

A Multi-level Model for a Vector-Borne Organ to Tissue life Cycle Dynamics

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Declaration

*I, **Awelani Sydney Mahada**, declare that this thesis submitted in partial fulfilment of the requirements for the conferral of the degree **Master of Science (Applied Mathematics)**, from the University of Venda, is wholly my own work unless otherwise referenced or acknowledged. This document has not been submitted for qualifications at any other academic institution.*



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Abstract

Introduction: Malaria is among the World's most lethal infectious disease. It is caused by a parasitic pathogen transmitted by the *Anopheles* mosquito, which inoculates sporozoites into the human host during a blood meal. The population dynamics of malaria are well-known for their complexity, stemming not only from the parasite's lifecycle, which involves two hosts (humans and mosquitoes) but also from the intricate replication and transmission cycles across different levels of the infectious disease system organization. Like other infectious disease systems, malaria infections inherit multilevel and multiscale systems, which pose significant challenges to efforts aimed at eliminating and ultimately eradicating the infection in a malaria-endemic population.

Methodology Mathematical modeling in the study of complex system has proven to be an invaluable tool for understanding and predicting the behaviour and dynamics of a complex system within the domain of complexity science. Thus, in this study, we propose a multiscale modelling framework that captures the dynamics of malaria across three organizational levels within infectious disease systems implicated in the spread of malaria in a community. We begin by formulating a mathematical model to describe the development and progression of malaria parasites within the liver and tissue(blood) stages of an infected human host. This is followed by the formulation of a multiscale model that integrates both the inside(i.e.,the organ-tissue level)host and the outside (i.e., the host level) host malaria dynamics.

Results Mathematical analysis for both the malaria models presented in this study was carried out and proved that all the models are mathematically and epidemiologically well-posed. We also compute the basic reproduction number R_0 for both models and use the R_0 to determine the local and global stability of the disease-free equilibrium as well as the local stability of endemic equilibrium of both models, respectively. We demonstrate that if $R_0 < 1$, then the disease-free equilibrium point of both models is locally and globally asymptotically stable, respectively. However, if $R_0 > 1$ the endemic equilibrium point of both models is locally asymptotically stable. The numerical results for both the models have demonstrated that the goal of intervention during malaria infection should be to reduce the rates at which merozoites and gametocytes invade healthy liver tissue as well as the blood cells. Hence it is recommended that interventions during malaria infection be directed on reducing the pace at which merozoites infect healthy blood cells and the density of merozoites in circulation.

Conclusion The study presents a method that incorporates the complexity of malaria pathogens which is significant not only for malaria treatment but also for other vector-borne disease system control treatment strategies.

Keywords: Merozoites, Gametocytes, Anopheles, Sporozoites, Hepatocytes, Gametes, Schizonts, Oocysts,

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Chapter 1

Introduction

Malaria is a disease that spreads unevenly through time and geography. The dynamics of the malaria disease and the geographic distribution of vectorial density are subject to variation based on climatic factors and environmental conditions. The correlation between host, vector, and climatic conditions is the cause of the malaria's rapid spread. The contact rate of vector-borne diseases is significantly impacted by climate variation ([Organization et al. \(2007\)](#)). The transmission of disease transmitted by vectors is determined by three different elements, namely the pathogen, the arthropod vector and the human host. The vectors serves as a carrier of the parasite and as an organism in which the parasite develops to an infectious stage before being transmitted to the vertebrate host. The study seek to develop a multiscale models of infectious disease systems taking malaria disease system as a case study. We are using three categories of multiscale models of infectious disease system in linking the sub-models which are coupled multiscale models, nested multiscale models and embedded multiscale models.

1.1 Background.

A renewed push to eradicate malaria as a public health issue has resulted from the dramatic declines in malaria transmission after the year 2000. This has changed the conversation dramatically, and as a result, more money is being spent on research and resources for strategies to reduce the size of the malaria map ([Organization et al. \(2007\)](#)). The WHO's approach to preventing malaria is based on several important pillars, including quick diagnosis and treatment with artemisinin combination therapy as well as surveillance to better focus initiatives. With remarkable outcomes, these interventions have been greatly increased in the last few years. However, significant disparities in access to these tried-and-true tools and coverage gaps still exist. It is obvious that malaria transmission will continue even if these tools are implemented at extremely high levels. This was illustrated in the spread of malaria will continue. A modeling research headed by Imperial College provided evidence of this ([Walker et al. \(2016\)](#)).

Many scientific efforts, including the development of a malaria vaccine, have been

made to lessen the impact of malaria worldwide. The development of malaria vaccines targets distinct phases of the parasite's life cycle in both humans and mosquitoes. Other initiatives include the development of mathematical models; Ross created the first model of malaria transmission. Ross ([Garira et al. \(2014\)](#)) states that malaria can be eliminated if the mosquito population is reduced to a specific level. Subsequently, Macdonald included superinfection and made some other model adjustments. He demonstrated that in regions of high malaria transmission, decreasing the mosquito population had minimal impact on the disease's epidemiology. Certain demographic groups are significantly more susceptible than others to both malaria and severe illness ([Organization et al. \(2007\)](#)). These comprise young children under five, pregnant women, HIV/AIDS patients, non-immune migrants, the mobile population, and tourists. Given their unique circumstances, national malaria control programs must take extra precautions to shield these population groups from malaria infection.

In contrast to 231 million cases in 2017, there were 228 million cases of malaria in 2018, according to the World Malaria Report ([Organization et al. \(2006\)](#)), which was published in December 2019. In 2018, 405 000 malaria deaths were estimated, down from 416 000 deaths in 2017. World Health Organization The burden of malaria worldwide is still disproportionately heavy on the African Region. Ninety-three percent of malaria deaths and ninety-three percent of cases occurred in the region in 2018. More than half of all malaria cases globally in 2018 were reported from six countries: Nigeria (25 percent), the Democratic Republic of the Congo (12 percent), Uganda (5 percent), Cote D'ivoire (4 percent), Mozambique (4 percent), and Niger (4 percent). Youngsters under five are the most susceptible to malarial infection. They were responsible for 272,00 malaria deaths globally in 2018, or 67 percent of all malaria deaths, [Organization \(2015\)](#). The asexual erythrocytic or blood stage parasites are the source of all clinical symptoms linked to malaria. Numerous waste products, both known and unknown, including hemozoin pigment and other harmful components, build up in the infected red blood cell as the parasites grows inside the erythrocyte. When the infected cells lyse and release invasive merozoites, these are released into the bloodstream. Hemorrhage and additional harmful elements, like glucose phages and other cells, generate cytokines and other soluble substances that cause fever and rigors and may have an impact on other serious malarial pathophysiology. [Organization et al. \(2006\)](#).

Erythrocytes infected with *Plasmodium falciparum* ([Garira and Mathebula \(2019\)](#)), especially those containing mature trophozoites, cling to the venular blood vessel wall's vascular endothelium and are unable to circulate freely in the blood. It is thought that this sequestration of infected erythrocytes in the brain's arteries ([Organization et al. \(2007\)](#)) contributes to the development of cerebral malaria, a severe illness syndrome with a high death rate. It takes some time for the first symptoms to manifest after an *Anopheles* mosquito bite during the incubation period. Most of the time, the incubation period lasts between seven and thirty days. *Plasmodium falciparum* is known to cause the shorter durations, while *Plasmodium malariae* is known to cause the longer ones ([Organization et al. \(2007\)](#)).

1.1.1 Life cycle of Malaria

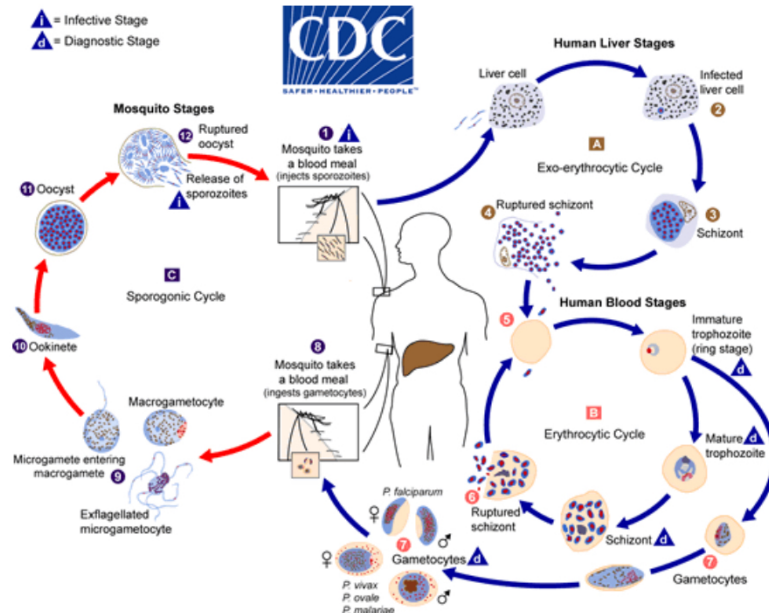


Figure 1.1: The transmission life cycle of malaria infectious disease. Life Cycle of Malaria Parasite Cdc, Haley Eichmann, 2024

Humans and female *Anopheles* mosquitoes contract malaria on a cyclical basis as part of the disease's natural history (Aly et al. (2009)). In humans see figure 1.1, the parasites proliferate and thrive in the blood's red blood cells after beginning in the liver cells. Repeated parasitic broods develop inside red blood cells in the bloodstream and eventually burst them, producing progeny parasites known as merozoites that carry on the cycle and infect more red blood cells (Aly et al. (2009)).

Malaria symptoms are brought on by blood stage parasites. When specific blood stage parasites (gametocytes, which come in both male and female forms) are consumed by a female *Anopheles* mosquito during blood feeding, they pair in the mosquito's stomach and start a cycle of development and multiplication (Allen and Kirk, 2004). A parasite type known as a sporozoite moves to the salivary glands of the mosquito after 10–18 days. Anti-coagulant saliva is injected along with the sporozoites, which travel to the liver and start a new cycle, when the *Anopheles* mosquito feeds on human blood. Therefore, the disease-carrying mosquito acts as a "vector" to spread the illness from one human to another. Although the parasite is transmitted by infected humans to the mosquito vector, the vector is not harmed by the parasites' presence (Allen and Kirk, 2004).

There are two hosts in the life cycle of the malaria parasite. A malaria-carrying

female *Anopheles* mosquito injects sporozoites into the human host during a blood meal (Bray and Garnham (1982)). After infecting liver cells, sporozoites develop into schizonts, which burst and release merozoites. Dormant stages of *P. ovale* and *P. vivax* might linger in the liver and trigger relapses by reentering the bloodstream weeks or even years later. The parasites multiply asexually in the erythrocytes following their first replication in the liver. Blood cells are infected by merozoites. Trophozoites in the ring stage develop into schizonts, which burst to release merozoites. A few parasites undergo sexual erythrocytic differentiation. According to Barreto (2006), blood stage parasites are to blame for the disease's clinical signs. *Anopheles* mosquitoes consume both male and female gametocytes while feeding on blood. The sporogonic cycle is the name for the parasites' ability to multiply within mosquitoes. The microgametes pierce the macrogametes in the mosquito's stomach to produce zygotes. The zygotes then develop into elongated, motile organisms that infiltrate the mosquito's midgut wall and mature into oocysts. The oocysts develop, burst, and release sporozoites, which travel to the salivary glands of the mosquito. The malaria life cycle is perpetuated by injecting sporozoites into a fresh human host (Bray and Garnham (1982)).

1.1.2 Symptoms and Diagnosis

Malaria is an acute febrile illness that often appears 10–15 days after an infected mosquito bites a non-immune individual (Garabed et al. (2019)). Malaria's early symptoms, which can include fever, chills, and headaches, can be mild. If treatment is not administered within 24 hours, *Plasmodium falciparum* malaria can deteriorate and often result in death Allen and Kirk (2004). One or more of these symptoms are frequently present in children with cerebral malaria, respiratory distress owing to metabolic acidosis, or severe anemia. Adults also frequently have multiorgan failure. In areas where malaria is endemic, people may develop a partial immunity to the disease, making infections symptomless conceivable.

Vector control is the main tactic used to stop and lessen the spread of malaria (Organization (2015)). This was shown in a large-scale study conducted from 2011 to 2016 in five countries under the coordination of the WHO. Frequent signs and symptoms of malaria generally involve a high temperature and chills. A malaria infection usually manifests as fever, chills, headaches, nausea, vomiting, lethargy, and stiffness in the muscles. On the other hand, some malaria parasite types can hibernate in your body for as long as a year. Barreto et al. (2006).

Diagnosing malaria still involves light microscopy of thick and thin stained blood smears. According to (Schwartz et al. (2001)), thick smears are 20–40 times more sensible than thin smears for screening plasmodium parasites, with a detection limit of 10–50 trophozoites. A erroneously low parasite count in the peripheral blood might occur from parasitized erythrocytes being sequestered in tissue capillaries in *falciparum* malaria (Garcia (1999)).

1.1.3 Malaria Prevention and Treatment

Malaria can be prevented and treated early to lessen illness and death. It helps to lessen the spread of malaria. The most effective prevention currently available is artemisinin-based combination therapy (ACT), especially for *Plasmodium falciparum* malaria. Before starting treatment, the World Health Organization advises that any suspected cases of malaria should be verified using parasite-based diagnostic testing (either microscopy or fast diagnostic test). Within thirty minutes or less, the results of the parasitological confirmation can be obtained. preventions based purely on symptoms should be explored in cases when a parasitological diagnosis is not achievable. The third edition of the "WHO Guidelines for the treatment of malaria" was released in April 2015 and contains more thorough suggestions, [Organization \(2015\)](#).

Severe malaria patients need to be treated in an intensive care unit. If clinically significant malaria develops, it typically does so 3–7 days after fever onset, though there have been isolated accounts of nonimmune individuals passing away within 24 hours of symptom onset. Due to delayed cytokine release, severe malaria may manifest even after initial treatment response and full clearance of parasitemia [Schwartz et al. \(2001\)](#). When adults contract severe malaria, cerebral malaria is the most prevalent clinical manifestation and cause of mortality. According to [Svenson et al. \(1995\)](#), the onset can be sudden and cause a widespread convulsion, or it can be slow and cause early disorientation and drowsiness, followed by a coma that lasts for several hours to many days. Practically speaking, cerebral malaria should be the course of treatment for any change in mental status. To rule out meningitis caused by bacteria, a lumbar puncture should be carried out. In order to differentiate between cerebral malaria and temporary postictal coma, patients must remain unconscious for a minimum of half an hour following a seizure. The prognosis is worse the deeper the coma ([Bruneel et al. \(2003\)](#)).

Low peripheral vascular resistance and increased cardiac output are common in shock patients. Despite severe sequestration of parasitized erythrocytes in the myocardium's microvasculature, cardiac pump function seems to have been remarkably sustained ([Svenson et al. \(1995\)](#)). Autonomic dysfunction may be secondary to postural hypotension. Severe hypertension can strike out of nowhere, generally accompanied by significant bleeding from the gastrointestinal tract or rupture of the spleen, sepsis, pulmonary edema, and metabolic acidosis. Children in highly endemic areas are more likely to suffer from severe anemia as a result of recurrent or persistent *Plasmodium* infections. Thrombocytopenia is a frequent condition that is typically unrelated to bleeding. Less than 10 percent of patients with severe malaria have been documented to have disseminated intravascular coagulation ([Barreto et al. \(2006\)](#)).

1.2 Problem Statement

There is a knowledge vacuum that requires the intervention of malaria infection at the tissue and organ of an infected human host, taking into account the influ-

ence and severity of malaria within an infected individual on the transmission of the malaria disease. There is some knowledge on how the pathogens attack the liver cells as soon as they enter the human host's liver organ. We call attention to the efforts undertaken to investigate the relationship between the within-host and between-host dynamics of infectious illnesses (Mideo et al. (2008)). Since endeavors require knowledge of processes at many infectious disease scales and how these scales are linked, the gap has been formed during the attempt to get an in-depth understanding of the transmission process of infectious illnesses, including malaria sickness, Garira et al., 2017 ACC. The understanding of the spread of numerous infectious illnesses, such as HIV, malaria, schistosomiasis, and tuberculosis, has improved because to mathematical models. Most mathematicians, however, model each of these illnesses' progressions independently. However, by mathematically tracking transmission dynamics within the human-host progression of these infectious diseases, we can determine the environmental measures that can be taken to reduce the number of free-living pathogens and what steps can be taken to combat pathogens within an infected person (Garira (2017)). A small number of mathematical studies that have been conducted on the infectious disease malaria have taken into account both the organ that transmits the malaria infection and the evolution of the pathogen at the tissue level. We observed a gap that requires the presence of malaria infection at the tissue and organ of an infected human host, taking into account the influence and severity of malaria within an infected individual on the transmission of the malaria disease. By creating a multiscale modeling framework that will assist in tracking the evolution of the malaria pathogen at the tissue and liver organ levels within the human host, we hope to close this gap in our knowledge. The following question will be attempted to be addressed by the research.

- Can we use a multiscale model of malaria transmission dynamics to assess if it is possible to stop or restrict the spread of malaria in a community where the merozoite life cycle is complex?

1.3 Aim and Objectives

The main aim of this study is to develop a multiscale modelling framework that characterize a malaria transmission dynamics and apply it across the microscale and macroscale replication-transmission cycle within the hosts. The study specifically seeks to accomplish the following objectives:

- To develop a mathematical models for the dynamics of malaria transmission that takes into account pathogen's development in the liver and the human host's tissue system.
- To incorporate a multiscale model of malaria transmission dynamics that integrate the pathogen's development at both the liver and the tissue host level with the pathogen transmission at the malaria population-level.

1.4 Methodology

The spread of the malaria disease system is tracked using a multiscale modeling framework. The research focuses on compartment models that explain the dynamics of malaria disease transmission between humans and mosquitoes. To track the efficacy of the immune response against the malaria disease system's transmission within the liver and bloodstream, we employ a multiscale modeling approach. The dynamics of infection inside a single host, where the immune process occurs, are linked to the within-human host process. The Study builds on coupled multiscale models of malaria which is developed into two phases, the first phase is to develop submodels for vertebrate-host and vector-host separately and second phase is to integrate the sub-models into single model within one or numerous variables of such model. The embedded multiscale modeling approach will be used in this study, since there is no replication of pathogen at within vector-host scale and the influence of between-vector and within-vector host scale through super infection is considered important. We will use the nested multiscale modelling approach for vertebrate-host because there is a replication of pathogen.

We will develop a mathematical-based multiscale model approach that involves the use of mathematical approaches to develop multiscale dynamics models. We will come up with differential equations from different sub-models that describes each scale. This differential equations will demonstrate the flow of information and illustrate the linking mechanism, the descriptions of variables and parameters will be presented in the tables. The model will be solved analytically by obtaining the reproductive number, disease-free equilibrium point, endemic equilibrium point, positivity, local and global stability analysis. We will adapt the computational-based multiscale model approach, where we use computer programs to derive approximate numerical solutions of the mathematical-based multiscale model approach. We will apply computational-based multiscale model approach to test the local and global sensitivity analysis and simulation of models using graphs.

1.5 Limitations of Multiscale Modelling

While multiscale modeling plays an important role in providing deeper biological insight into the complex interactions between disease process such as the disease triad through improved diagnosis facilitated by biomarker discovery, improved predictions on clinical outcomes of infections and provision of the multiscale ,system-based approach for evaluating the wider implications of therapeutic strategies, the approach is not without drawbacks. A few methods, such as concurrent Atomistic Continuum (CAC), Coupled Atomistic Discrete Dislocation (CADD), and the Coupled Extended Finite Element Method (XFEM), are able to simulate moving

defects in the coarse-scale domain to improve practicality and predictions. The analysis reveals that most methods suffer from the consequences of inconsistent materials descriptions between representations at different scales. The use of multiscale simulation in solving coupled thermal and mechanical problems is demonstrating potential; nevertheless, many concurrent multiscale approaches are currently unable to fully assess faults at the mesoscale, which is substantially outside the scope of standard atomistic methods.

The increased model complexity brought about by the computational approach—very few population-level parameters can be estimated analytically in a closed form—is another disadvantage of multiscale modeling. This indicates that outside of large computer-based systems, not much can be discovered by examining the impact of within-host operations on the between-host process. Despite all of these drawbacks, multiscale modeling is an invaluable computational tool that can present opportunities to infer the synergistic dynamics of malaria at the individual and population level. In addition, prior findings using multiscale models have largely revealed the shortcomings of single-based models, presenting the methodology as a significant mathematical tool whose associated complexities are commensurate with the biological insights they yield (Cai et al. (2017)).

1.6 Outline of the thesis

- Chapter 1, provides overview of infectious disease, particularly the biological background of Malaria, the transmission cycle and prevention of Malaria disease.
- Chapter 2, develops a mathematical model that depicts the dynamics of transmission for both the epidemiological and immunological stages of the infectious malaria disease.
- Chapter 3, provides the shortcomings of transmission dynamic models in comparison to multiscale models. We demonstrate that, in order to evaluate the efficacy of preventative measures for the sake of malaria health policy, the inside host infection model could not be expanded.
- Chapter 4, provides the construction of a multiscale model that combines the epidemiological and immunological models. The multiscale model that is produced is then used to determine the optimal combinations of interventions that could be used to stop the spread of malaria.
- Chapter 5, provides the Results, discussion, a conclusion, and recommendations.

Chapter 2

Multiscale Modelling Frame-Work for Linking Micro-scale and Macro-scale Models

2.1 Introduction

In this chapter, we present the review of the literature on mathematical modelling and the development of mathematical modelling has begun in the 1970s in fields such as physics, meteorology, and chemistry. Like any other mathematical modelling process the choice to use mathematical modelling approach as a tool for addressing real world problems is in itself a decision-making process which depends entirely on the goal behind the formulation of a model as well as the specific research questions to be answered. In other words the decision to apply mathematical models rests upon the structure of the underlying problems. For instance, there are situations in which the underlying problem may require the launch of complex models such as multiscale models. This study, propose the use of Multiscale modelling because the research question dictates that we carry out a comparative effectiveness of malaria intervention, which is a task for beyond the reach of well known traditional single-scale modelling approaches. Specific examples in which multiscale modelling is applied related to its application. In solving a meteorological by linking the interactions of soil and vegetation with the atmosphere. The results obtained from linking the effects of those three determinants brought another deeper insight in computational weather forecasts as the results were considered very realistic.

2.2 Macro and Micro scale mathematical models

Mathematical modelling dealing with complex models, deploys the multiscale modelling approach which is refers to the approach of modelling in which multiple models at different scales or levels are used simultaneously to explain a system. The multiscale models comprises of two major parts which are: the

immunology/micro-scale/lower scale (i.e the within cell, tissues, organ) sub-model, epidemiology/macro-scale/upper-scale (i.e. the between-cell scales, between-tissues scale, between-organs scale) sub-model and the linking mechanisms of these sub-models. Multiscale models of infectious disease systems have new mathematical approach which helps in developing a system approach to gain an insight of infectious diseases transmission dynamics with regards to the dependence of two scales on each other on between epidemiological/macro-scale/upper-scale (between -cell scale, between-tissue scale, between-organ scale, between-host scale) and immunological/micro-scale/lower-scale (within-cell scale, within-tissue scale, within-organ scale, within host scale). Infectious disease dynamics are governed by many integrated scales from complex within-cell/ within-tissue/ within-organ/ within-host infection processes to between-cell/ between-tissue/between-organ/ between-host, vectors and environments. An essential distinct property of infectious disease system that distinguishes them from other diseases is that they remain as the leading source of morbidity and mortality. There are many work done on major developments in the prevention and treatment of infectious disease systems i.e. diagnostics, therapeutics and vaccines and they remain a significant public health concern. Malaria infectious disease need to be explored deep to its complex levels, and in order to do that all five multiscale model categories of infectious diseases must be considered in order to find the best methodological category to be used in addressing a problem. The categories of multiscale models of infectious disease are explained as follows:

There are five main categories of multiscale models of infectious disease systems that integrate the two adjacent scales (micro-scale and macro-scale) at a time of an infectious disease systems, which are: individual-based multiscale models, nested multiscale models, embedded multiscale models, hybrid multiscale models and coupled multiscale models. these categories are summarised below.

(i) Individual-based multiscale models (IMSMs): are multiscale models of infectious disease systems with individual/micro-scale/lower-scale sub-models being used to describe the entire multiscale model of infectious disease systems across both the individual/micro-scale/lower-scale and the population/micro-scale/upper-scale sub-models. There is no feedback from the upper-scale submodels to the lower-scale sub-models.

(ii) Nested multiscale models are multiscale models (NMSMs) of infectious disease systems with unidirectional flow of information, where there is only flow of information from individual/micro-scale/lower-scale sub-models to the population/macro-scale/upper-scale sub-models. The lower-scale and upper-scale sub-models must be demonstrated by the same formalism or mathematical presentation. The lower-scale sub-models shares the pathogen with upper scale sub-models through pathogen shed/excreted, which demonstrate the movement of pathogen from lower-scale to upper-scale sub-models. The influence of upper-scale sub-models to lower-scale sub-models is through initial infection, which demonstrate the movement of pathogens from upper-scale sub-models to lower-scale sub-models.

(iii) Embedded multiscale models (EMSMs) are multiscale models of infectious disease systems with both individual/micro-scale/lower scale and population/macro-

scale/upper-scale sub-models influencing each other in a reciprocal way. The two sub-models must illustrate by the same formalism or mathematical presentation. The lower-scale sub-models influences upper-scale sub-models through pathogen shedding/excretion, whereas the upper-scale sub-models influences the lower-scale sub-models through super-infection.

(iv) Hybrid multiscale models (HMSMs) are multiscale models of infectious disease systems with individual/micro-scale/lower-scale and population/macro-scale/upper-scale sub-models demonstrated by different mathematical representations. These four categories of multiscale models of infectious disease systems consider single-host and single-pathogen.

(v) Couple multiscale models (CMSMs) are multiscale models of infectious disease systems which consider multi-strain infection, multi-pathogen infection, multi-group infections, multi-host infections, multi-level infections, multi-geographical environment, multi-biological environment infections. Couple multiscale model of infectious disease systems is different with other first four categories of multiscale models where they focus on one-host and one-pathogen relationships. Coupled multiscale model is a combination of the first four categories of multiscale models.

2.3 Multiscale Modelling of Vector-borne diseases

There are many studies on multiscale modelling approaches of malaria disease systems. These multiscale models contain within-human dynamics of parasite, within-mosquito dynamics of parasite, life-cycle of parasite, environmental factors, immune response and mosquito and human population dynamics. Many mathematical models of transmission dynamics of malaria disease systems have been studied. Although the models have brought insights into malaria biology, they have relatively little impact on the field studies or on the design of control programmes. Recent studies of malaria disease systems on separate scales were either immunological(within-host scale) or epidemiological (between-host scale), and some link the epidemiological and immunological system.

Lagros and Bonhoeffer worked on the evolution of resistance of a complex process that influenced transmission dynamics between-hosts as well as linking the infection dynamics within-hosts. Their aim was to investigate these two processes combined to influence the evolution of resistance in malaria parasite. In their final discussion, they obtain stochastic model by translating each deterministic component into the corresponding stochastic model, using Gillespie tau-leap algorithms. They establish that treatment coverage has a stronger impact on disease prevalence, whilst treatment efficacy primarily influences resistance spread, recommending that coverage should constitute the primary focus of control effort. Their results emphasise the importance of simultaneously modelling the evolution of resistance within-hosts and between-hosts. In their work they did not take into account the detail process occurring inside the liver and tissues within the human host as well as the control measures which have an impact on preventing and

controlling malaria infection.

Other recent studies on coupled multiscale models of infectious disease on vector-borne disease on vector-borne diseases which consider environmentally driven infectious diseases for example schistosomiasis by Garira and Guinea Worm by Netshikweta. Part of the pathogen life cycles of these environmentally driven infectious diseases is external to the two hosts. The pathogen life-cycle of an environmentally driven infectious diseases can be complete without passing to the vector host. The recent studies on coupled multiscale models on malaria disease systems by Garira and Mathebula and Augusto illustrate the method of linking within-host (human and mosquito) scale and between-host (human and mosquito) scale using nested approach. The coupled multiscale models by Garira and Mathebula and Augusto demonstrated that the within-host scale have an influence on between-host scale, whereas the between-host scale only influence the within-host scale through initial infection. These coupled multiscale models for vector-borne disease system did not take into account the influence of life-cycles of malaria pathogen inside the tissues and liver organ on the transmission of infectious disease system.

Cai and Martcheva in the work considered a nested immune-epidemiological model of malaria when they investigate the influence of within-host on population-level dynamics. In their model, they used age-since infection, where between-host dynamics they use age-structured partial differential equations and on within-host dynamics they use ordinary differential equations. The model is difficult to simulate since one must simulate separately their different components using specific methods.

2.4 Multiscale Model framework for Linking scales

Infectious disease modelling multiscale, multiscale modelling framework has been applied to address a variety of questions. One common question is "What is the impact of within-host dynamics on population-scale quantities such as the basic reproduction number and prevalence?". For example, Feng et al., 2012 used multiscale modelling to study the transmission of *Toxoplasma gondii*, an obligate intracellular, parasitic alveolate that causes the disease toxoplasmosis. For modelling, they linked the within-host dynamics with the between-host dynamics to produce a multiscale model which they further used to show the existence of backward bifurcations. Moreover, their model results showed that multiscale modelling had the potential to provide outcomes that could not have been obtained if they had independently considered the role of epidemiological and immunological processes on the dynamics of *Toxoplasma gondii*. In terms of implications of this study's results, infection was shown to persist at a population level even when the isolated between-host reproduction number was less than one; a result which elucidated the importance of within-host dynamics on between-host threshold quantities such as the basic reproductive number.

Augusto et al and Orive et al., 2019 developed a novel deterministic model link-

ing the dynamics of a within-host model to population-level dynamics for malaria transmission. The coupling and feedback for the model were created using the various life history stages of the malaria parasite both in the human host and the mosquito vector, consideration of both levels of dynamics in a two-hosts system was a novel feature of their model. At the population level, they assume that individuals in the community are homogeneous both in their mixing and in their response to the infection. In their study, the functions linking the two dynamics levels were assumed to be linear functions of the mosquito biting rate, and the finding of the numerical analyzes indicated that, as the biting rate increases, the merozoites population increases in the absence of the human host immune response. And the study further indicated that the present of immune response lead to the development of oscillations in the merozoites population since the immune cells add an internal feedback to the within-host system, the gap is very clear that, considering the more complex and perhaps a more realistic functions linking the dynamics levels such as a saturating feedback function was a best way to study through.

Welker and Martcheva presented a new immunoepidemiological model for zoonotic visceral leishmaniasis in dogs, in which the within-host model is linked and simulated infectiousness based on parasite load and the between-host model was structured by time-since-infection. Their results demanded the consideration of wide scope of pathogen development and the complexity of the problem, which invites the use of Coupling multiscale models of infectious disease system where most complex type of immune-epidemiological models are utilised.

2.5 Multiscale Modelling of Malaria disease

Malaria is a mosquito-borne disease that is instigated by protozoan parasites known as Plasmodium and its transmitted to humans by bite of an infected mosquito. The recent studies of malaria disease system on separate scales were either immunological or epidemiological. Recent work on vector-borne diseases which consider environmentally driven infectious diseases for example human schistosomiasis and Guinea Worm. Recent studies on coupled multiscale models of malaria disease system illustrate the method of linking within-host scale and between-host scale using the nested approach. Their models demonstrated that the within-host scales have influence on between host scale, whilst the between host scale only influence the within-host scale through initial infection.

In this work we develop a coupled multiscale modelling of malaria disease system for directly transmitted vector-borne disease. We use bidirectional flow of information from within-mosquito submodel to between-mosquito sub-model and vice versa, whilst the other side we use the unidirectional flow of information from within-human sub-model to between-host sub-model and the between-human influence the within-human through initial infection. We then integrate the two sub-models using the community pathogen load. Multiscale modelling is a modelling method in which a collection of particular models from various scales are linked into a single model using different integrating methods.

