determinants of the Hurwitz are positive, which implies that all the eigenvalues of the Jacobian matrix have negative real part. Hence disease-free equilibrium point is asymptotically stable and $R_0 < 1$.

4.3.7 Global stability of the disease free equilibrium

By theorem in sub-section 4.3.6 we know that the disease free equilibrium state is locally asymptotically stable wherever $R_0 < 1$ and unstable when $R_0 > 1$. In this section, we list two conditions that if met, also guarantee the global asymptotic stability of the disease free state. We write equation (4.2.1) in the form

$$\begin{cases} \frac{dX}{dt} = F(X, Z) \\ \\ \frac{dZ}{dt} = G(X, 0) = 0 \end{cases} \tag{4.3.53}$$

where $X = (S_H, S_V)$ comprises of the uninfected components and $Z = (E, L, P, I_V, P_V, I_H, , G_H)$, comprises of the infected and infectious components.

$$E_0 = \quad = (0, 0, 0, \frac{\alpha_p\alpha_l\alpha_E\Lambda_E}{2(\alpha_E + \mu_E)(\alpha_l + \mu_l)(\alpha_p + \mu_p)\mu_V}, 0, 0, \frac{\Lambda_H}{\mu_H}, 0, 0), \tag{4.3.54}$$

denotes the disease free equilibrium of the system. To guarantee global asymptotic stability, the conditions H_1 and H_2 below must be met [18].

H_1: for $\frac{dX}{dt} = F(X,0)$, $\quad X^*$ is globally asymptotically stable (g.a.s)

H_2: $G(X,Z) = AZ - G(X,Z) \geq 0$ for $(X,Z) \in \mathbb{R}_9^+$, where $A = D_Z G(X^*,0)$ is an M- matrix and $\mathbb{R}_9^+$ is the region where the model makes biological sense. Now we determine F(X,0) at disease free

$$F(X,0) = \begin{pmatrix} \frac{\alpha_p \alpha_l \alpha_E \Lambda_E}{2(\alpha_E+\mu_E)(\alpha_l+\mu_l)(\alpha_p+\mu_p)\mu_V} - \mu_V S_V \\ \\ \Lambda_H - \mu_H S_H \end{pmatrix} \tag{4.3.55}$$

and

$$A = \begin{pmatrix} b_1 & 0 & 0 & 0 & 0 & 0 & 0 \\ \alpha_E & b_2 & 0 & 0 & 0 & 0 & 0 \\ 0 & \alpha_l & b_3 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & b_4 & 0 & 0 & \frac{\beta_H \Lambda_V}{G_0 \mu_V} \\ 0 & 0 & 0 & N_S \alpha_S & b_5 & 0 & 0 \\ 0 & 0 & 0 & 0 & \frac{\beta_V \Lambda_H}{P_0 \mu_H} & b_6 & 0 \\ 0 & 0 & 0 & 0 & 0 & N_G \alpha_G & b_7 \end{pmatrix} \tag{4.3.56}$$

where

$$\begin{cases} b_1 = -(\alpha_E + \mu_E), \\ b_2 = -(\alpha_l + \mu_l, \\ b_3 = -(\alpha_p + \mu_p), \\ b_4 = -(\mu_V + \delta_V), \\ b_5 = -\mu_S, \\ b_6 = -(\mu_H + \alpha_H + \delta_H), \\ b_7 = -\mu_G. \end{cases} \tag{4.3.57}$$

$$G(X,Z) = \begin{pmatrix} \Lambda_E \\ 0 \\ 0 \\ (\frac{\Lambda_V}{G_0\mu_V} - \frac{S_V}{(G_0+\epsilon G_H)})\beta_H G_H \\ 0 \\ (\frac{\Lambda_H}{P_0\mu_H} - \frac{S_H}{(P_0+\epsilon P_V)})\beta_V P_V \\ 0 \end{pmatrix} \tag{4.3.58}$$

Since Since $\frac{\Lambda_H}{P_0\mu_H} \geq \frac{S_H}{P_0+\epsilon P_V}$ and $\frac{\Lambda_V}{G_0\mu_V} \geq \frac{S_V}{G_0+\epsilon G_H}$, then $\hat{G}(X,Z) \geq 0$ for all $(X,Z) \in \mathbb{R}_9^+$. It is clear that $\hat{G}(X,Z) \geq 0$ for all $(X,Z) \in \mathbb{R}_9^+$. It is also clear that matrix A is an M-matrix since the off diagonal elements of A are non-negative. We state the theorem which summarises the above result.

Also by theorem in the previous sub-section.

The fixed point $E_0 = (0,0,0,\frac{\alpha_p\alpha_l\alpha_E\Lambda_E}{2(\alpha_E+\mu_E)(\alpha_l+\mu_l)(\alpha_p+\mu_p)\mu_V},0,0,\frac{\Lambda_H}{\mu_H},0,0)$ is a globally asymptotically stable (g.a.s) equilibrium of system (4.2.1) if $R_0 \leq 1$ and the assumption H_1 and H_2 are satisfied.

4.3.8 The endemic equilibrium point(EEP)

At the endemic equilibrium both human and mosquito vectors are infected by sporozoites and Gametocytes respectively and the endemic equilibrium is given by $E^* =$

$(E^*, L^*, P^*, S_V^*, I_V^*, P_V^*, S_H^*, I_H^*, G_H^*)$.

We give expressions for the endemic equilibrium and their interpretation in the following subsection and prove its existence. The endemic value of mosquito eggs is given by equation

$$E^* = \frac{\Lambda_E}{\alpha_E + \mu_E} \tag{4.3.59}$$

We deduce from above equation that the equilibrium associated with mosquito eggs is proportional to the average time in days and the rate of supply of new eggs. The endemic value of the larva is given by the equation

$$L^* = \frac{\alpha_E E^*}{(\alpha_l + \mu_l)} = \frac{\alpha_E}{(\alpha_l + \mu_l)} \frac{\Lambda_E}{(\alpha_E + \mu_E)} \tag{4.3.60}$$

The equation above represent the larva. The larva require water and prefer clean unpolluted water. They frequently rise to the water surface to breathe. They feed on algae, bacteria and other microorganisms. The Pupa is given by the equation

$$P^* = \frac{\alpha_l L}{(\alpha_p + \mu_p)} = \frac{\alpha_l}{(\alpha_p + \mu_p)} \frac{\alpha_E}{(\alpha_l + \mu_l)} \frac{\Lambda_E}{(\alpha_E + \mu_E)} \tag{4.3.61}$$

The pupa also require water and need to resurface frequently to breathe. The endemic value of the adult mosquito vector is given by the equation

$$S_V^* = \frac{\alpha_P P^*}{2(\lambda_H^* + \mu_V)} = \frac{\alpha_p}{2(\lambda_H^* + \mu_V)} \frac{\alpha_l}{(\alpha_p + \mu_p)} \frac{\alpha_E}{(\alpha_l + \mu_l)} \frac{\Lambda_E}{(\alpha_E + \mu_E)} \tag{4.3.62}$$

The adult female feeds on nectar and other source of sugar, but also requires a blood meal for the protein needed to produce eggs. After the blood meal, the female usually rests until the eggs development. This process too depends on the temperature and usually takes $2 - 3$ days in the tropical condition. The endemic value of infected

mosquito is given by the equation

$$I_V^* = \frac{\lambda_V}{(\mu_V^* + \delta_V)} S_V = \frac{\lambda_V}{(\mu_V^* + \delta_V)} \frac{\alpha_p}{2(\lambda_H^* + \mu_V)} \frac{\alpha_l}{(\alpha_p + \mu_p)} \frac{\alpha_E}{(\alpha_l + \mu_l)} \frac{\Lambda_E}{(\alpha_E + \mu_E)} \quad (4.3.63)$$

From the above equation the infected mosquitoes' vector is the product of many quantities, where λ_V^* represents the force of infection, Λ_V represents recruitment of mosquito's vector, μ_V is the natural death of mosquito's vector and δ_V death rate of mosquito vectors by disease. The endemic value of the sporozoite is given by the equation

$$P_V^* = \frac{N_S \alpha_S}{\mu_S} I_V = \frac{N_S \alpha_S}{\mu_S} \frac{\lambda_V}{(\mu_V^* + \delta_V)} \frac{\alpha_p}{2(\lambda_H^* + \mu_V)} \frac{\alpha_l}{(\alpha_p + \mu_p)} \frac{\alpha_E}{(\alpha_l + \mu_l)} \frac{\Lambda_E}{(\alpha_E + \mu_E)} \quad (4.3.64)$$

The sporozoite is in the infected female mosquito, when it bite a human being, it injects the sporozoite. The endemic value of the infected human is given by the equation

$$I_H^* = \frac{\lambda_V^* S_H}{(\mu_H + \alpha_H + \delta_H)} = \frac{\lambda_V^* \Lambda_V}{\mu_H(\mu_H + \alpha_H + \delta_H) + \lambda_V^*(\mu_H + \delta_H)} \quad (4.3.65)$$

We deduce from above equation that the infected population is proportional to three quantities, the average time of stay in the infected compartment, the rate of infection of susceptible and the number of susceptible hosts. The endemic value of susceptible humans is given by the equation

$$S_H^* = \frac{\Lambda_H + \alpha_H I_H^*}{(\mu_H + \lambda_V^*)} = \frac{\Lambda_H}{(\mu_H + \lambda_V^*)} + \frac{\alpha_H \lambda_V^* \Lambda_H}{(\mu_H + \lambda_V^*)[\mu_H(\mu_H + \alpha_H + \delta_H) + \lambda_V^*(\mu_H + \delta_H)]} \quad (4.3.66)$$

Susceptible human is proportional to the average time of stay in the susceptible compartment and the rate of supply of few susceptible through birth. Individuals exit this compartment either through death or infection. The gametocytes taken by

the mosquito from infected human is given by equation

$$G_H^* = \frac{N_g \alpha_g I_H^*}{\mu_g} = \frac{N_g \alpha_g \lambda_V^* \Lambda_H}{\mu_H(\mu_H + \alpha_H + \delta_H) + \lambda_V^*(\mu_H + \delta_H)} \tag{4.3.67}$$

