Modelling Drug Resistance in Malaria

by

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Declaration

I, the undersigned, hereby declare that the work contained in this thesis is my own original work and has not previously, in its entirety or in part, been submitted at any university for a degree.

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Theresia Marijani Date

Abstract

A simple model for the spread of malaria is presented. The model that incorporates partial immunity in humans is extended to include two different strains namely a sensitive and a resistant strain in both human and mosquito populations. The models are analyzed for stability in terms of the reproduction number. In the extended model, we obtained two reproduction numbers arising from sensitive strain (R_{w^*}) and the resistant strain (R_{r^*}). We show that the disease free equilibrium point is locally asymptotically stable for $R_0 < 1$ and unstable for $R_0 > 1$. The endemic equilibrium point on the other hand is locally asymptotically stable for $R_0 > 1$. For the drug resistance model the analysis shows that if $R_{w^*} < 1$ and $R_{r^*} < 1$ the disease free equilibrium is locally asymptotically stable. We have used the center manifold theory to determine the stability of the endemic equilibrium point when R_0 is close to unit. We show that there is forward bifurcation when only the sensitive strain exists, and that the endemic equilibrium point is locally asymptotically stable whenever $R_{w^*} > 1$. Furthermore, we show that when only the resistant strain exists the model exhibits backward bifurcation. The presence of backward bifurcation may complicate the treatment control program due to the presence of a stable endemic state for $R_{r^*} < 1$. Some numerical simulations have been done and the findings show the role of strain dominance and implications with regards to malaria dynamics. We find that resistant strain dominance implies higher prevalence for malaria. The eradication of both drug sensitive and drug resistant malaria can be achieved if $R_{w^*} < 1$ and $R_{r^*} < 1$. We also observed that, reducing contact rates together with increased use of pesticides can reduce the malaria burden.

Opsomming

Die verspreiding van malaria word ondersoek d.m.v ´n wiskundige model. Die model sluit gedeeltelike immuniteit vir mense in, asook twee variante van malaria, een sensitief en een weerstandig teenoor malaria behandeling. Die modelle word geanaliseer vir die basiese aanwas getal en die stabilitieit van die aanwas getal word ondersoek. Vir die uitgebreide model word twee basiese aanwas getalle gevind, een vir die sensitiewe variant (R_{w^*}) en een vir ´n weerstandige variant (R_{r^*}). Ons wys dat die siekte vrye ekwilibrium punt lokaal stabiel is vir $R_0 < 1$ en onstabiel is vir $R_0 > 1$. Die endemiese ekwilibrium punt is egter lokaal asimptoties stabiel. Vir die weerstandige model wys ons dat wanneer $R_{w^*} < 1$ en $R_{r^*} < 1$, is die siekte vrye ekwilibrium punt lokaal asimptoties stabiel. Die sentrale meervoudige ruimte teorie word gebruik om die stabiliteits eienskappe van die endemiese ekwilibrium punt te bepaal wanner R_0 naby 1 is. Ons wys daar is ´n voorwaartse bifurkasie wanneer slegs die sensitiewe variant bestaan, en dat die endemiese equilibrium punt lokaal asimptoties stabiel is wanneer $R_{r^*} < 1$. Simulasie is gebruik om die rol van variant kompetiese en die impak daarvan op malaria beheer te ondersoek. Ons bevind dat ´n dominante behandeling weerstandige variant hoër prevalensie van malaira skep. Albei variante kan uigeroei word as $R_{w^*} < 1$ en $R_{r^*} < 1$ gebring kan word. Daar word verder bevind dat ´n verlaging in die malaria kontak koers en die gebruik van insek doders die malaria juk kan lig.

Dedication

I dedicate this thesis to my parents who have always inspired me through the saying "education is a never ending journey" and to my nephew Godwinhurryson (2 years old) who was at one time seriously ill with malaria but recovered two weeks after special treatment.

Acknowledgments

I would like to thank God for his glory and for all that he has done for me, thank you Lord! Furthermore, I would like to express sincere gratitude to all the people who have been very helpful to me during the time I spent in preparing this thesis.

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Chapter 1

Introduction

1.1 Epidemiology of malaria

Malaria is a serious infection of the red blood cells caused by protozoa of the genus plasimodium. There are four species of the malaria parasites that can infect humans and cause malaria namely; Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale and Plasmodium malariae. Plasmodium falciparum is the most widespread and dangerous of the four, if untreated it can lead to fatal cerebral malaria. Malaria is the most common disease throughout the tropics, subtropics and temperate regions, where climatic conditions allow for the continuous breeding of the mosquito [43]. Temperatures that allow suitable transmission range between $22°C$ and $32°C$. Temperature determines vector survival, incubation period and transmission. Low temperatures, below $18°C$, hinder mosquito survival and transmission, while high temperatures allow the mosquito survival and transmission. Mosquitoes are seen to breed more in temporary and turbid water bodies formed by rain. Rains are also related to humidity and saturation deficit that affect mosquito survival [4].

It is estimated that 40% of the world population lives in malaria endemic areas [9]. Most of them suffer clinical attacks and may survive after an illness lasting 10 to 20 days. During this period affected individuals may be unable to attend school, or work, thereby diminishing education attainment and productivity. Malaria is responsible for a 1.3% growth penalty per year in some African countries, due to loss of productivity. Mosquito-borne diseases kill up to 2.7 million people a year and 75% of them are African children

less than 5 years of age that live in poor conditions [21].

Malaria has been known since time immemorial, but it was centuries before the true cause was understood. Although people were unaware of the origin of malaria and the mode of transmission, protective measures against the mosquito have been used for many hundreds of years. The control of malaria started after the discovery of the malaria parasite by Laveran 1889 and the demonstration by Ross in 1897 that the mosquito was the vector for malaria [17]. These discoveries quickly led to control strategies and to the invention of Dichloro-Diphenyl-Trichloroethane (DDT) during world war II to fight malaria.

Malaria parasites are transmitted from one person to another through female anopheles mosquitoes. The disease is spread when an infected female anopheles mosquito bites a victim. It injects sporozoites of plasmodium from its salivary glands, into the blood stream of the host. The sporozoites migrate into the liver cells and develop into schizonts which arise via asexual reproduction, to a form which invades and attacks the red blood cells, the merozoites [2]. The merozoites then change to trophozoites and then to erythrocytic schizonts. This division takes about 2 days depending on species. The burst of the red blood cell releases more merozoites into the blood stream. The clinical symptoms of the disease will manifest in the host at this point, in the form of fever, headache, vomiting, chills, weakness and sweating. The symptoms may develop $10 - 35$ days after an infected mosquito bite. These symptoms tend to reappear depending on the immunity of the host. Some merozoites differentiate into male or female gametocytes. In this form, they can be taken up by mosquito when they bite the host. Inside the mosquito fertilization occurs, producing zygotes which develop into ookinetes. The ookinetes form oocysts which grow, divide and rupture to give sporozoites which migrate to the salivary glands of the mosquito. Then the infection cycle is ready to begin again when the vector feeds on the human host. The disease may also be transmitted from an infected mother to an unborn child, sharing of needles and syringes and blood transfusion [16, 22, 36].

Malaria can be prevented by taking anti-malaria drugs (prophylaxis) that protect against the disease one week before visiting malarious regions [33]. One way of preventing malaria is for a person to avoid being bitten by infected mosquitoes. An effective way of avoiding mosquito bites is to use treated mosquito nets. This has been useful to many rural parts of Africa in the fight against malaria. DDT and other pesticides have been used to kill

mosquitoes in many parts of the world. Malaria can also be prevented by staying indoors, and wearing clothes that cover the whole body [23]. People who have no or low immunity to malaria like young children, pregnant woman and visitors that travel to tropical areas are most at risk to get malaria that can result into serious illness. People that live in malaria endemic regions may acquire some immunity to the disease during their lifetime. A lot of vaccine initiatives by scientists have been on the cards. However, there has been very little success in producing such vaccines [24, 49]. Poverty, lack of knowledge and little or no access to health care also contributes to high malaria deaths worldwide [13].

Malaria can be treated with anti-malaria drugs. However, treatment depends on a number of factors, and it is worth noting that drug therapy depends on which type of malaria an individual has. Also, treatment depends on the region of the world in which the person was infected. The kinds of malaria parasite (has many strains) living in different parts of the world respond differently to different drugs [32]. The effective treatment for malaria is quinine. Quinine is effective to treat most forms of malaria in different parts of the world. Patients with serious malaria may require to go to hospital where special treatment like intravenous fluids, blood transfusions, kidney diagnosis and oxygen therapy can help [33].

The treatment of malaria has become difficult due to emergence of drug resistant strains of the mosquitoes. Parasites have become resistant to most of the anti-malaria drugs that are used. Prevention of malaria has also been complicated because mosquitoes have become resistant to some of the insecticides. Chloroquine was one of the commonly used drugs in malaria treatment. It was inexpensive, safe and initially highly effective in the 1950s and 1960s [27]. It has now been replaced by other anti-malaria drugs due to increased resistance. Other affordable pharmaceuticals that are user friendly are needed urgently. Increased drug resistance is caused by many factors. Some of these factors include:

- human behaviour: Purchase of drugs without prescription and drug use patterns influence the development of drug resistance. For example; in Tanzania, there is a common practice of buying anti-malaria drugs over the counter, and patients stop taking the drug as soon as they feel well instead of completing the treatment course [25].

- Mutation: This occurs when infected parasites are exposed to drugs. Mutation can

spread if a gametocytes carrying the mutation are ingested by feeding mosquito [48].

- Anti-malaria immunity: it seems the spread of drug resistant malaria is driven by the greater survival and competitiveness of resistant strains. This occurs during the time between administration of the drug and immune clearance of infections. The interval is increased when individuals with little or no parasite specific immunity such as young children are given anti-malaria drugs [6, 37].

1.2 Motivation

Malaria is the world's most dangerous parasitic infectious disease which remain a public health concern especially in African countries. The development of drug resistance poses one of the greatest threats to malaria control and has been linked to recent increases in malaria morbidity and mortality. We desire to formulate and analyze mathematical models of malaria drugs resistance, qualitatively and numerically, to determine threshold conditions under which malaria can be controlled and reversed.

1.3 Aims and objective of the study

The main goals for this thesis are:

- To review recent work on the modeling of malaria.
- To analyse and discuss a model for malaria with drug resistance.
- To carry out numerical simulations for all the models and discuss the implications of the results to the dynamics of malaria transmission.

1.4 Statement of the problem

Drug resistance has become the major public health problem worldwide. The widespread distribution of resistance in parasite strains is a major concern in chemoprophylaxis and

treatment. Mosquitoes, the vectors of malaria have also developed the resistance to the pesticides being used. It is against this background that we develop mathematical models that attempt to answer the following questions:

- under what conditions does malaria persist or can be controlled in presence of resistant strains?
- what are the model outcomes on the role of increased drug resistance in the human populations?
- what is the contribution of such models to public health intervention programmes?

1.5 Outline

This thesis begins with the introduction in which malaria is discussed as a disease. The second chapter, reviews general malaria models and models of drug resistance. A simple deterministic model of malaria with temporary immunity is presented in the third chapter which explains transmission dynamics of malaria between humans and the vectors. The model is then extended in the fourth chapter to include resistant and sensitive strains in both human and mosquito populations. In both Chapters 3 and 4, analytic and simulation results of the models are presented. A concluding chapter winds up the thesis.

Chapter 2

Literature Review

2.1 General malaria models

The historical perspective of malaria is given by Bailey. In the eighteenth century, the term *Mal-aria* meant "bad-air" in Italian. It was believed that malaria was a disease associated with swamps. The work of Ronald Ross, a malariologist, is also described. In their work, they showed the great contribution of Ross in modeling malaria disease dynamics by means of mathematical models. The work of Dietz is also given, who also used mathematical models that included immunology and its contribution to malaria dynamics [4].

A brief explanation of the life cycle of malaria is given by Aron and May [3]. They present a basic model for the transmission dynamics of malaria and its analysis. In their model, they introduced graphical, phase techniques that had not been used before. They emphasized on the dynamics of human hosts and mosquito vector relationship. Then, they elaborate their model by using the ideas of MacDonald's [30] original work in considering ways in which data may be used to choose correct models.

Anderson and May [2] described malaria as one of the major indirectly transmitted micro parasitic infections with the anopheles mosquito as the intermediate host. In their work, they looked at the complications that involved an intermediate host in the study of transmission, control and interpretation of the observed epidemiological patterns of malaria. They also considered the type of information available for estimating parameters and testing their predictive potential. They used the simple model of Ross-MacDonald.

They then introduced other additional factors and complications to facilitate and aid the interpretation of the observed trends.

The importance of mathematical modeling in contributing to malaria control is also described and explained by McKenzie and Samba [31], who discussed the great contributions of mathematics in intervention programs if individuals in the health fraternity were well informed about what mathematical models can do. They showed as an example, the Ross-MacDonald models of human immunity and how they contribute to malaria control.