The creation of multiscale models of infectious diseases, which include quantitative representations of transmission of an infectious disease system and can reveal its mechanisms of transmission, is one of the significant advances in the modeling of malarial disease in recent years [Garira \(2017\)](#). They contended that in order to improve human and animal health through the integration of knowledge from epidemiology and immunology research with a wide range of health research, including environmental health, molecular biology, population biology, and microbiology, this innovation necessitates a paradigm shift toward a sharper focus on understanding disease dynamics. A recent classification of an infectious disease system has served as the foundation for efforts to create multiscale infectious illness models ([Garira \(2017\)](#)). According to [Garira et al. \(2017\)](#), the framework divides multiscale models of infectious disease systems that can be developed at various levels of system organization, such as the host, tissue, or cell level, into five main generic categories: Individual-based multiscale models (IMSMs); nested multiscale models (NMSMs); embedding multiscale models (EMSMs); hybrid multiscale models (HMSMs); and embedded multiscale models (EMSMs). Nearly all mathematical models aimed to improve plasmodium falciparum control while concentrating on the blood stage of malaria parasite development. Numerous studies have been conducted on mathematical modeling of infectious diseases of the in-host malaria and its dynamics within the human host. Many have discovered how helpful these models are ([Barreto et al. \(2006\)](#)), and has established a firm foundation that makes it necessary to investigate the development of malaria parasites in liver (an organ) and tissue (blood).

From our model, we use the nested multiscale model to link the within-human sub-model and between-human sub-model. The between-human sub-model influence the within-human sub-model through the initial infection of the within-human, which involves the movement of sporozoites which are injected into the human blood system. Once the infection of the within-mosquito scale has successfully occurred, which the followed by pathogen replication atn the lower-scale. The lower-scale influences the upper-scale through the pathogen shedding/excretion. These involves the movement of gametocytes from the lower-scale to the upper-scale sub-model. After shedding of the pathogen is then followed by the pathogen transmission at the human population-level.

We use embedded multiscale model to interconnect the within-mosquito sub-model and between-mosquito sub-model, both scales influences each other in a reciprocal way. The malaria disease dynamics starts with super-infection of the lower-scale by the pathogen, which is the pathogen invasion of the within-mosquito scale. The process of super-infection links the upper scale to the lower-scale. Once the super-infection of the within-mosquito scale has successfully occurred, which then followed by pathogen replication at the lower-scale. The within-mosquito sub-model has impact on the between-mosquito sub-model through shedding or excretion. The lower scale influences the upper scale through scaled-up the lower-scale variables and parameters. After shedding of the pathogens is then followed by the pathogen transmission at the mosquito population-level. The between-mosquito sub-model has impact on the within-mosquito sub-model through super-infection, whereby the upper-scale has impact on the lower-

scale through scale-down upper-scale variables and parameters. After linking these sub-models, we will then develop a coupled multiscale model of malaria disease dynamics that integrate these two sub-models. This coupled multiscale model for malaria disease dynamics utilizing the community pathogen load as a common metric for infectiousness, disease transmission and an indicator of the effectiveness of the health interventions across scales. These community pathogen loads allow the scales to share the pathogen.

2.6 Summary

In this chapter, we review the literature associated with malaria infectious diseases. It is clear from the literature review that evaluative commenting is a widespread and deeply embedded practice in composition programs. This chapter provided a solid foundation for the current study by evaluating the body of literature in light of recent developments in the area to establish facts, in addition to providing clarification for the ongoing body of knowledge and understanding. It helped the researcher identify areas in which additional research was needed, like the formation of pathogens between human tissue and the liver organ, and the efficacy of the models currently in development in addressing the study objectives is not fully demonstrated. Consequently, in order to provide a meaningful understanding of the relative efficacy of various models, a multiscale model connecting the within-host and between-host scales must be developed. We want to concurrently conduct a comparative efficacy assessment of malaria and propose a multiscale modeling framework for connected within-host and between-host in the upcoming chapter.

Chapter 3

Mathematical Modelling For Malaria Microecosystem level Dynamics

3.1 Introduction

A recent study on the transmission of malaria has found two forms of vector-borne illness transmission pathways ([Allen and Kirk \(2004\)](#)). Type I vector-borne diseases are caused by infectious microorganisms that are free-living in their environment and facilitate transmission. Next, according to Barretto (2006), Type II vector-borne diseases are those in which there are only two hosts for the duration of the life cycle. Ticks, mosquitoes, and a host of other associated disorders are among the blood-feeding arthropods that most commonly transmit vector-borne diseases of type II. Within the Type II vector-borne illness system, there are two types or groups: (i) vector-borne disease systems devoid of a pathogen reproduction cycle at the microscale ([Aly et al. \(2009\)](#)). The pathogen load can only increase at the within-host scale through super-infection. (ii) The hosts in the other category of type II vector-borne disease systems mostly experience an increase in life stages due to the pathogen's microscale replication cycle. The life stage that has a milliscale pathogen reproductive cycle, such as malaria, since the host's pathogen load increases mostly due to the replication cycle of Merozoites in the malaria disease system. The multiscale model of the type II vector-borne illness system, in which there is no pathogen replication cycle within the host, is the focus of the study. We introduced the coupled multiscale model, which integrates the nested and embedded multiscale models, two major types of multiscale models of infectious disease systems. ([Schwartz, Sadetzki, Murad, and Raveh, 2001](#)) states that the pre-patent period, or the interval between sporozoite inoculation and detectable parasitemia, is 10 days for non-immune individuals infected with malaria, and the median incubation period, or the interval between sporozoite inoculation and symptom development, is approximately 11 days. Pre-patent and incubation periods, then, span roughly 5 to 10 days and 6 to 14 days, respectively. According to ([White et al. \(2014\)](#)), the incubation period is greatly extended by the immunity levels gained from prior exposures, antimalarial prophylaxis, or partial therapy that may lessen but does not prevent the disease all consider-

ably lengthen the incubation period. According to Broder Look, the majority of people have falciparum malaria symptoms one month after infection. (Kain et al., 1998) contends that non-falciparum malaria pathogens may incubate for significantly longer than falciparum malaria. Depending on the quantity of hypnozoites in the liver, both *P. vivax* and *P. ovale* malaria may relapse months or years after exposure. The dynamics of *Plasmodium falciparum* in the human host are the main topic of this chapter. Infected female anopheles injects sporozoites of the *Plasmodium falciparum* species into the human dermis during the mosquitoes' mandatory blood feeding (Aly et al. (2009)). The sporozoites are motile and enter the human liver through blood arteries. The creation of a parasitophorous vacuole surrounding the sporozoite occurs subsequent to the invasion of liver cells (Orwa T.O et al). They develop into preerythrocytic schizonts and divide by schizogony, which results in the release of the first generation of merozoites. Orwa et al. state that the infected red blood cells burst to release merozoites in a span of two days. The majority of the released merozoites enter vulnerable erythrocytes fast, initiating a new infection cycle. The hallmark symptoms of malaria are caused by waves of bursting erythrocytes and the invasion of new erythrocytes by the freshly released merozoites, which raise parasitemia (Bruneel et al. (2003)). The host is likely to get anemia or maybe pass away in the absence of an adequate immunological response or antimalarial medication. The remaining daughter merozoites mature into gametocytes, which are sexual forms. Currently, mathematical research is required to track this pathogen's intricate life cycle.

3.1.1 The In-Host Malaria model

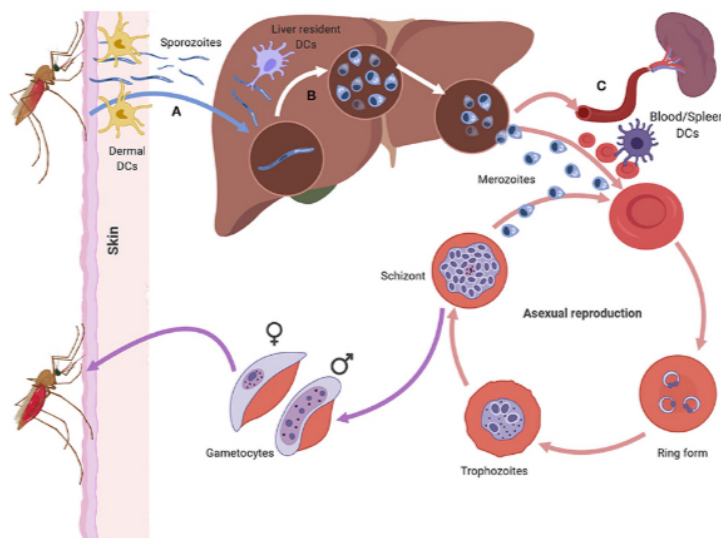


Figure 3.1: Malaria life cycle with the human-host, within the liver and in the blood stream. Variation in susceptibility to malaria demonstrated in liver cells. Christina Faust, 2016

Immunological models have been used to study and assess the dynamics of infections inside a single host (figure 3.1). The models usually show the interactions that occur between viruses and immune response cells in the host during an infection (Keeling and Danon (2009)). We now know more about the interactions between immune response cells and single-host infectious pathogens, such as bacteria, viruses, parasites, and protozoa, thanks to studies conducted utilizing immunological models. Immunological models are formulated mostly using partitional techniques. The book of (Garira and Chirove (2019)) has in-depth talks on the compartmentalization of immunological models; for the purpose of clarity, we offer a synopsis of the compartmentalization process. The body can be classified into primary compartments based on the different types of cells and immune cell species. Within-human malaria parasite population dynamics covers the evolution over time of eight populations within an infected human host. These populations are separated into two stages: the blood stage and the liver organ stage. The liver organ is composed of three populations: the liver cell population L_c , the infected liver cell population I_{Lc} , and the sporozoite-infected liver cell population S_p . For the dynamics of the three malaria parasite state populations, we adopt the following assumptions:

- On human organs already affected, there are no new infections. Since liver cells cannot heal from infection, we solely take into account the sporogenesis process, in which merozoites are released by infected hepatocytes.
- The liver is not exhibiting any immunological response.
- The within-liver sporozoite population S_p serves as a stand-in for each mosquito's potential for human infection.
- At time scale (s) parasite transmission dynamics, the population dynamics of the various malaria parasites at various phases of development take place, resulting in $S_p = S_p(s)$, $L_c = L_c(s)$, and $I_{Lc} = I_{Lc}(s)$.
- With all of this knowledge and these presumptions, the differential equation system for the dynamics of the malaria parasite population within liver organ is given by:

$$\begin{cases} \frac{dS_p(s)}{ds} = \Lambda_p - \mu_s S_p(s), \\ \frac{dL_c(s)}{ds} = \Lambda_h - \beta_s S_p L_c(s) - \mu_L L_c(s), \\ \frac{dI_{Lc}(s)}{ds} = \beta_s S_p L_c(s) - (\alpha_L + \mu_{Lc}) I_{Lc}(s), \end{cases} \quad (3.1.1)$$

The population of sporozoites is represented by the first equation of the submodel system (3.1.1), where Λ_p is the rate at which the sporozoites are injected in the

human blood and μ_s is the natural death rate of sporozoites; β_s is the rate at which sporozoites invade the liver cells, known as hepatocytes, and μ_L is the natural death of liver cells; α_L represents the rate at which sporozoites escape hepatocytes by bursting and releasing sex cells known as Merozoites, and μ_{Lc} is the natural decay rate infected liver cells. The dynamics of the merozoite population are explained by the three equation. According to our estimates, each bursting hepatocyte-infected liver organ releases an average of N_m merozoites; the rate at which merozoites are released from the liver organ is α_{mp} . As a result, the rate of increase of Merozoites within an infected liver is modeled by $N_m\alpha_{mp}I_{Lc}(s)$.

The merozoites released from the liver organ are the same merozoites infected the redblood cells in the blood stream, therefore M_{LB} is the pathogen load consists of merozoites from the liver organ and the merozoites entering the blood-stream. The pathogen load is a link between the liver organ and the blood-stream, it is considered the function of both I_{Lc} and I_{rb} . The equation M_{LB} is given as:

$$\frac{dM_{LB}}{ds} = f(I_{Lc} + I_{rb}) - \mu_h M_{LB}.$$

Where, $f(I_{Lc} + I_{rb}) = N_m\alpha_{mp}I_{Lc} + N_b\alpha_{Irb}I_{rb}$. Therefore, the Merozoites (pathogen load) will be given as:

$$\frac{dM_{LB}}{ds} = N_m\alpha_{mp}I_{Lc} + N_b\alpha_{Irb}I_{rb} - \mu_h M_{LB}.$$

The four populations within an infected human blood are the susceptible erythrocyte population S_b , the merozoite-infected erythrocyte population M_{LB} , the infected blood cell population I_{rb} , and the gametocyte-infected erythrocyte population G_b . The within-blood malaria parasite population dynamics describes the time evolution of these populations. The following is our assumption for these four within-blood populations.

- A super-infection of people does not exist.
- When a human is infected, there is no immune reaction.
- The population dynamics of the malaria parasites in the blood stage are the only ones that we specifically take into account, and the dynamics of the parasites in the liver stage are only partially represented by the initial mass of merozoites in the bloodstream.
- The four population within-host dynamics take place at time scale (s) parasite transmission dynamics, resulting in the following: $M_{LB} = M_{LB}(s)$, $S_b = S_b(s)$, $I_{rb} = I_{rb}(s)$, and $G_b = G_b(s)$.
- The within-host gametocytes population G_b is a proxy for individual human infectiousness to mosquitoes. Taking into account these assumptions, the model of describing the dynamics of the four within-host population is proposed to be,

$$\left\{ \begin{array}{l} \frac{dS_b(s)}{ds} = \Lambda_b - (\beta_b M_b(s) + \beta_L M_p) S_b(s) - \mu_e S_b(s), \\ \frac{dI_{rb}(s)}{ds} = [(1 - \pi) \beta_b M_b(s) + \beta_L M_p(s)] S_b(s) - (\mu_{Ib} + \alpha_{Irb}) I_{rb}(s), \\ \frac{dM_{LB}(s)}{ds} = N_m \alpha_{mp} I_{Lc}(s) + N_b \alpha_{Irb} I_{rb}(s) - \mu_h M_b(s), \\ \frac{dG_b(s)}{ds} = \pi \beta_b S_b(s) M_b(s) - (\alpha_o + \mu_b) G_b(s). \end{array} \right. \quad (3.1.2)$$

The first equation in the model system (3.1.2) explains the dynamics of vulnerable erythrocytes. It is anticipated that the population of susceptible red blood cells, or erythrocytes, will grow through the bone marrow's supply of red blood cells at a rate of Λ_b and will decrease through infection. $\beta_b M_{LB}$ models the rate at which free merozoites infect erythrocytes where β_b is the rate infection. The vulnerable erythrocytes are reduced through natural death at a constant rate μ_e . A merozoite that infects an erythrocyte has one of two potential fates, which are either become a trophozoite and repeat the cycle of merozoites production which can infect the blood cells at the rate β_L and reduced at the rate $\beta_L M_{LB}$ or transformed into trophozoites and then undergo gametocytogenesis, a process in which gametes are formed in the blood. The rates at which free merozoites from the liver and the blood stage infect erythrocytes β_b and β_L respectively are modeled by the variables $\beta_b S_b(s) M_{LB}(s)$ and $\beta_L S_b(s) M_{LB}(s)$. (Allen and Kirk, 2004). Therefore, we assume in the second equation that the erythrocyte $M_{LB}(s)$ is infected with merozoites, and that upon bursting, the merozoites will increase by a proportion α_{Irb} of the entire population of erythrocytes infected with merozoites. Consequently, the first term in the model system's second equation (3.1.2) .

As a result, $N_b \alpha_{Irb} M_{LB}(s)$ mimics the rate at which infected erythrocytes burst, increasing the number of merozoites in the human bloodstream. Since each merozoite has an average life span of days, the population of merozoites is assumed to decline through natural death at the rate μ_h . The dynamics of $G_b(s)$, the remaining fraction of the total population of erythrocytes infected with merozoites, are described in the fourth model system (3.1.2). Following erythrocyte infection by merozoites, this population of infected erythrocytes will change into trophozoites and proceed through a process called gametocytogenesis, which creates gametocytes inside the host erythrocyte. The rate of expansion of this population of erythrocytes infected with gametocytes is modelled by the first term in the fourth equation of the model system (3.1.2). The rate at which gametocytes within erythrocytes grow and become infectious to mosquitoes in this equation is α_o . It is expected that these erythrocytes infected with gametocytes will naturally decay at a rate of μ_b (Garira (2017)). Until they are consumed by a mosquito, which completes their development and produces either male or female gametes, the population of gametocyte-infected erythrocytes within an infected person remains

in an arrested developmental stage (Garira (2017)). Progress towards eliminating malaria has been impeded, according to Garira et al. (2017), by the paucity of malaria therapies that gametocytes, a human infectious reservoir that should be targeted to limit human mosquito malaria transmission. The following is the framework representing the transmission dynamics of the malaria infectious disease within the human host,

The compartmental framework/diagram put together all the assumption and demonstrated the flow of pathogen's life cycle within-human host. The within-human

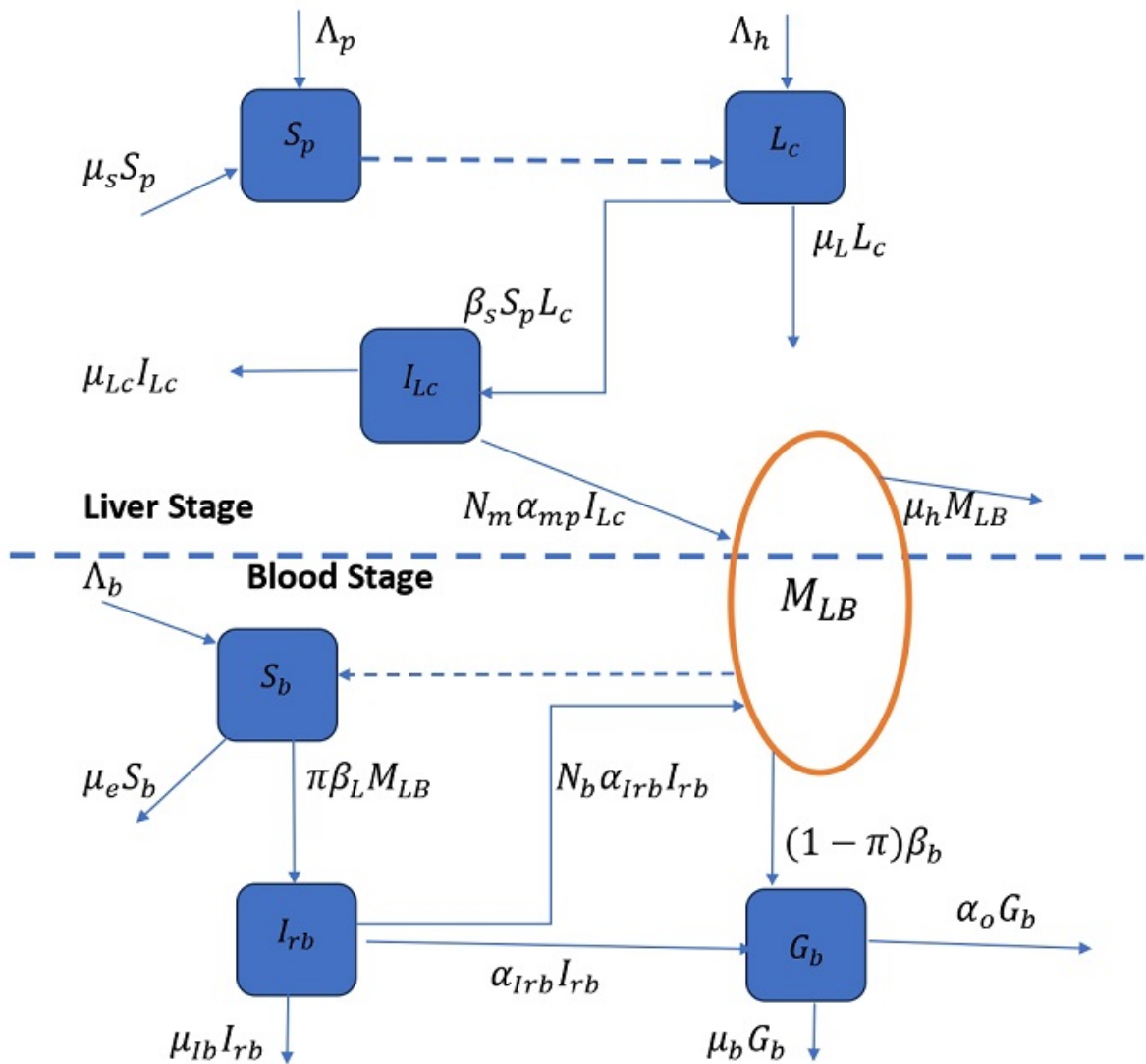


Figure 3.2: Compartmental diagram of Malaria life cycle within-human host transmission dynamics

malaria parasite population dynamics describes the time evolution of all eight

populations within an infected human host, is given by the following system of differential equation.

$$\left\{ \begin{array}{l} \frac{dS_p(s)}{ds} = \Lambda_p - \mu_s S_p(s), \\ \frac{dL_c(s)}{ds} = \Lambda_h - \beta_s S_p L_c(s) - \mu_L L_c(s), \\ \frac{dI_{Lc}(s)}{ds} = \beta_s S_p L_c(s) - (\alpha_L + \mu_{Lc}) I_{Lc}(s), \\ \frac{dS_b(s)}{ds} = \Lambda_b - \beta_b M_b(s) S_b(s) - \mu_e S_b(s), \\ \frac{dI_{rb}(s)}{ds} = (1 - \pi) \beta_b M_b(s) S_b(s) - (\mu_{Ib} + \alpha_{Irb}) I_{rb}(s), \\ \frac{dM_{LB}(s)}{ds} = N_m \alpha_L I_{Lc}(s) + N_b \alpha_{Irb} I_{rb}(s) - \mu_h M_b(s), \\ \frac{dG_b(s)}{ds} = \pi \beta_b S_b(s) M_b(s) - (\alpha_o + \mu_b) G_b(s). \end{array} \right. \quad (3.1.3)$$

The table 3.1 below represent and provide the description of the variables assumed for the transmission dynamics of the infectious malaria disease within the human host.

Variables	Descriptions
S_b	The population of susceptible red blood cells
M_b	The population of merozoites
I_{rb}	The population of free merozoites in the blood
G_b	The population of gametocytes infected red blood cells.
S_p	The population of sporozoites
S_b	The population of hepatocytes before sporozoites evade the liver cell
I_{lc}	The infected liver through infection of liver cells (hepatocytes)

Table 3.1: The list of variables in the blood stream and liver of the human host

As a result, $N_b \alpha_{Irb} I_{rb}(s)$ mimics the rate at which infected erythrocytes burst, increasing the number of merozoites in the human bloodstream. Since each merozoite has an average life span of days, the population of merozoites is assumed to decline through natural death at the rate μ_h . The dynamics of $G_b(s)$, the remaining fraction of the total population of erythrocytes infected with merozoites, are described in the eighth model system. Following erythrocyte infection by merozoites, this population of infected erythrocytes will change into trophozoites and proceed through a process called gametocytogenesis, which creates gametocytes inside the host erythrocyte. The rate of increase of this population of

erythrocytes infected with gametocytes is modelled by the first term in the fourth equation of the model system. The rate at which gametocytes within erythrocytes grow and become infectious to mosquitoes in this equation is α_o . It is expected that these erythrocytes infected with gametocytes will naturally decay at a rate of μ_b (Garira (2017)).

The model state variables are summarized in Table (3.2) below with the initial value conditions, The variables and parameters that describes the within-human

Parameters	Descriptions
β_b	Infection rate of erythrocytes by free merozoites
Λ_b	The rate of supply of red blood cells from bone marrow
μ_e	Natural decay rate of red blood cells
α_{Irb}	Proportion of merozoites infected erythrocytes
α_{mp}	The rate at which red blood cells burst to produce merozoites
μ_b	Natural decay rate of free Gametocytes
N_b	Number of merozoites produced and present in the blood stream
α_L	Proportion of sporozoites infected the liver cells
μ_d	Natural decay rate of gametocyte infected red blood within infected humans
μ_h	The natural decay of merozoites present in the blood stream
α_o	The number of gametocytes consumed per single bite
β_s	Infection rate of hepatocyte cells by free sporozoites
Λ_p	The rate of supply of hepatocyte cells from liver
μ_L	Natural decay rate of hepatocytes cells
π	The rate at which red blood cells burst to produce merozoites
N_m	Number of merozoites produced per liver cell incubation
μ_{Lc}	Rate at which liver cells die naturally

Table 3.2: Description of the parameters of the model system (3.1.3)

malaria transmission dynamics are in Table 3.1 and 3.2, respectively. The transmission dynamics of malaria are summarised in the compartmental diagram in the figure 3.1. In the next subsection we carry out the positivity of the solution.

3.2 Positivity of the Solution

We assume that all state variables and parameters for the model (3.1.3) are non-negative for all $s \geq 0$, so that they should not violate basic aspect of the biological reality. In this section, we therefore show that all the solutions of the model system (3.1.3) with positive initial conditions will remain non-negative for all $s \geq 0$.

$$\frac{dS_b(s)}{ds} = \Lambda_b - \beta_p S_b M_{LB} - \mu_e S_b, \quad (3.2.1)$$

which is true when;

$$\frac{dS_b(s)}{ds} \geq -(\beta_b M_{LB} - \mu_e) S_b,$$

so that

$$\frac{dS_b(s)}{S_b} = -(\beta_b M_{LB} - \mu_e) ds.$$

by letting,

$$S = \sup(s) \geq 0 : S_b > 0, M_{LB} > 0, I_{rb} > 0, G_b > 0 \in [0, s].$$

integrating inequality of equation (3.1.3), we then have:

$$\ln(S_b) \geq -(\mu_e M_{LB}(s) + \int_0^s \beta_b M_{LB}(s) \ln(S_b(0)).$$

hence,

$$S_b(s) \geq S_b(0) \cdot \exp\{-(\mu_e M_{LB}(s) + \int_0^s \beta_b M_{LB}(s))\} > 0.$$

similarly, it can be shown that solution of $I_{rb} > 0$, $M_{LB} > 0$ and $G_b > 0$ for all $s \geq 0$ on the model system (3.1.1). Considering the first equation:

$$\frac{dS_p(s)}{ds} = \Lambda_p - \mu_s S_p, \quad (3.2.2)$$

which is true when;

$$\frac{dS_p(s)}{ds} \geq -\mu_s S_p,$$

$$\frac{dS_p(s)}{S_p} = -(\beta_s - \mu_s) ds.$$

now we let,

$$S = \sup(s) \geq 0 : S_p > 0, L_c > 0, I_{lc} > 0 \in [0, s].$$

by integrating inequality of equation, we then have:

$$\ln(S_p) \geq -(\mu_s(s) + \int_0^s \mu_s(s) ds) + \ln(S_p(0)).$$

hence,

$$S_p(s) \geq S_p(0) \cdot \exp\{-(\mu_s S_p(s) + \int_0^s \mu_s(s) ds)\} > 0.$$

The same method used above can be used to test the first, third and the fourth equation within the liver organ. We introduce the feasible region in the next subsection for the dynamic model system (3.1.3).

3.2.1 The Feasible Region of Equilibria of model

The model system monitors the dynamic of malaria transmission within-human host, it is important and emperical that all the models stay positive as shown in (3.1.3) above. now,

$$\frac{dS_b(s)}{ds} = \Lambda_b - \beta_b S_b M_{LB} - \mu_e S_b$$

so that

$$\frac{dS_b(s)}{ds} \leq -(\beta_b M_{LB} - \mu_e) S_b,$$

this implies that,

$$\lim_{t \rightarrow \infty}(\sup(S_b(s))) \leq \frac{\Lambda_b}{\beta_b M_{LB} + \mu_e}.$$

Using the sixth equation of the system we obtain,

$$\begin{cases} \frac{dI_{rb}(s)}{ds} = (1 - \pi)\beta_b S_b M_{LB} - (\mu_{Ib} + \alpha_{Irb})I_{rb}, \\ = (1 - \pi)\beta_b S_b M_{LB} - (\mu_{Ib} + \alpha_{Irb})I_{rb}. \end{cases}$$

this implies that;

$$\lim_{t \rightarrow \infty}(\sup(I_{rb}(s))) \leq \frac{(1 - \pi)\beta_b S_b M_{LB}}{\mu_{Ib} + \alpha_{Irb}}.$$

using the sixth and the seventh equation of the system, we obtain the following respectively:

$$\lim_{t \rightarrow \infty}(\sup(M_{LB}(s))) \leq \frac{N_b \alpha_{mp} I_{rb}}{\mu_h}.$$

and

$$\lim_{s \rightarrow \infty}(\sup(G_b(s))) \leq \frac{\pi \beta_h S_b M_b}{(\alpha_o + \mu_b)}.$$

we let Ω be the feasible region for the model system, we now have:

$$\Omega = (S_p, L_c, I_{Lc}, S_b, I_{rb}, M_{LB}, G_b). \quad (3.2.3)$$

be an invariant region of the model system (3.2.3), where

$$\begin{aligned}
 0 &\leq S_p \leq \frac{\Lambda_p}{\mu_s}, \\
 0 &\leq L_c \leq \frac{\Lambda_h \mu_s}{\beta_s \Lambda_p - \mu_L \mu_s}, \\
 0 &\leq I_{Lc} \leq \frac{\beta_s \Lambda_p \Lambda_h}{(\alpha_l + \mu_{Lc})} \cdot \frac{1}{\beta_s \Lambda_p - \mu_L \mu_s}, \\
 0 &\leq S_b \leq \frac{\Lambda_b(\alpha_{mp} + \mu_c)(\beta_s \Lambda_p - \mu_L \mu_s) \mu_h}{\beta_L(N_m \alpha_L)(\beta_s N_b \alpha_{Irb}) + \beta_b + \mu_e} \cdot (\Phi_1), \\
 0 &\leq I_{rb} \leq \frac{\beta_L \Lambda_p}{\mu_{Ib} + \alpha_{Irb}} \cdot \frac{\Lambda_p(1 - \pi) \beta_b}{\mu_s(\mu_{Ib} + \alpha_{Irb})} \cdot \frac{\Lambda_b(\alpha_{mp} + \mu_c)(\beta_s \Lambda_p - \mu_L \mu_s) \mu_h}{\beta_L(N_m \alpha_L)(\beta_s N_b \alpha_{Irb}) + \beta_b + \mu_e} \cdot (\Phi_1), \\
 0 &\leq M_b \leq \frac{1}{\mu_b \beta_b} \cdot \frac{N_b \alpha_{Irb}}{\mu_h} \cdot \frac{\Lambda_b(\alpha_{mp} + \mu_c)(\beta_s \Lambda_p - \mu_L \mu_s) \mu_h}{\beta_L(N_m \alpha_L)(\beta_s N_b \alpha_{Irb}) + \beta_b + \mu_e} \cdot (\Phi_1), \\
 0 &\leq G_b \leq \frac{\pi \beta_b \Lambda_b M_b}{\mu_s(\alpha_o + \mu_b)} \cdot \frac{1}{\mu_b \beta_b} \cdot \frac{N_b \alpha_{Irb}}{\mu_h} \cdot \frac{\Lambda_b(\alpha_{mp} + \mu_c)(\beta_s \Lambda_p - \mu_L \mu_s) \mu_h}{\beta_L(N_m \alpha_L)(\beta_s N_b \alpha_{Irb}) + \beta_b + \mu_e} \cdot (\Phi_1).
 \end{aligned} \tag{3.2.4}$$

Where, $\Phi_1 = \frac{1}{\mu_l + \mu_s} \cdot \frac{N_m \alpha_L}{\alpha_{mp} + \mu_c} \cdot \frac{\beta_s \Lambda_p \Lambda_h}{(\alpha_l + \mu_{Lc})}$.

This implies that Ω is positively invariant and attracting region, since all solutions that will start in Ω will remain positive for all $s \geq 0$. Hence, model system is mathematically and immunologically well-posed, therefore it is sufficient to consider the dynamic of the flow generated by model system in this regions.