The above equation represent the total population of the human infected by gametocytes. The force of infection of mosquito vector is given by the equation

$$\lambda_V^* = \frac{\beta_V N_S \alpha_S \alpha_p \alpha_l \alpha_E \Lambda_E}{2P_0 \mu_S(\mu_V + \delta_V)(\lambda_H^* + \mu_V)(\alpha_p + \mu_p)(\alpha_l + \mu_l)(\alpha_E + \mu_E) + N_S \alpha_S \epsilon \lambda_H^* \alpha_p \alpha_l \alpha_E \Lambda_E} \tag{4.3.68}$$

The force of infection of human host is given by the following

$$\lambda_H^* = \frac{\beta_H N_G \alpha_G \lambda_V^* \Lambda_H}{G_0 \mu_G[(\mu_H + \lambda_V^*)(\mu_H + \alpha_H + \delta_H) - \lambda^* \alpha_H] + \epsilon N_G \alpha_G \lambda_V^* \Lambda_H} \tag{4.3.69}$$

From equation (9.62). Let

$$\begin{cases} f_1 = \beta_V N_S \alpha_S \alpha_P \alpha_l \alpha_E \Lambda_E \\ f_2 = 2P_0 \mu_S(\mu_V + \delta_V)(\alpha_P + \mu_p)(\alpha_l + \mu_l)(\alpha_E + \mu_E) \\ f_3 = N_S \alpha_S \in \alpha_p \alpha_l \alpha_E \Lambda_E \end{cases} \tag{4.3.70}$$

Equation (9.62) becomes

$$\lambda_V^* = \frac{f_1}{f_2(\lambda_H^* + \mu_V) + f_3 \lambda_H^*} \tag{4.3.71}$$

By substituting equation (9.63) into equation (9.65) (λ_H^*) we have that:

$$\lambda_V^* = \frac{f_1 G_0 \mu_G[(\mu_H + \delta_H)(\mu_H + \delta_H) + \alpha_H \mu_H] + \epsilon N_G \alpha_G \Lambda_H \lambda_V^*}{f_2 \beta_H N_G \alpha_G \lambda_V^* \Lambda_H + \mu_H G_0 \mu_G[(\mu_H + \delta_H)(\mu_H + \delta_H) + \alpha_H \mu_H] + \epsilon N_G \alpha_G \Lambda_H \lambda_V^* + f_3 \beta_H N_G \alpha_G \lambda_V^* \Lambda} \tag{4.3.72}$$

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Let

$$\begin{cases} f_4 = G_0\mu_G[(\mu_H + \delta_E)(\mu_H + \delta_H) + \alpha_H\mu_H] \\ a_1 = N_G\alpha_G \in \Lambda_H \\ a_2 = N_G\alpha_G\beta_H\Lambda_H \\ f_5 = G_0\mu_G\mu_H[(\mu_H + \delta_H)(\mu_H + \delta_H) + \alpha_H\mu_H] \end{cases} \tag{4.3.73}$$

Equation (9.66) becomes

$$\lambda_V^* = \frac{f_1 f_4 + a_1\lambda_V^*}{f_2 a_2\lambda_V^* + f_5 + a_1\lambda_V^* + f_3 a_2\lambda_V^*} \tag{4.3.74}$$

By solving λ_V^* we have that:

$$b_1\lambda_V^{*2} + b_2\lambda_V^* - f_1 f_4 = 0 \tag{4.3.75}$$

where

$$\begin{cases} b_1 = f_2 a_2 + a_1 + f_3 a_2 \\ b_2 = f_5 - a_1 \end{cases} \tag{4.3.76}$$

Therefore λ_V^* is given by

$$\lambda_V^* = \frac{-b_2 \pm \sqrt{b_2^2 + 4b_1 f_1 f_4}}{2b_1} \tag{4.3.77}$$

4.3.9 The existence of the endemic equilibrium state

In this section we present some results concerning the existence of an endemic equilibrium or constant solution for model system (4.2.1). To do this we shall make use of a threshold parameter, which we have already denoted by R_0.

Theorem: *The model system* (4.2.1) *formulated in terms of proportion has at least one endemic equilibrium solution given by*

$E^*=(E^*, L^*, P^*, S_V^*, I_V^*, P_V^*, S_H^*, I_H^*, G_H)$, *with* $E^*, L^*, P^*, S_V^*, I_V^*, P_V^*, S_H^*, I_H^*, G_H$, *all non-negative, whose existence and properties are determined by the threshold parameter* R_0.

Proof:

Let

$E^*=E, L, P, S_V, I_V, P_V, S_H, I_H, G_H$ be a constant solution of the model system (4.2.1).

We can easily express $(E^*, L^*, P^*, S_V^*, I_V^*, P*_V, S_H^*, I_H^*, G_H^*,)$ in the form of I_V^*

$$
\begin{cases}
E^*(I_V^*) = \frac{\Lambda_E}{(\alpha_E+\mu_E)}, \\
L^*(I_V^*) = \frac{\alpha_E}{(\alpha_l+\mu_l)} \frac{\Lambda_E}{(\alpha_E+\mu_E)}, \\
P^*(I_V^*) = \frac{\alpha_L}{(\alpha_p+\mu_p)} \frac{\alpha_E}{(\alpha_l+\mu_l)} \frac{\Lambda_E}{(\alpha_E+\mu_E)}, \\
S_V^*(I_V^*) = \frac{[z_1+z_2 I_V^*+z_3 I_V^*]\Phi_1 - z_4 I_V^* + z_5 I_V^*}{2Q_1 I_V^* + [2Q_2+2Q_3 I_V^*+2Q_4 I_V^*]\Phi_1 - 2Q_5 I_V^* + 2Q_6 I_V^*}, \\
P_V^*(I_V^*) = \frac{N_S \alpha_S I_V^*}{\mu_S}, \\
I_H^*(I_V^*) = \frac{N_S \alpha_S \beta_V \Lambda_H I_V^*}{[\mu_H(P_0\mu_S + N_S\alpha_S\epsilon I_V^*) + N_S\alpha_S\beta_V I_V^*](\mu_H+\alpha_H+\delta_H) - N_S\alpha_S\beta_V\alpha_H I_V^*}, \\
S_H^*(I_V^*) = \frac{P_0\mu_S + \epsilon N_S\alpha_S\Lambda_H I_V^*}{\mu_H(P_0\mu_S + N_S\alpha_S\epsilon I_V^*) + N_S\alpha_S\beta_V I_V^*} \times \\
\frac{\mu_H[(P_0\mu_S + N_S\alpha_S\epsilon I_V^*) + N_S\alpha_S\beta_V I_V^*](\mu_H+\alpha_H+\delta_H) - N_S\alpha_S\beta_V\alpha_H I_V^* + N_S\alpha_S\alpha_H\beta_V I_V^*}{\mu_H[(P_0\mu_S + N_S\alpha_S\epsilon I_V^*) + N_S\alpha_S\beta_V I_v^*](\mu_H+\alpha_H+\delta_H) - N_S\alpha_S\beta_V\alpha_H I_V^*}, \\
G_H^*(I_V^*) = \frac{N_G\alpha_G N_S\alpha_S\Lambda_H I_V^*}{[\mu_G\mu_H(P_0\mu_S + N_S\alpha_S\epsilon I_V^*) + N_S\alpha_S\mu_G\beta_V I_V^*](\mu_H+\alpha_H+\delta_H) - N_S\alpha_S\mu_G\beta_V\alpha_H I_V^*}, \\
\lambda_V^*(I_V^*) = \frac{N_S\alpha_S\beta_V I_V^*}{\mu_S P_0 + N_S\alpha_S\epsilon I_V^*)}, \\
\lambda_H^*(I_V^*) = \frac{f_1 I_V^*}{[f_2+f_3 I_V^*+f_4 I_V^*]\Phi_1 - f_5 I_V^* + f_6 I_V^*}.
\end{cases}
\tag{4.3.78}
$$

where

$$
\begin{cases}
z_1 = \mu_H \mu_G G_0 \alpha_p P_0 \mu_S, \\
z_2 = N_S \alpha_S \mu_H \mu_G G_0 \alpha_p \in, \\
z_3 = N_S \alpha_S \mu_G \alpha_p G_0 \beta_V, \\
z_4 = N_S \alpha_S \mu_G \beta_V \alpha_H G_0 \alpha_p, \\
z_5 = N_G \alpha_G N_S \alpha_S \alpha_p \in \Lambda_H, \\
\Phi_1 = (\mu_H + \alpha_H + \delta_H).
\end{cases} \tag{4.3.79}
$$

$$
\begin{cases}
Q_1 = N_G \alpha_G N_S \alpha_S \beta_H \Lambda_H, \\
Q_2 = \mu_H \mu_G G_0 \mu_V P_0 \mu_S, \\
Q_3 = N_S \alpha_S \mu_H \mu_G G_0 \mu_V \in, \\
Q_4 = N_S \alpha_S \mu_G \beta_V G_0, \\
Q_5 = N_S \alpha_S \mu_G \mu_V \beta_V \alpha_H G_0, \\
Q_6 = N_G \alpha_G N_S \alpha_S \mu_V \in \Lambda_H.
\end{cases} \tag{4.3.80}
$$

$$\begin{cases} f_1 = N_G \alpha_G N_S \alpha_S \beta_H \Lambda_H, \\ f_2 = \mu_H \mu_G G_0 \mu_V P_0 \mu_S, \\ f_3 = \mu_H \mu_G G_0 N_S \alpha_S \in, \\ f_4 = N_S \alpha_S \mu_G \beta_V G_0, \\ f_5 = N_S \alpha_S \mu_G \beta_V \alpha_H G_0, \\ f_6 = N_G \alpha_G N_S \alpha_S \in \Lambda_H. \end{cases} \tag{4.3.81}$$

Substituting $\lambda_H(I_V^*)$ and $S_V(I^*)$ into equation of I_V which is

$$\frac{dI_V(t)}{dt} = \lambda_H S_V - (\mu_V + \delta_V) I_V \tag{4.3.82}$$

$$(\mu_V+\delta_V)c_3c_4I_V^{*3}+[2(\mu_V+\delta_V)\Phi_1Q_2c_3+(\mu_V+\delta_V)f_2c_4-c_2]I_V^{*2}+[2(\mu_V+\delta_V)f_1\Phi_1Q_2-c_1]I_V^{*}=0 \tag{4.3.83}$$

where

$$\begin{cases} c_1 = f_1z_1\Phi_1 - f_4z_4, \\ c_2 = f_1z_2\Phi_1 + f_1z_3\Phi_1 + f_1z_5, \\ c_3 = f_3 + f_4 - f_5 + f_6, \\ c_4 = 2Q_1 + 2Q_3\Phi_1 + 2Q_4\Phi_1 - 2Q_5 + 2Q_6. \end{cases} \tag{4.3.84}$$

$$I_V^*(d_1I_V^{*2} + d_2I_V^* + d_3) = 0 \tag{4.3.85}$$

$$I_V^* = \frac{-d_2 \pm \sqrt{d_2^2 - 4d_1d_3}}{2d_1}. \tag{4.3.86}$$

$$\begin{cases} d_1 = (\mu_V + \delta_V)c_3c_4, \\ d_2 = 2(\mu_V + \delta_V)\Phi_1Q_2c_3 - (\mu_V + \delta_V)f_4c_4 - c_2, \\ d_3 = 2(\mu_V + \delta_V)f_1\Phi_1Q_2. \end{cases} \tag{4.3.87}$$

for the endemic equilibrium. Since $d_1d_3 < 0$ for $R_0 > 1$, we can easily deduce from (4.3.87) that only one positive endemic equilibrium exist expression for $R_0 > 1$. Consequently, there exists one unique endemic equilibrium for model system (4.2.1) whenever $R_0 > 1$.