The presentation of a compartmental mathematical model for the spread of malaria in human and mosquito populations is also given by Chitnis, Cushing and Hyman [9]. In their work, susceptible humans get infected at a certain probability when they get in contact with infected mosquitoes. They immediately become exposed, and later on become infectious. After recovery, they become susceptible again. This movement from one compartment to the other as the disease status change, divided the population into four compartments, susceptible, exposed, infectious and the recovered compartments or classes. In the model, they assumed that both the hosts and the vectors follow a logistic growth while humans having additional immigration and disease related death rate. In their analysis, they determined the disease free equilibrium point, which was locally asymptotically stable whenever the reproduction number was less than one. They proved the existence of at least one endemic equilibrium point in the domain of existence of the model. A similar model was proposed by Tumwiine, Mugisha and Luboobi [44]. In their model, loss of immunity resulted in the recovered individuals joining the susceptible class again. They [44] showed that the disease free equilibrium point was globally asymptotically stable when the reproduction number for the model was less than one.

The cohort model for predicting parasitemia of malaria was used with the common source model of Muench, Aron and May [3, 34]. They [43] incorporated time dependent immunity, true immunity, super infection and resistant strain parasites. The time dependent immunity (TDI) model was used as baseline study to investigate parameter behavior with changing time. They found that relatively small subclasses of the immune classes are mostly responsible for transmitting malaria to mosquitoes. They also showed that super infection is not a compelling factor in the dynamics of the disease and mosquitoes harboring resistant parasites may be few in an environment [43]. Models for the transmission of

malaria with chemo-prevention have also been studied. Stability analysis of the equilibria with the aim of finding threshold conditions under which malaria clears or persists in the human population are given. The results suggest that eradication of mosquitoes and prophylaxis prevention can significantly reduce the malaria burden [35].

2.2 Models of drugs resistance

Research on reducing malaria drug resistance has been done by many researchers [1, 38, 40, 41]. Mathematical models have been used to model the dynamics of drug sensitive and drug resistant malaria strains. The models describe the spread of resistance and they consider that resistance is conferred by an allele at one locus. They show that resistance does not spread if the fraction of infected individuals treated is less than a certain threshold value [20]. According to Laxminarayan [28], infection levels increase due to increasing treatment. This leads to a reduced level of infection for a short term because many patients will be under treatment. As more patients are treated, resistance increases. This is followed by gaining immunity with reduced effectiveness of drugs.

The emergence of anti-malaria drug resistance is dependent on the occurrence of a spontaneous genetic change (mutation or gene amplification) in a malaria parasite, which interferes with that parasites susceptibility to a drug. A single mutation may be sufficient to confer almost complete resistance to some drugs. There is often a series of mutations that confer increasing intolerance of the parasite to increasing drug concentrations, as in the cases of pyrimethamine and chloroquine [46].

Resistance to anti-malaria drugs has proved to be a challenging problem in malaria control in many parts of the world where malaria is endemic. Sensitivity of the parasites to chloroquine, the best and most widely used drug for treating malaria, has been on the decline. Newer anti-malaria were discovered in an effort to tackle this problem, but most of these drugs are either expensive or have undesirable side effects. Moreover, after a variable length of time, the parasites, especially the falciparum species, have started showing resistance to these drugs also. The epidemiological factors associated with the development and spread of drug resistant malaria have been recently explored by Wensdorfer in a paper in which he looked at parasite-drug-human-vector interactions that affect the occurrence

and dynamics of drug resistance [47].

A model of anti-malaria resistance that aimed at describing malaria epidemiology and predict the effect of potential policy interventions based on sound representations of the underlying biology was given by Yeung *et al.* [50]. The predictions in terms of the prevalence of malaria infections and the proportion of infections that are resistant were used to calculate future cost and effectiveness. The mathematical model was introduced in order to address the issue of difficulties in measuring the burden of drug resistance and predicting the impact of prevention strategies.

The economics of malaria resistance, raised an interesting scenario in the work presented by [28]. They developed a bioeconomic of malaria transmission and evolution of drug resistance. They examine questions of optimal treatment strategy and coverage when drug resistance places an additional constraint on choices available to a policy maker. Results show that, infection levels further increase in response to increasing resistance. Increase in infection levels is most rapid for higher rates of treatment coverage. The cost of malaria morbidity decreased with increasing treatment coverage even after resistance related impacts. They concluded that at high level of treatment coverage, resistance evolves so rapidly regardless of which strategy is followed. The faster acquisition of immunity with less effective drug plays a critical role in determining the superior strategy [28].

Parasitic resistance poses a huge threat to the efforts that are in place to control malaria. Various methods have been developed to control the vector. The use of insecticides in particular, paved way to the development of insecticides resistance in mosquitoes. Alternative methods of vector control, such as zooprophlaxis were suggested in [19]. Zooprophlaxis is the control of vector bone disease by attracting vector to domestic animals in order to protect human health. In their paper Kawaguchi, Sasaki and Mogi [19] examined whether the combined use of insecticide spray and zooprophlaxis can limit the development of insecticide resistance in mosquitoes. They developed a mathematical model with three populations, where mosquitoes feed on both humans and animals. Their model revealed that, by choosing a suitable insecticide spraying rate, cattle density and location in some situation malaria can be controlled without mosquitoes developing insecticide resistance. They suggest that separating humans and cattle is very important in controlling malaria via zooprophylaxis [19].

The use of regular doses of anti-malaria drugs that has been proposed as intermittent preventive treatment (IPT) to reduce morbidity and mortality of malaria pregnant women and infants. O'meara, Smith and McKenzie [37] investigated the implementation of IPT on the drug resistant malaria. Their mathematical model, evaluated the possible impact of treating individuals with anti malaria drugs at regular intervals regardless of their infection status. The model showed that immunity, treatment rate, drug decay kinetics and presumptive treatment rate are important factors in the spread of the drug resistance parasites. The results showed that it is important to considering both the half-life of a drug and the existing level of resistance when choosing a drug for IPT. Also IPT is more likely to accelerate the spread of resistance in high transmission areas.

Koela and Antia [20] presented an epidemiological framework to investigate the spread of anti-malaria resistance. In their model they showed how mathematical models based on Ross-MacDonald model of malaria transmission, can be used to examine the process and parameters that are critical in determining the spread of resistance. Their results showed that if drug treatment exceeds certain threshold, resistance will eventually become prevalent in the population [20].

In this work, we develop a mathematical model of drug resistance that uses the model by Koela and Antia [20] as a starting point. We include resistant strains in both the vector and host species. Specifically, we consider two strains, sensitive and and resistant strains. We assume that humans infected with the sensitive strain transmit this strain to mosquitoes and may recover with immunity and revert to the susceptible class. Likewise, mosquitoes infected with the sensitive strain are capable of infecting humans with the sensitive strain. Humans infected with the resistant strain are capable of infecting mosquitoes with the malaria resistant strain. Moreover, we assume in this model, that humans infected with the resistance strains do not recover. Mosquitoes infected with the malaria resistant strain are capable of infecting humans with the resistant strain. To simplify our model, we have ignored the latent class in the mosquito population because the period of latency is very small compared to the period of infectiousness.

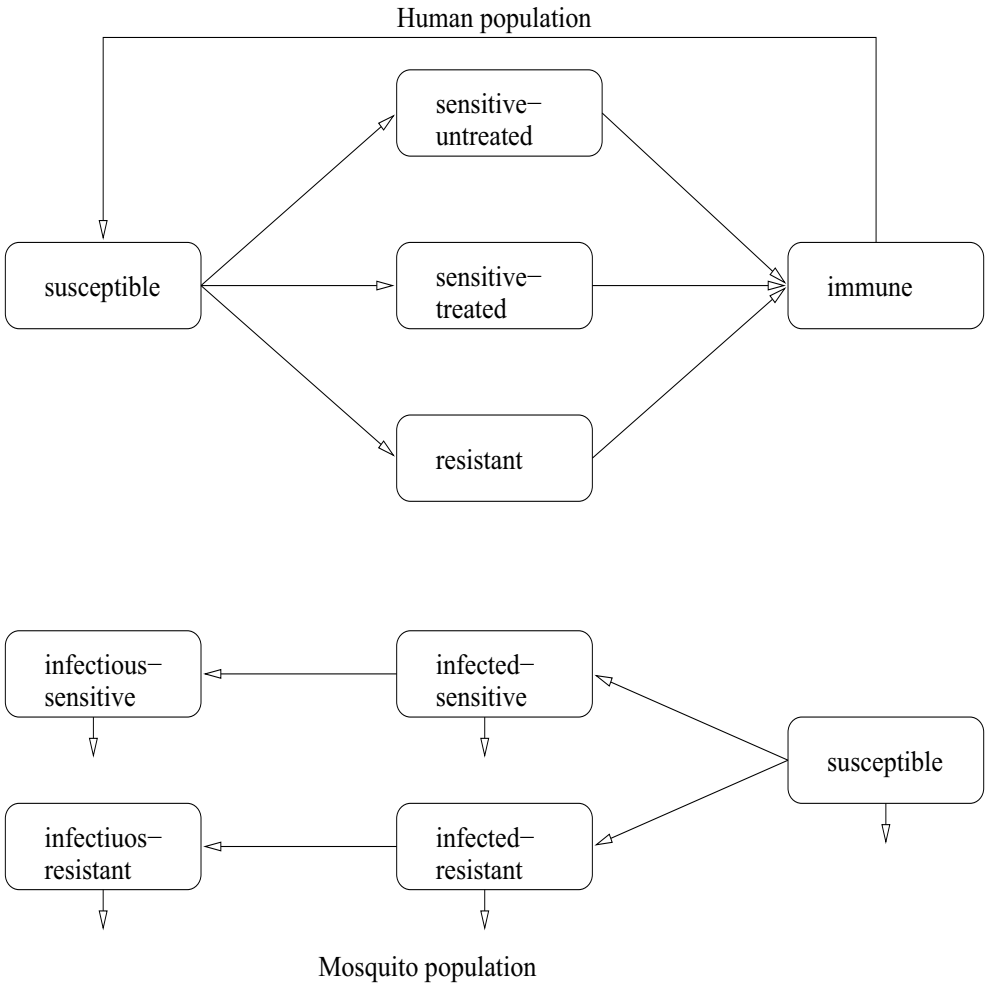


FIG. 2.1. The model of drug resistance made by Koela and Antia

Chapter 3

Simple model for malaria transmission

3.1 Introduction

We begin by considering a simple transmission model of malaria in this chapter. The diagrammatic flow of the human and mosquito populations as their disease status change is represented by FIG. 3.1. The model looks at the interaction of the human and mosquito populations in a bid to capture the dynamics of the spread of malaria. We obtain the model reproduction number using the next generation matrix approach [45]. The linearization of the model equations at the disease free and endemic equilibrium points is done to determine the stability of the equilibrium points.

3.2 Model formulation

Malaria models have been developed for a century, and our simple model is based on the Ross-MacDonald model that presents the basic features of malaria transmission. We have three classes that characterize the total human population (N_H); susceptible (S_H), those at risk of getting infected; infected humans (I_H), those who are infected with malaria and are capable of infecting the mosquito upon being bitten; recovered (R_H), those who have recovered from malaria and developed some immunity to the disease. The mosquito population is characterized by two classes: susceptible mosquitoes (S_{vv}), those that are at risk of being infected upon biting an infected human and infected mosquitoes (I_{vv}), those

that are infected with the disease and are capable of transmitting it to humans. Some of the parameters and their descriptions in the models are as follows;

TABLE. 3.1. The table that shows parameters and their definitions.