3.3 The Infection/Disease Free Equilibrium and its Stability

3.3.1 Disease-free Equilibrium

To obtain the disease free equilibrium point of the system. We set the left hand side of the equations equal to zero and further we assume that, $I_{rb} = M_{LB} = G_b = I_{Lc} = 0$ this means that the human population in totality, considering the

liver organ and the blood is free from the disease. thus

$$\begin{cases} \Lambda_p - \mu_s S_p(s) = 0, \\ \Lambda_h - \beta_s S_p L_c(s) - \mu_L L_c(s) = 0, \\ \beta_s S_p L_c(s) - (\alpha_L + \mu_{Lc}) I_{Lc}(s) = 0, \\ \Lambda_b - \beta_b M_b(t) - \mu_e S_b(s) = 0, \\ (1 - \pi) \beta_b M_b(s) S_b(s) - (\mu_{Ib} + \alpha_{Irb}) I_{rb}(s) = 0, \\ N_m \alpha_{mp} I_{Lc}(s) + N_b \alpha_{Irb} I_{rb}(s) - \mu_h M_b(s) = 0, \\ \pi \beta_b S_b(s) M_b(s) - (\alpha_o + \mu_b) G_b(s) = 0. \end{cases}$$

therefore,

$$E_0 = \left(\frac{\Lambda_p}{\mu_s}, \frac{\Lambda_h \mu_s}{\beta_s \Lambda_p + \mu_L \mu_s}, 0, \frac{\Lambda_b}{\mu_e}, 0, 0, 0 \right) \quad (3.3.1)$$

3.3.2 Computation of within-blood stream reproduction number

Whether studying infectious diseases through epidemiology or immunology, the fundamental reproduction number is crucial. It is employed to ascertain whether or not a specific disease will endure within a given community. The average number of secondary infections that result from the introduction of a single infected person into a community that is completely susceptible is known as the basic reproduction number. A disease-free equilibrium point (DFE) that is locally asymptotically stable exists if R_0 is less than a unit. This indicates that during the course of an infected person's infectious period, an average of fewer new infections will be produced by that person than by another. However, if it exceeds a unit, the illness will on average, develop fewer new infections than one. However, if it exceeds one, the disease will continue to spread since one sick person will typically infect one or more new people, and the DFE would become unstable, leading to the existence of a stable endemic equilibrium point (EPP). To determine the reproduction number of the system. We use the generation operator approach and the next generation matrix method. The model system(3.1.3) can be written in the form

$$\begin{aligned}\frac{dX}{ds} &= f(X, Y, Z), \\ \frac{dY}{ds} &= g(X, Y, Z),\end{aligned}\tag{3.3.2}$$

$$\frac{dZ}{ds} = h(X, Y, Z),\tag{3.3.3}$$

where

$$\begin{aligned}X &= (S_p, L_c, S_b), \\ Y &= (I_{Lc}, I_{rb}),\end{aligned}\tag{3.3.4}$$

$$Z = (M_b, G_b),\tag{3.3.5}$$

We represented the components X, Y, Z in this manner, X is non-infected, Y represents the infected but not infectious and Z represents infected and infectious. E_0 denotes the disease free- equilibrium such that $f(X^*, 0, 0) = g(X^*, 0, 0) = h(X^*, 0, 0)$. We further assume that $g(X^*, Y, Z)$ is equals to zero and then we determine the finction $Y = g(X^*, Z)$ in this order, thus:

$$\begin{cases} g_1(X^*, Z) = \frac{\beta_s \Lambda_p \Lambda_h}{(\alpha_L + \mu_{Lc})(\beta_s \Lambda_p + \mu_L \mu_s)}, \\ g_2(X^*, Z) = \frac{N_m \alpha_h \beta_s \Lambda_p \Lambda_h}{(\alpha_{mp} + \mu_c)(\alpha_L + \mu_{Lc})(\beta_s \Lambda_p + \mu_L \mu_s)}, \\ g_3(X^*, Z) = \frac{\beta_L N_m \alpha_h \beta_s \Lambda_p \Lambda_h + (1 - \pi) \beta_s \Lambda_p \cdot M_{LB}}{\mu_s (\alpha_{mp} + \mu_c) (\alpha_L + \mu_{Lc}) (\beta_b \Lambda_p + \mu_L \mu_s)}. \end{cases}\tag{3.3.6}$$

Now we let,

$$A = D_z h(X^*, g(X^*, 0), 0)\tag{3.3.7}$$

and further assume that A can be written in the form of $A = M - D$ such that $M \geq 0$ and $D > 0$ is a diagonal matrix. Therefore,

$$h(X, Y, Z) = \pi \beta_b S_b M_{LB} - (\alpha_o + \mu_b) G_b\tag{3.3.8}$$

then,

$$h(X, Y, Z) = \pi \beta_b S_b M_{LB} - (\alpha_o + \mu_b) G_b,\tag{3.3.9}$$

$$h(X^*, g(X^*, Z), Z) = \frac{\beta_s N_m \alpha_h \beta_s \Lambda_p \Lambda_h + (1 - \pi) \beta_s \Lambda_p \cdot Z}{\mu_s (\alpha_{mp} + \mu_c) (\alpha_L + \mu_{Lc}) (\beta_b \Lambda_p + \mu_L \mu_s)} - (\alpha_o + \mu_b) Z.\tag{3.3.10}$$

We can now differentiate the equation (3.3.10) above with respect to Z , we get.

$$D_z h(X^*, g(X^*, Z), Z) = \frac{\beta_s N_m \alpha_h \beta_s \Lambda_p \Lambda_h + (1 - \pi) \beta_b \Lambda_p}{\mu_s (\alpha_{mp} + \mu_c) (\alpha_L + \mu_{Lc}) (\beta_s \Lambda_p + \mu_L \mu_s)} - (\alpha_o + \mu_b)$$

as stated above, we then have;

$$\begin{cases} A = D_z h(X^*, g(X^*, 0), 0) \\ A = M - D \end{cases}$$

this implies that,

$$\begin{cases} M = \frac{\beta_s N_m \alpha_h \beta_s \Lambda_p \Lambda_h + (1 - \pi) \beta_b \Lambda_p}{\mu_s (\alpha_{mp} + \mu_c) (\alpha_L + \mu_{Lc}) (\beta_s \Lambda_p + \mu_L \mu_s)} \\ D = (\alpha_o + \mu_b) \end{cases}$$

The reproduction number (R_0) will be given by the spectral radius of the above mentioned matrix, MD^{-1} , therefore:

$$R_0 = \sqrt{\frac{\beta_s \Lambda_p N_m \alpha_L}{\mu_s \mu_h (\alpha_L + \mu_{Lc})} + \frac{(1 - \pi) \beta_b \Lambda_b N_b \alpha_{Irb}}{\mu_e \mu_h (\mu_{Ib} + \alpha_{Irb})}} \quad (3.3.11)$$

The results above are the average amount of infectious reservoir contributed to the community of Merozoites and gametocytes load by the infected human host during the mosquito blood meal, this expressions represent the basic reproductive number which we consider as the characterizing transmission potential of malaria at the start of the epidemic. The reproduction number can be written in its composition as,

$$R_0 = \sqrt{\frac{\beta_s \Lambda_p N_m \alpha_L}{\mu_s \mu_h (\alpha_L + \mu_{Lc})} + \frac{(1 - \pi) \beta_b \Lambda_b N_b \alpha_{Irb}}{\mu_e \mu_h (\mu_{Ib} + \alpha_{Irb})}} \quad (3.3.12)$$

The terms in the model R_0 can be interpreted as follows:

- (1) The term $\frac{\Lambda_p}{\mu_s}$ represents the total population of sporozoites entering the human body through the liver organ just before they evade the liver cells.
- (2) The second term $\frac{N_m N_b \alpha_L}{(\alpha_L + \mu_{Lc})}$ represents the total number of merozoites escaping the liver organ to blood stream.
- (3) The third term $\frac{(1 - \pi) \beta_s \beta_b \alpha_{Irb}}{\mu_h (\mu_{Ib} + \alpha_{Irb})}$ represents the expected number of infectious merozoites parasites resulting from bursting blood schizonts at the blood stage of malaria parasite.
- (4) the last term $\frac{\Lambda_b}{\mu_e}$ represents the expected ratio of or proportion of merozoites

that forms gametocytes which will compose the new cycle of malaria infections.

In conclusion, we observed that the terms are < 1 . So the R_0 implies that the number of secondary infections during malaria infections is largely influenced by the average number of merozoites released from the bursting blood schizonts most of which are responsible for secondary infection. In the next subsection, model system (3.1.1) will be used to workout the stability of the within-human malaria transmission dynamics.

3.3.3 Local Stability of the Disease Free Equilibrium

To determine the local stability of DFE of the system, we must provide the proof of the following theorem.

Theorem 3.1 *The disease free equilibrium point is asymptotically stable when $R_0 < 1$.*

Proof. We linearise all the equation of the system (3.1.1) in order to obtain a jacobian matrix, and test for stability of DFE by calculating the eigenvalues (λ) of the model system (3.1.1). It is important that if all the eigenvalues obtained are negative, this will imply that the model system (3.1.1) is locally asymptotical stable.

$$\begin{aligned} E^* &= (S_p^*, L_c^*, I_{Lc}^*, S_b^*, I_{rb}^*, M_{LB}^*, G_b^*) \\ &= \left(\frac{\Lambda_p}{\mu_s}, \frac{\Lambda_h \mu_s}{\beta_s \Lambda_p + \mu_L \mu_s}, 0, \frac{\Lambda_b}{\mu_e}, 0, 0, 0 \right) \end{aligned} \quad (3.3.13)$$

The jacobian matrix of the system(3.1.1) is given by:

$$J = \begin{pmatrix} -\mu_s & 0 & 0 & 0 & 0 & 0 & 0 \\ -\beta_s L_c & -\mu_L & 0 & 0 & 0 & 0 & 0 \\ \beta_s L_c & \beta_s S_p & -d_1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -d_2 & 0 & 0 & 0 \\ 0 & 0 & 0 & (1 - \pi)\beta_b M_b & -d_3 & 0 & 0 \\ 0 & N_m \alpha_{mp} & 0 & 0 & N_b \alpha_{Irb} & -d_4 & 0 \\ 0 & 0 & 0 & \pi \beta_b M_b & 0 & \pi \beta_b S_b & -d_5 \end{pmatrix}$$

where $d_1 = (\alpha_L + \mu_{Lc})$, $d_2 = (\beta_b S_b + \mu_e)$, $d_3 = (\mu_{Ib} + \alpha_{Irb})$, $d_4 = \alpha_{mp} \mu_L + \mu_L M_{LB}$ and $d_5 = (\alpha_o + \mu_b)$

Now, the jacobian matrix evaluated at the disease free- equilibrium is given by:

$$J_{E^*} = \begin{pmatrix} -\mu_s & 0 & 0 & 0 & 0 & 0 & 0 \\ b_1 & -\mu_L & 0 & 0 & 0 & 0 & 0 \\ b_1 & \frac{\beta_s \Lambda_p}{\mu_s} & -(\alpha_L + \mu_{Lc}) & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -(\beta_b + \mu_e) & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -(\mu_{Ib} + \alpha_{Irb}) & 0 & 0 \\ 0 & N_m \alpha_{mp} & 0 & 0 & N_b \alpha_{Irb} & -(\alpha_{mp} \mu_L + \mu_L \mu_b) & 0 \\ 0 & 0 & 0 & 0 & 0 & \frac{\pi \beta_b \Lambda_p}{\mu_s} & -(\alpha_o + \mu_b) \end{pmatrix}$$

where $b_1 = \frac{\beta_s \Lambda_h \Lambda_s}{\beta_s \Lambda_p + \mu_L \mu_s}$

$$|J(E^*) - \lambda I| = 0 \quad (3.3.14)$$

it is clear that the jacobian matrix has negative eigenvalues $\lambda_1 = -\mu_s, \lambda_2 = -\mu_L, \lambda_3 = -(\alpha_L + \mu_{Lc}), \lambda_4 = -(\beta_b + \mu_e), \lambda_5 = -(\alpha_{Irb} + \mu_{Ib}), \lambda_6 = -(\alpha_{mp} \mu_L + \mu_L \mu_b)$ and $\lambda_8 = -(\alpha_o + \mu_b)$. Upon deleting some rows and coulombs to reduce the above matrix, then the variable λ , which is the characteristic polynomial associated with matrix above is given by:

$$\lambda^2 + \phi_1 + \phi_0 = 0 \quad (3.3.15)$$

where:

$$\begin{cases} \phi_1 = (\mu_{Ib} + \alpha_{Irb}) + \mu_h. \\ \phi_0 = (\mu_{Ib} + \alpha_{Irb})\mu_h - \left[\frac{(1 - \pi)\beta_b \Lambda_b N_b \alpha_{Irb}}{\beta_b M_b + \mu_e} \right], \\ = \frac{(\mu_{Ib} + \alpha_{Irb})[\phi_1 - (\mu_{Ib} + \alpha_{Irb})]}{\alpha_{Irb} \mu_h} - \frac{(1 - \pi)\beta_b \Lambda_b N_b}{\beta_b M_{LB} + \mu_e}, \\ = \frac{(\mu_{Ib} + \alpha_{Irb})[\phi_1 - (\mu_{Ib} + \alpha_{Irb})]}{\alpha_{Irb} \mu_h} - R_0. \end{cases}$$

and now we consider the quadratic equation in (3.3.16) in order to determnie the sign of the remaining eigenvalues of the polynomial.

$$\lambda^2 + \phi_1 \lambda + \phi_0 \quad (3.3.16)$$

now the quadratic equation,

$$\lambda = -\frac{[(\mu_{Ib} + \alpha_{Irb}) + \mu_h] \pm \sqrt{[(\mu_{Ib} + \alpha_{Irb}) + \mu_h]^2 - 4\left(\frac{(\mu_{Ib} + \alpha_{Irb})[\phi_1 - (\mu_{Ib} + \alpha_{Irb})]}{\alpha_{Irb}\mu_h} - R_0\right)}}{2} \quad (3.3.17)$$

and it can be simplified and written as:

$$\lambda = -\frac{\phi_1 \pm \sqrt{\phi_1^2 - 4\phi_0}}{2} \quad (3.3.18)$$

Now for the model system (3.1.1), we considered the theorem in Driessche and Watmough, which states that, the disease free equilibrium can only be locally asymptotically stable if and only if $R_0 < 1$ and unstable otherwise.

It is very clear that all the eigenvalues are negative implying that E_0 is locally asymptotically stable. According to Van den Driessche theorem the basic R_0 is less than one, then the disease free equilibrium is locally asymptotically stable and the disease cannot invade the population.

3.4 Global Stability of the Disease Free Equilibrium

In this section, We show that the malaria-free equilibrium state E_0 is globally asymptotically stable when $R_0 < 1$. To do that, we first assume that model system (3.1.1) can be re-written in Pseudotriangular form as follows:

$$\begin{cases} \dot{X}_1 = A_1(X)(X - X_1^*) + A_2(X)X_2 \\ \dot{X}_2 = A_3(X)X_2 \end{cases}$$

where X_1 is the vector representing the state of different compartments of the liver organ and the blood cells that are not infected and do not transmit malaria infection. X_2 is the vector representing the states of malaria parasite and host cells that are responsible for malaria transmission. We then have,

$$\begin{cases} X = (X_1, X_2) \\ X_1 = (S_p, L_c, S_b) \\ X_2 = (I_{Lc}, I_{rb}, M_{LB}, G_h) \\ X_1^* = \left(\frac{\Lambda_p}{\mu_s}, \frac{\Lambda_h\mu_s}{\beta_s\mu_s + \mu_L\mu_s}, \frac{\Lambda_b}{\mu_e}\right) \end{cases}$$

from the X_1 , we have the following:

$$A_1(X) = \begin{pmatrix} -\mu_s & 0 & 0 \\ 0 & -(\beta_s \mu_s - \mu_L \mu_s) & 0 \\ 0 & 0 & \mu_h \end{pmatrix}$$

and

$$A_2(X) = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & -(\alpha_L + \mu_{Lc}) & 0 & 0 \\ -\beta_L S_b & 0 & (1 - \pi)\beta_b S_b & 0 \end{pmatrix}$$

then a direct computational shows that the eigenvalues of matrix $A_1(X)$ is real and negative. This indicates that the system $\dot{X}_1 = A_1(X)(X - X_1^*) + A_2(X)X_2$ is globally asymptotically stable at the disease free equilibrium (E_0). In the same way the X_2 give rise to the following matrix $A_3(X)$:

$$A_3(X) = \begin{pmatrix} -(\alpha_{mp} + \mu_c) & 0 & 0 & 0 \\ \beta_L S_b & -(\mu_{Ib} + \alpha_{Irb}) & (1 - \pi)\beta_b S_b & 0 \\ 0 & N_b \alpha_{Irb} & -\mu_h & 0 \\ 0 & 0 & \pi \beta_b S_b & -(\mu_o + \mu_b) \end{pmatrix}$$

now we apply matrix elementary row transformation so that some rows can be interchanged, then the matrix $A_3(X)$, becomes:

$$A_3(X) = \begin{pmatrix} -(\alpha_{mp} + \mu_c) & 0 & (1 - \pi)\beta_b S_b & 0 \\ 0 & -(\mu_{Ib} + \alpha_{Irb}) & 0 & \beta_L S_b \\ 0 & 0 & -\mu_h & 0 \\ \pi \beta_b S_b & N_b \alpha_{Irb} & 0 & -(\mu_o + \mu_b) \end{pmatrix}$$

Now, matrix $A_3(X)$ can clearly seen as Metzler matrix because all the matrix off-diagonal entries/ elements of $A_3(X)$ are positive. Therefore in order to establish the global stability of the disease free equilibrium, we need to show that the mat-

rix $A_3(X)$ is metzler stable by providing the proof of the lemma below.

Lemma 1. *Let M be a square Metzler matrix that is block decomposed:*

$$M = \begin{pmatrix} A & B \\ C & D \end{pmatrix}$$

where A and D are square matrices. The matrix M is Metzler stable if and only if A and $D - CA^{-1}B$ are Metzler stable. The matrix M is represented by matrix A_3 above such that:

$$A = \begin{pmatrix} -(\alpha_{mp} + \mu_c) & 0 \\ 0 & -(\mu_{Ib} + \alpha_{Irb}) \end{pmatrix},$$

$$B = \begin{pmatrix} (1 - \pi)\beta_b S_b & 0 \\ 0 & \beta_L S_b \end{pmatrix},$$

$$C = \begin{pmatrix} 0 & 0 \\ \pi\beta_b S_b & N_b \alpha_{Irb} \end{pmatrix},$$

and

$$D = \begin{pmatrix} -\mu_h & 0 \\ 0 & -(\mu_o + \mu_b) \end{pmatrix}.$$

therefore we have that:

$$D - CA^{-1}B = \begin{pmatrix} -\phi_1 & 0 \\ \phi_2 & -\phi_3 \end{pmatrix},$$

where $\phi_1 = \mu_h$, $\phi_2 = \frac{\beta_L \Lambda_b \pi}{\mu_e(\mu_{Ib} + \alpha_{Irb})}$,

$$\phi_3 = (\alpha_o + \mu_b) \frac{\beta_L \Lambda_b \pi}{\mu_e(\mu_{Ib} + \alpha_{Irb})} + \frac{\beta_L N_m \alpha_h \beta_s \Lambda_p \Lambda_h + (1 - \pi)\beta_b \Lambda_p}{\mu_s(\alpha_{mp} + \mu_c)(\alpha_L + \mu_{Lc})(\beta_b \Lambda_p + \mu_L \mu_s)(\alpha_o + \mu_b)}$$

Now for the matrix $D - CA^{-1}B$ to be Metzler stable, ϕ_3 should be strictly positive. therefore, we simplify ϕ_3 thus.

$$\left(\frac{(\alpha_o + \mu_b)\beta_L \Lambda_b \pi}{\mu_e(\mu_{Ib} + \alpha_{Irb})} \right) \left(\frac{\beta_L N_m \alpha_h \beta_s \Lambda_p \Lambda_h + (1 - \pi)\beta_b \Lambda_p}{\mu_s(\alpha_{mp} + \mu_c)(\alpha_L + \mu_{Lc})(\beta_b \Lambda_p + \mu_L \mu_s)(\alpha_o + \mu_b)} \right) \leq 1, \quad (3.4.1)$$

then,

$$\left(\frac{(\alpha_0 + \mu_b)\beta_L\Lambda_b\pi}{\mu_e(\mu_{Ib} + \alpha_{Irb})} \right) R_0 \leq 1 \quad (3.4.2)$$

which can be further expressed as:

$$R_0 \leq \frac{\mu_e(\mu_{Ib} + \alpha_{Irb})}{(\alpha_0 + \mu_b)\beta_L\Lambda_b\pi} < 1 \quad (3.4.3)$$

It is now clear that Matrix A is stable and matrix $D - CA^{-1}B$ is Metzler stable if and only if $R_0 < 1$

3.5 The Existence of Endemic Equilibrium State and its Stability

In this section we work out the existence of the endemic equilibrium state and test for the stability, both local and global stability will be tested.

3.5.1 Existence of Malaria Infection Equilibrium

The model has a positive malaria infection equilibrium E^* , and in endemic equilibrium state, all compartments are infected with malaria and the endemic equilibrium state is denoted by:

$$E^* = (S_P^*, L_c^*, I_{Lc}^*, S_b^*, I_{rb}^*, M_b^*, G_b^*) \quad (3.5.1)$$

where

$$\left\{ \begin{array}{l} S_p^* = \frac{\Lambda_p}{\mu_s}, \\ L_c^* = \frac{\Lambda_h \mu_s}{\beta_s \Lambda_p + \mu_L \mu_s}, \\ I_{Lc}^* = \frac{\Lambda_h}{(1 + \mu_L)(\alpha_L + \mu_{Lc})}, \\ S_b^* = \frac{\Lambda_b}{\beta_b M_b^* + \mu_e}, \\ I_{rb}^* = \frac{\Lambda_p}{\mu_s} \cdot \frac{(1 - \pi) \beta_b \Lambda_b M_{LB}^*}{\beta_b M_{LB}^* + \mu_e} \cdot \frac{1}{(\mu_{Ib} + \alpha_{Irb})}, \\ G_b^* = \frac{\pi \beta_b \Lambda_b M_{LB}^* (\alpha_o + \mu_b)}{\beta_L M_{LB}^* + \beta_b M_{LB}^* + \mu_e}, \end{array} \right. \quad (3.5.2)$$

S_p^* and M_{LB}^* are positive solutions of $F(S_p^*) = 0$ and $G(M_{LB}^*) = 0$ respectively, where

$$S_p^* = A_3 M_{LB}^{*2} + A_2 M_{LB}^* + A_1 \quad (3.5.3)$$

and,

$$M_{LB}^* = B_3 M_{LB}^{*2} + B_2 M_{LB}^* + B_1 \quad (3.5.4)$$

where, $A_3 = \beta_s \mu_s$, $A_2 = \beta_s (\Lambda_h - \Lambda_p) + \mu_s \mu_L$, $A_1 = -\Lambda_p \Lambda_h$, $B_3 = (1 - \pi) \mu_h$, $B_2 = (\beta_b N_b \alpha_{rb} + \mu_h (\mu_{Ib} + \alpha_{Irb}))$, $B_1 = -\mu_h \lambda^*$ and $\lambda(S_p^*) = \frac{\varphi S_p^*}{\mu_s}$. Now to determine the essential and sufficient conditions for the existence of malaria infection equilibrium state E^* by proving the following theorem.

Theorem 3.2. *The model system (3.1.3) has a unique malaria infection equilibrium, $E^* = (S_p^*, L_c^*, I_{Lc}^*, S_b^*, I_{rb}^*, M_{LB}^*, G_b^*)$ if $R_0 > 1$, $\Lambda_h > \Lambda_p$, $A_3 M_{LB}^{*2} + A_2 M_{LB}^* + A_1 = 0$ and $B_3 M_{LB}^{*2} + B_2 M_{LB}^* + B_1 = 0$ have roots $S_p^* > 0$ and $M_{LB}^* > 0$ respectively.*

Proof: Let $E^* = (S_p^*, L_c^*, I_{Lc}^*, S_b^*, I_{rb}^*, M_{LB}^*, G_b^*)$ be malaria infection equilibrium of the system (3.1.3). Substituting the expression for I_{rb}^* into equation M_{LB}^* , we have:

$$\frac{N_b \alpha_{Irb} (\beta_L \Lambda_p) [(1 - \pi) \beta_b \Lambda_b M_{LB}^*]}{\mu_s (\mu_{Ib} + \alpha_{Irb}) (\beta_L + \beta_b M_b^* + \mu_e)} - \mu_h M_{LB}^* \quad (3.5.5)$$

which gives, let $\gamma_m = \frac{N_b \alpha_{Irb} (\beta_L \Lambda_p) [(1 - \pi) \beta_b \Lambda_b]}{\mu_s (\mu_{Ib} + \alpha_{Irb}) (\beta_L + \beta_b + \mu_e)}$ and $a = \mu_h$ therefore,

$$\begin{cases} \gamma_m = \frac{N_b \alpha_{Irb} \beta_L \Lambda_p [(1 - \pi) \beta_b \Lambda_b]}{\mu_s (\mu_{Ib} + \alpha_{Irb}) (\beta_L + \beta_b M_b^* + \mu_e)} \\ = \frac{N_b \alpha_{Irb} \beta_L \Lambda_p [(1 - \pi) \beta_b \Lambda_b]}{\mu_s (\beta_L + \beta_b + \mu_e)} \cdot \frac{1}{(\mu_{Ib} + \alpha_{Irb})} \end{cases} \quad (3.5.6)$$

thus,

$$\frac{dM_{LB}^*}{dS} = \gamma_m M_b^* - a_1 M_b^*. \quad (3.5.7)$$

letting the left hand side be zero, we have

$$(\gamma_m - a_1) M_{LB}^* = 0 \quad (3.5.8)$$

therefore,

$$\begin{cases} M_b^* = \frac{a_1}{\gamma_m} \\ M_b^* = \frac{\mu_h \mu_s (\beta_L + \beta_b + \mu_e) (\mu_{Ib} + \alpha_{Irb})}{N_b \alpha_{Irb} \beta_L \Lambda_p [(1 - \pi) \beta_b \Lambda_b]} \end{cases} \quad (3.5.9)$$

its clear that that the merozoites in the blood stages are responsible fr generating the malaria infectious cycle, and sporozoites S_p responsible to pathogen development within the liver of human-host, then putting all the equations together we have of the blood stage are,

$$\begin{cases} S_b^* = \frac{\Lambda_b}{(\mu_{Ib} + \alpha_{Irb})} \cdot \frac{1}{R_o}, \\ I_{rb}^* = \frac{\mu_e \mu_h}{N_b \alpha_{Irb} \beta_b} (R_0 - 1), \\ M_{LB}^* = \frac{\mu_e}{\beta_b} (R_0 - 1) \\ G_b^* = \frac{\Lambda_b}{(\alpha_o + \mu_b) R_0} (R_0 - 1). \end{cases} \quad (3.5.10)$$

Therefore, if $R_0 < 1$ then $\Lambda_p > \Lambda_b$ and the quadratic equations $A_3 M_{LB}^{*2} + A_2 M_{LB}^* + A_1 = 0$ and $B_3 M_{LB}^{*2} + B_2 M_{LB}^* + B_1 = 0$ have respectively positive roots S_p^* and M_{LB}^* . We note that the infected red blood cells at the endemic equilibrium point is equal to the average time of stay in the infected redblood cells class.

3.5.2 Local Stability of Endemic state

To determine the local stability of infection equilibrium for the model system (3.1.1), we linearise equation of our model system in order to obtain the jacobian matrix. We then evaluate the jacobian matrix of the model system (3.1.1) at the infection equilibrium (E^*),

$$E^* = \left(\frac{\Lambda_b}{(\mu_{Ib} + \alpha_{Irb})} \cdot \frac{1}{R_0}; \frac{\mu_e \mu_h}{N_b \alpha_{Irb} \beta_b} (R_0 - 1); \frac{\mu_e}{\beta_b} (R_0 - 1); \frac{\Lambda_b}{(\alpha_o + \mu_b) R_0} (R_0 - 1) \right) \quad (3.5.11)$$

The jacobian matrix of the model system (3.1.1) evaluated at the infection equilibrium is given by:

$$J_{E_0} = \begin{pmatrix} -\mu_e R_0 & 0 & 0 & \frac{-\Lambda_b \beta_b}{(\mu_{Ib} + \alpha_{Irb}) R_0} \\ \mu_e (R_0 - 1) & -(\mu_{Ib} + \alpha_{Irb}) & 0 & \frac{\Lambda_b \beta_b}{(\mu_{Ib} + \alpha_{Irb}) R_0} \\ 0 & \alpha_{Irb} & -\mu_h & 0 \\ 0 & 0 & N_b \alpha_{Irb} & -(\alpha_o + \mu_b) \end{pmatrix}$$

We test for stability of the infection equilibrium (E^*) by calculating the eigenvalues (λ_s) of the above jacobian matrix. The characteristic equation for the jacobian matrix is given by:

$$P(\lambda) = m_0 \lambda^4 + m_1 \lambda^3 + m_2 \lambda^2 + m_3 \lambda + m_4 \quad (3.5.12)$$

where,

$$\begin{cases} m_0 = 1, \\ m_1 = y_1 + y_2 + y_3 + y_4, \\ m_2 = y_1 y_2 + (y_1 + y_2)(y_3 + y_4) + y_3 y_4, \\ m_3 = y_1 y_2 y_3 + y_1 y_2 y_4 + y_1 y_3 y_4, \\ m_4 = \frac{y_1 y_2 y_3 y_4 (R_0 - 1)}{R_0}. \end{cases}$$

for $(y_1, y_2, y_3, y_4) = (\mu_e, \alpha_{mp}, \mu_h, (\alpha_o + \mu_b))$. In order to determine the stability of the infection equilibrium E_* , we use the Routh-Hurwitz stability criteria to determine the sign of the eigenvalues of the characteristics polynomials. According to Routh-Hurwitz criteria, given a polynomial.

$$P(\lambda) = m_0 \lambda^n + m_1 \lambda^{n-1} + m_2 \lambda^{n-2} + m_3 \lambda^{n-3} + \dots + m_{n-1} \lambda + m_n \quad (3.5.13)$$

with a real constant coefficients m_i where $i = 1; 2; 3; \dots; n$ is considered. Now, from the equation (3.5.13), we will form Routh array as shown below:

$$\begin{array}{c|cccccccc}
 \lambda^n & m_0 & m_2 & m_4 & m_6 & . & . & . & . \\
 \lambda^{n-1} & m_1 & m_3 & m_5 & m_7 & 0 & . & . & . \\
 \lambda^{n-2} & a_1 & a_2 & a_3 & . & . & . & . & . \\
 \lambda^{n-3} & b_1 & b_2 & . & . & . & . & . & . \\
 \lambda^{n-4} & c_1 & . & . & . & . & . & . & . \\
 . & . & . & . & . & . & . & . & . \\
 . & . & . & . & . & . & . & . & . \\
 \lambda^2 & . & . & . & . & . & . & . & . \\
 \lambda^1 & . & . & . & . & . & . & . & . \\
 \lambda^0 & . & . & . & . & . & . & . & .
 \end{array} \quad (3.5.14)$$

m_i for ($i = 1; 2; 3; 4; \dots; n$) coefficient are taken from the characteristic equation $P(\lambda)$ and are arranged as shown in the Routh array above. Other elements are calculated from these element. Coefficient a_i for ($i = 1; 2; 3; 4; \dots; n$) are calculated as:

$$\begin{cases}
 a_1 = \frac{m_1 m_2 - m_3 m_0}{m_1}, \\
 a_2 = \frac{m_1 m_4 - m_5 m_0}{m_1}, \\
 a_3 = \frac{m_1 m_6 - m_7 m_0}{m_1},
 \end{cases}$$

using the Routh-Hurwitz criteria, the process is continued until we get a zero in the row with a_i coefficients. Similarly, b_i coefficients and c_i coefficients are calculated as follows:

$$\begin{cases}
 b_1 = \frac{m_3 a_1 - m_1 a_2}{a_1}, \\
 b_2 = \frac{m_1 a_1 - m_1 a_3}{a_1}, \\
 c_1 = \frac{b_1 a_2 - b_2 a_1}{b_1},
 \end{cases}$$

In our case, we define the Routh array table whose elements are the coefficient (m_i) of the characteristic polynomial $P(\lambda)$ in equation (3.5.13):

$$\begin{array}{c|ccc}
 \lambda^4 & m_0 & m_2 & m_4 \\
 \lambda^3 & m_1 & m_3 & 0 \\
 \lambda^2 & a_1 & a_2 & \\
 \lambda^1 & b_1 & & \\
 \lambda^0 & c_1 & &
 \end{array} \quad (3.5.15)$$

where;

$$\left\{ \begin{array}{l}
 a_1 = \frac{(y_2 + y_3 + y_4)(y_1^2 + y_1y_2 + y_1y_3 + y_1y_4 + y_2y_3 + y_2y_4 + y_3y_4)}{y_1 + y_2 + y_3 + y_4} > 0, \\
 a_2 = \frac{y_1y_2y_3y_4(R_0 - 1)}{R_0} > 0, \Leftrightarrow R_0 > 1, \\
 b_1 = \frac{m_3(m_1m_2 - m_3) - m_1^2m_4}{m_2m_1 - m_3} > 0, \\
 c_1 = m_4, \Leftrightarrow R_0 > 1,
 \end{array} \right.$$

Since $m_0; m_1; b_1; c_1 > 0$, we have shown that the signs in the first column of routh array are all the same and this confirms stability of the infection equilibrium. consequently, this completes our test for stability and subsequently conclude that the infection equilibrium for the model system is stable. And now we consider the within-mosquito transmission dynamics model system.