4.3.10 Local stability of the endemic equilibrium

The stability of the endemic equilibrium state of the model (4.2.1) can be analyzed using the centre manifold Theory described by ***Castillo-Chavez and song*** [19] 2004. To apply center manifold Theory we make the change of variable in model system (4.2.1).

Let $x_1 = E$, $x_2 = L$, $x_3 = P$,$x_4 = S_V$, $x_5 = I_V$, $x_6 = P_V$,$x_7 = S_H$,$x_8 = I_H$,$x_9 = G_H$.

Then, the system (4.2.1) can be written in vector form as

$$\frac{dX_i}{dt} = H(X_i), \tag{4.3.88}$$

where

$X_i = (x_1, x_2, ..., x_9)^T$ and $H = (h_1, h_2...h_9)$ are transpose matrices. The model system (4.2.1) becomes

$$
\begin{cases}
\frac{dx_1(t)}{dt} = \Lambda_E - (\alpha_E + \mu_E)x_1 = h_1, \\
\frac{dx_2(t)}{dt} = \alpha_E x_1 - (\alpha_l + \mu_l)x_2 = h_2, \\
\frac{dx_3(t)}{dt} = \alpha_l x_2 - (\alpha_p + \mu_p)x_3 = h_3, \\
\frac{dx_4(t)}{dt} = \frac{\alpha_p}{2}x_3 - \frac{\beta_H x_9}{(G_0 + \in x_9)}x_4 - \mu_V x_4 = h_4, \\
\frac{dx_5(t)}{dt} = \frac{\beta_H x_9}{(G_0 + \in x_9)}x_4 - (\mu_V + \delta_V)x_5 = h_5, \\
\frac{dx_6(t)}{dt} = N_S \alpha_S x_5 - \mu_S x_6 = h_6, \\
\frac{dx_7(t)}{dt} = \Lambda_H - \frac{\beta_V x_6}{(p_0 + \in x_6)}x_7 + \alpha_H x_8 - \mu_H x_7 = h_7, \\
\frac{dx_8(t)}{dt} = \frac{\beta_V x_6}{(p_0 + \in x_6)}x_7 - (\mu_H + \alpha_H + \delta_H)x_8 = h_8, \\
\frac{dx_9(t)}{dt} = N_G \alpha_G x_8 - \mu_G x_9 = h_9,
\end{cases}
\tag{4.3.89}
$$

where $N_H = x_7 + x_8 + x_9$ and $N_V = x_1 + x_2 + x_3 + x_4 + x_5 + x_6$ with $\beta^* = \beta_H$. Let β^* be bifurcation parameter of the system linearized at disease free equilibrium point when $\beta^* = \beta$ with $R_0 = 1$. Thus β^* can be solved from reproductive number when $R_0 = 1$ as

$$
\sqrt{\frac{N_S \alpha_S \alpha_p \alpha_l \alpha_E \beta_H \Lambda_H N_G \alpha_G \beta_V \Lambda_E}{2P_0 G_0 \mu_G \mu_H \mu_S \mu_V \mu_S (\alpha_E + \mu_E)(\alpha_l + \mu_l)(\alpha_p + \mu_p)(\mu_V + \delta_V)(\mu_H + \alpha_H + \delta_H)}} = 1 \tag{4.3.90}
$$

By squaring both sides we have

$$\frac{N_S\alpha_S\alpha_p\alpha_l\alpha_E\beta_H\Lambda_H N_G\alpha_G\beta_V\Lambda_E}{2P_0G_0\mu_G\mu_H\mu_S\mu_V\mu_S(\alpha_E+\mu_E)(\alpha_l+\mu_l)(\alpha_p+\mu_p)(\mu_V+\delta_V)(\mu_H+\alpha_H+\delta_H)}=1 \tag{4.3.91}$$

$$\beta^*=\frac{2P_0G_0\mu_G\mu_H\mu_V\mu_S(\alpha_E+\mu_E)(\alpha_l+\mu_l)(\alpha_p+\mu_p)(\mu_V+\delta_V)(\mu_H+\alpha_H+\delta_H)}{N_S\alpha_S\alpha_p\alpha_l\alpha_E\beta_H\Lambda_H N_G\alpha_G\beta_V\Lambda_E} \tag{4.3.92}$$

Then zero is a simple eigenvalue of the following Jacobian matrix, with the application of the bifurcation parameters. The Jacobian matrix associated with equation system (4.3.89) at E_0 is given by

$$J(E_0)=\begin{pmatrix} b_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \alpha_E & b_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \alpha_l & b_3 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{\alpha_p}{2} & -\mu_V & 0 & 0 & 0 & 0 & \frac{\beta_H\Lambda_H}{\mu_H G_0} \\ 0 & 0 & 0 & 0 & b_4 & 0 & 0 & 0 & -\frac{\beta_H\Lambda_H}{\mu_H G_0} \\ 0 & 0 & 0 & 0 & N_S\alpha_S & -\mu_H & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \frac{\beta_V\Lambda_V}{P_0\mu_V} & -\mu_H & \alpha_H & 0 \\ 0 & 0 & 0 & 0 & 0 & -\frac{\beta_V\Lambda_V}{P_0\mu_V} & 0 & b_5 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & N_G\alpha_G & -\mu_G \end{pmatrix} \tag{4.3.93}$$

where

$$\begin{cases} b_1 = -(\alpha_E + \mu_E), \\ b_2 = -(\alpha_l + \mu_l), \\ b_3 = -(\alpha_p + \mu_p), \\ b_4 = -(\mu_V + \delta_V), \\ b_5 = -(\mu_H + \alpha_H + \delta_H). \end{cases} \tag{4.3.94}$$

A right eigenvector associated with the eigenvalue zero is $w = (w_1, w_2, ..., w_6)$, We get

$$\begin{cases} -(\mu_H + \alpha + _H + \delta_H)w_1 = 0 \\ \alpha_E w_1 - (\alpha_l + \mu_l)w_2 = 0 \\ \alpha_l w_2 - (\alpha_p + \mu_p)w_3 = 0 \\ \frac{\alpha_2}{2} w_3 - \mu_v w_4 + \frac{\beta_H \Lambda_H}{\mu_H G_0} w_9 = 0 \\ -(\mu_V + \delta_V)w_5 - \frac{\beta_H \Lambda_H}{\mu_H G_0} w_9 = 0 \\ N_S \alpha_S w_5 - \mu_S w_6 = 0 \\ \frac{\beta_V \Lambda_V}{P_0 \lambda_V} w_6 - \mu_H w_7 + \alpha_H w_8 = 0 \\ -\frac{\beta_V \Lambda_V}{P_0 \mu_V} w_6 - (\mu_H + \alpha_H + \delta_H)w_8 = 0 \\ N_G \alpha_G w_8 - \mu_G w_9 = 0 \end{cases} \tag{4.3.95}$$

Solving the systems (4.3.95), we have the following eigenvector

$$\begin{cases} w_1 = 0, \\ w_2 = \frac{\alpha_E}{(\alpha_l+\mu_l)} w_1 = 0, \\ w_3 = \frac{\alpha_l}{(\alpha_p+\mu_p)} w_2 = 0, \\ w_4 = \frac{\beta_H \Lambda_H}{\mu_V \mu_H G_0}, \\ w_5 = \frac{\beta_H \Lambda_H}{(\mu_H G_0(\mu_V+\delta_V)} w_9, \\ w_6 = \frac{N_S \alpha_S}{\mu_S} w_5, \\ w_7 = \frac{\beta_V \Lambda_V + P_0 \mu_V \alpha_H w_8}{P_0 \mu_V \mu_H}, \\ w_8 = \frac{\beta_V \Lambda_V}{P_0 \mu_V (\mu_H+\alpha_H+\delta_H)} w_6, \\ w_9 = \frac{N_G \alpha_G}{\mu_G} w_8. \end{cases} \tag{4.3.96}$$

The left eigenvector satisfying $v.w = 1$ is $v = (v_1, v_2, ..., v_9)$. To find these left eigenvector associated with the eigenvalue 0, the above matrix should be transposed and gives matrix, J_{left}

$$J(E_0) = \begin{pmatrix} b_1 & \alpha_E & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & b_2 & \alpha_l & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & b_3 & \frac{\alpha_p}{2} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -\mu_V & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & b_4 & N_S\alpha_S & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\alpha_S & \mu_H & \frac{\beta_V\Lambda_V}{P_0\mu_V} & -\frac{\beta_V\Lambda_V}{P_0\mu_V} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -\mu_H & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \alpha_H & b_5 & N_G\alpha_G \\ 0 & 0 & 0 & \frac{\beta_H\Lambda_H}{\mu_H G_0} & -\frac{\beta_H\Lambda_H}{\mu_H G_0} & 0 & 0 & 0 & -\mu_G \end{pmatrix} \tag{4.3.97}$$

where

$$\begin{cases} b_1 = -(\alpha_E + \mu_E), \\ b_2 = -(\alpha_l + \mu_l), \\ b_3 = -(\alpha_p + \mu_p), \\ b_4 = -(\mu_V + \delta_V), \\ b_5 = -(\mu_H + \alpha_H + \delta_H). \end{cases} \tag{4.3.98}$$