Parameter	Definition
Π_H	The rate of recruitment of new susceptible humans
Π_{vv}	The rate of recruitment of new susceptible mosquitoes
ϵ	Per capital rate of loss of immunity
γ	Per capital rate at which humans acquire the immunity
σ	Per capital death rate due to diseases
ν	Per capital rate of recovery individual from temporary immunity
μ_H	Per capital natural death rate for humans
μ_{vv}	Per capital natural death rate for mosquitoes
β_H	The contact rate for susceptible humans and infected mosquitoes
β_{vv}	The contact rate for susceptible mosquitoes and infected humans
λ_H	The rate of birth of humans
λ_{vv}	The rate of birth of mosquitoes

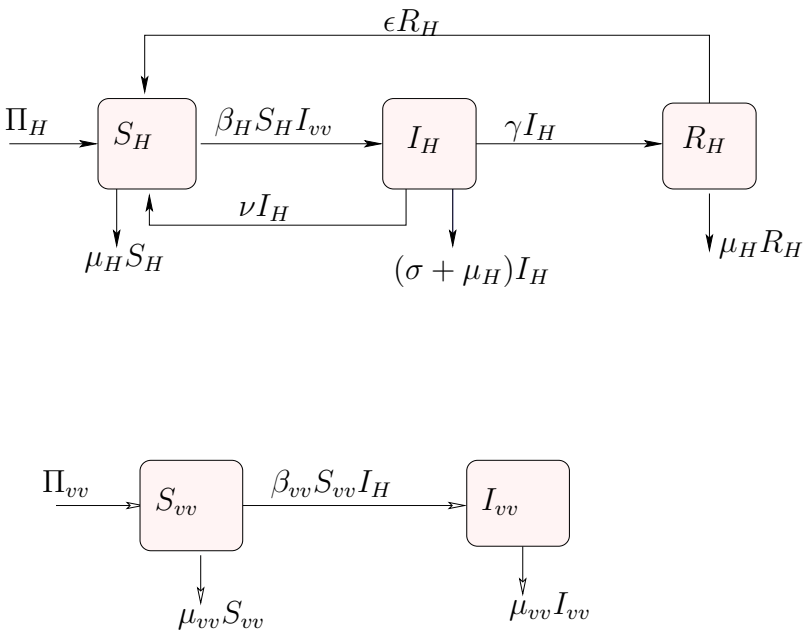


FIG. 3.1. A diagrammatic representation of a simple model for malaria transmission

The model diagram for malaria transmission given above shows the interactions among human and mosquito populations. The model is described by the following equations:

$$\left.\begin{aligned} \dot{S_H} &= \Pi_H - \beta_H S_H I_{vv} - \mu_H S_H + \nu I_H + \epsilon R_H, \\ \dot{I_H} &= \beta_H S_H I_{vv} - (\gamma + \mu_H + \sigma + \nu) I_H, \\ \dot{R_H} &= \gamma I_H - (\mu_H + \epsilon) R_H, \\ \dot{S_{vv}} &= \Pi_{vv} - \beta_{vv} S_{vv} I_H - \mu_{vv} S_{vv}, \\ \dot{I_{vv}} &= \beta_{vv} S_{vv} I_H - \mu_{vv} I_{vv}. \end{aligned}\right\} \tag{3.1}$$

3.3 Constant population model

Adding the first three equations of the system (3.1) gives;

$$\frac{d(S_H + I_H + R_H)}{dt} = \Pi_H - \mu_H N_H - \sigma I_H,$$

and adding the last two equations gives;

$$\frac{d(S_{vv} + I_{vv})}{dt} = \Pi_{vv} - \mu_{vv} N_{vv}.$$

We assume initially, that the growth of the susceptibles is not constant but proportional to the respective populations. We thus consider λ_H and λ_{vv} to be the birth parameters for the human and mosquito populations. So if we assume that $\Pi_H = \lambda_H N_H$ and $\Pi_{vv} = \lambda_{vv} N_{vv}$ and take $\sigma = 0$ then we have

$$\frac{dN_H}{dt} = (\lambda_H - \mu_H) N_H,$$

and

$$\frac{dN_{vv}}{dt} = (\lambda_{vv} - \mu_{vv}) N_{vv}.$$

Furthermore if we assume $\lambda_H = \mu_H$ and $\lambda_{vv} = \mu_{vv}$ then we have a constant population model. We will compare the models for $\sigma = 0$ and $\sigma \neq 0$ when we carry out numerical simulation. The case $\sigma = 0$ helps us to understand some underlying dynamics in the absence of disease related deaths.

3.3.1 Equilibria and model reproduction number

The system goes to an equilibrium point as $t \longrightarrow \infty$. The right hand side of the system (3.1) is equated to zero, so that,

$$\left.\begin{aligned} 0 &= \mu_H N_H - \beta_H S_H I_{vv} - \mu_H S_H + \nu I_H + \epsilon R_H, \\ 0 &= \beta_H S_H I_{vv} - (\gamma + \mu_H + \nu) I_H, \\ 0 &= \gamma I_H - (\mu_H + \epsilon) R_H, \\ 0 &= \mu_{vv} N_{vv} - \beta_{vv} S_{vv} I_H - \mu_{vv} S_{vv}, \\ 0 &= \beta_{vv} S_{vv} I_H - \mu_{vv} I_{vv}. \end{aligned}\right\} \tag{3.2}$$

Since

$$N_H = S_H + I_H + R_H, \tag{3.3}$$

$$N_{vv} = S_{vv} + I_{vv}. \tag{3.4}$$

System (3.2) becomes;

$$0 = \beta_H (N_H - (I_H + R_H)) I_{vv} - (\gamma + \mu_H + \nu) I_H, \tag{3.5}$$

$$0 = \gamma I_H - (\mu_H + \epsilon) R_H, \tag{3.6}$$

$$0 = \beta_{vv} (N_{vv} - I_{vv}) I_H - \mu_{vv} I_{vv}. \tag{3.7}$$

From equation (3.6) we get

$$R_H^* = \frac{\gamma I_H^*}{(\mu_H + \epsilon)}. \tag{3.8}$$

We substitute equation (3.8) into (3.5) to obtain;

$$0 = \beta_H (N_H^* - I_H^* - \frac{\gamma I_H^*}{(\mu_H + \epsilon)}) I_{vv}^* - (\gamma + \mu_H + \nu) I_H^*.$$

Making the I_{vv}^* the subject, gives

$$I_{vv}^* = \frac{(\gamma + \mu_H + \nu) I_H^*}{\beta_H (N_H^* - I_H^* - P I_H^*)}, \tag{3.9}$$

where $P = \frac{\gamma}{(\mu_H + \epsilon)}$.

Epidemiologically, P represents the proportion of individuals that will remain immune to malaria infection. $\frac{1}{\mu_H + \epsilon}$ represents the mean time an individual stays in the class of the

recovered individuals.
From the equations (3.7) and (3.9) we obtain;

$$0 = \beta_{vv}(N^*_{vv} - \frac{(\gamma+\mu_H+\nu)I^*_H}{\beta_H(N^*_H - I^*_H - PI^*_H)I_H})I^*_H - \mu_{vv}\frac{(\gamma+\mu_H+\nu)I^*_H}{\beta_H(N^*_H - I^*_H - PI^*_H)}. \tag{3.10}$$

Factorizing I^*_H gives either $I^*_H = 0$ or

$$0 = \beta_{vv}\left(N^*_{vv} - \frac{(\gamma+\mu_H+\nu)I^*_H}{\beta_H(N^*_H - I^*_H - PI^*_H)I^*_H}\right) - \mu_{vv}\frac{(\gamma+\mu_H+\nu)}{\beta_H(N^*_H - I^*_H - PI^*_H)}. \tag{3.11}$$

The case $I^*_H = 0$ results in the disease free equilibrium point $E_0 = (N^*_H, 0, 0, N^*_{vv}, 0)$.
We can easily obtain I^*_H from the following expression,

$$0 = \beta_{vv}\beta_H N_{vv}(N^*_H - (1+P)I^*_H) - \beta_{vv}(\gamma+\mu_H+\nu)I^*_H - \mu_{vv}(\gamma+\mu_H+\nu).$$

We thus have;

$$\begin{aligned} I^*_H &= \frac{\beta_{vv}\beta_H N^*_{vv}N^*_H - \mu_{vv}(\gamma+\mu_H+\nu)}{\beta_{vv}\beta_H N^*_{vv}(1+P) + \beta_{vv}(\gamma+\mu_H+\nu)}, \\ &= \frac{\mu_{vv}(\gamma+\mu_H+\nu)\left(\frac{\beta_{vv}\beta_H N^*_H N^*_{vv}}{\mu_{vv}(\gamma+\mu_H+\nu)} - 1\right)}{\beta_{vv}(\gamma+\mu_H+\nu) + \beta_{vv}\beta_H N^*_{vv}(1+P)}. \end{aligned} \tag{3.12}$$

Determination of the reproduction number

The reproduction number R_0 is obtained through the computation of the eigenvalues of a Jacobian matrix. We use next-generation approach presented in [45] to find the model reproduction number.

We rearrange the equation as follows, starting with the infected classes;

$$\left.\begin{aligned} \dot{I_H} &= \beta_H S_H I_{vv} - (\gamma+\mu_H+\nu)I_H, \\ \dot{I_{vv}} &= \beta_{vv} S_{vv} I_H - \mu_{vv} I_{vv}, \\ \dot{S_H} &= \mu_H N_H - \beta_H S_H I_{vv} + \epsilon R_H - \mu_H S_H + \nu I_H, \\ \dot{R_H} &= \gamma I_H - (\mu_H + \epsilon)R_H, \\ \dot{S_{vv}} &= \mu_{vv} N_{vv} - \beta_{vv} S_{vv} I_H - \mu_{vv} S_{vv}. \end{aligned}\right\} \tag{3.13}$$

$$\mathcal{F} = \begin{pmatrix} \beta_H S_H I_{vv} \\ \beta_{vv} S_{vv} I_H \end{pmatrix} \quad \text{and} \quad \mathcal{V} = \begin{pmatrix} (\gamma+\mu_H+\nu)I_H \\ \mu_{vv} I_{vv} \end{pmatrix}.$$

We have two infectious classes, hence $m = 2$ and our Jacobian is of the form;

$$\mathcal{DF}|_{(E_0)} = \begin{pmatrix} \frac{\partial f_1}{\partial I_H} & \frac{\partial f_1}{\partial I_v v} \\ \frac{\partial f_2}{\partial I_H} & \frac{\partial f_2}{\partial I_v v} \end{pmatrix}.$$

Here the matrices $\mathcal{DF}|_{(E_0)}$ and $\mathcal{DV}|_{(x_0)}$ of the system at the disease free equilibrium point are given by

$$F = \mathcal{DF}|_{(E_0)} = \begin{pmatrix} 0 & \beta_H N_H^* \\ \beta_{vv} N_{vv}^* & 0 \end{pmatrix},$$

$$V = \mathcal{DV}|_{(E_0)} = \begin{pmatrix} \gamma + \mu_H + \nu & 0 \\ 0 & \mu_{vv} \end{pmatrix}.$$

$$V^{-1} = \frac{1}{\mu_{vv}(\gamma + \mu_H + \nu)} \begin{pmatrix} \mu_{vv} & 0 \\ 0 & (\gamma + \mu_H + \nu) \end{pmatrix}.$$

An evaluation of the product of F and inverse of V gives

$$FV^{-1}|_{(E_0)} = \begin{pmatrix} 0 & \frac{\beta_H N_H^*}{\mu_{vv}} \\ \frac{\beta_{vv} N_{vv}^*}{\gamma + \mu_H + \nu} & 0 \end{pmatrix}.$$

The eigenvalues of FV^{-1} are obtained by considering the characteristic polynomial that result by evaluating

$$\begin{vmatrix} -\lambda & \frac{\beta_H N_H^*}{\mu_{vv}} \\ \frac{\beta_{vv} N_{vv}^*}{\gamma + \mu_H + \nu} & -\lambda \end{vmatrix} = 0.$$

The spectral radius $\rho(FV^{-1})$, i.e the largest eigenvalues of FV^{-1} is given by $\max(R_0)$ which is the model reproduction number;

$$\mathcal{R}_0 = \sqrt{\frac{\beta_H N_H^* \beta_{vv} N_{vv}^*}{(\gamma + \mu_H + \nu)\mu_{vv}}} = \sqrt{\frac{\beta_H N_H^*}{(\gamma + \mu_H + \nu)} . \frac{\beta_{vv} N_{vv}^*}{\mu_{vv}}} = \sqrt{R_{0H}^c R_{0V}^c} = \sqrt{R_0}. \tag{3.14}$$

$\mathcal{R}_0$ is thus the model reproduction number. It describe the number of secondary cases of malaria infections that will result from the introduction of infected human (mosquito) into

a whole susceptible population of mosquitoes (humans) during the period of infectivity. The model reproduction number $\mathcal{R}_0$ has a square root because of the two generations required for, an infected vector or host to generate an infection. R_0 is a product of two threshold parameters R^c_{0H} and R^c_{0V}, where $R^c_{0H} = \frac{\beta_H N^*_H}{(\gamma+\mu_H+\nu)}$ and $R^c_{0V} = \frac{\beta_{vv} N^*_{vv}}{\mu_{vv}}$. R^c_{0H} is the average number of secondary infections generated by one infected human during his/her period of infectiousness. R^c_{0V} is the average number of secondary infections generated by one infected mosquito during its period of infectiousness.

We now give a brief interpretation of the terms in the reproduction number $\mathcal{R}_0$.

$\frac{1}{(\gamma+\mu_H+\nu)}$ is the average time a human being stays in the infectious class. $\frac{1}{\mu_{vv}}$ is the duration a mosquito spends in the infected class. $\beta_H N^*_H$ and $\beta_{vv} N^*_{vv}$ represent the effective contacts that result in an infection for the human population and vector population respectively.

We can thus write the endemic equilibrium point in terms of R_0, so that equation (3.12) becomes;

$$I^*_H = Q(R_0 - 1), \tag{3.15}$$

where

$$Q = \frac{\mu_{vv}(\gamma + \mu_H + \nu)}{(\gamma + \mu_H + \nu)\beta_{vv} + \beta_{vv} N^*_{vv} \beta_H (1 + P)}. \tag{3.16}$$

Using back substitution case when $I^*_H \neq 0$ we obtain from (3.11) where

$$R^*_H = PQ(R_0 - 1)$$

and

$$I^*_{vv} = \frac{(\gamma + \mu_H + \nu)Q(R_0 - 1)}{\beta_H (N^*_H - Q(R_0 - 1)(1 + P))}.$$

We can obtain S^*_H and S^*_{vv} from the expressions;

$$S^*_H = N^*_H - (I^*_H + R^*_H)$$

and

$$S^*_{vv} = N^*_{vv} - I^*_{vv}$$

respectively.