3.5.3 The Global Stability of the Endemic malaria infection equilibrium

When $R_0 < 1$, the malaria infection equilibrium is locally asymptotically stable. This suggest that local stability of the malaria infection equilibrium when $R_0 > 1$ So we only investigate the global stability of malaria infection equilibrium. in order to do this, we use the techniques used by pedro et al (2014).

Theorem 3.3 *If R_0 , the model system (3.1.1) has unique positive malaria infection*

equilibrium, E^* such that:

$$\left\{ \begin{array}{l} \frac{S_p^* L_c^*}{S_p L_c} \geq \frac{L_c^*}{L_c} \geq 1, 0 < S_p < S_p^*, 0 < L_c < L_c^*, \\ \frac{S_p^* L_c^*}{S_p L_c} \geq \frac{S_p^*}{S_p} \geq 1, 0 < S_p < S_p^*, 0 < L_c < L_c^*, \\ \frac{S_b^* M_{LB}^*}{S_b M_{LB}} \geq \frac{M_{LB}^*}{M_{LB}} \geq 1, 0 < M_{LB} < M_{LB}^*, 0 < S_b < S_b^*, \\ \frac{S_b^* M_{LB}^*}{S_b M_{LB}} \geq \frac{S_b^*}{S_b} \geq 1, 0 < M_{LB} < M_{LB}^*, 0 < S_b < S_b^*, \end{array} \right.$$

then, E^* is globally asymptotically stable in $\hat{\Omega} = \Omega$.

proof: To establish the global stable of the malaria infectious equilibrium, we define the Lyapunov function of the form

$$L(x) = \sum z_i (x_i - x_i^* \ln \frac{x_i}{x_i^*}), i = 1, 2, 3, \dots, 8 \quad (3.5.16)$$

as proposed by Castillo-Chavez et al. (2002) where x_i is a number of cells in the i^{th} class, x_i^* are equilibrium values and z_i are constants. This approach has been found useful for numerous models as well as the complicated models of *invivo* dynamics (Korobeinikov, 2004). We constructed the following lypunov function

$$L = z_1 (S_p - S_p^* \ln \frac{S_p}{S_p^*}) + z_2 (L_c - L_c^* \ln \frac{L_c}{L_c^*}) \quad (3.5.17)$$

$$+ z_3 (I_{Lc} - I_{Lc}^* \ln \frac{I_{Lc}}{I_{Lc}^*}) + z_4 (M_{LB} - M_{LB}^* \ln \frac{M_{LB}}{M_{LB}^*}) \quad (3.5.18)$$

$$+ z_5 (S_b - S_b^* \ln \frac{S_b}{S_b^*}) + z_6 (I_{rb} - I_{rb}^* \ln \frac{I_{rb}}{I_{rb}^*}) + z_7 (M_{LB} - M_{LB}^* \ln \frac{M_{LB}}{M_{LB}^*}) \quad (3.5.19)$$

$$+ z_8 (G_p - G_p^* \ln \frac{G_p}{G_p^*})$$

Using the model system (3.1.1) at malaria infection equilibrium state into time

derivative of (3.5.19) gives

$$\frac{dL}{ds} = z_1 \mu_s S_p \left(1 - \frac{S_p^*}{S_p}\right)^2 + z_2 \mu_L L_c \left(1 - \frac{L_c^*}{L_c}\right)^2 \quad (3.5.20)$$

$$+ z_3 (\alpha_L + \mu_{Lc}) I_{Lc} \left(1 - \frac{I_{Lc}^*}{I_{Lc}}\right)^2 + z_4 (\alpha_{mp} + \mu_c) M_{LB} \left(1 - \frac{M_{LB}^*}{M_{LB}}\right)^2 \quad (3.5.21)$$

$$+ z_5 \mu_e S_p \left(1 - \frac{S_b^*}{S_b}\right)^2 + z_6 (\mu_{Ib} + \alpha_{Irb}) I_{rb} \left(1 - \frac{I_{rb}^*}{I_{rb}}\right)^2 + z_7 \mu_h M_{LB} \left(1 - \frac{M_{LB}^*}{M_{LB}}\right)^2 \quad (3.5.22)$$

$$+ z_8 (\alpha_o + \mu_b) G_p \left(1 - \frac{G_b^*}{G_b}\right)^2$$

where $f(\Omega) = z_1 \left[1 - \frac{S_p^*}{S_p}\right] \left[\frac{S_p^* L_c^*}{S_p L_c} - 1\right] + z_2 \beta_s S_p L_c \left[1 - \frac{L_c^*}{L_c}\right] \left[\frac{S_p^* L_c^*}{S_p L_c} - 1\right] + z_5 \beta_L M_{LB} S_b + \beta_b M_{LB} S_b \left[1 - \frac{S_b^*}{S_b}\right] \left[\frac{S_b^* M_{LB}^*}{S_b M_{LB}} - 1\right] + z_8 \pi \beta_b S_b M_{LB} \left[1 - \frac{G_b^*}{G_b}\right] \left[\frac{S_b^* G_b^*}{S_b G_b} - 1\right]$
and $\Omega = (S_p, L_c, I_{Lc}, S_b, I_{rb}, M_{LB}, G_b) > 0$, therefore by hypothesis of Theorem 3.3, we have

$$\begin{cases} z_1 \left[1 - \frac{S_p^*}{S_p}\right] \left[\frac{S_p^* L_c^*}{S_p L_c} - 1\right] \leq 0 \\ z_2 \beta_s S_p L_c \left[1 - \frac{L_c^*}{L_c}\right] \left[\frac{S_p^* L_c^*}{S_p L_c} - 1\right] \leq 0 \\ z_5 \beta_L M_{LB} S_b + \beta_b M_{LB} S_b \left[1 - \frac{S_b^*}{S_b}\right] \left[\frac{S_b^* M_{LB}^*}{S_b M_{LB}} - 1\right] \leq 0 \\ z_8 \pi \beta_b S_b M_{LB} \left[1 - \frac{G_b^*}{G_b}\right] \left[\frac{S_b^* G_b^*}{S_b G_b} - 1\right] \leq 0 \end{cases}$$

where $S_p = S_p^*, L_c = L_c^*, I_{Lc} = I_{Lc}^*, S_b = S_b^*, I_{rb} = I_{rb}^*, M_{LB} = M_{LB}^*, G_b = G_b^*$
therefore $f(\Omega) = S_p = S_p^*, L_c = L_c^*, M_{LB} = M_{LB}^*, G_b = G_b^*$. hence, $\frac{dL}{ds} \leq 0 \forall (S_p, L_c, I_{Lc}, S_b, I_{rb}, M_b, G_b) > 0$ and $\frac{dL}{ds} = 0$ only when $S_p = S_p^*, L_c = L_c^*, I_{Lc} = I_{Lc}^*, S_b = S_b^*, I_{rb} = I_{rb}^*, M_{LB} = M_{LB}^*, G_b = G_b^*$, whilst E^* is the only equilibrium state of the system (3.1.1). Therefore we deduce the following, the largest compact invariant set in Ω such that $\frac{dL}{ds} = 0$ is a singleton E^* which is the malaria infection equilibrium and it is globally asymptotically stable.

3.6 Numerical Analysis

The purpose of numerical analysis is to solve analytically the differential equations of the model system to adopt the approximate methods. These can be done by estimating the unknown at specific point in its interval of definition by arithmetic means or initial value. These numerical solutions do not establish physical laws but give clear picture of the dependence of desired variable on the various parameters of the problem and this will provide a study a number of benefits for decision making and drawing up a sound conclusion.

Parameters	Descriptions	Initial value
α_p	Rate at which sporozoites become infectious to the liver cells	0.025
Λ_h	Rate of supply of uninfected liver cells	3000
μ_s	Natural decay rate rate of sporozoites	0.0001
N_m	Number of merozoites produced per bursting liver cells	25
α_{mp}	Rate at which liver cells burst to produce merozoites	0.06
μ_L	Natural decay rate of liver cells	0.029
α_L	Rate at which liver cells burst	0.02
μ_{Lc}	Natural decay rate of infected liver cells	0.0078
N_k	Number of sporozoites produced per burting oocysts	3000
α_v	Rate at which sporooites become infectious to humans	0.025
μ_v	Natural decay rate of sporozoites	0.0001
Λ_h	Rate of supply of susceptible red blood cells	200
β_s	Infection rate of liver cells by sporozoites	0.000000 1
μ_b	Natural decay rate of susceptible erythrocytes	0.0083
π	Proportion of gametocyte infected erythrocytes	0.1
μ_m	Natural decay rate of free merozoites	0.001
α_m	Rate at which erythrocytes burst to produce merozoites	0.5
N_m	Number of merozoites produced per bursting erythrocytes	16
α_h	Rate at which gametocytes develop and become infectious	0.02
μ_h	Natural decay rate of gametocytes infected erythrocytes within infected humans within infected humans	0.0625

Table 3.3: The Within-mosquito and Within-human parameter values and their descriptions.

Figure 3.3 Shows that the more red blood cells are increased from its production source, the less the infected red blood cells in the blood stream.yet merozoites remain constant, which implies that increasing the red blood cells will not reduce the number of infected red blood cells and over time the infection process will proceeds unless infected cells get treated.

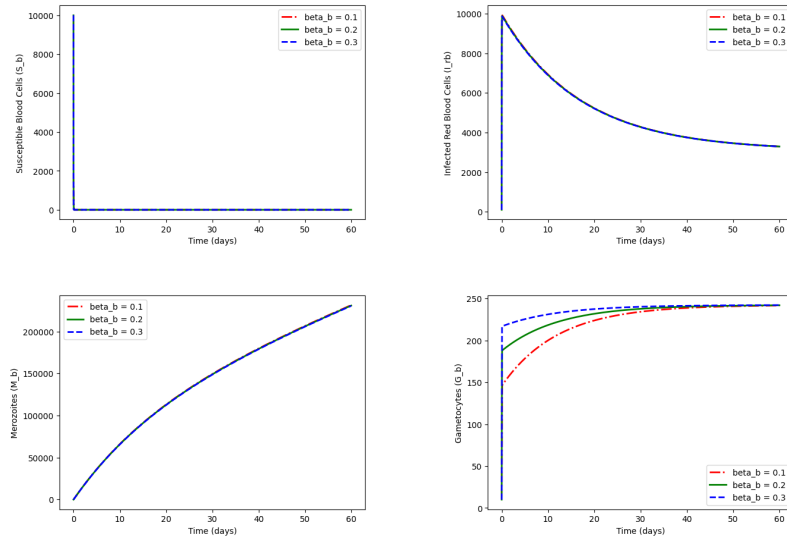


Figure 3.3: Numerical simulations showing dynamics of susceptible blood (S_b), infected red blood (I_{rb}), Merozoites in the blood stream (M_{LB}) and gametocytes in the blood (G_b) over time in days for various values of efficacy. $\beta_b : \beta_b = 0.1, \beta_b = 0.2$ and $\beta_b = 0.3$

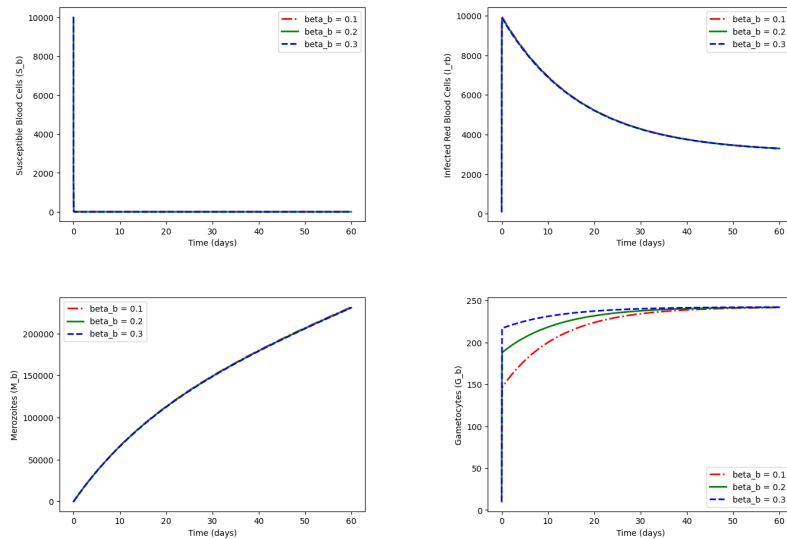


Figure 3.4: Numerical simulations showing dynamics of susceptible blood (S_b), infected red blood (I_{rb}), Merozoites in the blood stream (M_b) and gametocytes in the blood (G_b) over time in days for various values of efficacy. $\beta_b : \beta_b = 0.1, \beta_b = 0.2$ and $\beta_b = 0.3$

Figure 3.4 Shows that the more the efficacy the more red blood cells are increased from its source of production from the bone marrow, which is very true because if people are not in contact with infected mosquitoes the less the population of merozoites presence in the liver organ. Figure 3.5 Shows that the more red blood cells are increased from its production source, the less the infected red blood cells in the blood stream but merozoites remain in the system and constant,

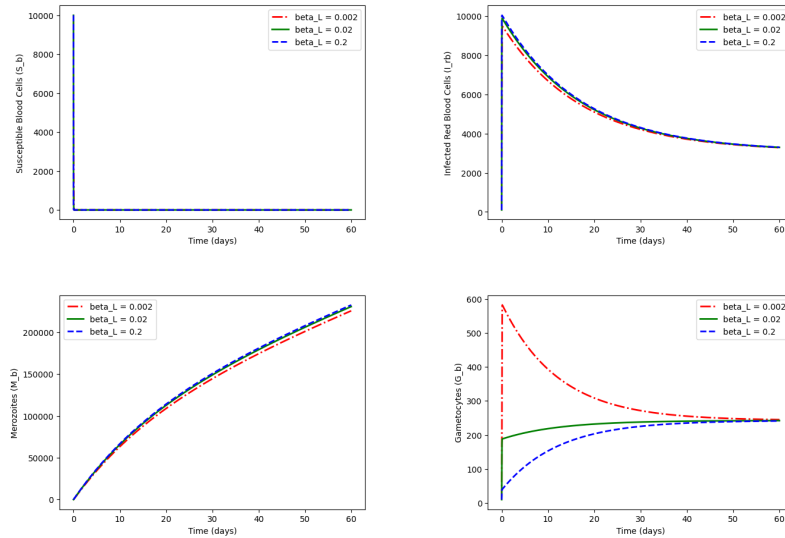


Figure 3.5: Numerical simulations showing dynamics of susceptible blood (S_b), infected red blood (I_{rb}), Merozoites in the blood stream (M_b) and gametocytes in the blood (G_b) over time in days for various values of efficacy. $\beta_b : \beta_L = 0.002, \beta_b = 0.02$ and $\beta_b = 0.2$

which implies that increases of gametocytes production in the blood stream. Figure 3.6 shows the rate of destruction of infected red-blood cells increases, we notice a slight decrease on merozoites. The solution imply that control measures aimed at giving health intervention that kills the infected red blood cells within the infected human red blood cells, which is good for the community because it reduce the transmission of malaria at the later stages. Figure 3.7 shows that the destruction rate of gametocytes by asexual production or immune respond in the last stages of malaria life stage of pathogen life-cycle within-human scale have an influence in reducing the transmission of malaria disease dynamics at community level that is on between-host scale. Figure 3.8 shows that the destruction rate of gametocytes by asexual production or immune respond in the last stages of malaria life stage of pathogen life-cycle within-human scale have an influence in reducing the transmission of malaria disease dynamics at community level that is on between-host scale. Figure 3.9 shows that the within-host scale variables are influenced by the between-host scale parameters. The simulation indicates that as the efficacy if liver cells by production inhibiting the merozoites increase and decrease. Hence, health interventions that inhibits merozoites within-human host scale will likely to minimise the transmission of malaria disease dynamics at between-host scale. Figure 3.10 shows that the within-host scale variables are influenced by the between-host scale parameters. The simulation indicates that as the efficacy if liver cells by production inhibiting the merozoites increase and decrease. Hence, health interventions that inhibits merozoites within-human host scale will likely to minimise the transmission of malaria disease dynamics at between-host scale that the more red blood cells are increased from its source of production from the bone marrow, the less the infected red blood cells in the blood stream but merozoites remain in the system and constant, which implies that in-

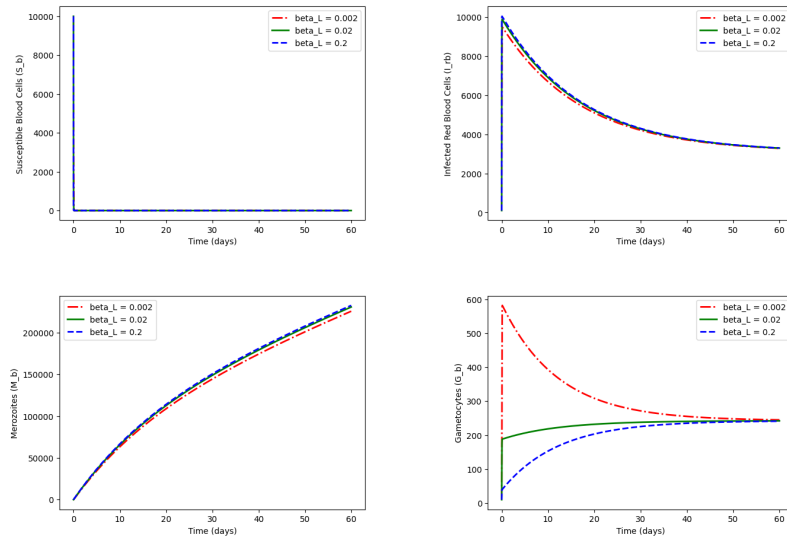


Figure 3.6: Numerical simulations showing dynamics of susceptible blood (S_b), infected red blood (I_{rb}), Merozoites in the blood stream (M_b) and gametocytes in the blood (G_b) over time in days for various values of efficacy. $\beta_b : \beta_L = 0.002, \beta_b = 0.02$ and $\beta_b = 0.2$

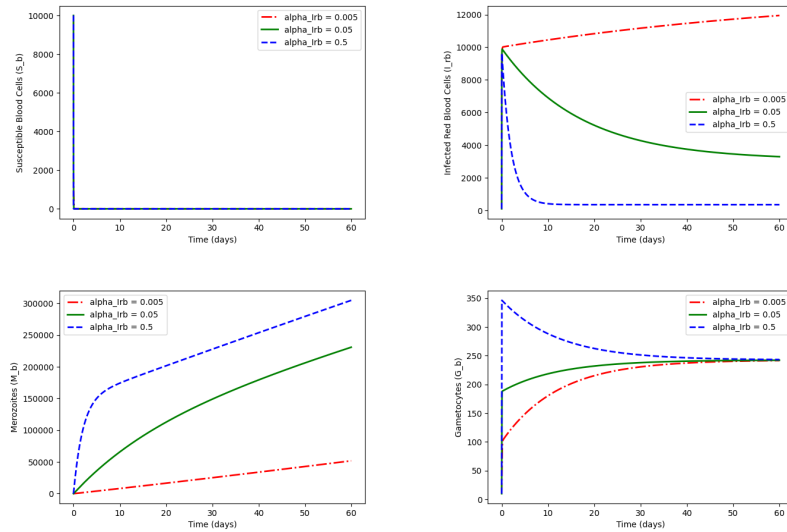


Figure 3.7: Numerical simulations showing dynamics of susceptible blood (S_b), infected red blood (I_{rb}), Merozoites in the blood stream (M_b) and gametocytes in the blood (G_b) over time in days for various values of efficacy. $\alpha_{Irb} : \alpha_{Irb} = 0.005, \alpha_{Irb} = 0.05$ and $\alpha_{Irb} = 0.5$

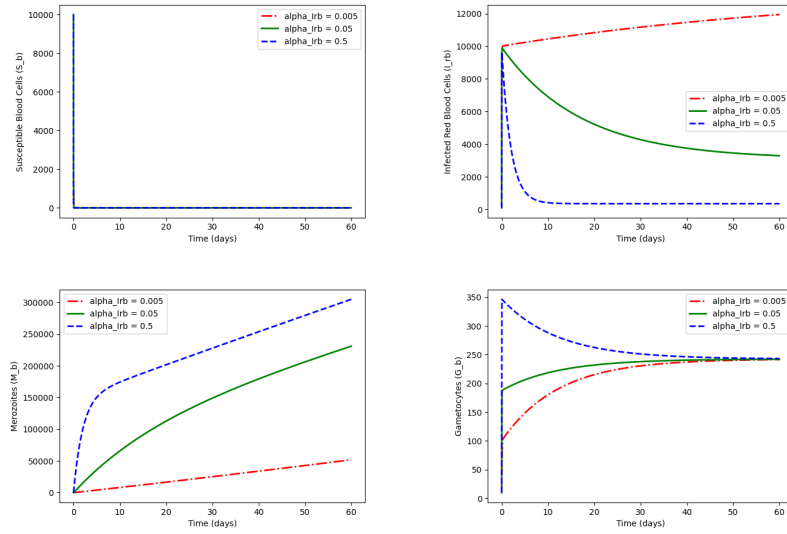


Figure 3.8: Numerical simulations showing dynamics of susceptible blood (S_b), infected red blood (I_{rb}), Merozoites in the blood stream (M_b) and gametocytes in the blood (G_b) over time in days for various values of efficacy. $\beta_b : \beta_b = 0.1, \beta_b = 0.2$ and $\beta_b = 0.3$

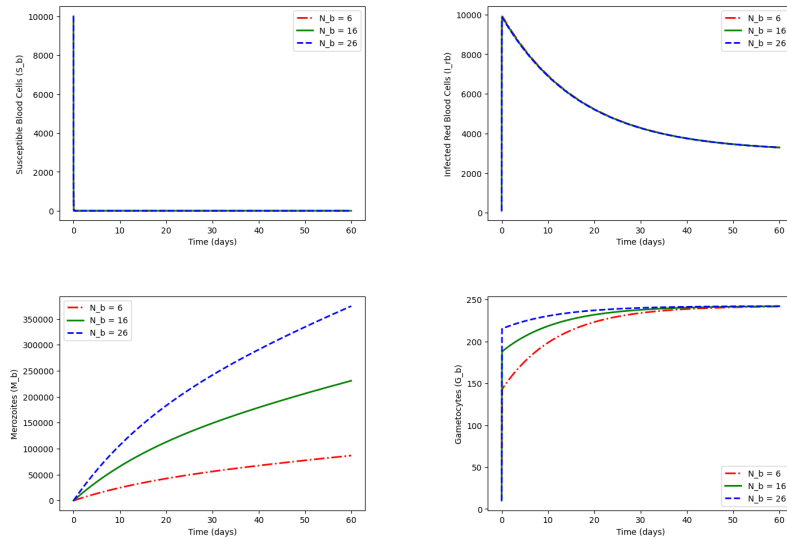


Figure 3.9: Numerical simulations showing dynamics of susceptible blood (S_b), infected red blood (I_{rb}), Merozoites in the blood stream (M_b) and gametocytes in the blood (G_b) over time in days for various values of efficacy. $N_b : N_b = 6, N_b = 16$ and $N_b = 26$

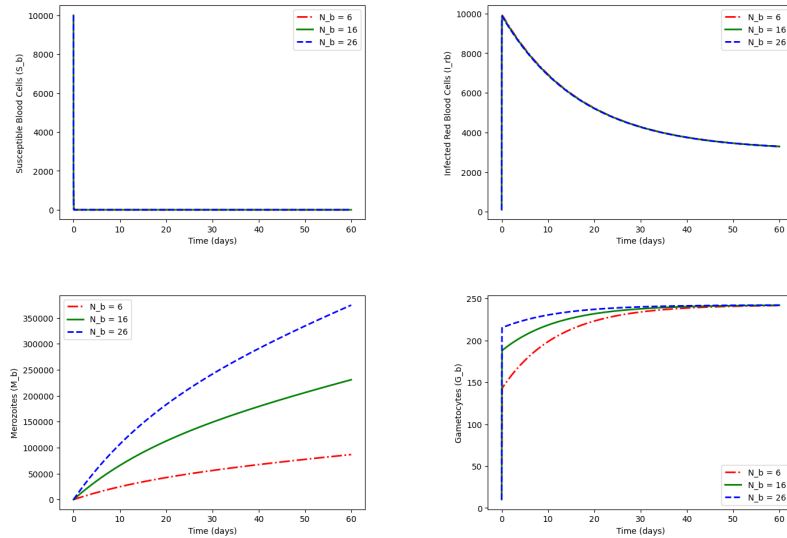


Figure 3.10: Numerical simulations showing dynamics of susceptible blood (S_b), infected red blood (I_{rb}), Merozoites in the blood stream (M_b) and gametocytes in the blood (G_b) over time in days for various values of efficacy. $\beta_b : \beta_b = 0.1, \beta_b = 0.2$ and $\beta_b = 0.3$

creasing the red blood cells will not reduce the number of infected red blood cells and over time the infection process will proceed unless infected cells also get treated simultaneously with preventing pathogen injection in the blood. Figure 3.11 shows that the more red blood cells are increased from its source of production from the bone marrow, the less the infected red blood cells in the blood stream but merozoites remain in the system and constant, which implies that increasing the red blood cells will not reduce the number of infected red blood cells and over time the infection process will proceed unless infected cells also get treated simultaneously with preventing pathogen injection in the blood.

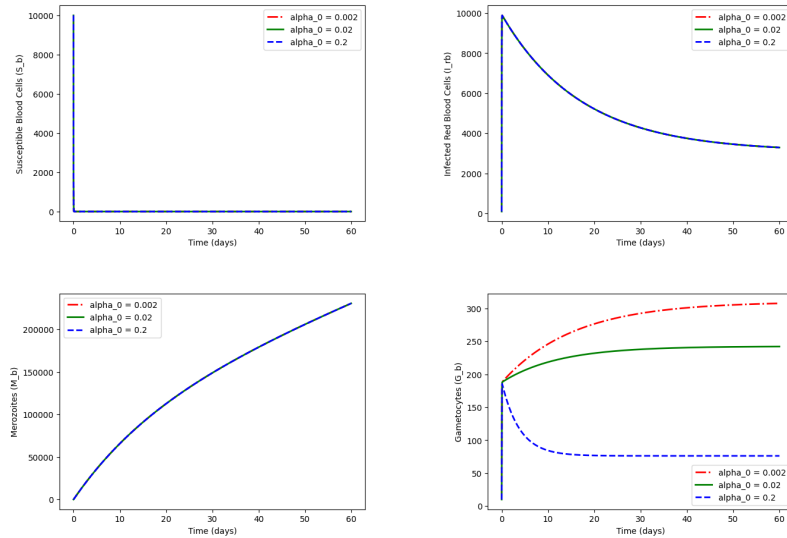


Figure 3.11: Numerical simulations showing dynamics of susceptible blood (S_b), infected red blood (I_{rb}), Merozoites in the blood stream (M_b) and gametocytes in the blood (G_b) over time in days for various values of efficacy. $\alpha_o : \beta_o = 0.002, \alpha_o = 0.02$ and $\alpha_o = 0.2$

3.7 Summary

The liver stage and the tissue stage (blood) of the parasite development are both included in the mathematical model of the within-human host malaria infection system (3.1.1) that is presented in this chapter. In contrast to the majority of models, which do not account for both the tissue and the organ, the majority of models regard macrophages as the most potent innate immune cells for removing malaria parasites from human blood. We broadened the scope of our research to include the liver in order to gain a better knowledge of the most important factors to take into account while eradicating infectious malarial illness. We established the mathematical and physiologically well-posedness of the constructed model in an invariant region Ω . Locally asymptotically stable equilibrium condition for malaria sickness is demonstrated when the within-host reproduction is locally asymptotically stable. If the threshold quantity R_0 is less than unity, then the malaria disease free equilibrium is guaranteed to be globally asymptotically stable. Using the Metzler matrix technique, the global stability of this equilibrium was examined. It was shown that the malaria free equilibrium is globally asymptotically stable when $R_0 < 1$; additionally, we mathematically demonstrated the local and global endemic states. Based on the numerical results, it is recommended that interventions during malaria infection be directed on reducing the pace at which merozoites infect healthy erythrocytes and the density of merozoites in circulation. These factors are accountable for the creation of new malaria life cycles that infiltrate blood cells. In the next chapter, we will develop a mathematical model for studying malaria transmission dynamics at between-host scale with the goal to motivate further the development of multiscale models.

Chapter 4

Mathematical Modelling for Host-level Malaria Dynamics

4.1 Introduction

The threat of infectious diseases to human health is still quite real. even if improvements in public health and medicine have contributed to the control of many endemic diseases. According to some research on the global burden of disease, infectious diseases accounted for more than 25 percent of the estimated 57 million deaths worldwide in 2002 ([Garira and Mafunda \(2019\)](#)). A bite or scratch from an infected animal falls under the category of infectious diseases, which include malaria, which has two hosts. Malaria is an infectious disease that spreads from human to person or from animal to animal. In this instance, the transmission of germs from host to host is facilitated by insects like mosquitoes. We refer to these carriers as vectors. The malaria parasite can be carried by mosquitoes ([Chiyaka et al. \(2008\)](#)). Several diseases can be significantly reduced in risk by vaccination. Vaccination can help lower the chance of contracting malaria, but as researchers, our goal is to eradicate infectious diseases by using mathematical methods to track the evolution of parasites within two hosts using multiscale modeling techniques [Garira and Chirove \(2019\)](#). Multiscale modeling is a type of modeling in which a system is simultaneously described by many multiscale models at various scales. Typically, the various models concentrate on various resolution scales. Multiscale modeling is typically required because the current macroscale models are insufficiently precise, and the microscale models are insufficiently efficient to provide significant amounts of information. By integrating the two points of view, Through the integration of both perspectives, our aim is to reach a fair equilibrium between precision and effectiveness. The majority of studies on infectious disease related to malaria show the linked multiscale models of infectious disease system, which are the most sophisticated kind of epidemiological models (Mathebula D and Garira, 2017). This type of multiscale modeling technique focuses on analyzing the transmission of infectious illnesses among several hosts by fusing theories of infection and within-host processes with the dynamics of within-host transmission. Either the integrated multiscale

modeling approach or the nested multiscale modeling approach can be used to couple submodels. Two approaches are used to produce the coupled multiscale modeling approach: first, separate submodels for the vector host and the vertebrate host are created. The second method involves combining the submodels into a single multiscale model that may contain one or more submodel variables. The development of coupled multiscale modeling of the infectious disease system is based on the compartmental diagrams, commonly known as the parallel integration framework. When several multiscale models of infectious illnesses are connected to create a single multiscale model, this is known as a parallel integrated compartmental framework [Barreto et al. \(2006\)](#). This chapter develops a multiscale model of the infectious illness system caused by malaria. The multiscale model is built on multiple multiscale model categories, including linked, nested, and embedded multiscale models. We create the multiscale model in the following subsection.

4.2 Multiscale Model Development

To demonstrate the use of the novel approach and its applicability for creating nested multiscale models of infectious disease systems, we create three distinct independent submodels for the dynamics of malaria transmission in this section. The transmission of malaria occurs through direct host-to-host contact.

We create a multiscale model that includes the dynamics of every population of living things implicated in the transmission of malaria, including the human host, the mosquito vector, and the pathogen *Plasmodium falciparum*, in order to estimate the baseline transmission dynamics of malaria. We create four separate submodels for the dynamics of malaria transmission at two different scales: one for the transmission within hosts and another for the transmission between hosts. These submodels are then integrated into a single multiscale model, which we further simplify by reducing the number of dimensions using slow and fast scale analysis.

4.2.1 The within-host submodels of malaria transmission dynamics

The within-human malaria parasite population dynamics describes the time evolution of all eight populations within an infected human host, was derived in chapter

3 above and is given as followings:

$$\left\{ \begin{array}{l} \frac{dS_p(s)}{ds} = \Lambda_p - \mu_s S_p(s), \\ \frac{dL_c(s)}{ds} = \Lambda_h - \beta_s S_p L_c(s) - \mu_L L_c(s), \\ \frac{dI_{Lc}(s)}{ds} = \beta_s S_p L_c(s) - (\alpha_L + \mu_{Lc}) I_{Lc}(s), \\ \frac{dS_b(s)}{ds} = \Lambda_b - (\beta_b M_b(s) + \beta_L M_p) S_b(s) - \mu_e S_b(s), \\ \frac{dI_{rb}(s)}{ds} = [(1 - \pi) \beta_b M_b(s) + \beta_L M_p(t)] S_b(s) - (\mu_{Ib} + \alpha_{Irb}) I_{rb}(s), \\ \frac{dM_{LB}(s)}{ds} = N_m \alpha_L I_{Lc}(S) + N_b \alpha_{Irb} I_{rb}(s) - \mu_h M_b(s), \\ \frac{dG_b(s)}{ds} = \pi \beta_b S_b(s) M_b(s) - (\alpha_o + \mu_b) G_b(s). \end{array} \right.$$

Within-Mosquito plasmodium falciparum parasite population dynamics sub-model.