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$$
\begin{cases}
-(\alpha_E + \mu_E)v_1 + \alpha_E v_2 = 0 \\
-(\alpha_l + \mu_l)v_2 + \alpha_l v_3 = 0 \\
-(\alpha_p + \mu_p)v_3 + \frac{\alpha_p}{2} v_4 = 0 \\
-\mu_V v_5 = 0 \\
-(\mu_V + \delta_V)v_5 + N_S \alpha_S v_6 = 0 \\
-\alpha_S v_5 + \mu_H v_6 + \frac{\beta_V \Lambda_V}{P_0 \mu_V} v_7 - \frac{\beta_V \Lambda_V}{P_0 \mu_V} v_8 = 0 \\
\mu_H v_7 = 0 \\
\alpha_H v_7 + -(\mu_H + \alpha_H + \delta_H)v_8 + N_G \alpha_G v_9 = 0 \\
\frac{\beta_H \Lambda_H}{\mu_H G_0} v_4 - \frac{\beta_H \Lambda_H}{\mu_H G_0} v_5 - \mu_G v_9 = 0
\end{cases}
\tag{4.3.99}
$$

From the left eigenvector we have the following results

$$\begin{cases} v_1 = \frac{\alpha_E}{(\alpha_E+\mu_E)} v_E, \\ v_2 = \frac{\alpha_l}{(\alpha_l+\mu_l} v_3, \\ v_3 = \frac{\alpha_p}{2(\alpha_p+\mu_p} v_4, \\ v_5 = 0, \\ v_6 = \frac{(\mu_V-\delta_V}{N_S\alpha_S} v_5, \\ v_7 = \frac{(\frac{\beta_V\Lambda_V}{P_0\mu_V}+\alpha_S v_5-\mu_H v_6)\mu_V\Lambda_V}{P_0\mu_V}, \\ v_8 = \frac{N_G\alpha_G}{\mu_H+\alpha_H+\delta_H} v_9, \\ v_9 = \frac{v_4-v_5}{\mu_G} \frac{\beta_H\Lambda_H}{\mu_H\mu_H G_0}. \end{cases} \tag{4.3.100}$$

We now compute the sign of a and b using the centre manifold, described by castillo- chavez and song 2004

$$\begin{cases} a = \sum_{k,i,j=2}^{3} v_k w_i w_j \frac{\partial^2 h_k}{\partial x_i \partial x_j}(0,0) + \sum_{k,i,j=2}^{6} v_k w_i w_j \frac{\partial^2 h_k}{\partial x_i \partial x_j}(0,0) \\ b = \sum_{k,i=2}^{3} v_k w_i \frac{\partial^2 h_k}{\partial x \partial \beta}(0,0) + \sum_{k,i=1=2}^{6} v_k w_i \frac{\partial^2 h_k}{\partial x \partial \beta}(0,0) \end{cases} \tag{4.3.101}$$

Since $v_5 = v_6 = 0$ for $k = 1,2,3,5,7,8,9$ and then $k = 1,2,3,5,7,8,9$ should be considered. That is, the following function will be used to compute a and b from the system (3.11.3)

$$h = \begin{cases} h_4 = \frac{x_p}{2}x_3 - \frac{\beta_H x_9 N_V}{(G_0+\epsilon x_9)} - \frac{\beta_H x_9 x_1}{(G_0+\epsilon x_9)} - \frac{\beta_H x_9 x_2}{(G_0+\epsilon x_9)} - \frac{\beta_H x_9 x_3}{(G_0+\epsilon x_9)} \\ \\ h_8 = \frac{\beta_V x_6 N_H}{(P_0+\epsilon x_6)} - \frac{\beta_V x_6 x_8}{(P_0+\epsilon x_9)} - \frac{\beta_V x_6 x_9}{(P_0+\epsilon x_6)} - (\mu_H + \alpha_H + \delta_H)x_8 \end{cases} \tag{4.3.102}$$

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

$$\frac{\partial^2 h}{\partial x_i \partial x_j} = \begin{cases} \frac{\partial^2 h_4}{\partial x_9 \partial x_1} = \frac{\beta_H}{G_0}, \\ \\ \frac{\partial^2 h_4}{\partial x_9 \partial x_2} = \frac{\beta_H}{G_0}, \\ \\ \frac{\partial^2 h_8}{\partial x_6 \partial x_8} = \frac{-\beta_V}{P_0}, \\ \\ \frac{\partial^2 h_8}{\partial x_6 \partial x_9} = \frac{-\beta_V}{P_0}. \end{cases} \tag{4.3.103}$$

Hence

$$\begin{cases} a = v_2 w_6 w_9 \frac{\partial^2 h_2}{\partial x_6 \partial x_9} + v_5 w_6 w_8 \frac{\partial^2 h_2}{\partial x_6 \partial x_8} \\ \quad = v_2 w_6 w_9 (\frac{-\beta_V}{P_0}) + v_7 w_6 w_8 (\frac{-\beta_V}{P_0}) \\ \quad = -(v_2 w_6 w_8 \frac{\beta_V}{P_0} + v_7 w_6 w_8 \frac{\beta_V}{P_0}) < 0 \end{cases} \tag{4.3.104}$$

Hence

$$\begin{cases} b = v_1 w_9 \frac{\partial^2 h_8}{\partial x_1 \partial_9} + v_2 w_9 \frac{\partial^2 h_8}{\partial x_2 \partial x_9} \\ \quad = v_1 w_9 (\frac{\beta_H}{G_0}) + v_2 w_9 (\frac{\beta_H}{G_0}) \\ \quad = v_1 w_9 \frac{\beta_H}{G_0} + v_2 w_9 \frac{\beta_H}{G_0} > 0 \end{cases} \tag{4.3.105}$$

Hence $a < 0$ and $b > 0$. Therefore the centre manifold Theory holds.

4.3.11 Sensitivity Analysis

To determine the relative importance of parameters to the initial transmission of the disease, we perform a sensitivity analysis of the basic reproduction number with respect to the parameter of the model.

$$R_0 = \sqrt{R_{0H}R_{0V}} = \sqrt{\frac{N_S\alpha_S\beta_H\alpha_p\alpha_l\alpha_E\Lambda_E N_G\alpha_G\beta_V\Lambda_H}{2P_0G_0\mu_G\mu_H\mu_S\mu_V(\alpha_p+\mu_p)(\alpha_l+\mu_l)(\alpha_E+\mu_E)(\mu_V+\delta_V)(\mu_H+\alpha_H+\delta_H)}}.$$

We evaluate the sensitive analysis of reproductive number with all parameter described in the table(3.3) as:

$$\Upsilon_u^{R_0} = \frac{\partial R_0}{\partial u} \times \frac{u}{R_0} \tag{4.3.106}$$

where $\frac{u}{R_0}$ normalise the coefficient by removing the effect of units(Njagarah and Nyabadza, 2013)

Parameter	Description	Sign	Value
N_G	Average number of gametocytes inside the infected human	+	0.5
α_G	Natural recovery of human to Gametocytes	+	0.5
β_H	Maximum exposure rate of humans	+	0.5
Λ_H	Supply rate susceptible humans	+	0.5
μ_G	Natural death rate Gametocytes	-	0.5
μ_H	Natural death rate of humans	-	0.504
δ_H	Disease induced death rate of humans	-	0.5
α_H	Natural recovery rate of humans	-	0.504
G_0	Saturated constant of Gametocytes	-	0.5

Table 4.2: Sensitive analysis of human host

Parameter	Description	Sign	Value
N_S	Average number of sporozoites inside the infected mosquito vector	+	0.5
α_S	Natural recover human to sporozoites	+	0.5
β_V	Maximum exposure rate of mosquito vector	+	0.5
μ_S	Natural death rate of sporozoites	-	0.5
μ_V	Natural death rate of mosquitoes	-	0.0192
δ_V	Infection induce death rate of mosquitoes	-	0.00003
P_0	Saturated constant of sporozoites	-	0.5

Table 4.3: Sensitive analysis of mosquito vectors with life cycle

Parameter	Description	Sign	Value
Λ_E	Supply rate of mosquito eggs	+	0.5
α_p	Natural recover of Pupa	+	0.3125
α_l	Natural recover of larva	+	0.0192
α_E	Natural death of mosquitoes eggs	+	0.362
μ_p	Natural death rate of pupa	-	0.3125

Table 4.4: Sensitive analysis of mosquito vectors with life cycle

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4.4 Numerical simulation

In this section, we present the numerical analysis of the model[9]. A numerical simulation of the model (4.2.1) is conducted to find out the dynamics of the disease in the human population. The simulation were conducted using python.

4.4.1 Table of simulation

Parameter	Meaning	Baseline value	Range explored	Units	Source or Rational
Λ_H	Supply rate of susceptible humans	0.00011	0.00011-0.00016	day^{-1}	Estimated
β_H	Maximum exposure rate of humans	0.5	0.5000-0.8000	day^{-1}	[73]
α_H	Natural recovery rate of humans	$\frac{1}{200}$	$\frac{1}{200}$	day^{-1}	[6]
μ_H	Natural death rate of humans	0.0000391	0.00004899	day^{-1}	[3, 31]
δ_H	Disease induced death rate of humans	0.00000426	0.00000426-0.000005333	day^{-1}	[2]
α_G	Natural recovery of human to Gametocytes	0.002	0.002-0.005	day^{-1}	Estimated
N_G	Number of gametocytes produced	0.089	0.089-0.099	day^{-1}	Estimated
μ_G	Natural death rate of Gametocytes	0.002	0.002-0.005	day^{-1}	Estimated

Table 4.5: Between-human host parameter values for model system

Parameter	Meaning	Baseline value	Range explored	Units	Source or Rational
β_V	Maximum exposure rate of mosquito vector	0.5	0.5000-0.8000	day^{-1}	[21]
μ_V	Natural death rate of mosquitoes	0.071	0.0071-0.00999	day^{-1}	[12]
α_S	Natural recover of human to sporozoites	$\frac{1}{200}$	$\frac{1}{200}$	day^{-1}	[6]
δ_V	Infection induce death rate of mosquitoes	0.00000426	0.00000426-0.000005333	day^{-1}	Estimated
μ_S	Natural death of sporozoites	0.01	0.01-0.09	day^{-1}	Estimated
N_S	Number of sporozoites	0.0789	0.0789-0.0899	day^{-1}	Estimated