We will thus have a unique endemic equilibrium point

$$E_1 = (S_H^*, R_H^*, I_H^*, S_{vv}^*, I_{vv}^*).$$

We can write the following Theorem on the existence of the equilibrium point E_1.

Theorem 3.3.1 *The endemic equilibrium point E_1, exist for $R_0 > 1$.*

3.3.2 Stability of the disease free equilibrium point, E_0

We linearize the model (3.1) at the disease free equilibrium point and obtain the Jacobian matrix,

$$\begin{pmatrix} -\mu_H & \nu & \epsilon & 0 & -\beta_H N_H^* \\ 0 & -(\gamma+\mu_H+\nu) & 0 & 0 & \beta_H N_H^* \\ 0 & \gamma & (\epsilon+\mu_H) & 0 & 0 \\ 0 & -\beta_{vv} N_{vv}^* & 0 & -\mu_{vv} & 0 \\ 0 & \beta_{vv} N_{vv}^* & 0 & 0 & -\mu_{vv} \end{pmatrix}.$$

This matrix has five eigenvalues. Three of them are given by;
$\eta_1 = -\mu_H$, $\eta_2 = -\mu_{vv}$, $\eta_3 = -(\mu_H + \epsilon)$. We note that $\eta_i < 0$ for $i = 1, 2, 3$.

The other two eigenvalues are obtained from the solution of;

$$\begin{vmatrix} -(\gamma+\mu_H+\nu)-\eta & \beta_H N_H^* \\ \beta_{vv} N_{vv}^* & -\mu_{vv}-\eta \end{vmatrix} = 0.$$

We thus have the characteristics equation,

$$\eta^2 + (\gamma+\mu_H+\nu+\mu_{vv})\eta + (\gamma+\mu_H+\nu)\mu_{vv} - \beta_{vv} N_{vv}^* \beta_H N_H^* = 0. \tag{3.17}$$

The solutions of (3.17) are,

$$\eta_4 = -(\gamma+\mu_H+\nu+\mu_{vv}) - \sqrt{(\gamma+\mu_H+\nu+\mu_{vv})^2 - 4((\gamma+\mu_H+\nu)\mu_{vv} - \beta_{vv} N_{vv}^* \beta_H N_H^*)},$$
$$\eta_5 = -(\gamma+\mu_H+\nu+\mu_{vv}) + \sqrt{(\gamma+\mu_H+\nu+\mu_{vv})^2 - 4((\gamma+\mu_H+\nu)\mu_{vv} - \beta_{vv} N_{vv}^* \beta_H N_H^*)}.$$

Therefore η_4 and η_5 can be written as follows, in terms of R_0

$$\begin{aligned}\eta_4 &= -(\gamma+\mu_H+\nu+\mu_{vv}) - \sqrt{(\gamma+\mu_H+\nu+\mu_{vv})^2 - 4(\gamma+\mu_H+\nu)\mu_{vv}(1-R_0)},\\ \eta_5 &= -(\gamma+\mu_H+\nu+\mu_{vv}) + \sqrt{(\gamma+\mu_H+\nu+\mu_{vv})^2 - 4(\gamma+\mu_H+\nu)\mu_{vv}(1-R_0)}.\end{aligned}$$

If $R_0 < 1$ then η_4 and η_5 are both negative. A consideration of the signs of the eigenvalues gives the following Theorem,

Theorem 3.3.2 *If $R_0 < 1$ then the disease free equilibrium point, E_0 is locally asymptotically stable otherwise it is unstable.*

3.3.3 Stability of the endemic equilibrium point, E_1

To determine the stability of E_1 we can reduce our model to a system of three equations using the following transformations: $R_H = N_H - S_H - I_H$ and $S_{vv} = N_{vv} - I_{vv}$. The reduced system is given by:

$$\left.\begin{aligned}S_H &= \lambda_H N_H - \beta_H S_H I_{vv} + \epsilon(N_H - S_H - I_H) - \mu_H S_H + \nu I_H,\\ I_H &= \beta_H S_H I_{vv} - (\gamma+\mu_H+\nu) I_H,\\ I_{vv} &= \beta_{vv}(N_{vv} - I_{vv}) I_H - \mu_{vv} I_{vv}.\end{aligned}\right\} \tag{3.18}$$

This system has the same stability properties as (3.1), and determination of equilibrium point is given in Appendix (B). To investigate the stability analysis of the endemic equilibrium point, we consider the Jacobian matrix at E_1 so that;

$$J_{E_1} = \begin{pmatrix} -(\beta_H I^*_{vv} + \epsilon + \mu_H) - b & -\epsilon + \nu & \beta_H S^*_H \\ \beta_H I^*_{vv} & -(\gamma+\mu_H+\nu) - b & \beta_H S^*_H \\ 0 & \beta_{vv}(N^*_{vv} - I^*_{vv}) & -(\beta_{vv} I^*_H + \mu_{vv}) - b \end{pmatrix}.$$

The characteristic equation of J_{E_1} is given by;

$$b^3 + Ab^2 + Bb + C = 0, \tag{3.19}$$

where

$$\begin{aligned}
A &= (\beta_H I^*_{vv} + \epsilon + \mu_H) + (\gamma + \mu_H + \nu) + \beta_{vv} I^*_H + \mu_{vv}, \\
B &= [(\gamma + \mu_H + \nu) + (\beta_{vv} I^*_H + \mu_{vv})][\beta_H I^*_{vv} + \epsilon + \mu_H] + (\gamma + \mu_H + \nu)(\beta_{vv} I^*_H + \mu_{vv}) \\
&\quad -\beta_{vv}\beta_H S^*_H (N^*_{vv} - I^*_{vv}) - (\nu - \epsilon)\beta_H I^*_{vv}, \\
C &= (\gamma + \mu_H + \nu)(\beta_{vv} I^*_H + \mu_{vv})(\beta_H I^*_{vv} + \epsilon + \mu_H) + \beta_{vv}\beta_H^2 I^*_{vv} S^*_H (N^*_{vv} - I^*_{vv}) \\
&\quad -(\beta_H I^*_{vv} + \epsilon + \mu_H)[\beta_{vv}\beta_H S^*_H (N^*_{vv} - I^*_{vv})] - (\nu - \epsilon)\beta_H I^*_{vv}(\beta_{vv} I^*_H + \mu_{vv}).
\end{aligned}$$

Expressing C in terms of the reproduction number, we get

$$\begin{aligned}
C &= (\mu_H + \epsilon)\mu_{vv}(\gamma + \mu_H + \nu)\left[\frac{\beta_H \beta_{vv} N^*_{vv} N^*_H}{\mu_{vv}(\gamma + \mu_H + \nu)} - 1\right], \\
&= (\mu_H + \epsilon)\mu_{vv}(\gamma + \mu_H + \nu)\left[R_0 - 1\right].
\end{aligned}$$

In this case $C > 0$ if $R_0 > 1$.
We also note that;

$$B = (\epsilon + \mu_H)(\gamma + \mu_H + \nu)\left(\frac{N^*_H}{S^*_H}\right) + (\beta_{vv} I^*_H + \mu_{vv})(\beta_H I^*_{vv} + \epsilon + \mu_H) + \beta_{vv}\beta_H S^*_H I^*_{vv} > 0,$$

and clearly $A > 0$,

and

$$\begin{aligned}
(AB) &- C \\
&= [(\beta_H I^*_{vv} + \epsilon + \mu_H) + (\gamma + \mu_H + \nu) + \beta_{vv} I^*_H + \mu_{vv}] \\
&\quad \left[(\epsilon + \mu_H)(\gamma + \mu_H + \nu)\left(\frac{N^*_H}{S^*_H}\right) + (\beta_{vv} I^*_H + \mu_{vv})(\beta_H I^*_{vv} + \epsilon + \mu_H) + \beta_{vv}\beta_H S^*_H I^*_{vv}\right] \\
&\quad - \left[(\mu_H + \epsilon)\mu_{vv}(\gamma + \mu_H + \nu)(R_0 - 1)\right].
\end{aligned}$$

Here $(AB - C) > 0$ if $R_0 > 1$. By the Routh-Hurwitz stability criteria, we thus state the following Theorem,

Theorem 3.3.3 *The endemic equilibrium point, E_1 is locally asymptotically stable for $R_0 > 1$, otherwise it is unstable.*

3.4 Non constant population model

High mortality rates due to malaria have been recorded world wide. A more realistic consideration is given when we allow for deaths due to the disease. A removal of deaths due to the diseases is a gross underestimate of the effect of malaria on an infected individual.

3.4.1 Equilibria and model reproduction number

We now consider the case $\sigma \neq 0$ such that the population is not constant. We calculate the equilibria as we have done for the case $\sigma = 0$.

From the system (3.1) the equations becomes.

$$\left.\begin{aligned} 0 &= \Pi_H - \beta_H S_H I_{vv} + \epsilon R_H - \mu_H S_H + \nu I_H, \\ 0 &= \beta_H S_H I_{vv} - \gamma I_H - \mu_H I_H - \sigma I_H - \nu I_H, \\ 0 &= \gamma I_H - \mu_H R_H - \epsilon R_H, \\ 0 &= \Pi_{vv} - \beta_{vv} S_{vv} I_H - \mu_{vv} S_{vv}, \\ 0 &= \beta_{vv} S_{vv} I_H - \mu_{vv} I_{vv}. \end{aligned}\right\} \tag{3.20}$$

As before

$$\begin{aligned} N_H &= S_H + I_H + R_H, \\ N_{vv} &= S_{vv} + I_{vv}. \end{aligned}$$

The growth of human population is obtained from the differential equation

$$\frac{dN_H}{dt} = \Pi_H - \mu_H N_H - \sigma I_H.$$

In the absence of the disease

$$E_2 = (\frac{\Pi_H}{\mu_H}, 0, 0, \frac{\Pi_{vv}}{\mu_{vv}}, 0),$$

the population tends to $\frac{\Pi_H}{\mu_H}$ i.e $N_H \longrightarrow \frac{\Pi_H}{\mu_H}$ as $t \longrightarrow \infty$.

The vector population is obtained by the differential equation

$$\frac{dN_{vv}}{dt} = \Pi_{vv} - \mu_{vv}N_{vv}, \quad N_{vv} = \frac{\Pi_{vv}}{\mu_{vv}}.$$

Determination of reproduction number

In this section we use the method of next-generation method.

$$\mathcal{F} = \begin{pmatrix} \beta_H S_H^* I_{vv}^* \\ \beta_{vv} S_{vv}^* I_H^* \end{pmatrix} \quad \text{and} \quad \mathcal{V} = \begin{pmatrix} (\gamma + \mu_H + \sigma + \nu) I_H^* \\ \mu_{vv} I_{vv}^* \end{pmatrix}.$$

The matrix $\mathcal{DF}$ and $\mathcal{DV}$ at the disease-free equilibrium (E_2) are given by;

$$F = \begin{pmatrix} 0 & \frac{\beta_H \Pi_H}{\mu_H} \\ \frac{\beta_{vv}\Pi_{vv}}{\mu_{vv}} & 0 \end{pmatrix}.$$

$$V = \begin{pmatrix} \gamma + \mu_H + \sigma + \nu & 0 \\ 0 & \mu_{vv} \end{pmatrix},$$

$$V^{-1} = \frac{1}{\mu_{vv}(\gamma + \mu_H + \sigma + \nu)} \begin{pmatrix} \mu_{vv} & 0 \\ 0 & (\gamma + \mu_H + \sigma + \nu) \end{pmatrix}.$$

$$FV^{-1} = \begin{pmatrix} 0 & \frac{\beta_H \Pi_H}{\mu_H \mu_{vv}} \\ \frac{\beta_{vv}\Pi_{vv}}{\mu_{vv}(\gamma+\mu_H+\sigma+\nu)} & 0 \end{pmatrix}.$$

The eigenvalue of FV^{-1} is as follows;

$$\begin{vmatrix} -\chi & \frac{\beta_H \Pi_H}{\mu_H \mu_{vv}} \\ \frac{\beta_{vv}\Pi_{vv}}{\mu_{vv}(\gamma+\mu_H+\sigma+\nu)} & -\chi \end{vmatrix} = 0.$$

The spectral radius $\rho(FV^{-1})$ which is $\max(R_0)$ as given below;

$$\mathcal{R}_{0*} = \sqrt{\frac{\beta_H \Pi_H \beta_{vv} \Pi_{vv}}{(\gamma + \mu_H + \sigma + \nu)\mu_H \mu_{vv}^2}} = \sqrt{\frac{\beta_H \Pi_H}{\mu_H(\gamma + \mu_H + \sigma + \nu)} . \frac{\beta_{vv}\Pi_{vv}}{\mu_{vv}^2}} = \sqrt{R_{0H*}.R_{0V*}} = \sqrt{R_{0*}}. \tag{3.21}$$

The $\mathcal{R}_{0*}$ is the product of R_{0H*} and R_{0V*}. R_{0H*} is the average number of secondary infections generated by one infected human during his/her period of infectiousness. R_{0V*} is the average number of secondary infections generated by one infected mosquito during its period of infectiousness.