Mosquitoes are the definitive hosts for the malaria parasites, where the sexual phase of the parasite's life cycle occurs in a process involving morphologically distinct life stages ([Bray and Garnham \(1982\)](#)) called sporogony and culminates in the development of infectious form of the parasite called sporozoites. In this subsection, the within-mosquito malaria parasite population dynamics during sporogony is modelled by the time evolution of five parasite developmental stages in the infected erythrocytes, $G_v(s)$, the population of gametes, $G_m(s)$, the population of zygotes $Z_v(s)$, the population of oocysts, $O_v(s)$, and the population of sporozoites, $P_v(s)$. We make the following assumptions for the dynamics of the five malaria parasite stage populations.

- (i) There is no super-infection of mosquito. (ii) The within-mosquito sporozoites population P_v is proxy for individual mosquito infectiousness to human.
- (iii) The population dynamics of the different malaria parasites at different stages of development occurs at fast time scale(s) compared to mosquito-to-human and human-to-mosquito parasite transmission dynamics so that $G_v = G_v(s), Z_v = Z_v(s), O_v = O_v(s)$ and $P_v = P_v(s)$.
- (iv) We assume that within an infected mosquito, male and female gametes only fuse as pairs to form zygotes and those gametes that fail to locate a gamate of opposite sex to fuse with will, with time, die a natural death and therefore will not

participate in zygote formation. (Garira (2017))

These assumptions lead to the following system of differential equation for the within-mosquito malaria parasite population dynamics.

$$\begin{cases} \frac{dG_v(s)}{ds} = -(\alpha_g + \mu_g)G_v(s), \\ \frac{dG_m(s)}{ds} = N_g\alpha_g G_v(s) - (\alpha_s + \mu_s)G_m(s), \\ \frac{dZ_v(s)}{ds} = \frac{1}{2}\alpha_s G_m(s) - (\alpha_z + \mu_z)Z_v(s), \\ \frac{dO_v(s)}{ds} = \alpha_z Z_v(s) - (\alpha_k + \mu_k)Z_v(s), \\ \frac{dP_v(s)}{ds} = N_k\alpha_k O_v(s) - (\alpha_v + \mu_v)P_v(s). \end{cases}$$

Gametes are created inside the host erythrocyte during a developmental process known as gametogenesis, which is experienced by the gametocyte-infected erythrocytes. The rate at which gametocyte-infected erythrocytes rupture, releasing sex cells known as gametes, is α_g in the first equation of the submodel system, while the natural decay rate of gametocyte-infected erythrocyte within an infected mosquito is μ_g . The dynamics of the gamete population inside an infected mosquito are described by the second equation in the sub-model system. We assume that each bursting gametocyte releases an average of N_g gametes upon bursting from infected erythrocytes. As a result, the rate of gamete growth within an infected mosquito is modeled by $N_g\alpha_g G_v(s)$. It is assumed that the rate of decay of these gametes is μ_s . Additionally, at a fixed α_s , male and female gametes fuse to generate zygotes, depleting these gametes. The dynamics of zygotes are described by the third equation in the sub-model system. Within an infected mosquito, the mean population of zygotes $Z_v(s)$ is produced by gametes going through a developmental phase where they mature, couple up, and fuse to form zygotes at a rate of $\frac{\alpha_s}{2}$. In order to describe the pairing of male and female gametes and their subsequent fusing to generate zygotes, the fraction $\frac{1}{2}$ is introduced

and multiplied by the parameter α_s . We suppose that the zygotes either undergo additional developmental modifications to become ookinetes, which infiltrate the mosquito mid-gut lining and finally grow into oocysts, or they die spontaneously at a rate μ_z . The dynamics of the oocyst population are described by the fourth equation in the sub-model system. The average population of oocysts is created by the developmental changes that zygotes undergo, first becoming ookinetes and then, at a rate, becoming oocysts. As a result, the first term in the fourth equation of the sub-model system models the rate at which the population of oocysts increases due to the developmental changes that ookinetes undergo to become oocysts, and the second term models the rate at which this population decreases due to either natural decay at a rate of μ_k or the assumed rate of α_k

through oocyst bursting to produce sporozoites. The dynamics of sporozoites are described by the fifth equation in the sub-model system. After the plasmodium develops fully inside the mosquito vector, a colony of sporozoites is produced. We assume that the average number of sporozoites released upon bursting by each oocyst, which bursts at a rate of α_k , is N_k . As a result, the rate of increase of sporozoites within an infected mosquito is modeled by $N_k \alpha_k O_v(s)$. The final equation represents α_v , which is the rate at which mature sporozoites shed into the salivary glands of infected mosquitoes, forming the infectious reservoir of a single mosquito. It is assumed that the excreted/shed sporozoite population decays, with an average life-span of $\frac{1}{\alpha_v}$ days for each sporozoite.

4.2.2 The between-hosts submodels of malaria transmission dynamics.

The transmission dynamics of the between host scale model include two distinct submodels, namely the mosquito-to-human malaria transmission sub-model and the human-to-mosquito malaria transmission sub-model.

1. Mosquito-to-human malaria transmission sub-model.

The SIS model describes this sub-model. The submodel is derived from the observation of the dynamics of two populations: susceptible humans S_H and infected humans I_H . This allows us to calculate the total population of humans as follows: $N_H = S_H + I_H$. For this submodel, we make the following assumptions.

- (i) The human population does not possess herd immunity due to prior exposure to malaria infection or vaccine.
- (ii) Malaria infections can spontaneously heal in the affected human population.
- (iii) The number of infected mosquitoes determines the transmission parameter β_V , so that $\beta_V = \beta_V(I_V)$.
- (iv) It is assumed that the dynamics of S_H and I_H happen on a slow time scale. t in comparison to the malaria parasite population dynamics within-human and within-mosquito sub-models so that $S_H = S_H(t)$ and $I_H = I_H(t)$.

The following sub-model for the dynamics of malaria transmission from mosquitoes to humans is the result of these assumptions.

$$\begin{cases} \frac{dS_H(t)}{dt} = \Lambda_H - \beta_V(I_V)S_H(t) - \mu_H S_H(t) + \gamma_H I_H, \\ \frac{dI_H(t)}{dt} = \beta_V(I_V)S_H(t) - (\mu_H + \gamma_H + \sigma_H)I_H(t). \end{cases} \quad (4.2.1)$$

The first equation in submodel (4.2.1) describes the dynamics of susceptible humans. The population of susceptible humans is assumed to increase at a constant rate Λ_H through birth. This population is depleted through infections of susceptible humans at a variable rate $\beta_V(I_V)$ and natural death at a constant rate μ_H . The population of susceptible humans also increase through natural recovery of infected individuals at a rate γ_H . The second equation in sub-model (4.2.1) describes

the dynamics of infected human. This population increases through infection of susceptible humans and decrease through natural death at a rate μ_H . Through disease induced death at a rate σ_H and through recovery at a rate γ_H .

2. Human-to-Mosquito malaria transmission sub-model.

This sub-model is described by SI model and describes the transmission of malaria parasite from infected human to susceptible mosquitoes. We make the following assumptions for this sub-model.

- (i) The infected mosquitoes do not recover naturally from malaria infection.
- (ii) The transmission parameter β_H is a function of the number of infected humans so that $\beta_H = \beta_H(I_H)$.
- (iii) The dynamics of S_V and I_V are assumed to occur at a slow scale t compared to the within-human and within-mosquito sub-models so that $S_V = S_V(t)$ and $I_V = I_V(t)$.

Taking this assumptions into consideration the sub-model for the human-to-mosquito malaria transmission dynamics becomes.

$$\begin{cases} \frac{dS_V(t)}{dt} = \Lambda_V - \beta_H(I_H)S_V(t) - \mu_V S_V(t), \\ \frac{dI_V(t)}{dt} = \beta_H(I_H)S_V(t) - (\mu_V + \sigma_V)I_V(t). \end{cases} \quad (4.2.2)$$

The first equation in the sub-model system (4.2.2) describes the dynamics of susceptible mosquitoes. The first term on the right-hand side of this equation models the increase of susceptible population of mosquitoes through birth. The susceptible population of mosquitoes decreases through natural death at a constant rate μ_V , and through infection by humans at a variable rate $\beta_H(I_H)$. The second equation in sub-model system (4.2.2) describes the dynamics of infected mosquitoes. The population of infected mosquitoes at a rate $\beta_H(I_H)$. The same population decreases through natural death at a constant rate μ_V and also through infection induced death at a constant rate σ_V .

4.2.3 Integration of the four separate sub-models of malaria transmission dynamics into a single multiscale model

The four sub-models that individually describe the transmission of malaria at various scales were introduced in the preceding subsections. The integration of these into a single multiscale model is now demonstrated. For environmentally transmitted infectious disease systems, general pathogens shedding/excretion links the within-host scale to the between-host scale, whereas infection/superinfection links the between-host scale to the within-host scale (Garira et al. (2014); Garira (2017)). We apply these concepts to the current situation, where the human-to-mosquito and mosquito-to-human malaria transmission dynamics submodels are coupled to the within-human and within-mosquito submodels, respectively, in a unidirectional manner. We accomplish the integration of the four sub-models in

two processes. Making assumptions about the relationship between the dependent variables of the within-human and within-mosquito parasite population dynamics, G_h, P_v, M_h , and the parameters of the human-to-mosquito and mosquito-to-human malaria parasite transmission at epidemiological levels is the first step in the integration of the four sub-models (4.2.1), (4.2.2), (4.2.3), and (4.2.4). scale which are $\beta_V(I_V), \beta_H(I_H), \delta, \gamma$ and δ_H . The second step involves applying ecosystems concepts to the within-mosquito and within-human malaria parasite population dynamics (Rynkiewicz et al., 2015; Sicard et al., 2014; Lofgren et al., 2016) to derive the appropriate equations. derivations and assumptions are as follows.

1. In the context of malaria infection, host survival or death and host recovery can be considered as suitable metrics of the emergent ecosystem properties due to merozoites since the merozoites stage of the malaria parasite is responsible for morbidity and mortality (Rynkiewicz et al., 2015; Sicard et al., 2014; Lofgren et al., 2016). This is because the human host is an ecosystem. Thus, in the mosquito-to-human sub-model (4.2.1), we assume that the disease-induced human death rate δ_H and the recovery rate γ_H for malaria-infected humans are functions of the within-human merozoite population dynamics, such that $\delta_H = \delta_H M_h$ and $\delta_H = \delta_H M_h(s)$.

2 According to Rynkiewicz et al. (2015), Sicard et al. (2014), Lofgren et al. (2016), and Day et al. (1998), the mosquito's mortality is caused by the malaria parasite's sporozoite stage, which is also responsible for the infection-induced death of the mosquito. Therefore, in the context of malaria infection, when the mosquito vector is considered an ecosystem, mosquito survival or death can be considered as a suitable metric of the emergent ecosystem property due to sporozoites. Thus, in the human-to-mosquito sub-model (4.2.2), we assume that the infection-induced mortality rate of mosquitoes δ_V is a function of the within-mosquito sporozoite population dynamics, such that $\delta_V = \delta_V(P_v)$.

3. Additionally, it is assumed that the transmission parameter in the sub-model of mosquito-to-human malaria transmission, β_V , is not solely dependent on the vector population $I_V(t)$ and the sporozoite population $P_v(s)$, but also on the infectiousness at the population or community level $P_v(s)I_V(t)$. Furthermore, we interpret $P_v(s)I_V(t)$ as a new variable at the epidemiological scale, which is a product of the number of infected mosquitoes and the average sporozoite load of each individual infected mosquito. In this case, the community sporozoite load, or $P_V(t)$, represents the total infectious reservoir of mosquitoes in the community. The transmission parameter for the mosquito-to-human malaria transmission sub-model is $\beta_V = \beta_V(P_V(t))$ in terms of community sporozoite load. We further assume a Holling type II functional form of the function $\beta_V(P_V)$ so that the force of infection, denoted here by $\lambda_V(t)$, associated with infectivity of the community to humans becomes

$$\lambda_V(t) = \beta_V(P_V(t)) = \frac{\beta_V P_V(t)}{P_0 + P_V(t)} \quad (4.2.3)$$

where β_V is the exposure rate to a community with a population P_V of sporozoites per unit time and is in this study considered as a measure of human biting rate

(Hansen and Buckee, 2013) P_0 is the community sporozoite load that yields 50 percent chance of getting a human host infected with malaria after a bite by a mosquito in a particular community and

$$\lambda_V(P_V(t)) = \frac{P_V(t)}{P_0 + P_V(t)} \quad (4.2.4)$$

is the likelihood that a person in a community with a community sporozoite load of $P_V(t)$ will contract malaria from a random mosquito vector bite. We again utilize the concepts of an ecosystem approach to the within-mosquito parasite population dynamics in order to derive the differential equation governing $P_V(t)$ (Rynkiewicz et al., 2015; Sicard et al., 2014; Lofgren et al., 2016). We will be able to relate the novel epidemiological variable $P_V(t)$, to the within-mosquito parasite population dynamics explicitly through the use of the ecosystem approach. Specifically, it allows us to link, at the within-mosquito scale, the differential equation for $P_V(t)$ to the differential equation for $P_v(s)$. Using the model system (4.2.4), we know that the differential equation $P_v(s)$ is

$$\frac{dP_v(s)}{ds} = N_k \alpha_k O_v(s) - (\alpha_v + \mu_v) P_v(s). \quad (4.2.5)$$

In order to understand the within-mosquito population dynamics of sporozoites, we must apply the ecosystem concepts found in Rynkiewicz et al. (2015), Sicard et al. (2014), and Lofgren et al. (2016). We assume that mosquitoes in a given geographic area or community are small habitats/environments in the community where sporozoites can multiply and grow until they mature to become infectious to humans. As a result, at any given time s , the rate of contamination in each of these habitats is α_v , as this represents the pace at which sporozoites proliferate and become infectious within each mosquito. Now since at any time t we have a total of $I_V(t)$ of these contaminated habitats contaminated with an average of $P_v(s)$ sporozoites, then the rate of change of community sporozoite load $P_V(t)$, in the entire community made of $I_V(t)$ small habitats in the community becomes

$$\frac{dP_V(t)}{dt} = P_v(s) \alpha_V I_V(t) - \alpha_V P_V(t) \quad (4.2.6)$$

where α_V is the rate of sporozoite elimination in a particular geographical area so that the process of elimination of community sporozoite load in a particular geographical area takes an average of $\frac{1}{\alpha_V}$ days. Since $P_V(t)$ is the total infectious reservoir of mosquitoes in a particular community defined here as community sporozoite load, then $\frac{1}{\alpha_V}$ days is the average time to eliminate the total infectious reservoir of mosquitoes and render all mosquitoes in a particular community non-infectious. Taking into account these derivations and assumptions the mosquito-to-human malaria transmission sub-model which is now coupled to the within-

mosquito parasite population dynamics becomes

$$\begin{cases} \frac{dS_H(t)}{dt} = \Lambda_H - \frac{\beta_V P_V(t)}{P_0 + P_V(t)} S_H(t) - \mu_H S_H(t) + \gamma(M_h(s)) I_H(t), \\ \frac{dI_H(t)}{dt} = \frac{\beta_V P_V(t)}{P_0 + P_V(t)} S_H(t) - [\mu_H + \gamma_H(M_h(s)) + \delta_H(M_h(s))] I_H(t), \\ \frac{dP_V(t)}{dt} = P_v(s) \alpha_V I_V(t) - \alpha_V P_V(t). \end{cases} \quad (4.2.7)$$

As an aggregate population-level biomarker of a community's sporozoite burden over a given time period, community sporozoite load $P_V(t)$ is a measure of the total infectious reservoir of mosquitoes in the community and is being proposed as a useful metric for evaluating the overall impact of malaria health interventions aimed at the mosquito vector and quantifying their impact on transmission of malaria from mosquitoes to humans. We therefore suggest that this new public health measure of malaria transmission be operationalized in the evaluation of the path from control to elimination for malaria transmission in a specific community as a way to be consistent with a metric similar to that used for HIV/AIDS (Miller et al., 2013; Castel et al., 2012; Garira and Mafunda, 2019). (a) an indicator of community's level of infectiousness and transmission probability of malaria to humans, (b) a measure of the effectiveness of malaria interventions targeted at the mosquito vector, and (c) a proximal marker of malaria incidence among mosquitoes and their potential to propagate malaria to humans.

4. Finally, we assume that the transmission parameter in the human-to-mosquito malaria transmission sub-model, β_H is not just a function of the infected human population alone $I_H(t)$, but is a product of the infected human population $I_H(t)$ and gametocyte population $G_h(s)$ so that $\hat{\beta}_H = \beta_H(G_h(s)I_H(t))$. The net effect of this assumption is to up-scale individual human infectiousness $G_h(s)$ to population level or community level infectiousness $G_h(s)I_H(t)$. In addition, the quantity $G_h(s)I_H(t)$ is a new variable at epidemiological scale which we now denote by $G_H(t)$ so that $G_H(t) = G_h(s)I_H(t)$, which is a product of the average individual infected humans's gametocyte load and the number of infected humans. Here $G_H(t)$ is the total infectious reservoir of humans in the community which we refer to in this study as a community gametocyte load. In terms of community gametocyte load, the transmission sub-model becomes $\beta_H = \beta_H(G_H(t))$. We further also assume a Holling type II functional form of the function $\beta_H(G_H)$ so that the force of infection, denoted here by $\lambda_H(t)$, associated with infectivity of the community to mosquito becomes

$$\lambda_H(t) = \beta_H(G_H(t)) = \frac{\beta_H G_H(t)}{G_0 + G_H(t)} \quad (4.2.8)$$

where β_H is the exposure rate to community with a population G_H of gametocytes per unit time and is in this study considered as a measure of mosquito biting rate

(Hansen and Buckee, 2013). G_0 is the community gametocyte load that yields 50 percent chance of getting a mosquito vector infected with a particular community and

$$\lambda_H[G_H(t)] = \frac{G_H(t)}{G_0 + G_H(t)}, \quad (4.2.9)$$

is the probability that a random bite of a human host by a mosquito vector in a particular community with a community gametocyte load $G_H(t)$ will infect the mosquito with malaria in that community. In order to derive the differential equation governing $G_H(t)$, we again appeal to the ideas of an ecosystem approach to the within-human parasite population dynamics (Rynkiewicz et al., 2015; Sicard et al., 2014 and Lofgren et al., 2016). The ecosystem approach to the within-human parasite population dynamics will enable us to couple the new epidemiological variable $G_H(t)$, to the within-human parasite population dynamics. In particular, it enables us to couple the differential equation for $G_H(t)$ to the differential equation for gametocyte $G_h(s)$ at the within-human scale. From model system (4.2.3), we know that differential equation for $G_h(s)$ is

$$\frac{dG_h(s)}{ds} = \pi\beta_h R_h(s)M_h(s) - (\alpha_h + \mu_h)G_h(s) \quad (4.2.10)$$

Applying the ecosystem concepts in Rynkiewicz et al., 2015; Sicard et al., 2014 and Lofgren et al., 2016 to the within-human population dynamics of gametocytes, we assume that human in a particular geographical area of community are small homogeneous habitats in which gametocytes can multiply and grow until they mature to become infectious to mosquitoes. so at any time s each of these habitats is contaminated at a rate α_h since this is the rate at which gametocytes grow and mature to become infectious within each of the human hosts. Now, since at any time t we have a total of $I_H(t)$ of these contaminated habitats contaminated with an average of $G_h(s)$ gametocyte, then the rate of change of community made of $I_H(t)$ homogeneous small habitats in the community becomes

$$\frac{dG_H(t)}{dt} = G_h(s)\alpha_h I_H - \alpha_H G_H(t). \quad (4.2.11)$$

where α_H is the rate of elimination of this total infectious reservoir of humans in the community so that the process of gametocyte elimination in a particular geographical area takes an average of $\frac{1}{\alpha_H}$ days. Since $G_H(t)$ is the total infectious reservoir of humanin a particular community defined here as a community gametocytes load, then $\frac{1}{\alpha_H}$ days is the average time to eliminate the total infectious reservoir of humans and render all humans in a particular community non-infectious to mosquitoes. Taking into account these derivations and assumptions the human-to-mosquito malaria transmission sub-model which is now coupled to

the within-human parasite population dynamics becomes

$$\begin{cases} \frac{dS_V(t)}{dt} = \Lambda_V - \frac{\beta_H G_H(t)}{G_0 + G_H(t)} S_V(t) - \mu_V S_V(t), \\ \frac{dI_V(t)}{dt} = \frac{\beta_H G_H(t)}{G_0 + G_H(t)} S_V(t) - [\mu_v + \delta_V(P_v(s))] I_V(t), \\ \frac{dG_H(t)}{dt} = G_h(s) \alpha_h I_H - \alpha_H G_H(t). \end{cases} \quad (4.2.12)$$

Community sporozoite load $G_H(t)$, which is a measure of the total infectious reservoir of mosquitoes in the community, is defined as an aggregate population-level biomarker of a community's sporozoite burden over a specific time period and is being proposed as a useful metric for assessing the overall impact of malaria health interventions targeted at the mosquito vector and quantifying their impact on transmission of malaria from mosquitoes to humans. In line with a similar metric for HIV/AIDS (Miller et al., 2013; Castel et al., 2012; Garira and Mafunda, 2019), we therefore propose that this new public health measure of malaria transmission should be operationalized in the assessment of the path from control to elimination for malaria transmission in a particular community as (a) an indicator of community's level of infectiousness and transmission probability of malaria to humans, (b) a measure of the effectiveness of malaria interventions targeted at the mosquito vector, and (c) a proximal marker of malaria incidence among mosquitoes and their potential to propagate malaria to mosquito vectors.

Putting together all the various derivations and assumptions, the complete multiscale model for malaria transmission dynamics for human-to-human or mosquito-to-mosquito is given by the following system of ordinary differential equation. Putting together all the various derivations and assumptions the multiscale model for malaria transmission dynamics from human to human or mosquito to mosquito is

given by the system of ordinary differential equations (2.5.11).

$$\left\{ \begin{array}{l} \frac{dS_H(t)}{dt} = \Lambda_H - \frac{\beta_V P_V}{P_0 + P_V} S_H(t) - \mu_H S_H(t) + \gamma_H I_H, \\ \frac{dI_H(t)}{dt} = \frac{\beta_V P_V}{P_0 + P_V} S_H(t) - (\mu_H + \gamma_H + \delta_H) I_H(t), \\ \frac{dS_p(s)}{ds} = \Lambda_p - \mu_s S_p(s), \\ \frac{dL_c(s)}{ds} = \Lambda_h - \beta_s S_p L_c(s) - \mu_L L_c(s), \\ \frac{dI_{Lc}(s)}{ds} = \beta_s S_p L_c(s) - (\alpha_L + \mu_{Lc}) I_{Lc}(s), \\ \frac{dS_b(s)}{ds} = \Lambda_b - (\beta_b M_b(s) + \beta_L M_p) S_b(s) - \mu_e S_b(s), \\ \frac{dI_{rb}(s)}{ds} = [(1 - \pi) \beta_b M_b(s) + \beta_L M_p(t)] S_b(s) - (\mu_{Ib} + \alpha_{Irb}) I_{rb}(s), \\ \frac{dM_{LB}(s)}{ds} = N_m \alpha_{mp} I_{Lc}(s) + N_b \alpha_{Irb} I_{rb}(s) - \mu_h M_{LB}(s), \\ \frac{dG_b(s)}{ds} = \pi \beta_b S_b(s) M_b(s) - (\alpha_o + \mu_b) G_b(s), \\ \frac{dG_H}{dt} = N_H \alpha_H I_H - \alpha_H G_H(t), \\ \frac{dS_V(t)}{dt} = \Lambda_V - \frac{\beta_H G_H}{G_0 + G_H} S_V(t) - \mu_V S_V, \\ \frac{dI_V(t)}{dt} = \frac{\beta_H G_H}{G_0 + G_H} S_V(t) - (\mu_v + \sigma_V) I_V, \\ \frac{dG_v(s)}{ds} = -(\alpha_g + \mu_g) G_v(s), \\ \frac{dG_m(s)}{ds} = N_g \alpha_g G_v - (\alpha_s + \mu_s) G_m(s), \\ \frac{dZ_v(s)}{ds} = \frac{1}{2} \alpha_s G_m - (\alpha_z + \mu_z) Z_v(s), \\ \frac{dO_v(s)}{ds} = \alpha_z Z_v(s) - (\alpha_k + \mu_k) Z_v(s), \\ \frac{dP_v(s)}{ds} = N_k \alpha_k O_v(s) - (\alpha_v + \mu_v) P_v(s), \\ \frac{dP_V}{dt} = N_V \alpha_V I_V - \alpha_V P_V(t). \end{array} \right. \quad (4.2.13)$$

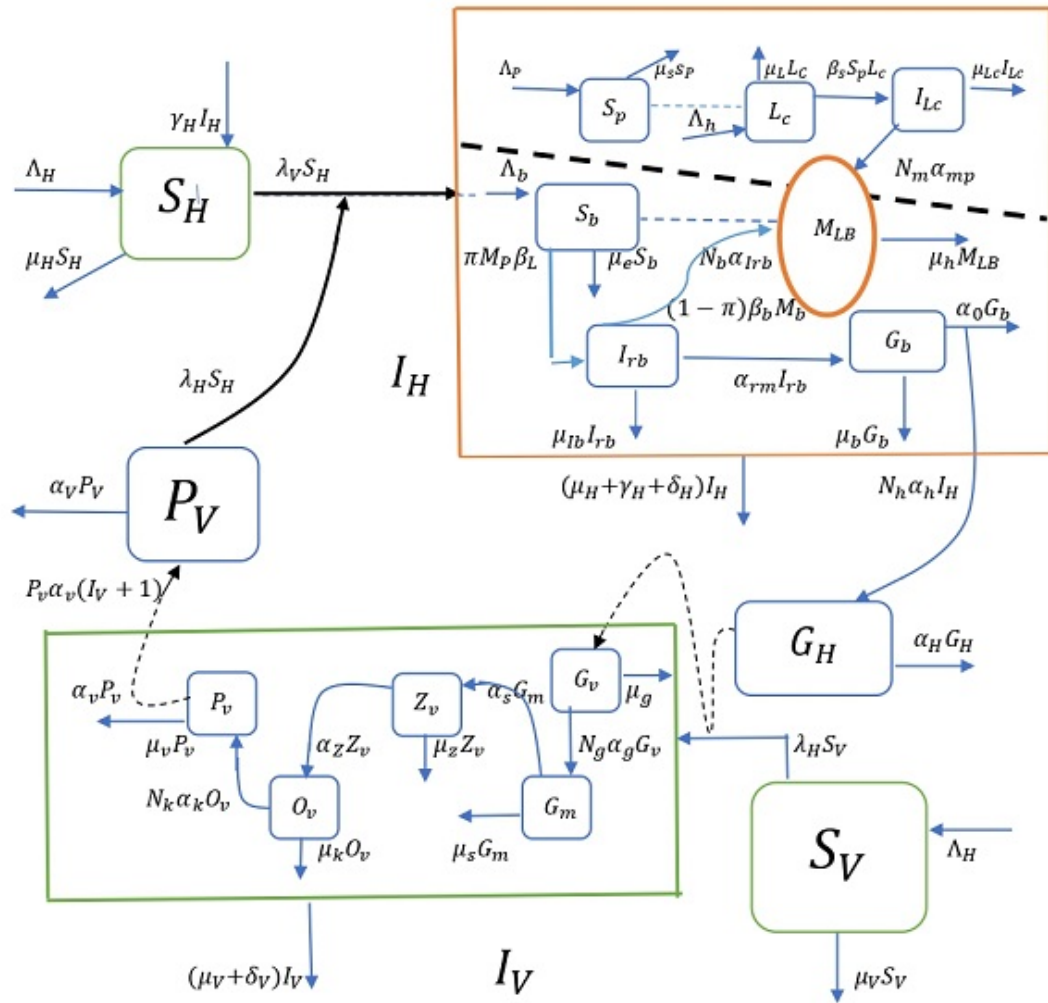


Figure 4.1: The compartmental framework of malaria transmission dynamics.

Because the nested and embedded multiscale models make up the connected multiscale model system (4.2.15), we simplify the model system (4.2.15) in the following section. Assuming that humans and mosquitoes are small, homogenous habitats within the community where sporozoites and gametocytes proliferate and develop into infectious entities, we generated the multiscale model system (4.2.15). We determined how pathogen population dynamics at the within-host scale scale up to the between-host scale by treating each host as a homogenous habitat. The aforementioned assumption bears little weight in terms of developing a modeling science base for vector-borne diseases that are directly transmitted, as opposed to one that already exists for diseases transmitted by the environment, in which the load of community pathogens in the environment is explicitly accounted for in the model (Garira et al., 2014; Netshikweta and Garira,

2007).