Table 4.6: Between-mosquito host parameter values for model system

Parameter	Meaning	Baseline value	Range explored	Units	Source or Rational
Λ_E	Supply rate of mosquito eggs	200	200-400	day^{-1}	Estimated
α_E	Natural death of mosquitoes eggs	0.079	0.079-0.099	day^{-1}	Estimated
μ_E	Natural death of eggs	0.03	0.03-0.09	day^{-1}	Estimated
α_l	Natural recover of larva	0.05	0.05-0.09	day^{-1}	Estimated
μ_l	Natural death rate of larva	0.002	0.002-0.009	day^{-1}	Estimated
α_p	Natural recover of Pupa	0.003	0.003-0.009	day^{-1}	Estimated
μ_p	Natural death rate of pupa	0.005	0.008	day^{-1}	Estimated

Table 4.7: Table for the development of the mosquito vector

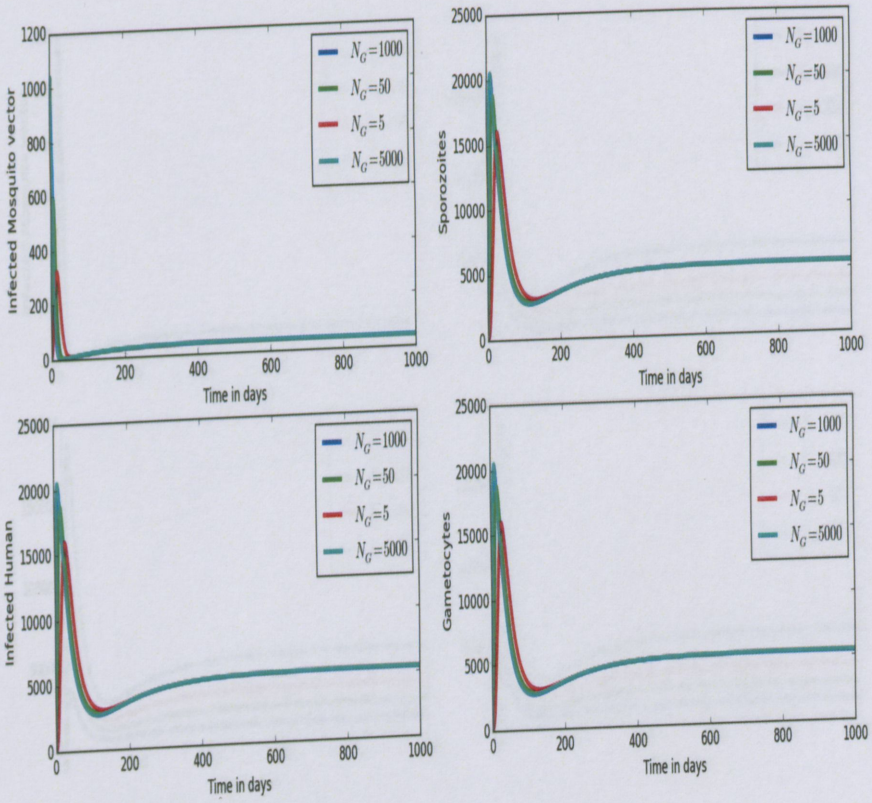


Figure 4.2: A numerical simulation of the malaria model system (4.2.1) with the values of the parameters given in table 4.5, 4.6 and 4.7. These parameters correspond to the reproductive number. The behavior of infected mosquito vector differ for different value of β_H. The behavior of sporozoite, Susceptible human and infected human will be the same for different value of β_E. The initial condition is: $E = 1000$, $L = 70$, $P = 70$, $S_V = 4000$, $I_V = 5$, $P_V = 100$; $S_H = 2000$; $I_H = 30$, $G_H = 10$ which correspond to $\Lambda_E = 200$, $\Lambda_H = 1000$, $\alpha_E = 0.0079$, $\mu_E = 0.03$, $\alpha_l = 0.05$, $\mu_l = 0.002$, $\alpha_p = 0.003$, $\mu_p = 0.005$, $\alpha_l = 0.003$, $\beta_V = 0.5$, $\mu_V = 0.00000391$, $\alpha_S = 0.005$, $\beta_V = 0.00000426$, $\beta = 0.5$, $\alpha_H = 0.005$, $\mu_H = 0.0000391$, $\delta_H = 0.00000426$, $\alpha_G = 0.002$, $\mu_G = 0.002$ $P_0 = 40$, $N_S = 0.0789$, $N_G = 0.089$, $G_0 = 20$, $\in = 0.05$. The simulation were conducted using python.

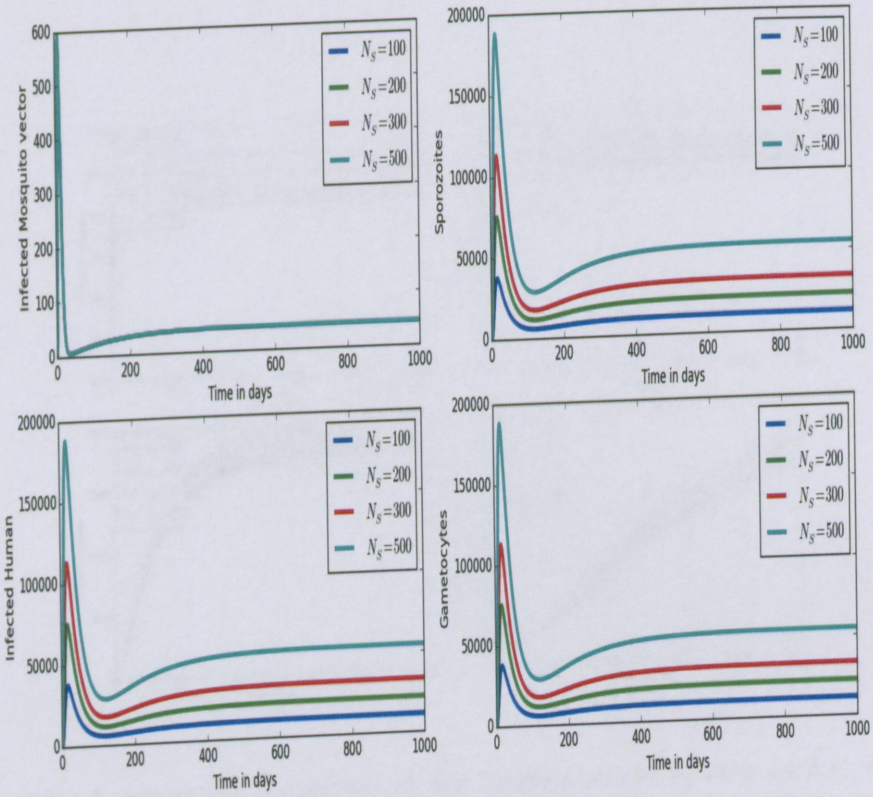


Figure 4.3: A numerical simulation of the malaria model system (4.2.1) with the values of the parameters given in table 4.5, 4.6 and 4.7. These parameters correspond to the reproductive number. The behavior of infected mosquito vectors differ for different value of β_H. The behavior of sporozoite, Susceptible human and infected human will be the same for different value of β_E. The initial condition is: $E = 1000$, $L = 70$, $P = 70$, $S_V = 4000$, $I_V = 5$, $P_V = 100$; $S_H = 2000$; $I_H = 30$, $G_H = 10$ which correspond to $\Lambda_E = 200$, $\Lambda_H = 1000$, $\alpha_E = 0.0079$, $\mu_E = 0.03$, $\alpha_l = 0.05$, $\mu_l = 0.002$, $\alpha_p = 0.003$, $\mu_p = 0.005$, $\alpha_l = 0.003$, $\beta_V = 0.5$, $\mu_V = 0.00000391$, $\alpha_S = 0.005$, $\beta_V = 0.00000426$, $\beta = 0.5$, $\alpha_H = 0.005$, $\mu_H = 0.0000391$, $\delta_H = 0.00000426$, $\alpha_G = 0.002$, $\mu_G = 0.002$ $P_0 = 40$, $N_S = 0.0789$, $N_G = 0.089$, $G_0 = 20$, $\in = 0.05$. The simulation were conducted using python.

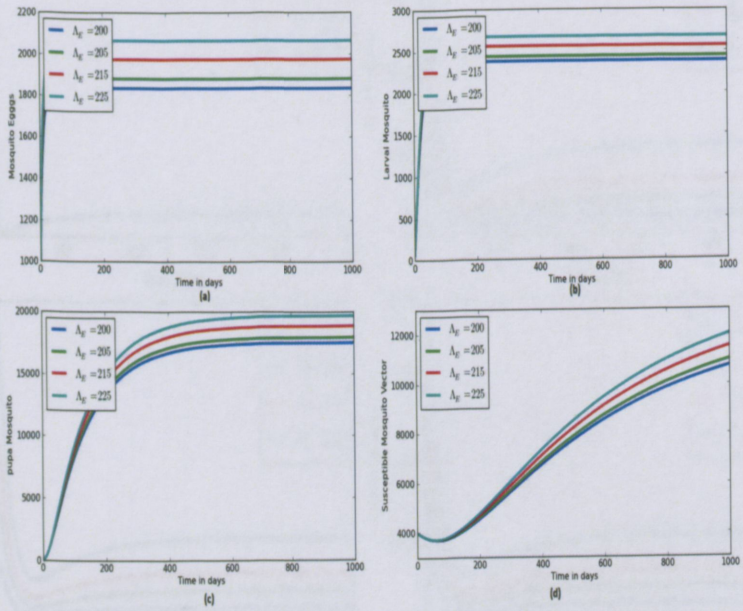


Figure 4.4: A numerical simulation of the malaria model system (4.2.1) with the values of the parameters given in table 4.5, 4.6 and 4.7. These parameters correspond to the reproductive number. The behavior of mosquito Eggs, Larva mosquito, Pupa mosquito and susceptible mosquito vector differ for different value of Λ_E. The initial condition is: $E = 1000$, $L = 70$, $P = 70$, $S_V = 4000$, $I_V = 5$, $P_V = 100$; $S_H = 2000$; $I_H = 30$, $G_H = 10$ which correspond to $\Lambda_E = 200$, $\Lambda_H = 1000$, $\alpha_E = 0.0079$, $\mu_E = 0.03$, $\alpha_l = 0.05$, $\mu_l = 0.002$, $\alpha_p = 0.003$, $\mu_p = 0.005$, $\alpha_l = 0.003$, $\beta_V = 0.5$, $\mu_V = 0.00000391$, $\alpha_S = 0.005$, $\beta_V = 0.00000426$, $\beta_E = 0.5$, $\alpha_H = 0.005$, $\mu_H = 0.0000391$, $\delta_H = 0.00000426$, $\alpha_G = 0.002$, $\mu_G = 0.002$ $P_0 = 40$, $N_S = 0.0789$, $N_G = 0.089$, $G_0 = 20$, $\in = 0.05$. The simulation were conducted using python.