An interpretation of the terms in the reproduction number $\mathcal{R}_{0*}$.

$\frac{1}{(\gamma+\mu_H+\sigma+\nu)}$ is the average time a human being stays in the infectious class.

The endemic equilibrium point (EEP) of the system is given by $E_3 = (S_H^*, I_H^*, R_H^*, S_{vv}^*, I_{vv}^*)$ where

$$\begin{aligned}
S_H^* &= N_H^* - (1+P)Q_1(R_{0*} - 1), \\
I_H^* &= Q_1(R_{0*} - 1), \\
R_H^* &= PQ_1(R_{0*} - 1), \\
S_{vv}^* &= N_{vv}^* - \frac{(\gamma + \mu_H + \sigma + \nu)Q_1(R_{0*} - 1)}{\beta_H(N_H^* - Q_1(R_{0*} - 1)(1+P))}, \\
I_{vv}^* &= \frac{(\gamma + \mu_H + \sigma + \nu)Q_1(R_{0*} - 1)}{\beta_H(N_H^* - Q_1(R_{0*} - 1)(1+P))},
\end{aligned}$$

following the steps presented in section (3.3.1). But here $Q_1 = \frac{\mu_{vv}(\gamma+\mu_H+\sigma+\nu)}{(\gamma+\mu_H+\sigma+\nu)\beta_{vv}+\beta_{vv}N_{vv}^*\beta_H(1+P)}$. We thus have the following result on the existence of the point E_3,

Theorem 3.4.1 *The endemic equilibrium point, E_3 exist for $R_{0*} > 1$.*

Proposition 1 *A comparison of R_0 and R_{0*} gives the relation of $R_{0*} < R_0$ for $N_H^* = \frac{\Pi_H}{\mu_H}$. We make a claim that*

$$R_{0*} < R_0 \Longrightarrow \frac{\Pi_H \Pi_{vv}(\mu_H + \gamma + \nu) - N_H^* N_{vv}^*(\mu_H + \gamma + \sigma + \nu)\mu_H \mu_{vv}}{(\mu_H + \gamma + \sigma + \nu)(\mu_H + \gamma + \nu)\mu_H \mu_{vv}^2} < 0.$$

$$\Pi_H \Pi_{vv}(\mu_H + \gamma + \nu) - N_H^* N_{vv}^*(\mu_H + \gamma + \sigma + \nu)\mu_H \mu_{vv} - N_H^* N_{vv}^* \mu_H \mu_{vv} \sigma < 0,$$

$$(\mu_H+\gamma+\nu)[\Pi_H\Pi_{vv}-N_H^*N_{vv}^*\mu_H\mu_{vv}]-N_H^*N_{vv}^*\mu_H\mu_{vv}\sigma<0,$$

$$(\mu_H+\gamma+\nu)\mu_H\mu_{vv}\left(\frac{\Pi_H}{\mu_H}\frac{\Pi_{vv}}{\mu_{vv}}-N_H^*N_{vv}^*\right)-N_H^*N_{vv}^*\mu_H\mu_{vv}\sigma<0.$$

Note as

$$t\longrightarrow\infty\quad N_H^*\longrightarrow\quad\frac{\Pi_H}{\mu_H},\quad N_{vv}^*=\frac{\Pi_{vv}}{\mu_{vv}}.$$

$\frac{\Pi_H}{\mu_H}$ *is thus the maximum population that* N_H^* *can be. So* $N_H^*\leq\frac{\Pi_H}{\mu_H}$. *For the* $N_H^*=\frac{\Pi_H}{\mu_H}$ *the claim is true.*

This means that the constant population model overestimates the average number of secondary infections.

3.4.2 Stability of the disease free equilibrium point, E_2

At the disease free equilibrium point the Jacobian matrix is given by;

$$J_{E_2}=\begin{pmatrix}-\mu_H & \nu & \epsilon & 0 & -\frac{\beta_H\Pi_H}{\mu_H}\\ 0 & -(\gamma+\mu_H+\sigma+\nu) & 0 & 0 & \frac{\beta_H\Pi_H}{\mu_H}\\ 0 & \gamma & (\epsilon+\mu_H) & 0 & 0\\ 0 & -\frac{\beta_{vv}\Pi_{vv}}{\mu_{vv}} & 0 & -\mu_{vv} & 0\\ 0 & \frac{\beta_{vv}\Pi_{vv}}{\mu_{vv}} & 0 & 0 & -\mu_{vv}\end{pmatrix}.$$

The eigenvalues of the matrix J_{E_2} are;
$\chi_1=-\mu_H$, $\chi_2=-\mu_{vv}$, $\chi_3=-(\mu_H+\epsilon)$, and the solution of the characteristic equation obtained from;

$$\begin{vmatrix}-(\gamma+\mu_H+\sigma+\nu)-\chi & \frac{\beta_H\Pi_H}{\mu_H}\\ \frac{\beta_{vv}\Pi_{vv}}{\mu_{vv}} & -\mu_{vv}-\chi\end{vmatrix}=0.$$

The characteristic equation is given by

$$\chi^2+a_1\chi+a_0=0,$$

where

$a_1 = \gamma + \mu_H + \sigma + \nu + \mu_{vv}$ and $a_0 = (\gamma + \mu_H + \sigma + \nu)\mu_{vv} - \frac{\beta_{vv}\Pi_{vv}}{\mu_{vv}}\frac{\beta_H \Pi_H}{\mu_H}$.

We thus have;

$$\begin{aligned} \chi_4 &= -a_1 - \sqrt{a_1^2 - 4(\gamma + \mu_H + \sigma + \nu)\mu_{vv}(1 - R_{0*})}, \\ \chi_5 &= -a_1 + \sqrt{a_1^2 - 4(\gamma + \mu_H + \sigma + \nu)\mu_{vv}(1 - R_{0*})}. \end{aligned}$$

The eigenvalues are all negative provided $R_{0*} < 1$, We can thus summarize our results in the following Theorem;

Theorem 3.4.2 *The disease free equilibrium point, E_2 is locally asymptotically stable if $R_{0*} < 1$ otherwise it is unstable.*

3.4.3 Stability analysis of the endemic equilibrium point, E_3

The Jacobian matrix for non constant population model is as follows;

$$J_{E_3} = \begin{pmatrix} -\mu_H & 0 & -\sigma & 0 & 0 \\ \epsilon & -(\beta_H I^*_{vv} + Y_1) & \nu - \epsilon & 0 & -\beta_H S^*_H \\ 0 & \beta_H I^*_{vv} & -Y_2 & 0 & \beta_H S^*_H \\ 0 & 0 & 0 & -\mu_{vv} & 0 \\ 0 & 0 & \beta_{vv}(N^*_{vv} - I^*_{vv}) & \beta_{vv} I^*_H & -(\beta_{vv} I^*_H + \mu_{vv}) \end{pmatrix}.$$

Let $Y_1 = \mu_H + \epsilon$ and $Y_2 = \gamma + \mu_H + \sigma + \nu$. The eigenvalues of J_{E_3} are given by
$d_1 = -\mu_{vv}$,
and the solution of the characteristic equation is obtained from;

$$\begin{vmatrix} -\mu_H - d & 0 & -\sigma & 0 \\ \epsilon & -(\beta_H I^*_{vv} + Y_1) - d & \nu - \epsilon & -\beta_H S^*_H \\ 0 & \beta_H I^*_{vv} & -Y_2 - d & \beta_H S^*_H \\ 0 & 0 & \beta_{vv}(N^*_{vv} - I^*_{vv}) & -(\beta_{vv} I^*_H + \mu_{vv}) - d \end{vmatrix} = 0,$$

$$d^4 + A_1 d^3 + B_1 d^2 + C_1 d + D_1 = 0,$$

where the characteristic equation is thus given by

$$\begin{aligned}
A_1 &= \alpha+\epsilon+\nu+\sigma+I^*_{vv}\beta_H+I^*_H\beta_{vv}+3\mu_H+\mu_{vv},\\
B_1 &= \epsilon(\sigma+\nu+\gamma)+I^*_{vv}\beta_H(\gamma+\epsilon+\sigma)+(I^*_H\beta_{vv}+\mu_{vv})\epsilon+2\mu_H(I^*_H\beta_{vv}+\mu_{vv})+3\mu_H^2\\
&\quad +S^*_HI^*_{vv}\beta_H\beta_{vv}+I^*_HI^*_{vv}\beta_H\beta_{vv}+2\mu_H(\gamma+\epsilon+\nu+\sigma)+I^*_{vv}\beta_H(\mu_H+\mu_{vv})>0,\\
C_1 &= I^*_H\beta_{vv}\epsilon(\gamma+\nu+\sigma+2\mu_H)+I^*_{vv}\beta_H(I^*_H\beta_{vv}+\mu_{vv})(\sigma+\epsilon+\gamma+2\mu_H)\\
&\quad +I^*_{vv}\beta_H\mu_H(\epsilon+\sigma+\mu_H+\gamma+2\nu)+S^*_HI^*_{vv}\beta_H\beta_{vv}(2\mu_H+\epsilon)-N^*_{vv}S^*_H\beta_H\beta_{vv}(2\mu_H+\epsilon)\\
&\quad +I^*_{vv}\beta_H\epsilon\sigma+I^*_H\beta_{vv}\mu_H[2(\gamma+\sigma)+3\mu_H]+\mu_H^2(\gamma+\epsilon+\nu+\sigma+\mu_H)\\
&\quad +\mu_{vv}\epsilon(\nu+\sigma+\gamma)+\mu_H\epsilon(\gamma+\nu+\sigma)+\mu_H\mu_{vv}[2(\gamma+\epsilon+\nu+\sigma)+3\mu_H],
\end{aligned}$$

$D_1 = I^*_H(K_1)$,
with

$$\begin{aligned}
K_1 &= \left(\frac{\beta_{vv}N^*_{vv}}{\beta_{vv}I^*_H+\mu_{vv}}\right)\beta_H\beta_{vv}[\sigma(\mu_H+\epsilon)+\mu_H(\gamma+\epsilon+\mu_H)]+\mu_H\beta_{vv}(\gamma+\mu_H\sigma+\nu)(\mu_H+\epsilon)\\
&\quad +\left(\frac{\beta_{vv}N^*_{vv}}{\beta_{vv}I^*_H+\mu_{vv}}\right)\beta_H\mu_H\mu_{vv}(\gamma+\epsilon+\sigma+\mu_H).
\end{aligned}$$

Note that $D_1>0$ for $R^*_0>0$ since $K_1>0$.
Due to complexity and the size of the expressions for B_1, C_1 and D_1, we make the following conclusions without going through further calculations;
If

$$A_1>0,\ B_1>0,\ C_1>0,\ D_1>0,\ A_1B_1-C_1>0 \tag{3.22}$$

and

$$(A_1B_1-C_1)C_1-A_1^2D_1>0. \tag{3.23}$$

then all the eigenvalues of J_{E_3} have negative real parts. This follows from the Routh-Hurwitz criterion. We thus state the following Theorem on the local stability of E_3

Theorem 3.4.3 *The endemic equilibrium points, E_3 is locally asymptotically stable if condition described in (3.22 and 3.23) are satisfied.*

3.5 Numerical simulations

Our numerical results are obtained using Matlab. Numerical simulations enable us to observe disease progression patterns and quantity some key epidemiological parameters. To illustrate our numerical results, we begin by outlaying some epidemiological parameter values, some based on the model assumptions as some obtained from published literature. These results are used to confirm some of the key analytic findings of the model. We now give a brief discussion on how some of the parameters were estimated. We quickly acknowledge the difficulty in estimating some of these parameters. Estimates of some of the parameters are unknown especially parameters associated with disease transmission probability that vary depending on several factors. These factors depend on the host, the environment and the vector itself. Environmental factors such as temperature, rainfall patterns and humidity determine the mosquito survival and infectivity.

Malaria is more prevalent in regions where mosquito breeding is favorable like tropical areas such as sub-Sahara Africa. The mortality rate for humans is assumed to be in the range $1/60 - 1/50$ per year. We assume survival of mosquitoes to be between 4 and 21 days as given in [12, 33]. The effective contact rate for both the hosts and vectors are assumed to lie in the interval $(0, 1)$ [10]. The death rate due to malaria is assumed as $(0.004, 0.008)$ per day. We assumed an estimated recovery rate which is the same as rate of acquiring immunity to be $(0.04, 0.25)$ per day. The rate of arrival of new susceptible mosquito is estimated from $(245, 2500)$ per day and for human population is estimated to be $(0.033, 0.52)$ per day.

For our simulations, firstly we begin by considering the constant population model. We assume a small community population of 10000 people and the following initial conditions for the human population $(S_H, I_H, R_H) = (9990, 10, 0)$. For the vector population, we assume a hypothetical value for the mosquito population $N_{vv} = 25000$. This is by no means from a real scenario but the population is chosen just for simulation purposes. The initial conditions chosen are $(S_{vv}, I_{vv}) = (24970, 30)$.