4.2.4 Simplification of the Multiscale malaria

The multiscale model system (4.2.15) is given with submodels within-Mosquito in terms of fast time scale (s) as compared to mosquito to human and human to mosquito submodels. The mosquito to human and human to mosquito are given at slow time scale (t), therefore we simplify this multiscale model by making a slow and fast time scale analysis to the system. Now we use ι as the constant highlighting the fast time scale of the within-mosquito submodels, ([Garira \(2017\)](#)).

$$\left\{ \begin{array}{l} \iota \frac{dG_v(s)}{ds} = -(\alpha_g + \mu_g)G_v(s), \\ \iota \frac{dG_m(s)}{ds} = N_g \alpha_g G_v - (\alpha_s + \mu_s)G_m(s), \\ \iota \frac{dZ_v(s)}{ds} = \frac{1}{2} \alpha_s G_m - (\alpha_z + \mu_z)Z_v(s), \\ \iota \frac{dO_v(s)}{ds} = \alpha_z Z_v(s) - (\alpha_k + \mu_k)Z_v(s), \\ \iota \frac{dP_v(s)}{ds} = N_k \alpha_k O_v(s) - (\alpha_v + \mu_v)P_v(s), \\ \iota \frac{dP_V}{dt} = N_V \alpha_V I_V - \alpha_V P_V(t). \end{array} \right. \quad (4.2.14)$$

where $t = \iota S$, so that the within mosquito malaria transmission dynamics submodels can be written in terms of the slow time scale.

$$\left\{ \begin{array}{l} \frac{dS_H(t)}{dt} = \Lambda_H - \frac{\beta_V P_V}{P_0 + P_V} S_H(t) - \mu_H S_H(t) + \gamma_H I_H, \\ \frac{dI_H(t)}{dt} = \frac{\beta_V P_V}{P_0 + P_V} S_H(t) - (\mu_H + \gamma_H + \delta_H) I_H(t), \\ \frac{dG_H}{dt} = N_h \alpha_H I_H - \alpha_H G_H(t), \\ \frac{dS_V(t)}{dt} = \Lambda_V - \frac{\beta_H G_H}{G_0 + G_H} S_V(t) - \mu_V S_V, \\ \frac{dI_V(t)}{dt} = \frac{\beta_H G_H}{G_0 + G_H} S_V(t) - (\mu_v + \sigma_V) I_V, \\ \frac{dG_v(t)}{dt} = -(\alpha_g + \mu_g) G_v(t), \\ \frac{dG_m(t)}{dt} = N_g \alpha_g G_v - (\alpha_s + \mu_s) G_m(t), \\ \frac{dZ_v(t)}{dt} = \frac{1}{2} \alpha_s G_m - (\alpha_z + \mu_z) Z_v(t), \\ \frac{dO_v(t)}{dt} = \alpha_z Z_v(t) - (\alpha_k + \mu_k) Z_v(t), \\ \frac{dP_v(s)}{dt} = N_k \alpha_k O_v(t) - (\alpha_v + \mu_v) P_v(t), \\ \frac{dP_V(t)}{dt} = N_V \alpha_V I_V - \alpha_V P_V(t). \end{array} \right. \quad (4.2.15)$$

Where

$$N_h = G_b = \frac{\beta_L N_m \alpha_h \beta_s \Lambda_p \Lambda_h + (1 - \pi) \beta_b \Lambda_p}{\mu_s (\alpha_{mp} + \mu_c) (\alpha_L + \mu_{Lc}) (\beta_b \Lambda_p + \mu_L \mu_s) (\alpha_o + \mu_b)} \quad (4.2.16)$$

and the reproductive number of the within an infected human is given below:

$$R_0 = \frac{\beta_L N_m \alpha_h \beta_s \Lambda_p \Lambda_h + (1 - \pi) \beta_b \Lambda_p}{\mu_s (\alpha_{mp} + \mu_c) (\alpha_L + \mu_{Lc}) (\beta_b \Lambda_p + \mu_L \mu_s) (\alpha_o + \mu_b)} \quad (4.2.17)$$

4.2.5 The Feasible region of the equilibrium state of the model

For feasible region, all the parameters and the state variables for the model system (4.2.17) are assumed to be positives to be consistent with human and mosquito population and can be determined that all positive solutions with initial conditions remain closed and positive. Now $N_H = S_H + I_H$ which gives

$$\frac{N_H}{dt} \leq \Lambda_H - \mu_H N_H \quad (4.2.18)$$

so that,

$$\lim_{t \rightarrow \infty} \sup(N_H(t)) \leq \frac{\Lambda_H}{\mu_H} \quad (4.2.19)$$

and now using the same method, we let $N_V = S_V + I_V$, therefore:

$$\frac{N_V}{dt} \leq \Lambda_V - \mu_V N_V \quad (4.2.20)$$

so that,

$$\lim_{t \rightarrow \infty} \sup(N_V(t)) \leq \frac{\Lambda_V}{\mu_V} \quad (4.2.21)$$

Now considering the sixth equation of the model system (4.2.17), we have:

$$\frac{dG_v(t)}{dt} = -(\alpha_g + \mu_g)G_v(t), \quad (4.2.22)$$

which is true when

$$\frac{dG_v(t)}{dt} \geq -(\alpha_g + \mu_g)G_v(t),$$

so that

$$\frac{dG_v(s)}{G_v} = -(\alpha_g + \mu_g)ds.$$

by letting,

$$S = \sup(s) \geq 0 : G_v > 0, G_m > 0, Z_v > 0, O_v > 0, P_v > 0 \in [0, s].$$

Now we integrate inequality of equation (3.5.14), we thus have:

$$\ln(G_v) \geq -(\alpha_g + \mu_g) + \int_0^s e^{-(\alpha_g + \mu_g)} ds + \ln(G_v(0)).$$

hence,

$$G_v(s) \geq G_v(0) \cdot \exp\{-(\alpha_g + \mu_g) + \int_0^s e^{-(\alpha_g + \mu_g)} dt\} > 0.$$

similarly, it can be shown that solution of $G_m > 0, Z_v > 0, O_v > 0$ and $P_v > 0$ for all $t \geq 0$. We can clearly see that, similar expressions can be attained for the

remaining models variables. We therefore able to express that all feasible solutions of the model system (4.2.17) are positive and eventually enter the invariant attracting region.

$$\Omega = (S_H, I_H, G_H, S_V, I_V, G_v, G_m, Z_v, O_v, P_v, P_V) \quad (4.2.23)$$

where

$$\begin{aligned} 0 &\leq S_H + I_H \leq \frac{\Lambda_H}{\mu_H}, \\ 0 &\leq S_V + I_V \leq \frac{\Lambda_V}{\mu_V}, \\ 0 &\leq G_H \leq \frac{N_h \alpha_h \Lambda_H}{\alpha_H \mu_H}, \\ 0 &\leq G_v \leq G_v(0) e^{-(\alpha_g + \mu_g)} \frac{1}{\psi V} \frac{N_h \alpha_h \Lambda_H}{G_0 \mu_H \alpha_H + N_h \alpha_h \Lambda_H} \frac{\beta_H(\mu_V - \mu_V)}{\Lambda_V + \mu_V}, \\ 0 &\leq G_m \leq G_v(0) e^{-(\alpha_g + \mu_g)(s)} \cdot \frac{N_g \alpha_g}{\alpha_s + \mu_s} \frac{N_h \alpha_h \Lambda_H}{G_0 \mu_H \alpha_H + N_h \alpha_h \Lambda_H} \frac{\beta_H(\mu_V - \mu_V)}{\Lambda_V + \mu_V}, \\ 0 &\leq Z_v \leq \frac{G_v(0) e^{-(\alpha_g + \mu_g)(s)}}{2} \cdot (\vartheta_1) \frac{N_h \alpha_h \Lambda_H}{G_0 \mu_H \alpha_H + N_h \alpha_h \Lambda_H} \frac{\beta_H(\mu_V - \mu_V)}{\Lambda_V + \mu_V}, \\ 0 &\leq O_v \leq \frac{G_v(0) e^{-(\alpha_g + \mu_g)(s)}}{2} \cdot (\vartheta_2) \frac{N_h \alpha_h \Lambda_H}{G_0 \mu_H \alpha_H + N_h \alpha_h \Lambda_H} \frac{\beta_H(\mu_V - \mu_V)}{\Lambda_V + \mu_V}, \\ 0 &\leq P_v \leq \frac{1}{2} \cdot \frac{G_v(0) e^{-(\alpha_g + \mu_g)(s)}}{\alpha_v + \mu_v} \cdot (\vartheta_3) \frac{N_h \alpha_h \Lambda_H}{G_0 \mu_H \alpha_H + N_h \alpha_h \Lambda_H} \frac{\beta_H(\mu_V - \mu_V)}{\Lambda_V + \mu_V}, \\ 0 &\leq P_V \leq \frac{1}{2} \cdot \frac{G_v(0) e^{-(\alpha_g + \mu_g)(t)}}{\alpha_v + \mu_v} \cdot (\vartheta_4) \frac{N_h \alpha_h \Lambda_H}{G_0 \mu_H \alpha_H + N_h \alpha_h \Lambda_H} \frac{\beta_H(\mu_V - \mu_V)}{\Lambda_V + \mu_V}. \end{aligned} \quad (4.2.24)$$

Where, $\vartheta_1 = \frac{1}{\alpha_z + \mu_z} \cdot \frac{\alpha_s}{\alpha_s + \mu_s} \cdot \frac{N_g \alpha_g}{\alpha_g + \mu_g}$, $\vartheta_2 = \frac{1}{\alpha_k + \mu_k} \cdot \frac{\alpha_z}{\alpha_z + \mu_z} \cdot \frac{\alpha_s}{\alpha_s + \mu_s} \cdot \frac{N_g \alpha_g}{\alpha_g + \mu_g}$, $\vartheta_3 = \frac{N_k \alpha_k}{\alpha_k + \mu_k} \cdot \frac{\alpha_z}{\alpha_z + \mu_z} \cdot \frac{\alpha_s}{\alpha_s + \mu_s} \cdot \frac{N_g \alpha_g}{\alpha_g + \mu_g}$, $\vartheta_4 = \frac{N_k \alpha_k}{\alpha_k + \mu_k} \cdot \frac{\alpha_z}{\alpha_z + \mu_z} \cdot \frac{\alpha_s}{\alpha_s + \mu_s} \cdot \frac{\alpha_v}{\alpha_v + \mu_v} \cdot \frac{N_g \alpha_g}{\alpha_g + \mu_g}$.

for $\Lambda_V > \mu_V$ which implies that Ω is positively invariant. It is sufficient to consider the dynamics of the flow generated by the model system (4.2.17) in the invariant region. This means that, every solution of the multiscale model system (4.2.17) with initial condition in Ω remain in Ω for all $t > 0$.

4.2.6 The reproductive number

The malaria multiscale model system (4.2.17) reproduction number denoted by R_0 is computed using the technique of the next generation operator. We consider $I_H, I_V, G_v, G_m, Z_v, O_v, P_v$ as the parasite infested compartments. We then write

the model system in the form

$$\begin{cases} \frac{dX}{dt} = f(X, Y, Z) \\ \frac{dY}{dt} = g(X, Y, Z) \\ \frac{dZ}{dt} = h(X, Y, Z) \end{cases} \quad (4.2.25)$$

where

$$\begin{cases} X = (S_H, S_V) \\ Y = (I_H, I_V, G_v, G_m, Z_v, O_v, P_v) \\ Z = (P_V, G_H) \end{cases} \quad (4.2.26)$$

Components of X denote the susceptible components, Y denote, the infected but not infectious componets and Z denote the infectious component responsible for transmitting the malaria. We define $\hat{g}(X^*, Z)$ by

$$\hat{g}(X^*, Z) = \hat{g}_1(X^*, Z), \hat{g}_2(X^*, Z), \hat{g}_3(X^*, Z), \hat{g}_4(X^*, Z), \hat{g}_5(X^*, Z), \hat{g}_6(X^*, Z), \hat{g}_7(X^*, Z)$$

with

$$\begin{aligned} \hat{g}_1(X^*, Z) &= \frac{1}{\mu_H + \gamma_H + \delta_H} \frac{\beta_V \Lambda_H}{\mu_H} \frac{P_V}{P_0 + P_V}, \\ \hat{g}_2(X^*, Z) &= \frac{1}{\mu_V + \delta_V} \frac{\beta_H \Lambda_V}{\mu_V} \frac{G_H}{G_0 + G_H}, \\ \hat{g}_3(X^*, Z) &= G_v(0) e^{(\alpha_g + \mu_g)} \frac{1}{\psi V} \frac{\beta_H(\mu_V - \mu_V)}{\Lambda_V + \mu_V} \frac{1}{I_V + 1} \frac{G_H}{G_0 + G_H}, \\ \hat{g}_4(X^*, Z) &= \frac{N_g \alpha_g}{\alpha_s + \mu_s} \cdot G_v(0) e^{(\alpha_g + \mu_g)} \frac{1}{\psi V} \frac{\beta_H(\mu_V - \mu_V)}{\Lambda_V + \mu_V} \frac{1}{I_V + 1} \frac{G_H}{G_0 + G_H}, \\ \hat{g}_5(X^*, Z) &= \frac{1}{2} \frac{N_g \alpha_g}{\alpha_s + \mu_s} \cdot G_v(0) e^{(\alpha_g + \mu_g)} \frac{\alpha_s}{\alpha_z + \mu_z} \cdot \frac{1}{\psi V} \frac{\beta_H(\mu_V - \mu_V)}{\Lambda_V + \mu_V} \frac{1}{I_V + 1} \frac{G_H}{G_0 + G_H}, \\ \hat{g}_6(X^*, Z) &= \frac{1}{2} \frac{N_g \alpha_g}{\alpha_s + \mu_s} \cdot G_v(0) e^{(\alpha_g + \mu_g)} \frac{\alpha_s}{\alpha_z + \mu_z} \cdot \frac{\alpha_z}{\alpha_z + \mu_z} \frac{1}{\alpha_k + \mu_k} \cdot \frac{1}{\psi V} \frac{\beta_H(\mu_V - \mu_V)}{\Lambda_V + \mu_V} \frac{1}{I_V + 1} \frac{G_H}{G_0 + G_H}, \\ \hat{g}_7(X^*, Z) &= \frac{1}{2} \frac{N_g \alpha_g}{\alpha_s + \mu_s} \cdot G_v(0) e^{(\alpha_g + \mu_g)} \cdot (\Phi_2) \cdot \frac{1}{\psi V} \frac{\beta_H(\mu_V - \mu_V)}{\Lambda_V + \mu_V} \frac{1}{I_V + 1} \frac{G_H}{G_0 + G_H}, \end{aligned} \quad (4.2.27)$$

$$\text{where, } \Phi_2 = \frac{\alpha_s}{\alpha_z + \mu_z} \cdot \frac{\alpha_z}{\alpha_z + \mu_z} \frac{N_k \alpha_k}{\alpha_k + \mu_k} \frac{1}{\alpha_v + \mu_v}.$$

and now we consider the $\frac{dP_V}{dt}$ and $\frac{dG_H}{dt}$ the let $w_1 = \frac{dP_V}{dt}$, $w_2 = \frac{dG_H}{dt}$ and now by substituting the values of $I_H, I_V, G_v, G_m, Z_v, O_v, P_v$ we get,

$$\begin{cases} w_1 = \frac{1}{2} \frac{N_g \alpha_g}{\alpha_s + \mu_s} \cdot G_v(0) e^{(\alpha_g + \mu_g)} \cdot (\Phi_2) \cdot \frac{1}{\psi V} \frac{\beta_H(\mu_V - \mu_V)}{\Lambda_V + \mu_V} \frac{1}{I_V + 1} \frac{G_H}{G_0 + G_H} - \alpha_V P_V, \\ w_2 = \frac{N_h \alpha_h}{\mu_H + \gamma_H + \delta_H} \frac{\beta_V \Lambda_H}{\mu_H} \frac{G_H}{G_0 + G_H} - \alpha_H G_H. \end{cases} \quad (4.2.28)$$

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

$$A = \begin{pmatrix} \frac{\partial w_1}{\partial P^V} & \frac{\partial w_1}{\partial G^H} \\ \frac{\partial w_2}{\partial P^V} & \frac{\partial w_2}{\partial G^H} \end{pmatrix},$$

then, $A = \begin{pmatrix} \alpha_V & \frac{1}{2} \omega \frac{N_g \alpha_g}{\alpha_s + \mu_s} \cdot \frac{\alpha_s}{\alpha_z + \mu_z} \cdot \frac{\alpha_z}{\alpha_z + \mu_z} \frac{N_k \alpha_k}{\alpha_k + \mu_k} \frac{\alpha_v}{\alpha_v + \mu_v} \cdot \phi \\ \frac{N_h \alpha_h}{\mu_H + \gamma_H + \delta_H} \frac{\beta_V \Lambda_H}{\mu_H} \frac{G_H}{G_0 + G_H} & \alpha_H \end{pmatrix}$,
 where,

$$\omega = G_v(0) \varrho^{(\alpha_g + \mu_g)} \text{ and } \phi = \frac{1}{\psi V} \frac{\beta_H(\mu_V - \mu_V)}{\Lambda_V + \mu_V} \frac{1}{I_V + 1} \frac{G_H}{G_0 + G_H}$$

We deduce matrix M and D to be

$$M = \begin{pmatrix} 0 & \frac{1}{2} \omega \frac{N_g \alpha_g}{\alpha_s + \mu_s} \cdot \frac{\alpha_s}{\alpha_z + \mu_z} \cdot \frac{\alpha_z}{\alpha_z + \mu_z} \frac{N_k \alpha_k}{\alpha_k + \mu_k} \frac{\alpha_v}{\alpha_v + \mu_v} \cdot \phi \\ \frac{N_h \alpha_h}{\mu_H + \gamma_H + \delta_H} \frac{\beta_V \Lambda_H}{\mu_H} \frac{G_H}{G_0 + G_H} & 0 \end{pmatrix},$$

$$\text{and } D = \begin{pmatrix} \alpha_V & 0 \\ 0 & \alpha_H \end{pmatrix},$$

$$\text{which implies that } D^{-1} = \begin{pmatrix} \frac{1}{\alpha_V} & 0 \\ 0 & \frac{1}{\alpha_H} \end{pmatrix}.$$

The basic reproduction number is given by the spectral radius of the matrix MD^{-1} , which is $R_0 = \Delta(MD^{-1})$ then

$$R_0 = \sqrt{\left(\frac{1}{2} \omega \frac{N_g \alpha_g}{\alpha_s + \mu_s} \cdot \frac{\alpha_s}{\alpha_z + \mu_z} \cdot \frac{\alpha_z}{\alpha_z + \mu_z} \frac{N_k \alpha_k}{\alpha_k + \mu_k} \frac{\alpha_v}{\alpha_v + \mu_v} \cdot \phi \right) \cdot \left(\frac{N_h \alpha_h}{\mu_H + \gamma_H + \delta_H} \frac{\beta_V \Lambda_H}{\mu_H} \frac{G_H}{G_0 + G_H} \right)} \quad (4.2.29)$$

$$J(E^0) = \begin{pmatrix} -\mu_H & \gamma_H & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -k_1 \\ 0 & -b_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & k_1 \\ 0 & N_h\alpha_h & -\alpha_H & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -k_2 & -\mu_V & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & k_2 & 0 & -b_2 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & b_3 & 0 & 0 & -b_4 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & N_g\alpha_g & -d_5 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \frac{1}{2}\alpha_s & -d_6 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -d_7 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & N_k\alpha_k & -d_8 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \alpha_v & -\alpha_V \end{pmatrix} \quad (4.2.30)$$

where

$$k_1 = \frac{\beta_V \Lambda_H}{\mu_H P_0}, k_2 = \frac{\beta_H \Lambda_V}{\mu_V G_0}, b_1 = (\mu_H + \gamma_H + \delta_H), b_2 = (\delta_V + \mu_V), b_3 = \frac{\beta_H (\Lambda_V - \mu_V)}{\mu_V \psi G_0}, b_4 = G_v(0) \varrho^{(\alpha_g + \mu_g)}, b_5 = \alpha_s + \mu_s, b_6 = \alpha_z + \mu_z, b_7 = \alpha_k + \mu_k \text{ and } b_8 = \alpha_v + \mu_v.$$

The disease free equilibrium state is locally asymptotically stable if and only if all the the roots of the characteristic equation are negative or have negative real parts. hence,

$$\lambda_1 = -\mu_H, \lambda_2 = -\alpha_V, \lambda_3 = -G_v(0) \varrho^{(\alpha_g + \mu_g)}, \lambda_4 = -(\alpha_k + \mu_k), \lambda_5 = -(\alpha_s + \mu_s), \lambda_6 = -(\alpha_v + \mu_v), \lambda_7 = -(\delta_V + \mu_V), \lambda_8 = -\mu_V, \lambda_9 = -(\alpha_z + \mu_z), \lambda_{10} = -\frac{1}{2}[(2\mu_H + \gamma_H + \delta_H) + \sqrt{(\mu_H + \gamma_H + \delta_H)^2 - 4\mu_H(\mu_H + \gamma_H + \delta_H)}]$$

Therefore, all the eigenvalues of the jacobian matrix $J(E^0)$ are negative when $R_0 < 1$, then it means that E^0 is locally asymptotically stable when $R_0 < 1$

4.2.7 The Endemic Equilibrium state

In order to determine the endemic equilibrium state of the model system (4.2.17), we solve the equations of the sub-model system (4.2.17) using the integrating factor theorem, and intergrate them into a single differential equation. then we let $\alpha_g + \mu_g = \lambda_g$ on the first equation of the sub-model system (3.5.13)

$$\begin{aligned} \frac{dG_v(s)}{ds} &= -(\alpha_g + \mu_g)G_v(t), \\ \frac{dG_v(t)}{dt} &= -\lambda_g G_v(t), \\ G_v &= G_v(0)e^{-(\alpha_g + \mu_g)t} \end{aligned} \quad (4.2.31)$$

now considering the second equation, with the intergrating factor $e^{(\alpha_s + \mu_s)t}$

$$\begin{aligned}
 \frac{dG_m(t)}{dt} &= N_g \alpha_g G_v - (\alpha_s + \mu_s) G_m(t), \\
 \frac{dG_m(t)}{dt} + (\alpha_s + \mu_s) G_m &= N_g \alpha_g G_v(s), \\
 e^{(\alpha_s + \mu_s)t} \frac{dG_m}{ds} + G_m(s)(\alpha_s + \mu_s) e^{(\alpha_s + \mu_s)t} &= N_g \alpha_g G_v e^{(\alpha_s + \mu_s)s} \\
 \int_0^t \frac{d}{dt} (G_m e^{(\alpha_s + \mu_s)t}) dt &= N_g \alpha_g G_v(0) \int_0^t e^{(\alpha_s + \mu_s + \alpha_s + \mu_s)t} dt \\
 G_m &= \frac{N_g \alpha_g G_v(0)}{[(\alpha_s + \mu_s) - (\alpha_g + \mu_g)]} \cdot e^{-(\alpha_g + \mu_g)} \\
 &+ \frac{[(\alpha_s + \mu_s) - (\alpha_g + \mu_g)] G_m(0) - N_g \alpha_g G_v(0)}{[(\alpha_s + \mu_s) - (\alpha_g + \mu_g)]} \cdot e^{-(\alpha_s + \mu_s)t}.
 \end{aligned} \tag{4.2.32}$$

The third equation will be:

$$\begin{aligned}
 Z_v &= \frac{\frac{1}{2} \alpha_s}{[(\alpha_s + \mu_s) - (\alpha_g + \mu_g)]} e^{-(\alpha_g + \mu_g)} \left(\frac{N_g \alpha_g G_v(0)}{[(\alpha_s + \mu_s) - (\alpha_g + \mu_g)]} \cdot e^{-(\alpha_g + \mu_g)} \right. \\
 &+ \left. \frac{[(\alpha_s + \mu_s) - (\alpha_g + \mu_g)] G_m(0) - N_g \alpha_g G_v(0)}{[(\alpha_s + \mu_s) - (\alpha_g + \mu_g)]} \cdot e^{-(\alpha_s + \mu_s)t} \right) \\
 &+ Z_v(0) - \frac{\frac{1}{2} \alpha_s}{[(\alpha_s + \mu_s) - (\alpha_g + \mu_g)]} \left(\frac{N_g \alpha_g G_v(0)}{[(\alpha_s + \mu_s) - (\alpha_g + \mu_g)]} \right. \\
 &+ \left. \frac{[(\alpha_s + \mu_s) - (\alpha_g + \mu_g)] G_m(0) - N_g \alpha_g G_v(0)}{[(\alpha_s + \mu_s) - (\alpha_g + \mu_g)]} \right) \cdot e^{-(\alpha_s + \mu_s)t}
 \end{aligned}$$

The forth equation will be:

$$\begin{aligned}
 O_v = & \frac{\frac{1}{2}\alpha_s\alpha_z}{[(\alpha_s + \mu_s) - (\alpha_g + \mu_g)]} \left(\frac{N_g\alpha_g G_v(0)}{[(\alpha_z + \mu_z) - (\alpha_g + \mu_g)][(\alpha_k + \mu_k) - (\alpha_g + \mu_g)]} \cdot e^{-(\alpha_g + \mu_g)t} \right. \\
 & + \frac{[(\alpha_s + \mu_s) - (\alpha_g + \mu_g)]G_m(0) - N_g\alpha_g G_v(0)}{[(\alpha_z + \mu_z) - (\alpha_s + \mu_s)][(\alpha_k + \mu_k) - (\alpha_s + \mu_s)]} \cdot e^{-(\alpha_s + \mu_s)t} + \frac{1}{[(\alpha_k + \mu_k) - (\alpha_z + \mu_z)]} \\
 & + \left(Z_v(0) - \frac{\frac{1}{2}\alpha_z\alpha_s}{[(\alpha_s + \mu_s) - (\alpha_g + \mu_g)]} \left(\frac{N_g\alpha_g G_v(0)}{[(\alpha_z + \mu_z) - (\alpha_g + \mu_g)]} \right) \right. \\
 & + \left. \frac{[(\alpha_s + \mu_s) - (\alpha_g + \mu_g)]G_m(0) - N_g\alpha_g G_v(0)}{[(\alpha_s + \mu_s) - (\alpha_g + \mu_g)]} \right) \cdot e^{-(\alpha_s + \mu_s)t} \\
 & + \left(O_v(0) - \frac{\frac{1}{2}\alpha_z\alpha_s}{[(\alpha_s + \mu_s) - (\alpha_g + \mu_g)]} \left(\frac{N_g\alpha_g G_v(0)}{[(\alpha_z + \mu_z) - (\alpha_g + \mu_g)][(\alpha_k + \mu_k) - (\alpha_z + \mu_z)]} \right) \right) \\
 & + \frac{[(\alpha_s + \mu_s) - (\alpha_g + \mu_g)]G_m(0) - N_g\alpha_g G_v(0)}{[(\alpha_z + \mu_z) - (\alpha_s + \mu_s)][(\alpha_k + \mu_k) - (\alpha_s + \mu_s)]} \cdot e^{-(\alpha_s + \mu_s)t} + \frac{1}{[(\alpha_k + \mu_k) - (\alpha_z + \mu_z)]} \\
 & + \frac{1}{[(\alpha_k + \mu_k) - (\alpha_z + \mu_z)]} \left(Z_v(0) - \frac{\frac{1}{2}\alpha_z\alpha_s}{[(\alpha_s + \mu_s) - (\alpha_g + \mu_g)]} \left(\frac{N_g\alpha_g G_v(0)}{[(\alpha_z + \mu_z) - (\alpha_g + \mu_g)]} \right) \right)
 \end{aligned}$$

The fifth equation will be:

$$\begin{aligned}
 P_v = & \frac{\frac{1}{2}N_k\alpha_k\alpha_s\alpha_z}{[(\alpha_s + \mu_s) - (\alpha_g + \mu_g)]} \left(\frac{N_g\alpha_g G_v(0)}{[(\alpha_z + \mu_z) - (\alpha_g + \mu_g)][(\alpha_k + \mu_k) - (\alpha_g + \mu_g)]} \cdot e^{-(\alpha_g + \mu_g)t} \right. \\
 & + \frac{[(\alpha_s + \mu_s) - (\alpha_g + \mu_g)]G_m(0) - N_g\alpha_g G_v(0)}{[(\alpha_z + \mu_z) - (\alpha_s + \mu_s)][(\alpha_k + \mu_k) - (\alpha_s + \mu_s)]} \cdot e^{-(\alpha_s + \mu_s)t} \\
 & + \frac{1}{[(\alpha_k + \mu_k) - (\alpha_z + \mu_z)][(\alpha_v + \mu_v) - (\alpha_z + \mu_z)]} \\
 & + \left(Z_v(0) - \frac{\frac{1}{2}\alpha_z\alpha_s}{[(\alpha_s + \mu_s) - (\alpha_g + \mu_g)]} \left(\frac{N_g\alpha_g G_v(0)}{[(\alpha_z + \mu_z) - (\alpha_g + \mu_g)]} \right) \right. \\
 & + \left. \frac{[(\alpha_s + \mu_s) - (\alpha_g + \mu_g)]G_m(0) - N_g\alpha_g G_v(0)}{[(\alpha_s + \mu_s) - (\alpha_g + \mu_g)]} \cdot e^{-(\alpha_s + \mu_s)t} \right. \\
 & + \left(O_v(0) - \frac{\frac{1}{2}\alpha_z\alpha_s}{[(\alpha_s + \mu_s) - (\alpha_g + \mu_g)]} \left(\frac{N_g\alpha_g G_v(0)}{[(\alpha_z + \mu_z) - (\alpha_g + \mu_g)][(\alpha_k + \mu_k) - (\alpha_z + \mu_z)]} \right) \right. \\
 & + \left. \frac{[(\alpha_s + \mu_s) - (\alpha_g + \mu_g)]G_m(0) - N_g\alpha_g G_v(0)}{[(\alpha_z + \mu_z) - (\alpha_s + \mu_s)][(\alpha_k + \mu_k) - (\alpha_s + \mu_s)]} \cdot e^{-(\alpha_s + \mu_s)t} + \frac{1}{[(\alpha_k + \mu_k) - (\alpha_z + \mu_z)]} \right. \\
 & + \left. \frac{1}{[(\alpha_k + \mu_k) - (\alpha_z + \mu_z)][(\alpha_v + \mu_v) - (\alpha_z + \mu_z)]} \right) (Z_v(0) \\
 & - \frac{\frac{1}{2}\alpha_z\alpha_s}{[(\alpha_s + \mu_s) - (\alpha_g + \mu_g)]} \left(\frac{N_g\alpha_g G_v(0)}{[(\alpha_z + \mu_z) - (\alpha_g + \mu_g)]} \right)) \\
 & + \left(P_v(0) - \frac{\frac{1}{2}N_k\alpha_k\alpha_s\alpha_z}{[(\alpha_s + \mu_s) - (\alpha_g + \mu_g)]} \left(\frac{N_g\alpha_g G_v(0)}{[(\alpha_z + \mu_z) - (\alpha_g + \mu_g)][(\alpha_k + \mu_k) - (\alpha_g + \mu_g)]} \cdot e^{-(\alpha_g + \mu_g)t} \right. \right. \\
 & + \frac{[(\alpha_s + \mu_s) - (\alpha_g + \mu_g)]G_m(0) - N_g\alpha_g G_v(0)}{[(\alpha_z + \mu_z) - (\alpha_s + \mu_s)][(\alpha_k + \mu_k) - (\alpha_s + \mu_s)]} \cdot e^{-(\alpha_s + \mu_s)t} \\
 & + \frac{1}{[(\alpha_k + \mu_k) - (\alpha_z + \mu_z)][(\alpha_v + \mu_v) - (\alpha_z + \mu_z)]} \\
 & + \left(Z_v(0) - \frac{\frac{1}{2}\alpha_z\alpha_s}{[(\alpha_s + \mu_s) - (\alpha_g + \mu_g)]} \left(\frac{N_g\alpha_g G_v(0)}{[(\alpha_z + \mu_z) - (\alpha_g + \mu_g)]} \right) \right. \\
 & + \left. \frac{[(\alpha_s + \mu_s) - (\alpha_g + \mu_g)]G_m(0) - N_g\alpha_g G_v(0)}{[(\alpha_s + \mu_s) - (\alpha_g + \mu_g)]} \cdot e^{-(\alpha_s + \mu_s)t} \right. \\
 & + \left(O_v(0) - \frac{\frac{1}{2}\alpha_z\alpha_s}{[(\alpha_s + \mu_s) - (\alpha_g + \mu_g)]} \left(\frac{N_g\alpha_g G_v(0)}{[(\alpha_z + \mu_z) - (\alpha_g + \mu_g)][(\alpha_k + \mu_k) - (\alpha_z + \mu_z)]} \right) \right. \\
 & + \left. \frac{[(\alpha_s + \mu_s) - (\alpha_g + \mu_g)]G_m(0) - N_g\alpha_g G_v(0)}{[(\alpha_z + \mu_z) - (\alpha_s + \mu_s)][(\alpha_k + \mu_k) - (\alpha_s + \mu_s)]} \cdot e^{-(\alpha_s + \mu_s)t} + \frac{1}{[(\alpha_k + \mu_k) - (\alpha_z + \mu_z)]} \right. \\
 & + \left. \frac{1}{[(\alpha_k + \mu_k) - (\alpha_z + \mu_z)][(\alpha_v + \mu_v) - (\alpha_z + \mu_z)]} \right) (Z_v(0) \\
 & - \frac{\frac{1}{2}\alpha_z\alpha_s}{[(\alpha_s + \mu_s) - (\alpha_g + \mu_g)]} \left(\frac{N_g\alpha_g G_v(0)}{[(\alpha_z + \mu_z) - (\alpha_g + \mu_g)]} \right)) \\
 & - \frac{\frac{1}{2}\alpha_z\alpha_s}{[(\alpha_s + \mu_s) - (\alpha_g + \mu_g)]} \left(\frac{N_g\alpha_g G_v(0)}{[(\alpha_z + \mu_z) - (\alpha_g + \mu_g)]} \right))
 \end{aligned}$$

(4.2.33)

The equilibrium point of the model system (4.2.17) is obtained by setting the right-hand side of the equations to zero. We obtained the following.

$$\left\{ \begin{array}{l} \hat{S}_H = \frac{\Lambda_H(\delta_H + \gamma_H + \mu_H)(P_0 + \hat{P}_V)}{j_1(P_0 + P_V) + j_2\hat{P}_V}, \\ \hat{I}_H = \frac{\beta_V\Lambda_H\hat{P}_V}{j_1(P_0 + P_V) + j_2\hat{P}_V} \\ \hat{S}_V = \frac{\Lambda_V[N_h\alpha_h\beta_V\Lambda_H\hat{P}_V + \alpha_HG_0[j_1(P_0 + P_V) + j_2\hat{P}_V]]}{N_h\alpha_h\beta_V\Lambda_H\hat{P}_V(\beta_H + \mu_V) + \mu_V\alpha_HG_0[j_1(P_0 + P_V) + j_2\hat{P}_V]}, \\ \hat{I}_V = \frac{N_h\alpha_h\beta_V\beta_H\Lambda_H\hat{P}_V}{(\mu_V + \delta_V)[N_h\alpha_h\beta_V\Lambda_H\hat{P}_V(\beta_H + \mu_V) + \mu_V\alpha_HG_0[j_1(P_0 + P_V) + j_2\hat{P}_V]]}, \\ \hat{G}_H = \frac{N_h\alpha_h\beta_V\hat{P}_V}{\alpha_H[j_1(P_0 + P_V) + j_2\hat{P}_V]}, \\ \hat{G}_v = \frac{\psi_0N_h\alpha_h\beta_V\beta_H\Lambda_H\hat{P}_V[j_1\alpha_HG_0P_0(\Lambda_V - \mu_V) + j_3\hat{P}_V]}{[j_4\hat{P}_V + j_1\alpha_HG_0P_0]\psi(\hat{I}_V + 1)\psi_1(j_5\hat{P}_V + j_1\mu_V\alpha_HG_0P_0)}, \\ \hat{G}_m = \frac{\psi_0N_g\alpha_gN_h\alpha_h\beta_V\beta_H\Lambda_H\hat{P}_V[j_1\alpha_HG_0P_0(\Lambda_V - \mu_V) + j_3\hat{P}_V]}{(\alpha_s + \mu_s)[j_4\hat{P}_V + j_1\alpha_HG_0P_0]\psi(\hat{I}_V + 1)\psi_1(j_5\hat{P}_V + j_1\mu_V\alpha_HG_0P_0)}, \\ \hat{Z}_v = \frac{\psi_0N_h\alpha_h\alpha_s\beta_V\beta_H\Lambda_H\hat{P}_V[j_3\hat{P}_V + j_1\alpha_HG_0P_0(\Lambda_V - \mu_V)]}{2(\alpha_s + \mu_s)(\alpha_z + \mu_z)[j_4\hat{P}_V + j_1\alpha_HG_0P_0]\psi(\hat{I}_V + 1)\psi_1(j_5\hat{P}_V + j_1\mu_V\alpha_HG_0P_0)}, \\ \hat{O}_v = \frac{\psi_0N_h\alpha_h\alpha_s\alpha_z\beta_V\beta_H\Lambda_H\hat{P}_V[j_3\hat{P}_V + j_1\alpha_HG_0P_0(\Lambda_V - \mu_V)]}{2(\alpha_k + \mu_k)(\alpha_s + \mu_s)(\alpha_z + \mu_z)[j_4\hat{P}_V + j_1\alpha_HG_0P_0]\psi(\hat{I}_V + 1)\psi_1(j_5\hat{P}_V + j_1\mu_V\alpha_HG_0P_0)}, \\ \hat{P}_v = \frac{y_1\hat{P}_V[j_3\hat{P}_V + j_1\alpha_HG_0P_0(\Lambda_V - \mu_V)]}{y_2(\hat{I}_V + 1)(j_5\hat{P}_V + j_1\mu_V\alpha_HG_0P_0)[j_4\hat{P}_V + j_1\alpha_HG_0P_0]}, \\ \hat{P}_V = \frac{y_1\alpha_v\hat{P}_V[j_3\hat{P}_V + j_1\alpha_HG_0P_0(\Lambda_V - \mu_V)]}{y_2\alpha_V(j_5\hat{P}_V + j_1\mu_V\alpha_HG_0P_0)[j_4\hat{P}_V + j_1\alpha_HG_0P_0]}, \\ = \frac{-\Delta_2 + \sqrt{\Delta_2^2 - 4\Delta_1\Delta_3}}{2(\Delta_1)}. \end{array} \right.$$

where

$$\left\{ \begin{array}{l} j_1 = \mu_H(\delta_H + \gamma_H + \mu_H), \\ j_2 = \beta_V(\delta_H + \mu_H), \\ j_3 = \alpha_H G_0(j_1 + j_2)(\Lambda_V - \mu_V) + N_h \alpha_h \beta_V \Lambda_H [\Lambda_V - (\beta_H + \mu_V)], \\ j_4 = N_h \alpha_h \beta_V \Lambda_H + \alpha_H G_0(j_1 + j_2), \\ j_5 = N_h \alpha_h \beta_V \Lambda_H (\beta_H + \mu_V) + \mu_V \alpha_H G_0(j_1 + j_2), \\ \psi_0 = (1 - e^{-(\alpha_g + \mu_g)t}) \frac{N_g \alpha_g}{(\alpha_s + \mu_s)} G_v(0) e^{-(\alpha_g + \mu_g)t}, \\ y_1 = \frac{1}{2} N_k \alpha_k N_g \alpha_g \alpha_s \alpha_z N_h \alpha_h \beta_H \beta_V \Lambda_H, \\ y_2 = \psi(\alpha_v + \mu_v)(\alpha_s + \mu_s)(\alpha_k + \alpha_k)(\alpha_g + \mu_g), \\ \Delta_1 = j_3 j_4 y_2 \alpha_V, \\ \Delta_2 = j_1 y_2 \alpha_H \alpha_V G_0 P_0 (\mu_V j_4 + j_5) - j_3 y_1 \alpha_v, \\ \Delta_3 = -j_1^2 \alpha_H^2 G_0^2 P_0^2 y_2 \alpha_V \mu_V [R_0 - 1]. \end{array} \right.$$

We now conclude that there exist a positive endemic equilibrium points when $R_0 > 1$, since: 1. $\hat{P}_V$ represents the non-feasible equilibrium point, $\hat{P}_V = 0$ if and only if $R_0 = 1, \Delta_1 > 0, \Delta_2 > 0, \Delta_3 = 0$

2. $\hat{P}_V < 0$ is not a positive equilibrium point because of Descartes rule of signs, there is no sign of change from the coefficients, when if and only if $R_0 < 1, \Delta_1 > 0, \Delta_2 > 0, \Delta_3 > 0$.