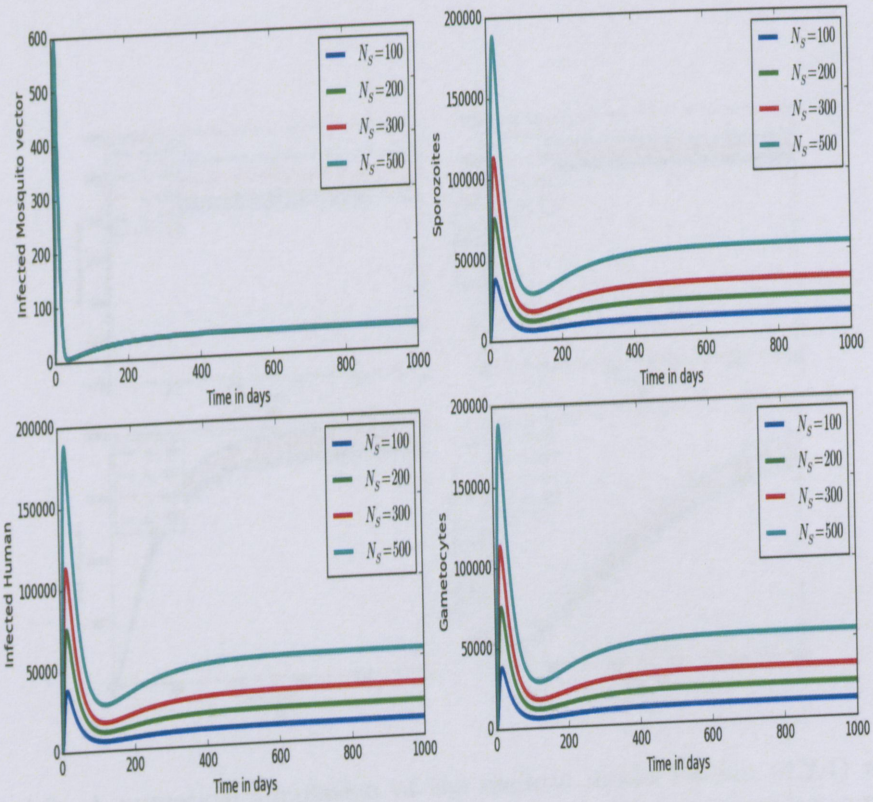


Figure 4.5: A numerical simulation of the malaria model system (4.2.1) with the values of the parameters given in table 4.5, 4.6 and 4.7. These parameters correspond to the reproductive number. The behavior of infected mosquito vector differ for different value of β_H. The behavior of sporozoite, Susceptible human and infected human will be the same for different value of β_E. The initial condition is: $E = 1000$, $L = 70$, $P = 70$, $S_V = 4000$, $I_V = 5$, $P_V = 100$; $S_H = 2000$; $I_H = 30$, $G_H = 10$ which correspond to $\Lambda_E = 200$, $\Lambda_H = 1000$, $\alpha_E = 0.0079$, $\mu_E = 0.03$, $\alpha_l = 0.05$, $\mu_l = 0.002$, $\alpha_p = 0.003$, $\mu_p = 0.005$, $\alpha_l = 0.003$, $\beta_V = 0.5$, $\mu_V = 0.00000391$, $\alpha_S = 0.005$, $\beta_V = 0.00000426$, $\beta = 0.5$, $\alpha_H = 0.005$, $\mu_H = 0.0000391$, $\delta_H = 0.00000426$, $\alpha_G = 0.002$, $\mu_G = 0.002$ $P_0 = 40$, $N_S = 0.0789$, $N_G = 0.089$, $G_0 = 20$, $\in = 0.05$. The simulation were conducted using python.

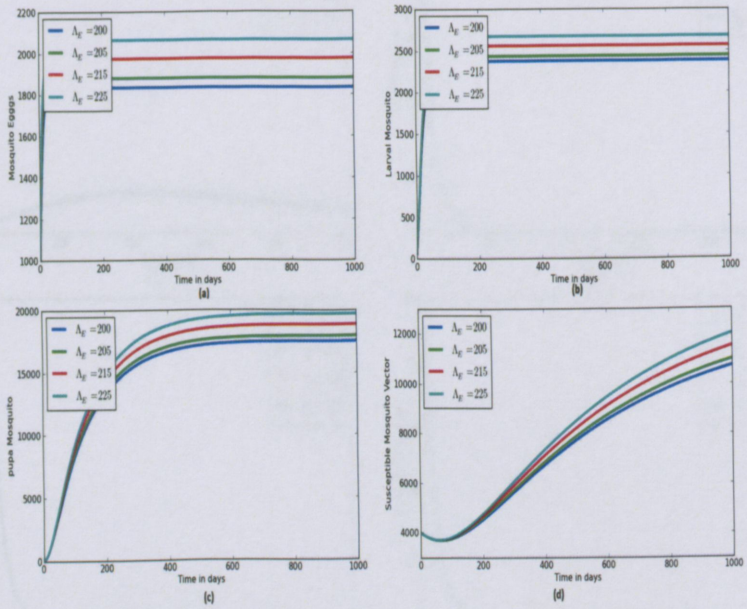


Figure 4.6: A numerical simulation of the malaria model system (4.2.1) with the values of the parameters given in table 4.5, 4.6 and 4.7. These parameters correspond to the reproductive number. The behavior of mosquito Eggs, Larva mosquito, Pupa mosquito and susceptible mosquito vector differ for different value of Λ_E. The initial condition is: $E = 1000$, $L = 70$, $P = 70$, $S_V = 4000$, $I_V = 5$, $P_V = 100$; $S_H = 2000$; $I_H = 30$, $G_H = 10$ which correspond to $\Lambda_E = 200$, $\Lambda_H = 1000$, $\alpha_E = 0.0079$, $\mu_E = 0.03$, $\alpha_l = 0.05$, $\mu_l = 0.002$, $\alpha_p = 0.003$, $\mu_p = 0.005$, $\alpha_l = 0.003$, $\beta_V = 0.5$, $\mu_V = 0.00000391$, $\alpha_S = 0.005$, $\beta_V = 0.00000426$, $\beta_E = 0.5$, $\alpha_H = 0.005$, $\mu_H = 0.0000391$, $\delta_H = 0.00000426$, $\alpha_G = 0.002$, $\mu_G = 0.002$ $P_0 = 40$, $N_S = 0.0789$, $N_G = 0.089$, $G_0 = 20$, $\in = 0.05$. The simulation were conducted using python.

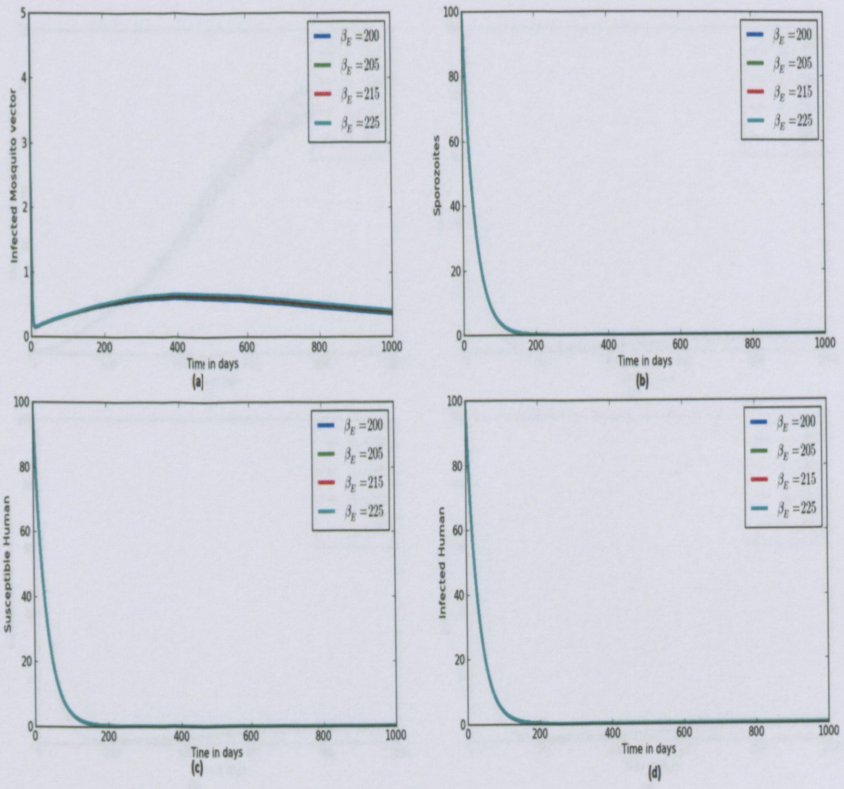


Figure 4.7: A numerical simulation of the malaria model system (4.2.1) with the values of the parameters given in table 4.5, 4.6 and 4.7. These parameters correspond to the reproductive number. The behavior of infected mosquito vectors differ for different value of β_H. The behavior of sporozoite, Susceptible human and infected human will be the same for different value of β_E. The initial condition is: $E = 1000$, $L = 70$, $P = 70$, $S_V = 4000$, $I_V = 5$, $P_V = 100$; $S_H = 2000$; $I_H = 30$, $G_H = 10$ which correspond to $\Lambda_E = 200$, $\Lambda_H = 1000$, $\alpha_E = 0.0079$, $\mu_E = 0.03$, $\alpha_l = 0.05$, $\mu_l = 0.002$, $\alpha_p = 0.003$, $\mu_p = 0.005$, $\alpha_l = 0.003$, $\beta_V = 0.5$, $\mu_V = 0.00000391$, $\alpha_S = 0.005$, $\beta_V = 0.00000426$, $\beta = 0.5$, $\alpha_H = 0.005$, $\mu_H = 0.0000391$, $\delta_H = 0.00000426$, $\alpha_G = 0.002$, $\mu_G = 0.002$ $P_0 = 40$, $N_S = 0.0789$, $N_G = 0.089$, $G_0 = 20$, $\in = 0.05$. The simulation were conducted using python.