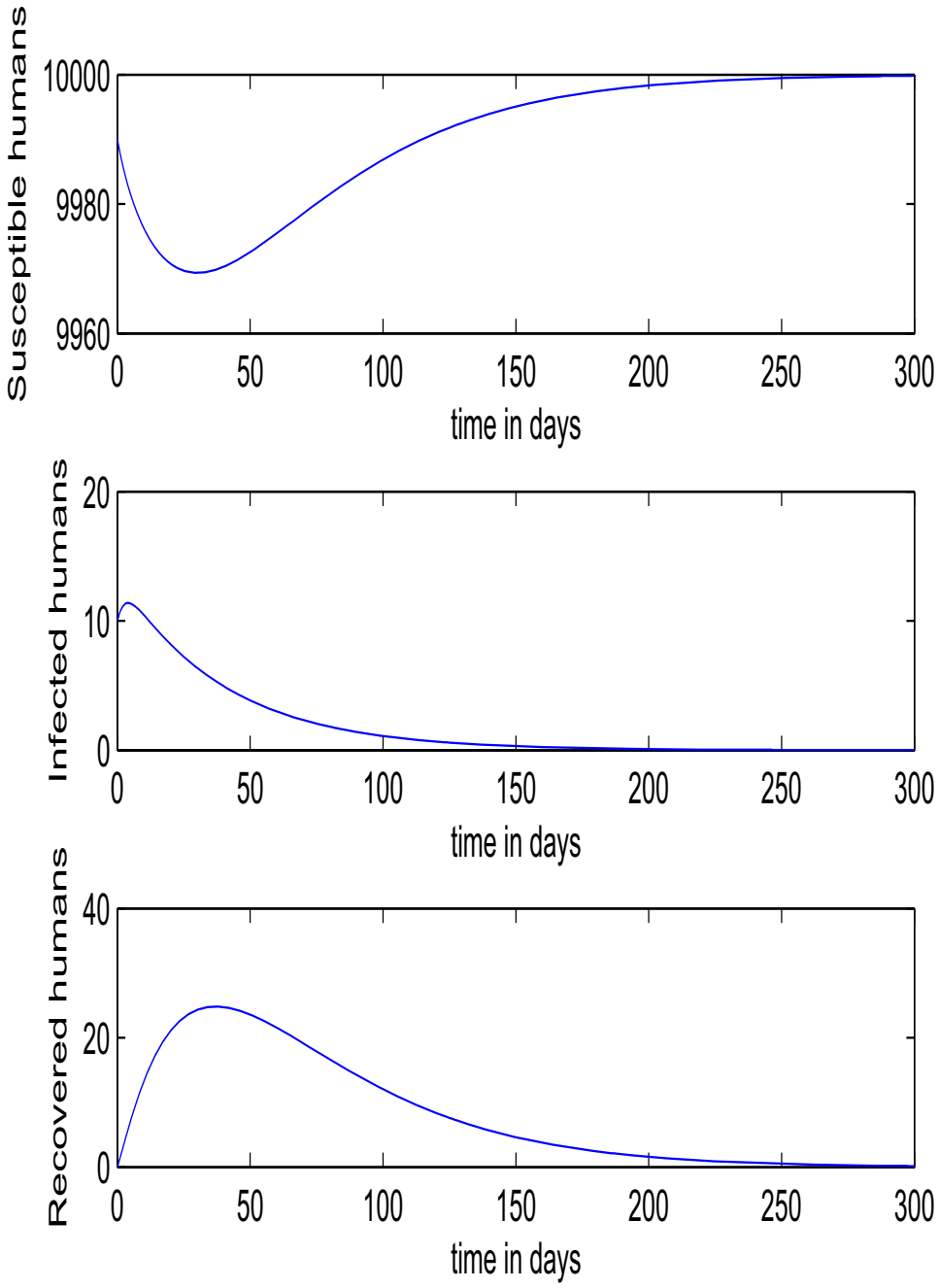


FIG. 3.2 (a)

We begin by considering the disease free state. For $R_0 = 0.8625$, then the dynamics of malaria in the human population is represented by FIG. 3.2 (a) and the vector populations

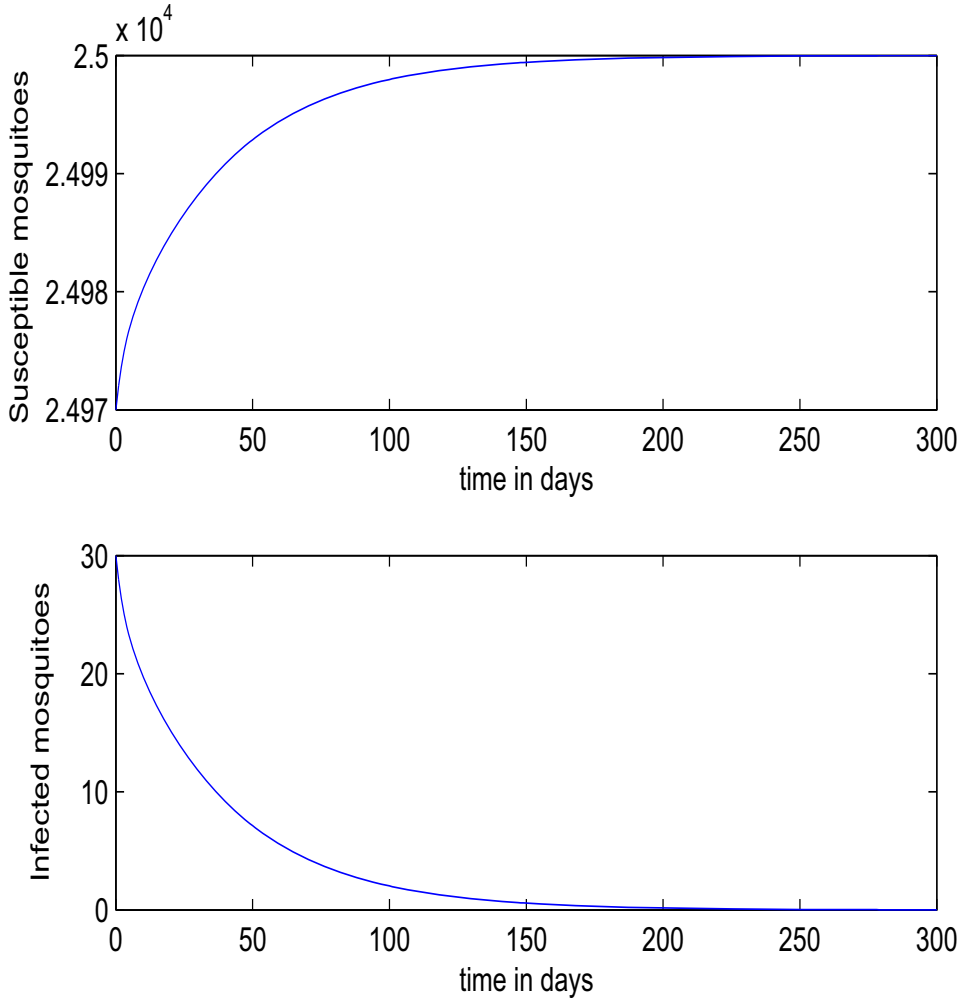


FIG. 3.2 (b)

FIG. 3.2. Represents a disease free state for the constant population, with the following parameter values: $\mu_H = 0.000054, \mu_{vv} = 0.16, \epsilon = 0.03, \gamma = 0.14, \beta_H = 0.00001, \beta_{vv} = 0.00001, \nu = 0.07$ and $R_0 = 0.8625$.

by FIG. 3.2 (b). The disease clears from both populations. Only the susceptible humans and mosquitoes remaining. This result is in agreement with Theorem (3.3.2). Using the same initial conditions and $R_0 = 2.9456$, the dynamics of the disease are represented by FIG. 3.3 (a) and (b). The graphs show that the infected individuals do not vanish from the populations. This corresponds to an endemic state as given in Theorem (3.3.3).

Secondly we consider the non constant population model. Using the same initial conditions

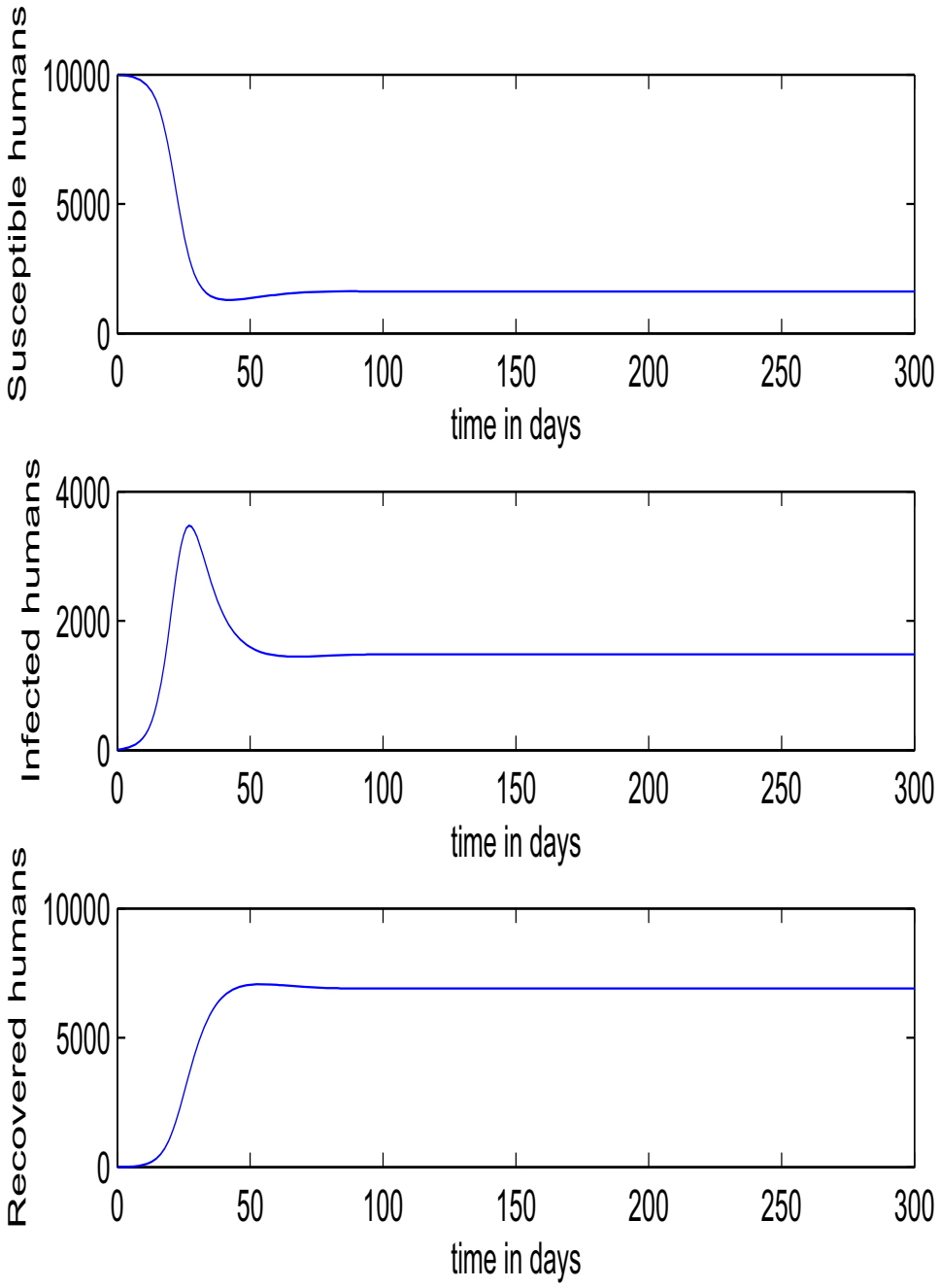


FIG. 3.3 (a)

but different parameter values, it follows from the FIG. 3.4 that, both humans and vectors populations are approaching disease free equilibrium by having $R_0 = 0.8435$. This result