3. $\hat{P}_V > 0$ is a positive equilibrium point because of Descartes rule of signs, the coefficients Δ_2 could be positive or negative, $R_0 > 1, \Delta_1 > 0, \Delta_2 > 0, \Delta_3 < 0$.

4.2.8 Local Stability analysis of endemic equilibrium point

The endemic equilibrium state is given by:

$$E^* = (\hat{S}_H, \hat{I}_H, \hat{G}_H, \hat{S}_V, \hat{I}_V, \hat{G}_v, \hat{G}_m, \hat{Z}_v, \hat{O}_v, \hat{P}_v, \hat{P}_V). \quad (4.2.34)$$

The infected steady state exists when and only when $R_0 > 1$. Then will proof the following theorem.

Theorem 4.2 *The endemic equilibrium point E^* of the system (4.2.17) is locally asymptotically stable when $R_0 > 1$.*

Proof. The calculated jacobian matrix is given by:

$$J(E^0) = \begin{pmatrix} -q_1 & \gamma_H & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -a_1 \\ a_2 & -q_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_1 \\ 0 & N_h \alpha_h & -\alpha_H & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -q_3 & -q_4 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & q_3 & q_4 & -q_5 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & q_6 & q_7 & q_8 & -q_9 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & N_g \alpha_g & -q_{10} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \frac{1}{2} \alpha_s & -q_{11} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -q_{12} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & N_k \alpha_k & -q_{13} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \alpha_v & -\alpha_v \end{pmatrix} \quad (4.2.35)$$

where,

$$\begin{aligned} q_1 &= \mu_H + \frac{\beta_V \hat{P}_V}{P_0 + \hat{P}_V}, q_2 = (\delta_H + \gamma_H + \mu_H), q_3 = \frac{\beta_H G_0 \hat{S}_V}{(G_0 + \hat{G}_H)^2}, q_4 = \frac{\beta_H \hat{G}_H}{G_0 + \hat{G}_H} + \\ \mu_V, q_5 &= \frac{\beta_H \hat{G}_H}{G_0 + \hat{G}_H}, q_6 = \frac{\beta_H G_0 (\hat{S}_V - 1)}{(G_0 + \hat{G}_H)^2 \psi_V (\hat{I}_V + 1)}, q_7 = \frac{\beta_H \hat{G}_H}{(G_0 + \hat{G}_H) \psi_V (\hat{I}_V + 1)}, q_8 = \\ \frac{\beta_H G_0 (\hat{S}_V - 1)}{(G_0 + \hat{G}_H)^2 \psi_V (\hat{I}_V + 1)}, q_9 &= G_v(0) e^{-(\alpha_g + \mu_g)t}, q_{10} = (\alpha_s + \mu_s), q_{11} = (\alpha_z + \mu_z), q_{12} = \\ (\alpha_k + \mu_k), q_{13} &= (\alpha_v + \mu_v). \end{aligned}$$

The eigenvalues are given as follows, by using the R_0 , the characteristic equation at the endemic equilibrium state E^* is given by,

$$|J(E^*) - \lambda I| = 0$$

therefore,

$$\begin{aligned} \lambda_1 &= -\alpha_H, \lambda_2 = -\alpha_V, \lambda_3 = -G_v(0) e^{-(\alpha_g + \mu_g)t}, \lambda_4 = -(\alpha_k + \mu_k), \lambda_5 = -(\alpha_s + \\ \mu_s), \lambda_6 &= -(\alpha_v + \mu_v), \lambda_7 = -(\delta_V + \mu_V), \lambda_8 = -(\alpha_z + \mu_z), \lambda_9 = \frac{-[\beta_H \hat{G}_H + \mu_V (G_0 + \hat{G}_H)]}{(G_0 + \hat{G}_H)} \end{aligned}$$

$$\begin{aligned} \text{and } \lambda_{10} &= \frac{1}{2(P_0 + \hat{P}_V)} [(\delta_H + \gamma_H + 2\mu_H)(P_0 + \hat{P}_V) + \beta_V \hat{P}_V] \\ &- [(\delta_H + \gamma_H + 2\mu_H)(P_0 + \hat{P}_V) + \beta_V \hat{P}_V]^2 - 4(P_0 + \hat{P}_V)[\mu_H(\delta_H + \gamma_H + 2\mu_H)(P_0 + \hat{P}_V) + \end{aligned}$$

$$\beta_V \hat{P}_V (\delta_H + \mu_H)^{\frac{1}{2}}],$$

The disease free equilibrium is stable when all the eigenvalues obtained from $j(E^*)$ are negatives or have negative real part. $\lambda_1, \lambda_2, \dots, \lambda_9$ are strictly negatives and the disease free points are stable.

4.3 Sensitivity Analysis of the Transmission Metrics of Baseline Multiscale Model

Sensitivity analysis is a critical component of multiscale model studies' parameter value analysis, helping to address the uncertainty surrounding the parameter value range from the perspective of their assumptions. This enables us to ascertain the outputs' sensitivity to variations in the particular parameter. To determine the relative change in the basic reproduction number R_0 when each parameter of the model system (4.2.15) changes, we perform a sensitivity analysis in this section. This will give the study several advantages for making decisions and coming to a reliable conclusion. We can only obtain the detailed information and, as a result, the predictions may be significantly more accurate through sensitivity analysis. This will give the study several advantages for making decisions and coming to a reliable conclusion. We can only obtain the detailed information and, as a result, the predictions may be significantly more accurate through sensitivity analysis. It helps us as researchers identify areas that need to be improved in the future. For every model parameter in the model system, we employed the normalised forward sensitivity index of the R_0 (4.2.15). We let R_0 be a differentiable function on the parameter say (v) on a random selection, so that the normalised forward sensitivity index of R_0 at (v) will be defined as:

$$\Upsilon_v^{R_0} = \frac{\partial R_0}{\partial v} = \frac{v}{R_0} \quad (4.3.1)$$

therefore, considering the sensitivity index of R_0 with respect to human infection rate β_H is given by

$$\Upsilon_{\beta_H}^{R_0} = \frac{\partial R_0}{\partial \beta_H} = \frac{\beta_H}{R_0} = 0.3 \quad (4.3.2)$$

Using the equation (4.6.1) similar expression can be derived for the remaining parameters. Therefore the resulting sensitivity indices of R_0 to the different model parameter are shown below in table. we can see the index of parameter β_H is positive. the sign of the index value indicates weather, the parameter increases the reproduction number or reduces the reproduction number. This means that, increasing human infection rate β_H reduces R_0 and likewise to the rest of the parameters.

Table 4.1: The parameter descriptions for model system (4.2.15)

No.	Para.	P_V	G_H	R_0
1	Λ_H	-0.4888	0.568	0.50
2	Λ_V	0.7165	0.6322	0.6481
3	β_V	-0.4892	0.4510	0.50
4	μ_H	0.491	-0.4651	-0.502
5	γ_H	0.469	-0.432	-0.479
6	P_0	0.489	-0.450	-0.50
7	δ_H	0.0172	-0.121	-0.018
8	G_0	0.488	0.431	-0.50
9	β_H	0.092	0.081	0.500
10	μ_V	-0.796	-0.702	-0.648
11	δ_V	0	0	0
12	α_H	0.4888	-0.568	-0.500
13	ϕ	-1.0093	-0.890	-0.500
14	α_V	-1.0093	-0.890	-0.500
15	α_z	0.210	0.185	0.351
16	α_h	-0.0660	0.0768	0.0675
17	α_g	-0.497	-0.4393	0.00032
18	μ_z	-0.7088	-0.62541	-0.35112
19	μ_g	-0.000656	-0.000579	-0.000325
20	α_s	0.509	0.449	0.4993
21	N_m	-7.04407709441952e-9	8.19464231795426e-9	7.20486103531783e-9
22	μ_s	-1.0079918	-0.8893	-0.499
23	N_g	0.5107	0.450	0.500
24	N_k	0.5107	0.4506	0.500
25	α_v	-0.494	-0.4363	0.0019
26	α_k	-0.4505	-0.39750	0.02380
27	μ_k	-0.0480	-0.04240	-0.02380
28	μ_h	0.06605	-0.0768	-0.0675675
29	μ_v	-0.004021	-0.00355	-0.001992
30	Λ_h	-0.488	0.568	0.500
31	β_h	-7.04407694965236e-9	8.19464227516475e-9	7.20486132269917e-9
32	μ_b	7.04407712270992e-9	-8.19464250545660e-9	-7.20486121493116e-9
33	π	-0.488	0.56868	0.499
34	μ_m	7.04407712270991e-9	-8.19464250545660e-9	-7.20486121493116e-9
35.	α_m	0	0	0

From the table above, we observe that the reproduction number is sensitive to the changes of parameters. Therefore increasing the death rate of mosquitoes by using the insecticides, will eventually reduces the transmission of malaria disease.

4.4 Numerical Analysis

The main purpose of this section is to solve analytically the differential equations of model system (4.2.15) to adopt the approximate methods. These can be done through numerical analysis leading to the estimation of the unknown at specific points in its interval of definition by arithmetic means or initial value. These numerical solutions do not establish physical laws, in general but give the clear picture of the dependence of desired variable on the various parameters of the problem. The behavior of the system (4.2.15) was simulated in order to illustrate the analytical results we obtained in this study. We used the estimated parameter values presented in table (4.2) for sensitivity and numerical analysis. Some of parameters values used from published literatures and some were estimated as values of some parameters generally not reported in literature.

Table 4.2: Description of the parameters of the model system (4.2.15)

Parameters	Descriptions	Initial value
β_b	Infection rate of erythrocytes by free merozoites	0.1
Λ_b	The rate of supply of red blood cells from bone marrow	200
μ_b	Natural decay rate of red blood cells	0.0083
π	Proportion of gametocyte infected erythrocytes	0.1
α_{rm}	The rate at which red blood cells burst to produce merozoites	0.5
μ_e	Natural decay rate of free merozoites	0.001
N_m	Number of merozoites produced per bursting erythrocytes	16
α_0	Rate at which gametocytes develop and become infectious	0.02
μ_h	Natural decay rate of gametocyte infected red blood within infected humans	0.0625

Table 4.3: The between-host parameter values and their descriptions.

Parameters	Descriptions	Initial value
α_V	Rate of elimination of community sporozoites load	0.9
Λ_V	Rate of supply of susceptible mosquitoes	6000
β_V	The contact rate of humans with infectious reservoir of mosquitoes	0.2
G_0	Half saturation constant for community gametocyte load	5×10^8
μ_V	Natural death rate of mosquitoes	0.12
δ_V	Infection induced death rate of mosquitoes	0.00000426
Λ_H	Rate of supply of susceptible humans	1000
β_H	The contact rate of mosquitoes with infectious reservoir of humans	0.3
α_H	Rate of elimination of community gametocyte load	0.0000913
μ_H	Natural death reate of humans	0.00004
γ_H	Natural recovery rate of humans	0.25
P_0	Half saturation constant for community sporozoite load	100 000 000
δ_H	Disease induced death rate of humans	0.0027

Parameters	Descriptions	Initial value
α_g	Rate at which gametocyte infected erythrocytes burst	96
Λ_v	Rate of uptake of gametocytes through super infection of mosquito	300
μ_g	Death rate of gametocytes	0.0625
N_g	Number of gametes produced per gametocyte infected erythrocyte	2
α_s	Fertilization of gametes	0.08
μ_s	Natural decay rate of gametes	58.0
α_z	Rate at which zygotes develop into oocysts	0.4240
μ_z	Natural decay rate of zygotes	1
α_k	Bursting rate of oocysts to producer sporozoites	0.2
μ_k	Natural decay rate of oocysts	0.01
N_k	Number of sporozoites produced per burting oocysts	3000
α_v	Rate at which sporooites become infectious to humans	0.025
μ_v	Natural decay rate of sporozoites	0.0001
Λ_h	Rate of supply of susceptible red blood cells	200
β_h	Infection rate of erythrocytes by free merozoites	0.1
μ_b	Natural decay rate of susceptible erythrocytes	0.0083
π	Proportion of gametocyte infected erythrocytes	0.1
μ_m	Natural decay rate of free merozoites	0.001
α_m	Rate at which erythrocytes burst to produce merozoites	0.5
N_m	Number of merozoites produced per bursting erythrocytes	16
α_h	Rate at which gametocytes develop and become infectious	0.02
μ_h	Natural decay rate of gametocytes infected erythrocytes within infected humans within infected humans	0.0625

Table 4.4: The Within-mosquito and Within-human parameter values and their descriptions.

The graphs in Fig. (4.2) illustrate the solution profile of the population of Infected humans, community of gametocytes load, the population of infected mosquitoes and the community of sporozoites load α_v : $\alpha_v = 0.025$; $\alpha_v = 0.0525$; $\alpha_v = 0.0825$. The numerical results show that higher rates of infection at the human population level results in increased population of parasites in the community of gametocytes and sporozoites. This can be prevented by putting in place insecticides or repellent nets to reduce contact between humans and mosquitoes, this reduces tranmission of the disease at both humans and mosquitoes population.

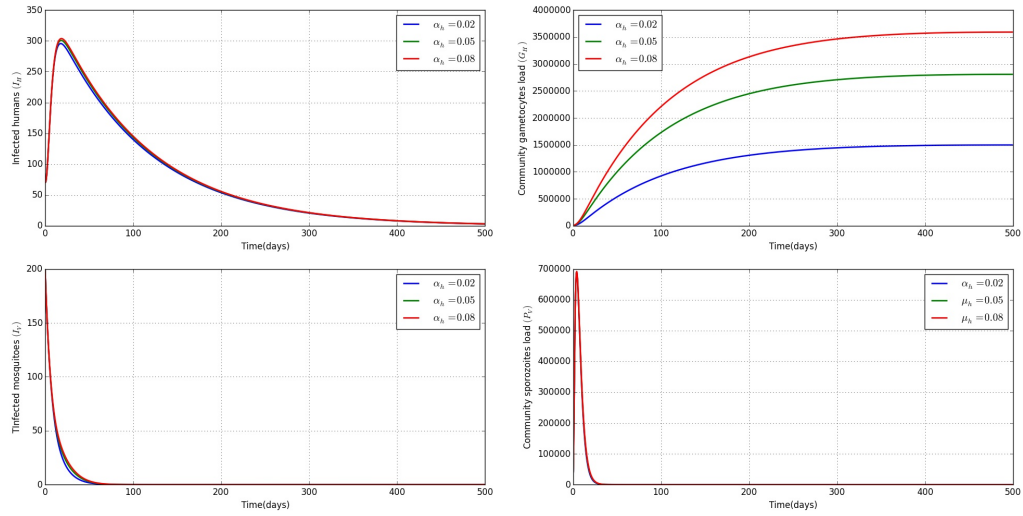


Figure 4.2: Graphs showing population dynamics of infected human and mosquitoes, the population of gametocytes and population of sporozoites, illustrate the solution profile of the population of Infected humans, community of gametocytes load, the population of infected mosquitoes and the community of sporozoites load α_V : $\alpha_V = 0.025$; $\alpha_V = 0.0525$; $\alpha_V = 0.0825$.

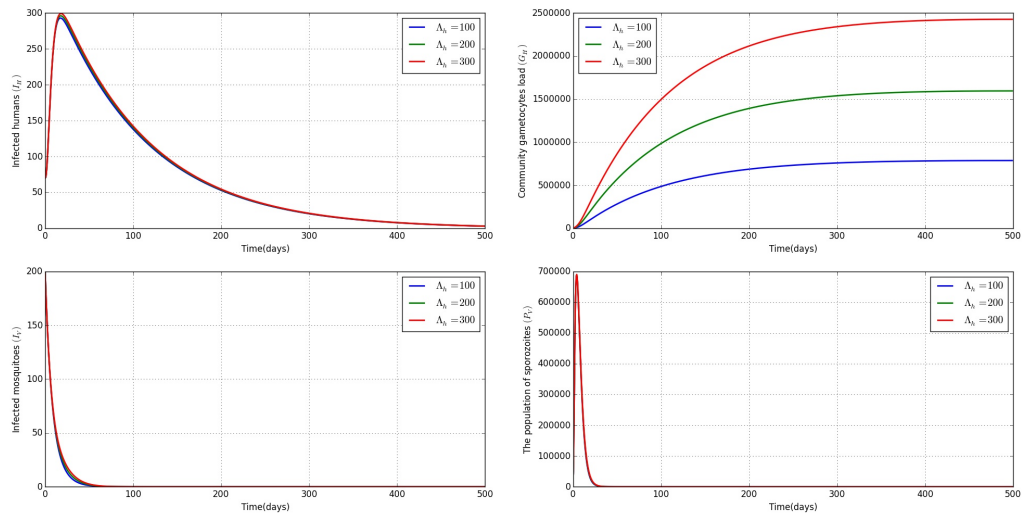


Figure 4.3: Graphs showing population dynamics of infected human and mosquitoes, the population of gametocytes and population of sporozoites.

The graphs in Fig. (4.3) illustrate the solution profile of the population of Infected humans, community of gametocytes load, the population of infected mosquitoes and the community of sporozoites load μ_k : $\mu_k = 0.01$; $\mu_k = 0.05$; $\mu_k = 0.09$. The numerical results show that higher rates of infection at the human population level results in increased population of parasites in the community of gametocytes and

sporozoites. The natural decay rate of oocysts doesn't eliminate the pathogens within the humans and mosquitoes population.

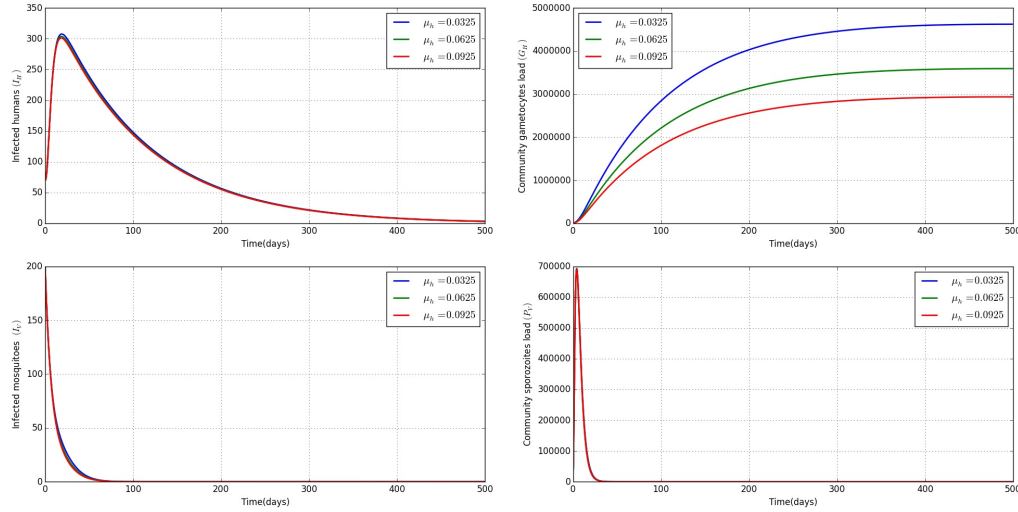


Figure 4.4: Graphs showing population dynamics of infected human and mosquitoes, the population of gametocytes and population of sporozoites, illustrate the solution profile of the population of Infected humans, community of gametocytes load, the population of infected mosquitoes and the community of sporozoites load μ_k : $\mu_k = 0.01$; $\mu_k = 0.05$; $\mu_k = 0.09$.

The graphs in Fig. (4.4) illustrate the solution profile of the population of Infected humans, community of gametocytes load, the population of infected mosquitoes and the community of sporozoites load μ_g : $\mu_g = 0.0525$; $\mu_g = 0.0625$; $\mu_g = 0.0725$. The numerical results show that higher rates of infection at the human population level results in increased population of parasites in the community of gametocytes and sporozoites. The natural death rate of gametocytes doesn't eliminate the pathogens within the humans and mosquitoes population.

The graphs in Fig. (4.5) illustrate the solution profile of the population of Infected humans, community of gametocytes load, the population of infected mosquitoes and the community of sporozoites load α_s : $\alpha_s = 0.015$; $\alpha_s = 0.01$; $\alpha_s = 0.08$. The numerical results show that higher rates of infection at the human population level results in increased population of parasites in the community of gametocytes and sporozoites. The number of fertilised gametes can only be prevented by medications in the form of vaccines or any other medications.

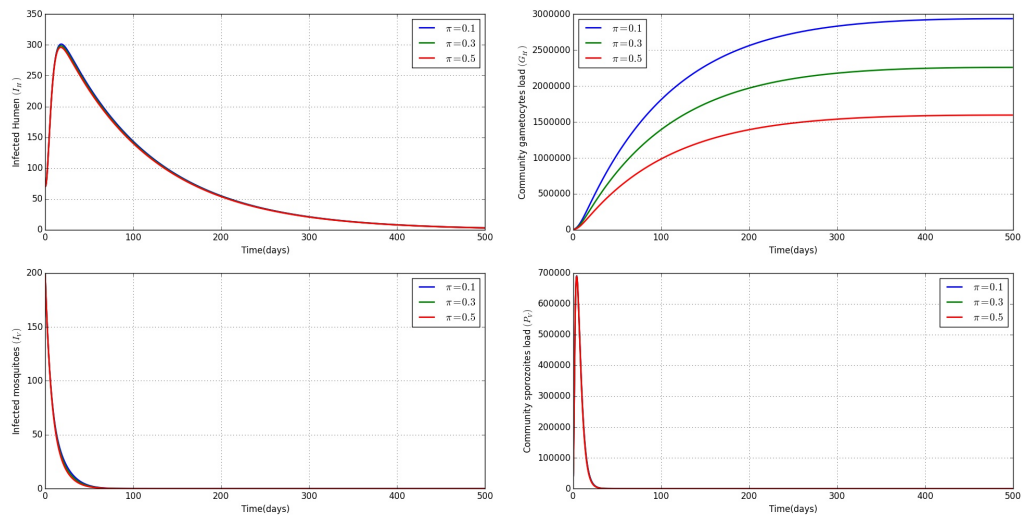


Figure 4.5: Graphs showing population dynamics of infected human and mosquitoes, the population of gametocytes and population of sporozoites and illustrate the solution profile of the population of Infected humans, community of gametocytes load, the population of infected mosquitoes and the community of sporozoites load μ_g : $\mu_g = 0.0525$; $\mu_g = 0.0625$; $\mu_g = 0.0725$.

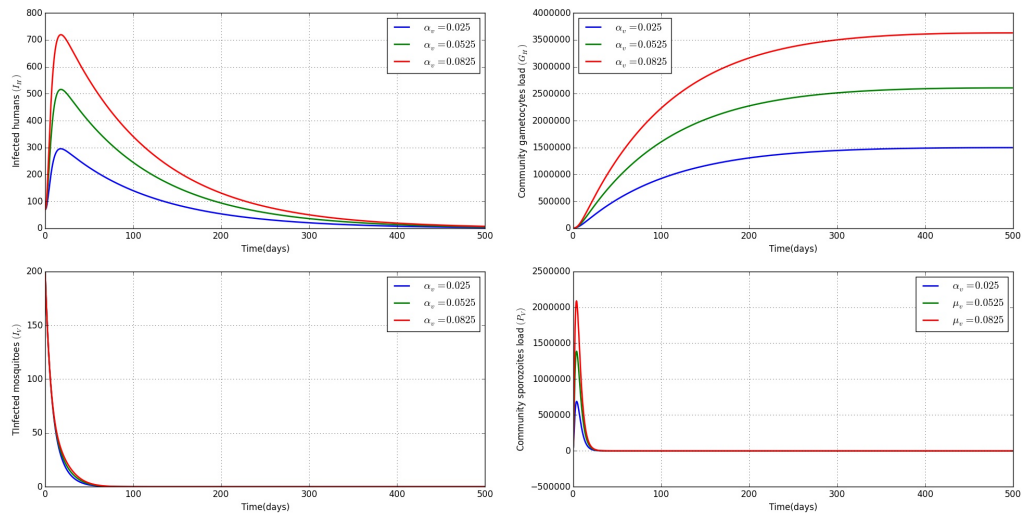


Figure 4.6: Graphs showing population dynamics of infected human and mosquitoes, the population of gametocytes and population of sporozoites, and illustrate the solution profile of the population of Infected humans, community of gametocytes load, the population of infected mosquitoes and the community of sporozoites load α_s : $\alpha_s = 0.015$; $\alpha_s = 0.01$; $\alpha_s = 0.08$.

The graphs in Fig. (4.6) illustrate the solution profile of the population of Infected humans, community of gametocytes load, the population of infected mosquitoes

and the community of sporozoites load N_k : $N_k = 2000$; $N_k = 1000$; $N_k = 3000$. The numerical results show that higher rates of infection at the human population level results in increased population of parasites in the community of gametocytes and sporozoites. The number of sporozoites produced per bursting oocysts can only be prevented by medications in the form of vaccines or any other medications

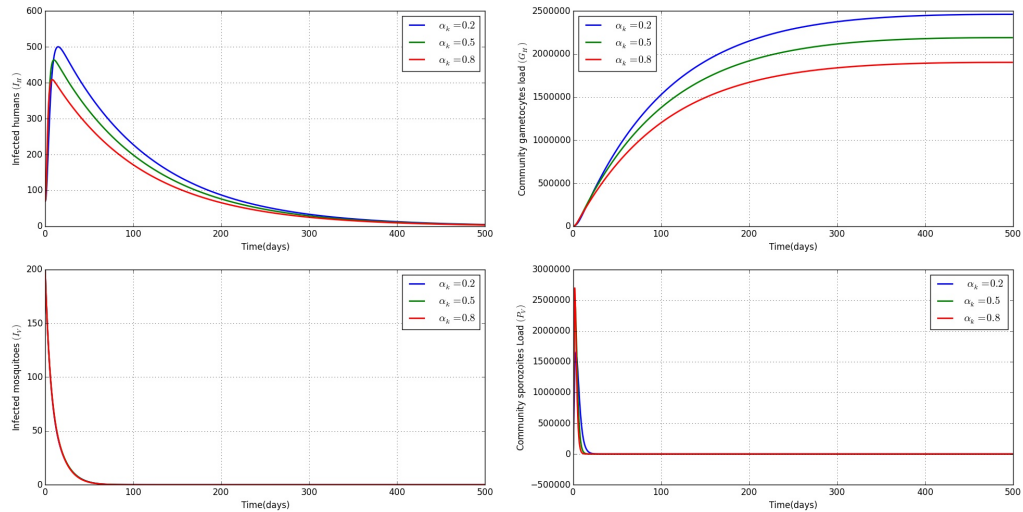


Figure 4.7: The illustrate the solution profile of the population of Infected humans, community of gametocytes load, the population of infected mosquitoes and the community of sporozoites load N_k : $N_k = 2000$; $N_k = 1000$; $N_k = 3000$.

The graphs in Fig. (4.7) illustrate the solution profile of the population of Infected humans, community of gametocytes load, the population of infected mosquitoes and the community of sporozoites load α_g : $\alpha_g = 56$; $\alpha_g = 76$; $\alpha_g = 96$. The numerical results show that higher rates of infection at the human population level results in increased population of parasites in the community of gametocytes and sporozoites. The rate at which gametocytes infected erythrocytes can also be prevented by medications in the form of vaccines or any other medications.

The graphs in Fig. (4.8) illustrate the solution profile of the population of Infected humans, community of gametocytes load, the population of infected mosquitoes and the community of sporozoites load α_z : $\alpha_z = 0.4240$; $\alpha_z = 0.8240$; $\alpha_z = 1.2240$. The numerical results show that higher rates of infection at the human population level results in increased population of parasites in the community of gametocytes and sporozoites. The rate at which zygotes develop into oocysts can also be prevented by medications in the form of vaccines or any other medications.