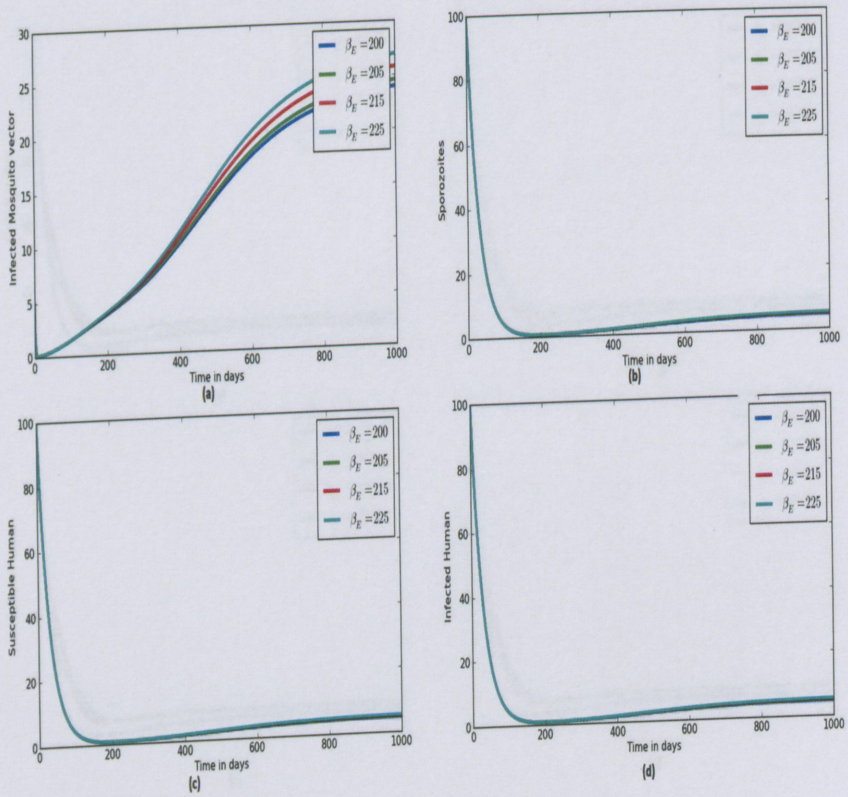


Figure 4.8: A numerical simulation of the malaria model system (4.2.1) with the values of the parameters given in table 4.5, 4.6 and 4.7. These parameters correspond to the reproductive number. The behavior of infected mosquito vectors, Sporozoites, Susceptible human differ for different value of β_E. The initial condition is: $E = 1000$, $L = 70$, $P = 70$, $S_V = 4000$, $I_V = 5$, $P_V = 100$; $S_H = 2000$; $I_H = 30$, ˜ $G_H = 10$ which correspond to $\Lambda_E = 200$, $\Lambda_H = 1000$, $\alpha_E = 0.0079$, $\mu_E = 0.03$, $\alpha_l = 0.05$, $\mu_l = 0.002$, $\alpha_p = 0.003$, $\mu_p = 0.005$, $\alpha_l = 0.003$, $\beta_V = 0.5$, $\mu_V = 0.00000391$, $\alpha_S = 0.005$, $\beta_V = 0.00000426$, $\beta = 0.5$, $\alpha_H = 0.005$, $\mu_H = 0.0000391$, $\delta_H = 0.00000426$, $\alpha_G = 0.002$, $\mu_G = 0.002$ $P_0 = 40$, $N_S = 0.0789$, $N_G = 0.089$, $G_0 = 20$, $\in = 0.05$. The simulation were conducted using python.

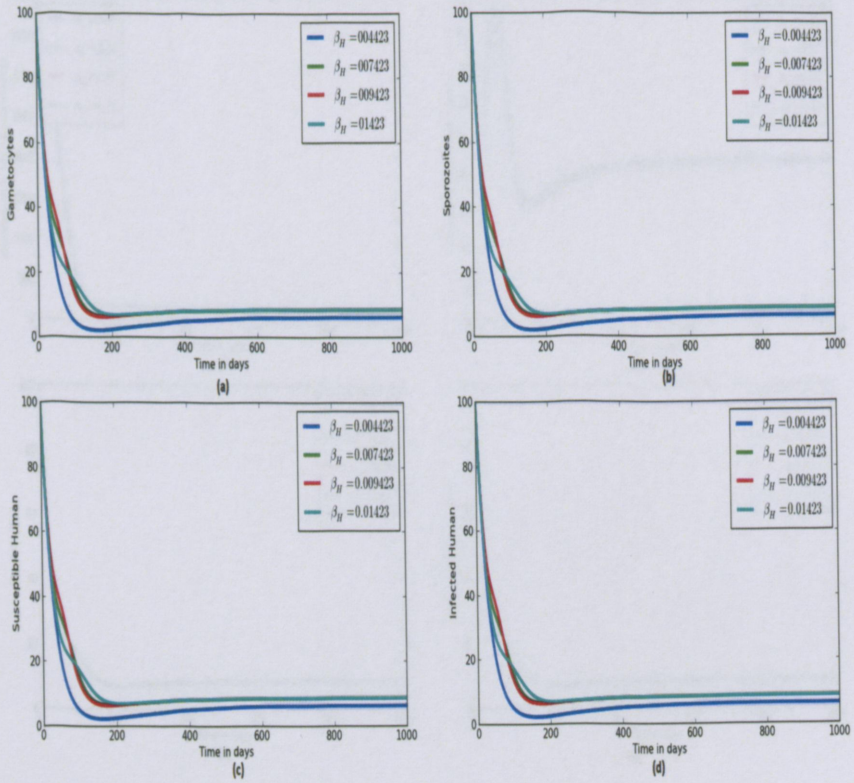


Figure 4.9: A numerical simulation of the malaria model system (4.2.1) with the values of the parameters given in table 4.5, 4.6 and 4.7. These parameters correspond to the reproductive number. The behavior of Gametocytes, Sporozoites, Susceptible human and Infected human differ for different value of β_H. The initial condition is: $E = 1000$, $L = 70$, $P = 70$, $S_V = 4000$, $I_V = 5$, $P_V = 100$; $S_H = 2000$; $I_H = 30$, $G_H = 10$ which correspond to $\Lambda_E = 200$, $\Lambda_H = 1000$, $\alpha_E = 0.0079$, $\mu_E = 0.03$, $\alpha_l = 0.05$, $\mu_l = 0.002$, $\alpha_p = 0.003$, $\mu_p = 0.005$, $\alpha_l = 0.003$, $\beta_V = 0.5$, $\mu_V = 0.00000391$, $\alpha_S = 0.005$, $\beta_V = 0.00000426$, $\beta = 0.5$, $\alpha_H = 0.005$, $\mu_H = 0.0000391$, $\delta_H = 0.00000426$, $\alpha_G = 0.002$, $\mu_G = 0.002$ $P_0 = 40$, $N_S = 0.0789$, $N_G = 0.089$, $G_0 = 20$, $\in = 0.05$. The simulation were conducted using python.

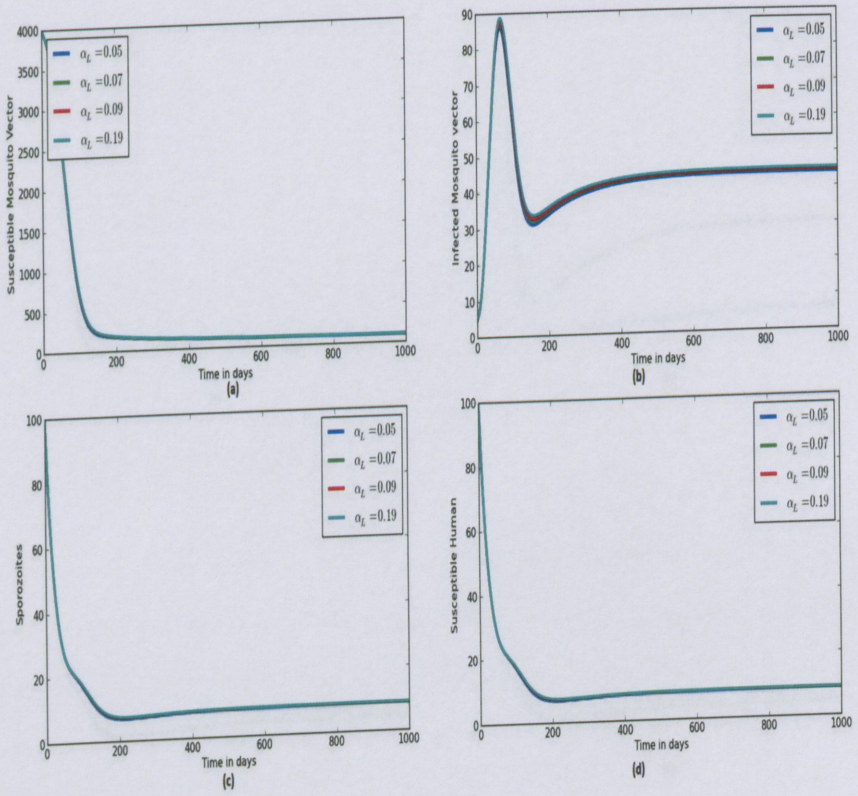


Figure 4.10: A numerical simulation of the malaria model system (4.2.1) with the values of the parameters given in table 4.5, 4.6 and 4.7. These parameters correspond to the reproductive number. The behavior of Susceptible mosquito vectors, Infected mosquito vectors, Sporozoites and susceptible human differ for different value of α_l. The initial condition is: $E = 1000$, $L = 70$, $P = 70$, $S_V = 4000$, $I_V = 5$, $P_V = 100$; $S_H = 2000$; $I_H = 30$, $G_H = 10$ which correspond to $\Lambda_E = 200$, $\Lambda_H = 1000$, $\alpha_E = 0.0079$, $\mu_E = 0.03$, $\alpha_l = 0.05$, $\mu_l = 0.002$, $\alpha_p = 0.003$, $\mu_p = 0.005$, $\alpha_l = 0.003$, $\beta_V = 0.5$, $\mu_V = 0.00000391$, $\alpha_S = 0.005$, $\beta_V = 0.00000426$, $\beta = 0.5$, $\alpha_H = 0.005$, $\mu_H = 0.0000391$, $\delta_H = 0.00000426$, $\alpha_G = 0.002$, $\mu_G = 0.002$ $P_0 = 40$, $N_S = 0.0789$, $N_G = 0.089$, $G_0 = 20$, $\in = 0.05$. The simulation were conducted using python.