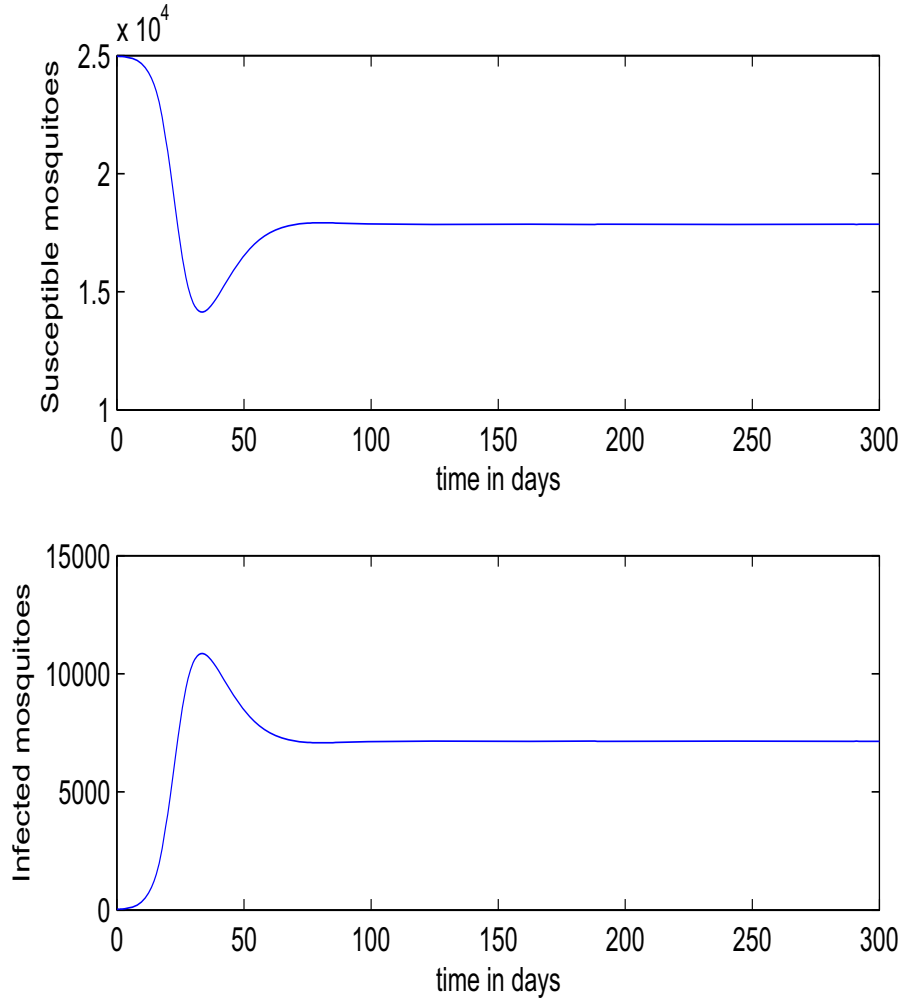


FIG. 3.3 (b)

FIG. 3.3. Depicts endemic equilibrium state for the constant population with the following parameter values: $\mu_H = 0.000054, \mu_{vv} = 0.1, \epsilon = 0.03, \gamma = 0.14, \beta_H = 0.000027, \beta_{vv} = 0.000027, \nu = 0.07$ and $R_0 = 2.9456$.

can be compared to Theorem (3.4.2). We then consider a situation where disease exists in the populations with $R_0 = 2.5925$ as shown in FIG. 3.5 for both human and mosquito population. This allows us to compare with Theorem (3.4.3) of stability of the endemic equilibrium point.

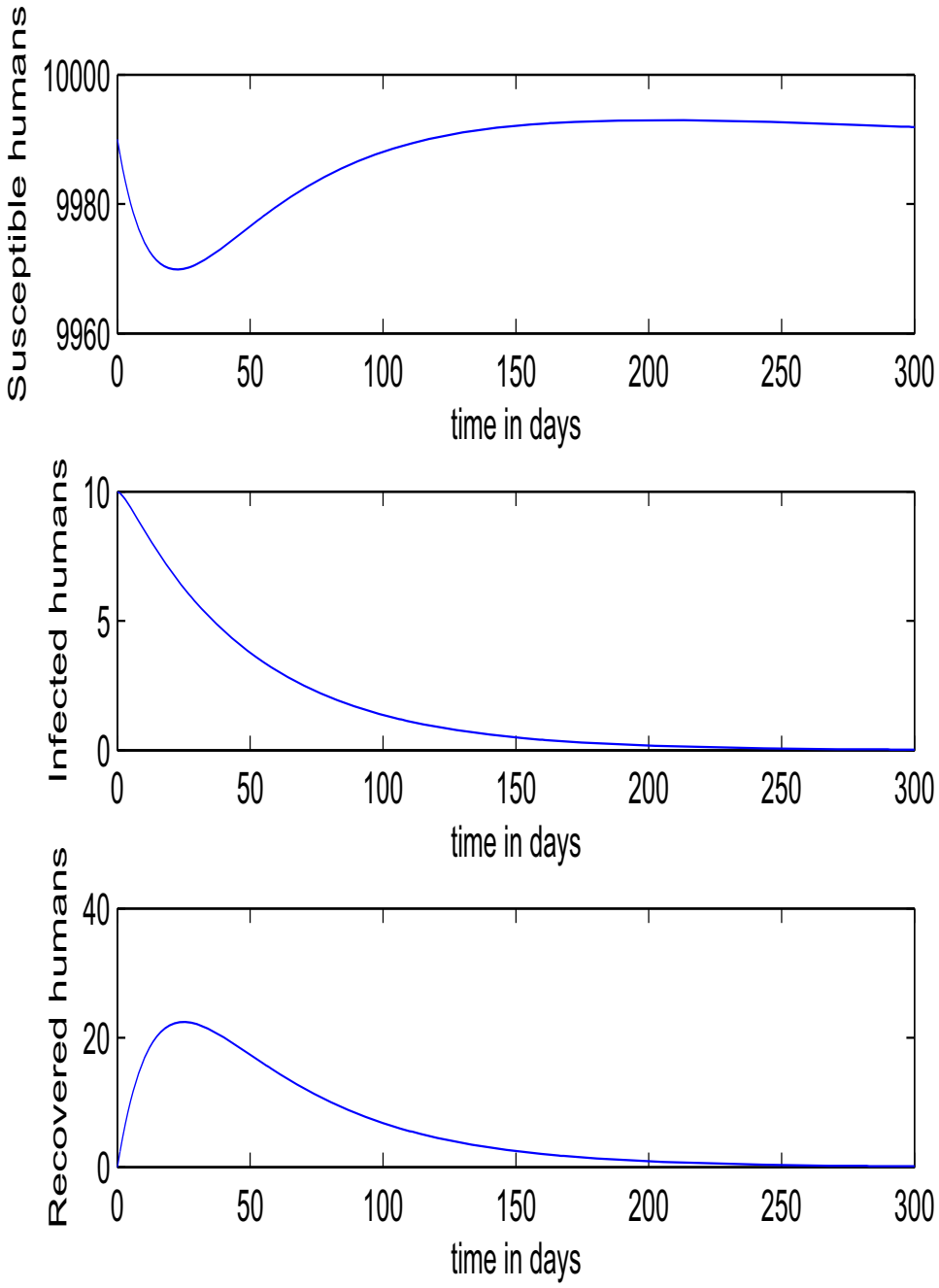


FIG. 3.4 (a)

We now investigate the role of some key epidemiological parameters. We investigate the effect of varying μ_{vv} the death rate of mosquitoes. We desire to find out whether this

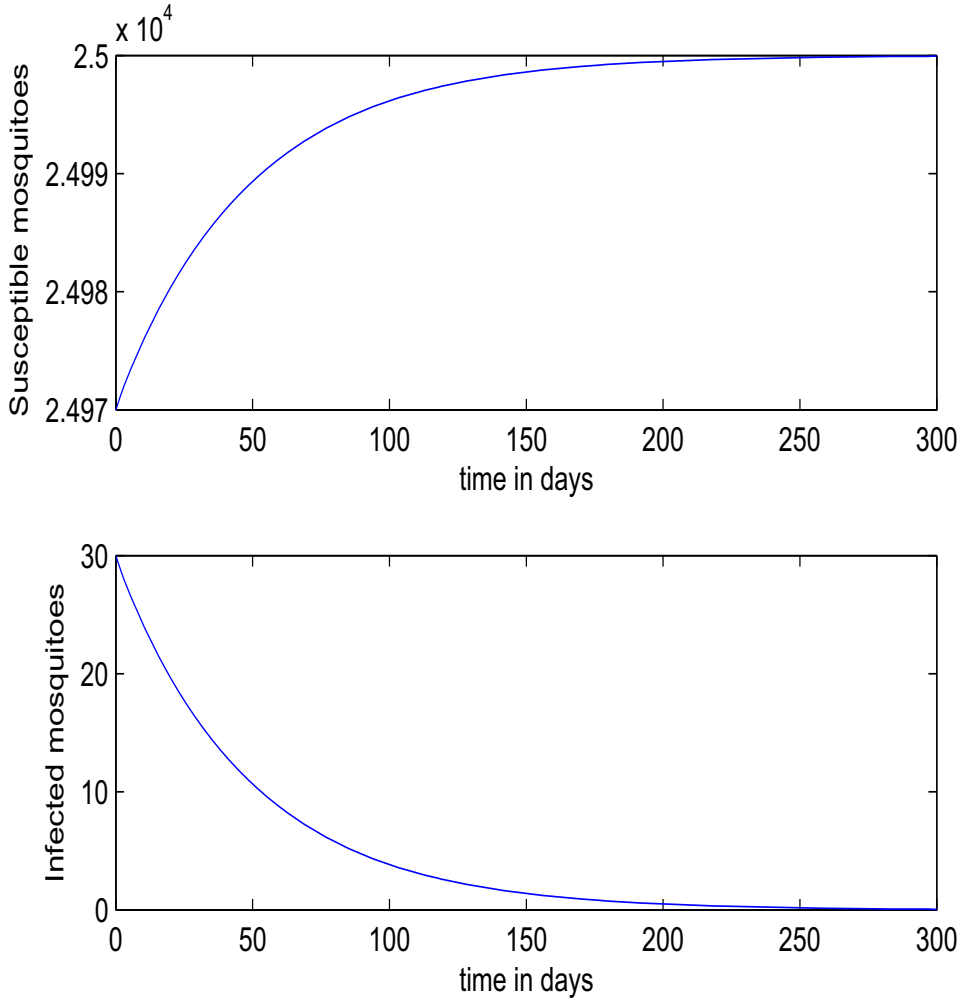


FIG. 3.4 (b)

FIG. 3.4. A disease free for a variable simple model with parameter values: $\mu_H = 0.000054, \mu_{vv} = 0.1, \epsilon = 0.07, \gamma = 0.25, \beta_H = 0.000009, \beta_{vv} = 0.000009, \nu = 0.02, \Pi_{vv} = 2500, \Pi_H = 0.52, \sigma = 0.004$ and $R_0 = 0.8435$.

parameter should be increased, and what would happen to the prevalence of malaria in the human population. An increased mortality rate of mosquitoes may be taken to mean increased use of insectsides or chemicals that result in the death of more mosquitoes. The FIG. 3.6 (a), shows the prevalence of malaria for varying mortality rates μ_{vv} of the mosquitoes. It shows that as we increase the mortality rate of the mosquitoes the prevalence of malaria decrease.

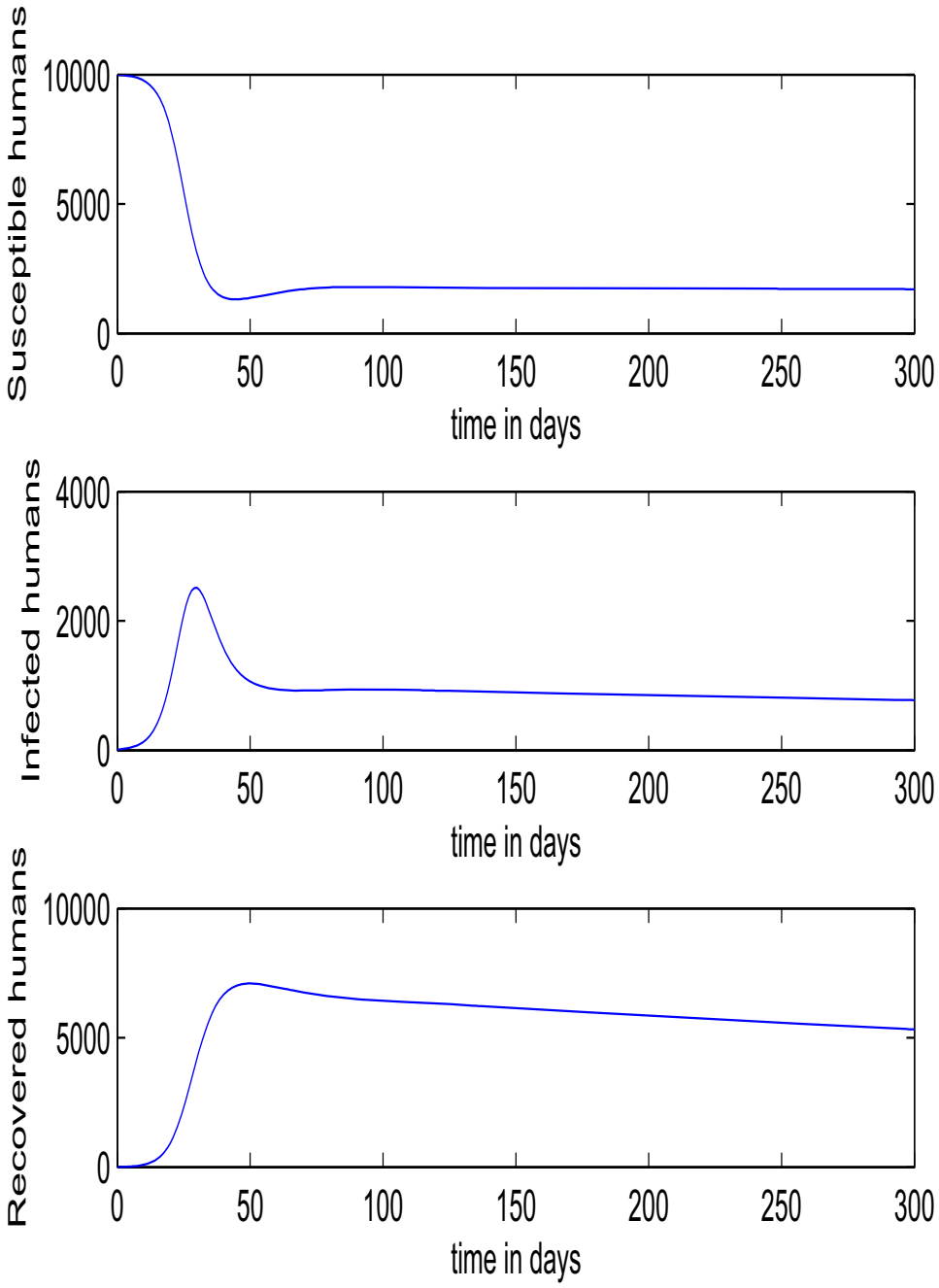


FIG. 3.5 (a)