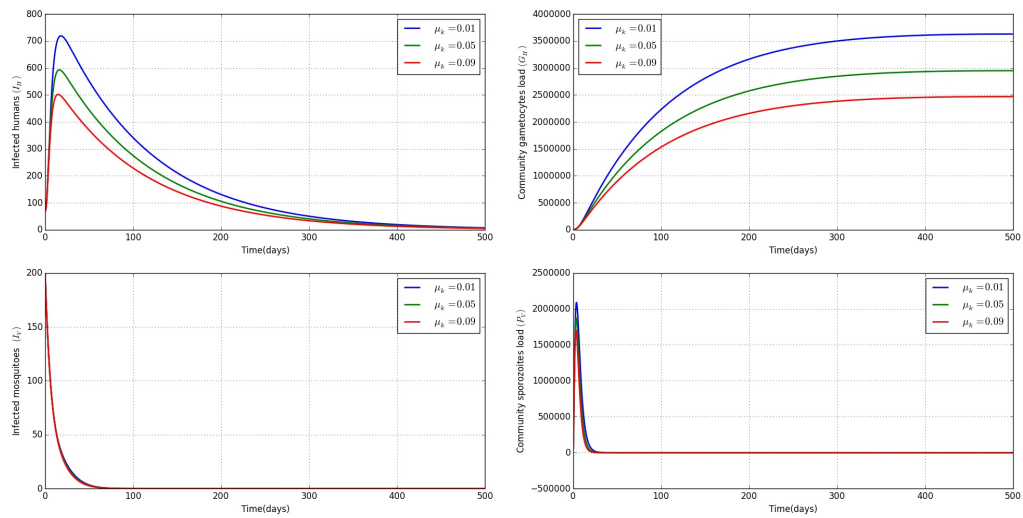


Figure 4.8: The illustrate the solution profile of the population of Infected humans, community of gametocytes load, the population of infected mosquitoes and the community of sporozoites load α_g : $\alpha_g = 56$; $\alpha_g = 76$; $\alpha_g = 96$.

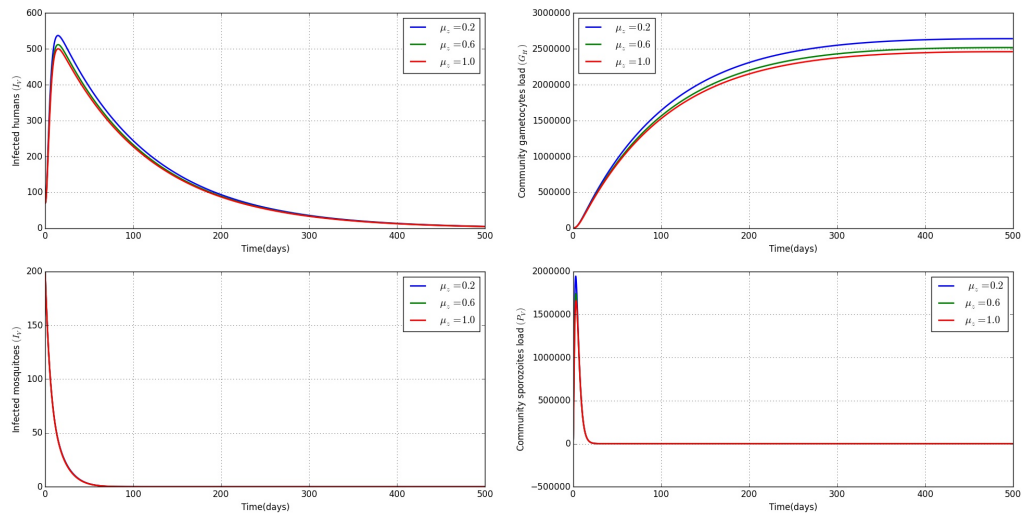


Figure 4.9: The illustrate the solution profile of the population of Infected humans, community of gametocytes load, the population of infected mosquitoes and the community of sporozoites load α_z : $\alpha_z = 0.4240$; $\alpha_z = 0.8240$; $\alpha_z = 1.2240$.

The graphs in Fig. (4.9) illustrate the solution profile of the population of Infected humans, community of gametocytes load, the population of infected mosquitoes and the community of sporozoites load N_g : $N_g = 2$; $N_g = 6$; $N_g = 10$. The numerical results show that higher rates of infection at the human population level results in increased population of parasites in the community of gametocytes and

sporozoites. The number of gametes produced per gametocytes infected erythrocytes burst can also be prevented by medications in the form of vaccines or any other medications.

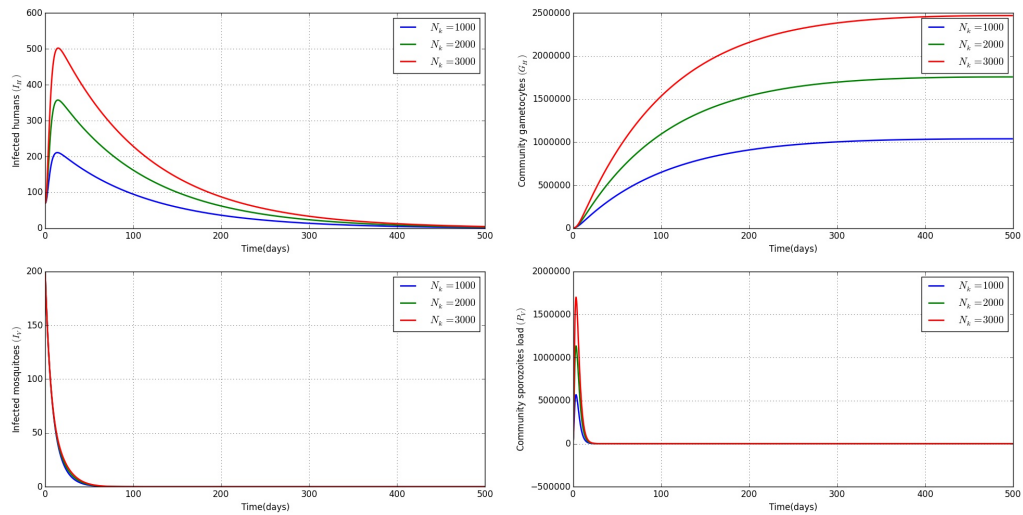


Figure 4.10: The illustrate the solution profile of the population of Infected humans, community of gametocytes load, the population of infected mosquitoes and the community of sporozoites load N_g : $N_g = 2$; $N_g = 6$; $N_g = 10$.

The graphs in Fig. (4.10) illustrate the solution profile of the population of Infected humans, community of gametocytes load, the population of infected mosquitoes and the community of sporozoites load μ_s : $\mu_s = 18$; $\mu_s = 38$; $\mu_s = 58$. The numerical results show that higher rates of infection at the human population level results in increased population of parasites in the community of gametocytes and sporozoites. The natural decay rate of gametes can be prevented by medications in the form of vaccines or any other medications.

The graphs in Fig. (4.11) illustrate the solution profile of the population of Infected humans, community of gametocytes load, the population of infected mosquitoes and the community of sporozoites load μ_z : $\mu_z = 0.2$; $\mu_z = 0.6$; $\mu_z = 1.0$. The numerical results show that higher rates of infection at the human population level results in increased population of parasites in the community of gametocytes and sporozoites. The natural decay rate of zygotes does not reduce or take away the pathogens within the infected individual population.

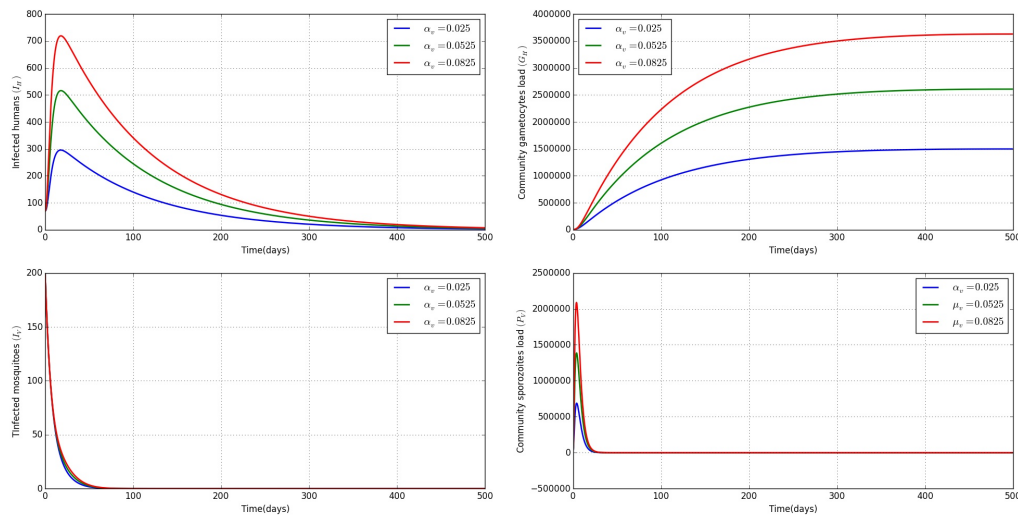


Figure 4.11: The illustrate the solution profile of the population of Infected humans, community of gametocytes load, the population of infected mosquitoes and the community of sporozoites load μ_s : $\mu_s = 18$; $\mu_s = 38$; $\mu_s = 58$.

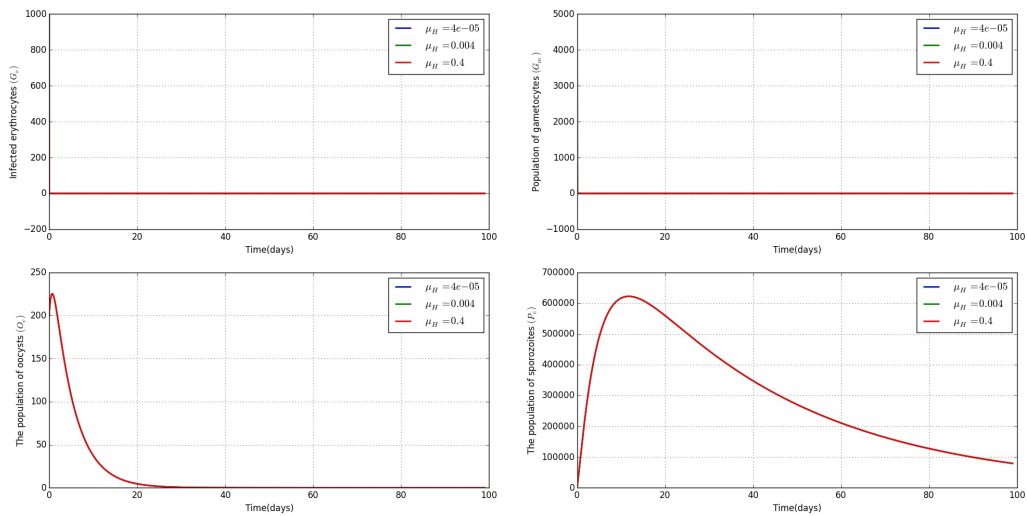


Figure 4.12: Graphs of numerical solutions of model system (4.2.15) showing the evolution in time of (a) population of infected humans (I_H), community of gametocytes load (G_H), population of infected mosquitoes (I_V) and the community of sporozoites load (P_V), for different values of the rate at which zygotes develop into oocysts. α_z :
 $\alpha_z = 0.2$; $\alpha_z = 0.5$; $\alpha_z = 0.8$

The graphs in Fig. (4.12) illustrate the solution profile of the population of Infected humans, community of gametocytes load, the population of infected mosquitoes and the community of sporozoites load α_z : $\alpha_z = 0.2$; $\alpha_z = 0.5$; $\alpha_z = 0.8$. The

numerical results show that higher rates of infection at the human population level results in increased population of parasites in the community of gametocytes and sporozoites. The rate at which zygotes develop into oocysts can be prevented by the use of vaccines to cut the pathogens further development within the infected individual population.

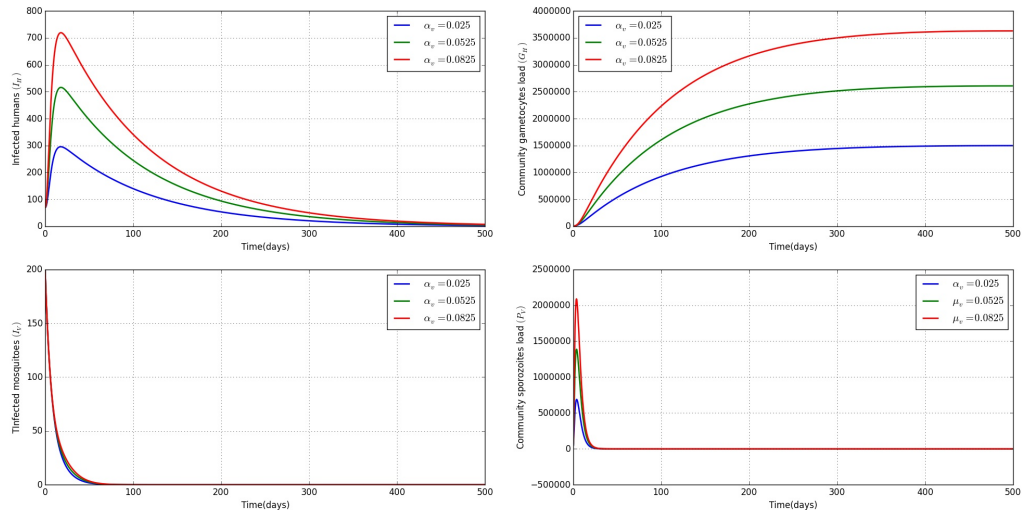


Figure 4.13: Graph illustrate the solution of model system (4.2.15) showing the evolution in time of infected humans, the community of gametocytes, infected mosquitoes and the community of sporozoites.

The graphs in Fig. (4.13) illustrate the solution profile of the population of Infected humans, community of gametocytes load, the population of infected mosquitoes and the community of sporozoites load μ_v : $\mu_v = 0.0001$; $\mu_v = 0.0005$; $\mu_v = 0.0009$. The numerical results show that higher rates of infection at the human population level results in increased population of parasites in the community of gametocytes and sporozoites. The natural decay rate of sporozoites does not reduce or take away the pathogens within the infected individual population.

The graphs in Fig. (4.14) illustrate the solution profile of the population of Infected humans, (b) community of gametocytes load, the population of infected mosquitoes and the community of sporozoites load G_v : $G_v = 0$; $G_v = 1000$; $G_v = 2000$. The numerical results show that higher rates of infection at the human population level results in increased population of parasites in the community of gametocytes and sporozoites. The rate of infected gametocytes infecting mosquito population increases the population of infected mosquitoes and the circle of infection carries on with this two populations.

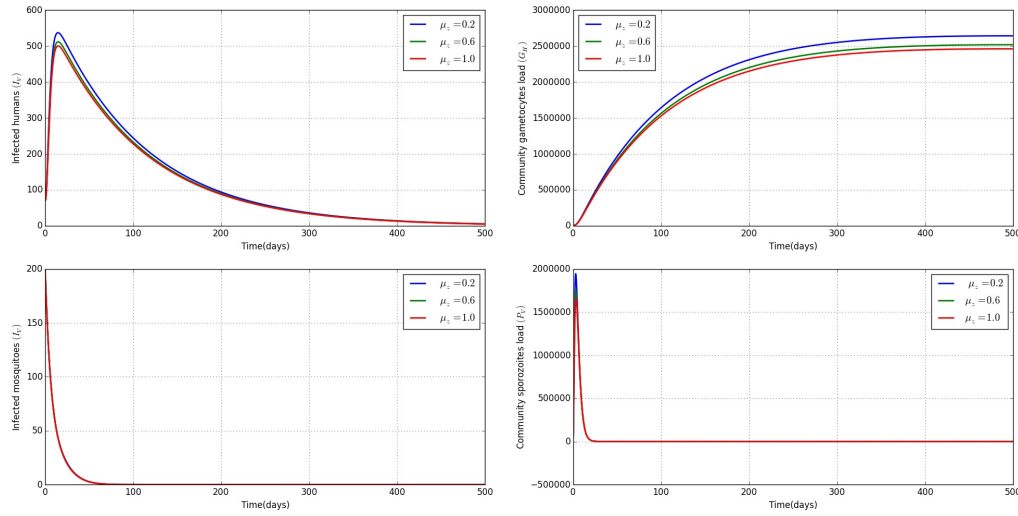


Figure 4.14: The illustrate the solution profile of the population of Infected humans, community of gametocytes load, the population of infected mosquitoes and the community of sporozoites load μ_v : $\mu_v = 0.0001$; $\mu_v = 0.0005$; $\mu_v = 0.0009$.

4.4.1 Summary

In this chapter, we integrated the within-host scale of malaria infectious disease using a method for developing a cascade of nested multiscale models of infectious disease systems, using the community pathogen load as the standard metric for the community level of infectiousness and the indicator of the efficacy of health and other related interventions. Through study, important mathematical features of the model were looked into. We determined the fundamental reproduction number of the model and utilized it to show that the infection-free equilibrium is stable. We established the uniqueness of the endemic equilibrium point and obtained the explicit formulas for the model's endemic equilibria. The within-mosquito sub-model system was employed to derive the differential equation $P_v(s)$ through the integrating factor method. The appropriate equations were then derived by applying ecosystems concepts to the within-mosquito and within-human malaria parasite population dynamics (Rynkiewicz et al., 2015; Sicard et al., 2014; Lofgren et al., 2016). The numerical results demonstrate that the goal of intervention during malaria infection should be to reduce the rates at which merozoites and gametocytes invade healthy liver tissue as well as erythrocytes. Additionally, employing antimalarial medications like ACT to raise the mortality rate of merozoites would be required for the prompt and efficient elimination of parasitemia. This will also guarantee a lower density of infected red blood cells, which are necessary for the life cycle of liver organ malaria and the subsequent production of merozoites.

Chapter 5

Discussion and Conclusion

In the battle against malaria, the globe has come a long way thanks to research and healthcare initiatives. The World Malaria Report (WHO 2016c) indicates that there is a decline in malaria cases and fatality rates. Malaria continues to be a major global health concern despite these advancements, with countries that have successfully stopped the spread of the disease finding it difficult to sustain their achievements. Large-scale interventions are used in malaria control areas with moderate to high transmission to lessen the disease's impact on public health. Targeted treatments in elimination contexts seek to halt local transmission in the precise locations where it becomes more concentrated, i.e., tiny geographic areas or certain subpopulations that can be more difficult and expensive to reach. In addition to having the potential to influence policy decisions and direct research into the control and eradication of various infectious diseases, including helminth disease, mathematical models are widely acknowledged as a valuable tool for assessing the efficacy of various control or elimination strategies. Unlike previous attempts at eradication, contemporary efforts expressly recognize that eliminating malaria necessitates a multi-year effort including numerous interventions, disciplines, techniques, and organizations. The creation of a new nested multiscale modeling framework for the malaria disease system, which can be used to evaluate the relative efficacy of health interventions with previously proven efficacy for use with a wider target population or at the community level in advance of community-based randomized controlled trials, is the study's significant contribution to scientific knowledge. In order to characterize the epidemiology of malaria and other infectious diseases in general and to develop innovative management strategies, multiscale modeling is essential. ,guiding the care of disease, determining the targets for novel medications and vaccinations, and then assessing the results of these medical measures. Community pathogen is used in the proposed multiscale modeling technique as a metric for the degree of infectiousness and transmission likelihood in the community, as well as an indicator of the efficacy of interventions. The utilization of a model to derive community pathogen load measurements is a practical and economical approach that public health personnel can employ to supplement the use of readily available empirical data.

When the reproductive number is less than unity, there is a free disease steady

state that is locally and globally asymptotically stable, according to the analysis of the multiscale model. When the reproductive number is greater than unity, there may be three endemic equilibria. The overall objective of the analysis in this work was demonstrated to be effectively achieved by the methods that produce the approximate or precise answers to the behavior of malaria pathogens. Using the normalized forward sensitivity indices with respect to the basic reproductive number, we examine the significance of the model parameters to the prevalence and spread of malaria infection within a community. The study has benefited greatly from sensitivity analysis and numerical results, which show that parameters related to the environment, within-host and between-host relationships, and the dynamics of malaria infection transmission at the population level all have a substantial impact. Most notably, the multiscale modeling technique made it possible to systematically compare the efficacy of malaria preventative measures in a way that has not been possible in modeling studies that do not use multiscale modeling to analyze the dynamics of malaria transmission.

In Conclusion, we formulated and analyzed a mathematical model for the in human host and in human dynamics of malaria parasite in the liver and blood stage. A positive invariant region, where the model is epidemiologically and mathematically well-posed was established. Using the next generation method, basic reproduction number of the model was computed. The existence and stability of two non-negative equilibrium points which are disease free equilibrium and disease infection equilibrium were established. Furthermore, we proved that disease free equilibrium is locally asymptotically stable if $R_0 < 1$ and globally asymptotically stable if $R_0 \leq 1$. We noted that disease progress from liver to blood with or without the impact of immune cells to suppress production of merozoites in higher that of antibodies to block invasion of sporozoites and merozoites into liver and blood cells respectively. The numerical simulation prove the existence of disease free equilibrium, which is global asymptotically stable irrespective of the initial values do state variables have. our work is an example on how mathematical models can be used to get insight of complex system like malaria life cycle. Therefore, it provides basis for mathematical models to study the in-host and in-mosquito dynamics. This study provided with proof that mathematical models that link the within-host scale and the between-host scale can be useful in evaluating the comparative effectiveness of malaria health interventions that operate at different scale domains of this infectious disease system. Although the focus of this study was on malaria, the framework is important enough to be applicable to many other vector-borne disease. In future work we propose the extension of this model by incorporating the effects of antimalarial drugs.

References

- R. J. Allen and K. Kirk. Cell volume control in the plasmodium-infected erythrocyte. *Trends in parasitology*, 20(1):7–10, 2004.
- A. S. Aly, A. M. Vaughan, and S. H. Kappe. Malaria parasite development in the mosquito and infection of the mammalian host. *Annual review of microbiology*, 63:195–221, 2009.
- R. M. Anderson, R. M. May, et al. Coevolution of hosts and parasites. *Parasitology*, 85(Pt 2):411–426, 1982.
- O. Angulo, F. Milner, and L. Segal. A sir epidemic model structured by immunological variables. *Journal of Biological Systems*, 21(04):1340013, 2013.
- M. L. Barreto, M. G. Teixeira, and E. H. Carmo. Infectious diseases epidemiology. *Journal of Epidemiology & Community Health*, 60(3):192–195, 2006.
- L. Blumberg, R. Lee, J. Lipman, and S. Beards. Predictors of mortality in severe malaria: a two-year experience in a non-endemic area. *Anaesthesia and intensive care*, 24(2):217–223, 1996.
- R. Bray and P. Garnham. The life-cycle of primate malaria parasites. *British medical bulletin*, 38(2):117–122, 1982.
- D. Brewster, D. Kwiatkowski, and N. White. Neurological sequelae of cerebral malaria in children. *Lancet (London, England)*, 336(8722):1039–1043, 1990.
- F. Bruneel, L. Hocqueloux, C. Alberti, M. Wolff, S. Chevret, J.-P. Bédos, R. Durand, J. Le Bras, B. Régnier, and F. Vachon. The clinical spectrum of severe imported falciparum malaria in the intensive care unit: report of 188 cases in adults. *American journal of respiratory and critical care medicine*, 167(5):684–689, 2003.
- H.-J. Bungartz and M. Griebel. Sparse grids. *Acta numerica*, 13(1):147–269, 2004.
- L. Cai, N. Tuncer, and M. Martcheva. How does within-host dynamics affect population-level dynamics? insights from an immuno-epidemiological model of malaria. *Mathematical Methods in the Applied Sciences*, 40(18):6424–6450, 2017.

- E. U. Canning and R. Sinden. The organization of the ookinete and observations on nuclear division in oocysts of plasmodium berghei. *Parasitology*, 67(1):29–40, 1973.
- C. Castillo-Chavez, Z. Feng, W. Huang, et al. On the computation of r_0 and its role in global stability. *IMA Volumes in Mathematics and Its Applications*, 125: 229–250, 2002.
- C. C. Chavez, Z. Feng, and W. Huang. On the computation of r_0 and its role on global stability. *Mathematical Approaches for Emerging and Re-Emerging Infection Diseases: An Introduction. The IMA Volumes in Mathematics and Its Applications*, 125:31–65, 2002.
- C. Chiyaka, W. Garira, and S. Dube. Modelling immune response and drug therapy in human malaria infection. *Computational and Mathematical Methods in Medicine*, 9(2):143–163, 2008.
- S. M. Ciupe and J. M. Heffernan. In-host modeling. *Infectious Disease Modelling*, 2(2):188–202, 2017.
- G. C. Cook and A. Zumla. *Manson's tropical diseases*. Elsevier Health Sciences, 2008.
- P. D. Crompton, S. K. Pierce, L. H. Miller, et al. Advances and challenges in malaria vaccine development. *The Journal of clinical investigation*, 120(12): 4168–4178, 2010.
- P. A. Eckhoff. A malaria transmission-directed model of mosquito life cycle and ecology. *Malaria journal*, 10(1):1–17, 2011.
- S. Eric Chin, D.N & Olafsson. *Problems and Solutions in Mathematical Science*. John Willey & Sons, 2017.
- D. A. Fedosov, W. Pan, B. Caswell, G. Gompfer, and G. E. Karniadakis. Predicting human blood viscosity in silico. *Proceedings of the National Academy of Sciences*, 108(29):11772–11777, 2011.
- R. Garabed, A. Jolles, W. Garira, C. Lanzas, J. B. Gutierrez, and G. Rempala. Multi-scale dynamics of infectious diseases. *Interface Focus*, 10, 2019.
- L. S. Garcia. Classification of human parasites, vectors, and similar organisms. *Clinical infectious diseases*, 29(4):734–736, 1999.
- W. Garira. A complete categorization of multiscale models of infectious disease systems. *Journal of Biological Dynamics*, 11:378 – 435, 2017.
- W. Garira. A primer on multiscale modelling of infectious disease systems. *Infectious Disease Modelling*, 3:176 – 191, 2018.
- W. Garira and F. Chirove. A general method for multiscale modelling of vector-borne disease systems. *Interface Focus*, 10, 2019.

- W. Garira and M. C. Mafunda. From individual health to community health: towards multiscale modeling of directly transmitted infectious disease systems. *Journal of Biological Systems*, 27(01):131–166, 2019.
- W. Garira and D. Mathebula. A coupled multiscale model to guide malaria control and elimination. *Journal of theoretical biology*, 475:34–59, 2019.
- W. Garira, D. Mathebula, and R. Netshikweta. A mathematical modelling framework for linked within-host and between-host dynamics for infections with free-living pathogens in the environment. *Mathematical biosciences*, 256:58–78, 2014.
- H. Ginsburg, S. Ward, and P. Bray. An integrated model of chloroquine action. *Parasitology Today*, 15(9):357–360, 1999.
- E. Hansen and C. O. Buckee. Modeling the human infectious reservoir for malaria control: does heterogeneity matter? *Trends in parasitology*, 29(6):270–275, 2013.
- B. Hellriegel. Modelling the immune response to malaria with ecological concepts: short-term behaviour against long-term equilibrium. *Proceedings of the Royal Society of London. Series B: Biological Sciences*, 250(1329):249–256, 1992.
- R. Howells and E. Davies. Nuclear division in the oocyst of plasmodium berghei. *Annals of Tropical Medicine & Parasitology*, 65(4):451–459, 1971.
- K. W. Hunter, L. P. Smith, G. T. Strickland, and W. A. Blackburn. Hypergamma-globulinemia and erythrocyte autoantibody complicate enzyme immunoassay of antimalarial antibody. *Journal of Immunoassay and Immunochemistry*, 2(2): 99–108, 1981.
- E. Jatta, M. Jawara, J. Bradley, D. Jeffries, B. Kandeh, J. B. Knudsen, A. L. Wilson, M. Pinder, U. D'Alessandro, and S. W. Lindsay. How house design affects malaria mosquito density, temperature, and relative humidity: an experimental study in rural gambia. *The Lancet Planetary Health*, 2(11):e498–e508, 2018.
- K. C. Kain, M. A. Harrington, S. Tennyson, and J. S. Keystone. Imported malaria: prospective analysis of problems in diagnosis and management. *Clinical infectious diseases*, 27(1):142–149, 1998.
- M. Keeling and L. Danon. Mathematical modelling of infectious diseases. *British Medical Bulletin*, 92(1), 2009.
- D. W. Lounsbury and S. G. Mitchell. Introduction to special issue on social ecological approaches to community health research and action. *American journal of community psychology*, 44(3):213–220, 2009.
- M. Martcheva, N. Tuncer, and C. St Mary. Coupling within-host and between-host infectious diseases models. *Biomath*, 4(2):1510091, 2015.

- F. E. McKenzie and W. H. Bossert. An integrated model of plasmodium falciparum dynamics. *Journal of theoretical biology*, 232(3):411–426, 2005.
- B. Menn, S. Lorentz, and T. J. Naucke. Imported and travelling dogs as carriers of canine vector-borne pathogens in germany. *Parasites & vectors*, 3(1):1–7, 2010.
- I. Merikanto, E. Kronholm, M. Peltonen, T. Laatikainen, T. Lahti, and T. Partonen. Relation of chronotype to sleep complaints in the general finnish population. *Chronobiology international*, 29(3):311–317, 2012.
- N. Mideo, S. Alizon, and T. Day. Linking within-and between-host dynamics in the evolutionary epidemiology of infectious diseases. *Trends in ecology & evolution*, 23(9):511–517, 2008.
- V. S. Moorthy, M. F. Good, and A. V. Hill. Malaria vaccine developments. *The lancet*, 363(9403):150–156, 2004.
- P. Muentener, P. Schlagenhauf, and R. Steffen. Imported malaria (1985-95): trends and perspectives. *Bulletin of the World Health Organization*, 77(7):560, 1999.
- G. S. Murphy and E. C. Oldfield III. Falciparum malaria. *Infectious disease clinics of North America*, 10(4):747–775, 1996.
- R. Netshikweta and W. Garira. A multiscale model for the world’s first parasitic disease targeted for eradication: guinea worm disease. *Computational and mathematical methods in medicine*, 2017, 2017.
- W. H. Organization. *Guidelines for the treatment of malaria*. World Health Organization, 2015.
- W. H. Organization, W. H. Organization, et al. Indoor residual spraying: use of indoor residual spraying for scaling up global malaria control and elimination: Who position statement. Technical report, World Health Organization, 2006.
- W. H. Organization et al. A field manual for low and moderate endemic countries. *Geneva: The World Organization*, 2007.
- A. L. Ouédraogo, P. A. Eckhoff, A. J. Luty, W. Roeffen, R. W. Sauerwein, T. Bousema, and E. A. Wenger. Modeling the impact of plasmodium falciparum sexual stage immunity on the composition and dynamics of the human infectious reservoir for malaria in natural settings. *PLoS pathogens*, 14(5): e1007034, 2018.
- J. Sachs and P. Malaney. The economic and social burden of malaria. *Nature*, 415(6872):680–685, 2002.
- E. Schwartz, S. Sadetzki, H. Murad, and D. Raveh. Age as a risk factor for severe plasmodium falciparum malaria in nonimmune patients. *Clinical infectious diseases*, 33(10):1774–1777, 2001.

- J. E. Svenson, J. D. MacLean, T. W. Gyorkos, and J. Keystone. Imported malaria: clinical presentation and examination of symptomatic travelers. *Archives of Internal Medicine*, 155(8):861–868, 1995.
- Z. Tabo, L. S. Luboobi, and J. Ssebuliba. Mathematical modelling of the in-host dynamics of malaria and the effects of treatment. *Journal of Mathematics and Computer Science*, 17(1):1–21, 2017.
- M. I. Teboh-Ewungkem and T. Yuster. A within-vector mathematical model of plasmodium falciparum and implications of incomplete fertilization on optimal gametocyte sex ratio. *Journal of theoretical biology*, 264(2):273–286, 2010.
- F. Tediosi, N. Maire, T. Smith, G. Hutton, J. Utzinger, A. Ross, and M. Tanner. An approach to model the costs and effects of case management of plasmodium falciparum malaria in sub-saharan africa. *The American journal of tropical medicine and hygiene*, 75(2_suppl):90–103, 2006.
- P. G. Walker, J. T. Griffin, N. M. Ferguson, and A. C. Ghani. Estimating the most efficient allocation of interventions to achieve reductions in plasmodium falciparum malaria burden and transmission in africa: a modelling study. *The Lancet Global Health*, 4(7):e474–e484, 2016.
- M. T. White, S. Karl, K. E. Battle, S. I. Hay, I. Mueller, and A. C. Ghani. Modelling the contribution of the hypnozoite reservoir to plasmodium vivax transmission. *Elife*, 3:e04692, 2014.

Appendix A

MATLAB CODES