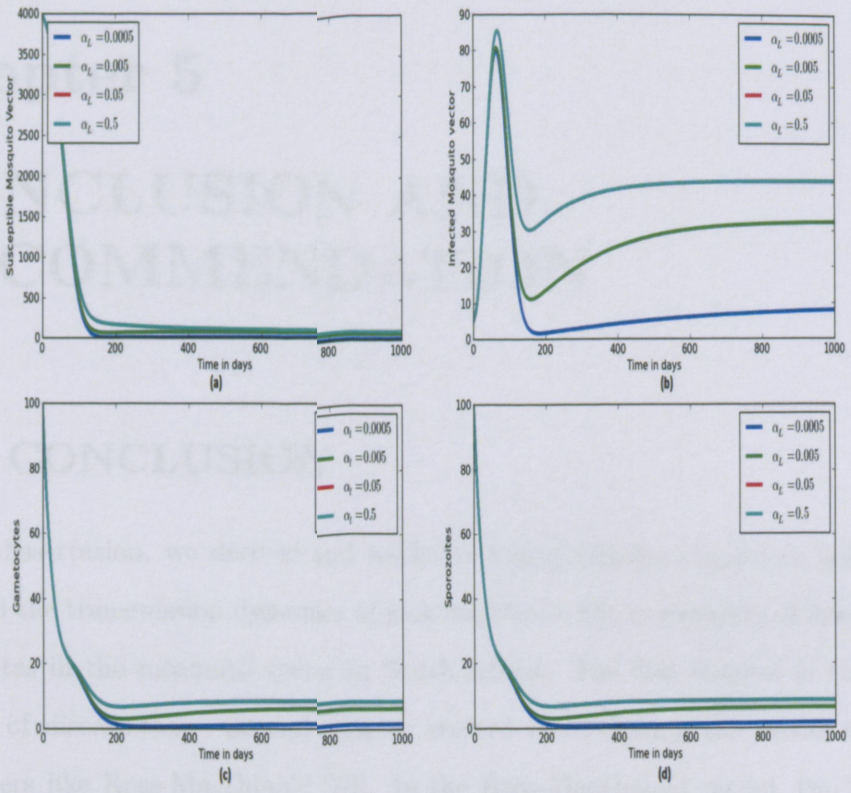


Figure 4.11: A numerical simulation of the malaria model system (4.2.1) with the values of the parameters given in table 4.5, 4.6 and 4.7. These parameters correspond to the reproductive number. The behavior of the of susceptible mosquito vector, infected mosquito vector,Gametocytes and sporozoites differ for different value of α_l. The initial condition is: $E = 1000$, $L = 70$, $P = 70$, $S_V = 4000$, $I_V = 5$, $P_V = 100$; $S_H = 2000$; $I_H = 30$, $G_H = 10$ which correspond to $\Lambda_E = 200$, $\Lambda_H = 1000$, $\alpha_E = 0.0079$, $\mu_E = 0.03$, $\alpha_l = 0.05$, $\mu_l = 0.002$, $\alpha_p = 0.003$, $\mu_p = 0.005$, $\alpha_l = 0.003$, $\beta_V = 0.5$, $\mu_V = 0.00000391$, $\alpha_S = 0.005$, $\beta_V = 0.00000426$ $\beta = 0.5$, $\alpha_H = 0.005$, $\mu_H = 0.0000391$, $\delta_H = 0.00000426$, $\alpha_G = 0.002$, $\mu_G = 0.002$ $P_0 = 40$, $N_S = 0.0789$, $N_G = 0.089$, $G_0 = 20$, $\epsilon = 0.05$. The simulation were conducted using python.

Chapter 5

CONCLUSION AND RECOMMENDATION

5.1 CONCLUSION

In this dissertation, we derived and analysed a mathematical model to better understand the transmission dynamics of gametocytes in the community of human and sporozoites in the mosquito vector in South Africa. The first chapter is the introduction of dissertation. Second chapter started by reviewing the model of other researchers like Ross-MacDonald [70]. In the Ross-MacDonald model, two populations of human host and mosquito vectors were considered and modelled by a system of differential equations. In chapter 3 we presented and analyzed multi-scale modelling of malaria infection, where we consider the average number of humans who are infected by gametocytes at time t $N_g(t)$ and the average number of mosquito vectors who are infected by sporozoites at time t $N_s(t)$. This model is a system of six non-linear differential equations. Ordinary differential equations were used to model malaria where humans and mosquito interact and infect each other. Mathematically, we modelled malaria as a 6-dimension system of ordinary differential equations, where

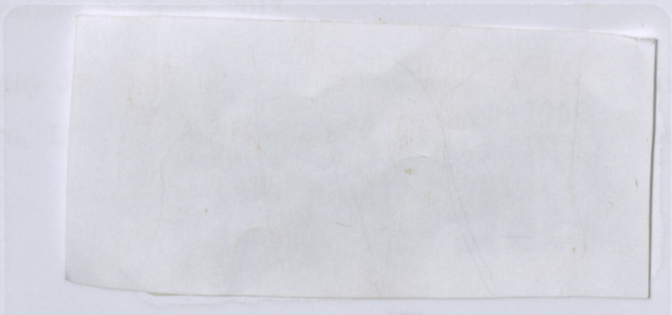
we have Susceptible humans, $S_H(t)$, Infected humans, $I_H(t)$, Gametocytes, $G_H(t)$. In the mosquito vectors we have Susceptible mosquito, $S_V(t)$, Infected Mosquito, $I_V(t)$ and Infected Mosquito, $P_V(t)$. We first proved the existence of domain, where the model is epidemiologically and mathematically well-posed. We showed the existence of steady state or equilibrium point where there is no malaria parasite in the human populations or plasmodium parasite in the mosquito populations. We defined the reproduction number, R_0 that is epidemiologically accurate that provides the expected number of new infections(in mosquitoes or humans) from one infectious individual (human or mosquito) over the duration of the infectious period given that all other members of the population were susceptible populations. Which implies that the average number of infected individual is less than one person throughout his/her infectious period and in this case the disease is wiped out. On the other hand if the average number of infected individuals is more than one, then the disease persists in the populations. In the result we see that the reproduction number, which is less than 1, it means that the disease is stable. We calculate local stability of the disease free equilibrium, we obtain by calculating the eigenvalues of the Jacobian matrix of the linearized system and we see that all the eigenvalues are negative which implies that it is locally asymptotical stable. We also calculate the endemic equilibrium point where both human and mosquito vectors are infected by the sporozoites and Gametocytes respectively. Chapter 4 is the extension of chapter 3, where we consider the life-cycle of mosquito vectors. The model has nine non-linear differential equations which describe the spreading of malaria with six state variable for mosquito vectors and three state variable for human host. Ordinary differential equations were used to model malaria where humans and mosquito interact and infect each other. Anopheles

mosquito are essential for development, multiplication, and spread of plasmodium. When an infectious mosquito bites a human, the parasite in the form of sporozoite in the saliva of mosquito enter the human. The sporozoites then migrate to the liver and then to the red blood cells. The model of life cycle of mosquito vectors and human host has both the invariant and positivity solution. We showed that there exists a domain where the model is epidemiologically and mathematically well-posed. We show the existence of steady state solution, where there is no malaria parasite in the human populations or plasmodium parasite in the mosquito populations. We defined the reproductive number,that is epidemiologically accurate in that it provides the expected number of new infections(in mosquitoes or humans) from one infectious individual (human or mosquito) over the duration of the infectious period given that all other members of the population are susceptible population. The existence and stability of steady-state solution were investigated. The endemic equilibrium point and the existence of endemic equilibrium point where calculated, to investigate the spreading of malaria. The Sensitivity analysis and numerical simulation where conducted to confirm the analytical results and explore the behaviour of the formulated model.

All the control strategies that we discussed, is qualitative relationship between the control strategies to the parameters and to include the cost of the control strategies to directly relate the reduction in disease prevalence and transmission to the cost involved. Other future goals include improving the model to capture important features of malaria transmission that our model does not include: Seasonal effects: Seasonally varying environmental effects, such as rainfall, temperature, and humidity affect many

of the important factors in malaria transmission. These environment-dependent parameters include the mosquito birth rate and the mosquito rate of progression from the latent period. We can model these seasonal effects by making some of these parameters periodic function of time. Analysing this periodically-force model, including changes in the reproductive number and endemic states, would provide a more accurate picture of malaria transmission than is currently obtained from models using parameter values that are averaged over the seasons. Mosquito population model: The mosquito life cycle has discrete stages and the development times for these stages are dependent on the environment. We can improve models for mosquito population dynamics by including these separate juvenile stages, while incorporating environmental and seasonal effects. Also, anthropophilic mosquito species,like An. gambian, depend on humans for their reproduction. Transmission-rate dependent period of immunity: Resistance to malaria has been shown to be dependent on prevalent levels of transmission. We include this effect in our model by making the rate of loss of immunity. Superinfection: Similar to other infections caused by macro parasites, malaria displays some properties of superinfection where reinfection when one is already infected can worsen the effects of the diseases. Age structure: Age structure is important in the dynamics malaria, as most deaths occurs in infants and the average parasitemia levels of infected individual's decreases with age. Immune response also changes with age. Adding age structure also allows us to study the effects of the various control strategies on the age distribution of disease prevalence. We can model age structure, either through discrete age groups or continuously through converting the system of equations to partial differential equations. Spatial structure: Spatial spread is an important feature in the dynamics of malaria, from local transmission

in a given region, to the global spread of drug-resistant strains of plasmodium. We can include spatial dynamics through the replication of the basic model at different nodes, representing various locations, with some human/mosquito migration between the nodes. Ultimately, we would like to validate this model by applying it to a specific malaria-endemic part of the world. We want to compare predicted endemic states obtained from the model using parameter value for that location to the actual local prevalence data. This will allow us to make informed decision about the type and level of intervention strategies that provide the most effective coverage in that area.



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