As we increase the killing of mosquitoes we reduce the prevalence of malaria to the population. So, eradication of mosquitoes can be a useful control measure in the control of

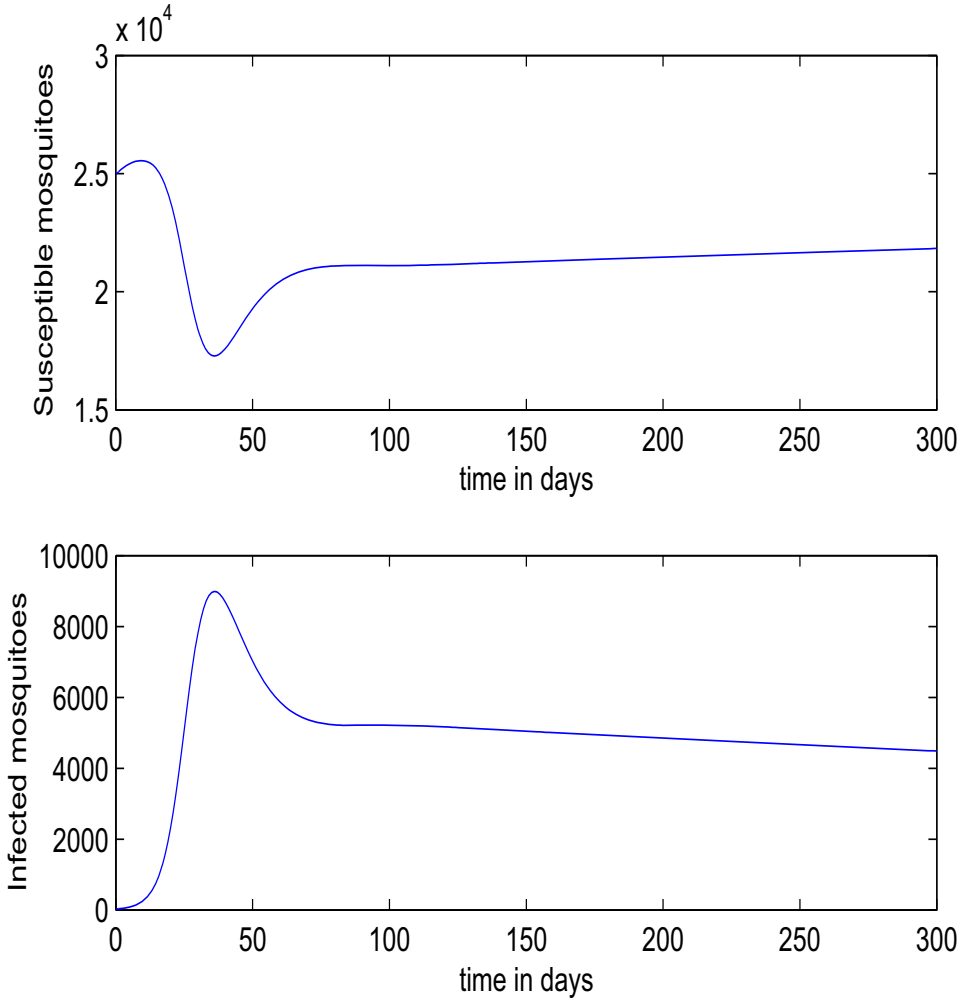
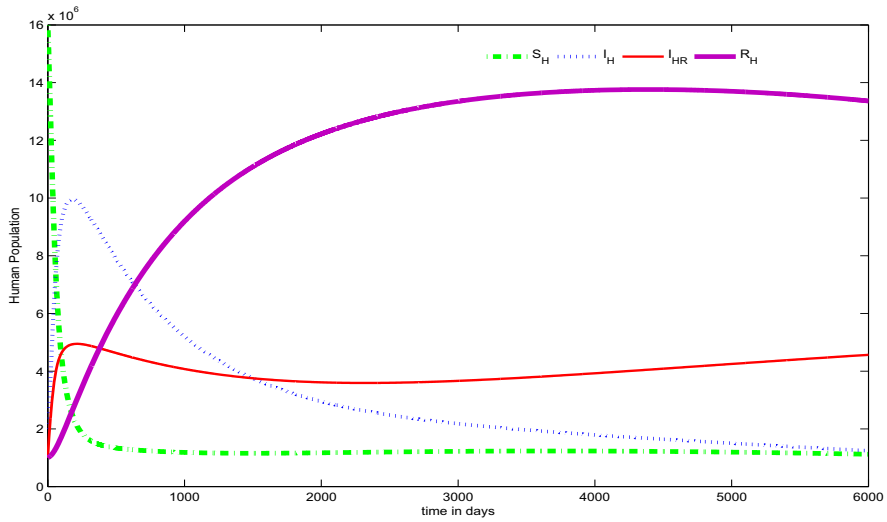


FIG. 3.5 (b)

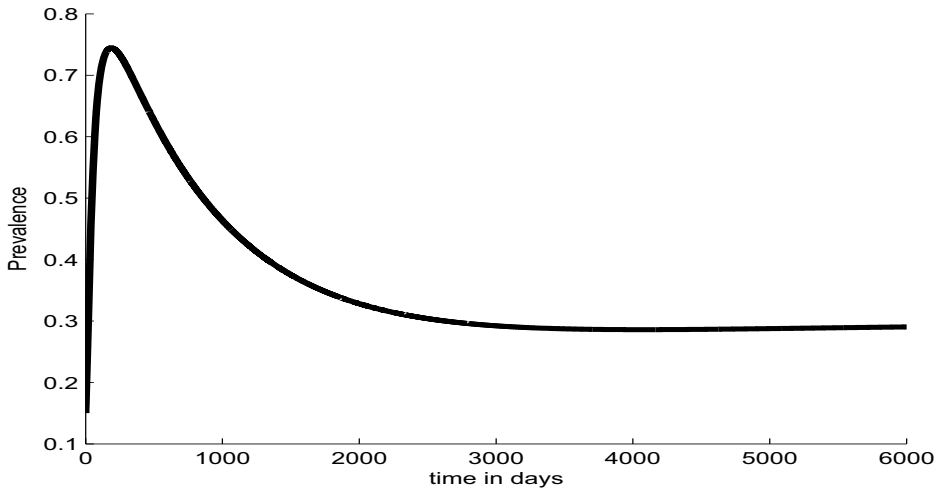
FIG. 3.5. An endemic equilibrium for a variable simple model with parameter values: $\mu_H = 0.000054, \mu_{vv} = 0.095, \epsilon = 0.03, \gamma = 0.2, \beta_H = 0.000025, \beta_{vv} = 0.000025, \nu = 0.04, \Pi_{vv} = 2500, \Pi_H = 0.52, \sigma = 0.008$ and $R_0 = 2.5925$.

malaria. This however is dependent on the resources due to the cost involved. Also of importance in the dynamics of malaria, is the rate of recovery (γ). γ determines the effectiveness of drugs used for chemoprevention. If γ is high, then a drug will be deemed useful in controlling the disease and vise-versa. γ is also a measure of how individuals use the drugs. Improper use could result in drug resistance. FIG. 3.6 (b), shows that as γ increases, the prevalence of malaria decreases. This shows that as more humans recover from infection and gain immunity, the prevalence of the disease decreases.

FIG. 4.6 shows the reverse of FIG. 4.5 i.e $R_{w^*} < R_{r^*}$. When the resistant strain dominates, the sub-population I_{HR} increases over time. FIG. 4.6 shows similar results to FIG. 4.5 but now the prevalence peaks at a higher value and settles at a higher prevalence value. The prevalence curve, FIG. 4.6 (b) shows the potential danger posed by drug resistant malaria.



(a)



(b)

FIG. 4.6. (a) Shows a plot of the human populations, (b) is the corresponding prevalence curve with $R_{w^*} = 2.0443$ and $R_{r^*} = 2.2105$. Parameter values: $\beta_H = 0.04$, $\beta_r = 0.1$, $\beta_{vv} = 0.1$, $\beta_{r1} = 0.02$, $\gamma = 0.0078$, $\epsilon = 0.0001$, $\delta = 0.001$, $\nu = 0.0012$, $\mu_H = 0.000046$, $\mu_{vv} = 0.07$, $\Pi_H = 5000$, $\Pi_{vv} = 250000$.

Vector control has been one of the most successful ways of controlling malaria despite the costs involved. Insecticides sprayed to kill mosquitoes have proved to be effective in controlling the vector. In our model, the parameter μ_{vv}, can be used to model vector control. $\frac{1}{\mu_{vv}}$ is the mean vector life span, with $\mu_{vv} = 0.1$ implying a lifespan of 10 days. Increasing μ_{vv} is synonymous to decreasing the life span of the vector. Control measures such as spraying, decrease the life span of the vector. FIG. 4.7 shows prevalence curves corresponding to different values of μ_{vv}. The figure depicts the situation where increasing the value of μ_{vv} leads to a decrease in the prevalence for μ_{vv}, $\frac{\mu_{vv}}{2}$,$\frac{\mu_{vv}}{3}$,$\frac{\mu_{vv}}{4}$. The corresponding values of the reproduction numbers are also shown. FIG. 4.8 shows the contour plots for

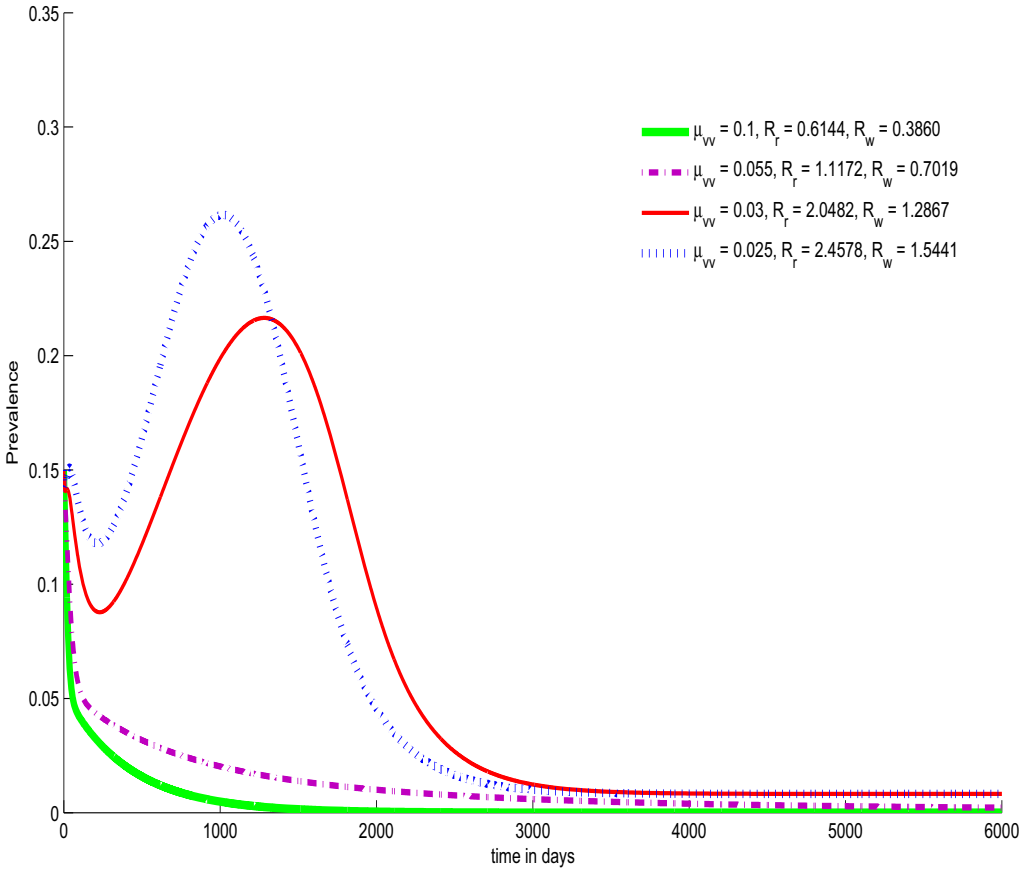


FIG. 4.7. The human prevalence of the malaria disease with different values of μ_{vv} with time in days. Parameter values: $\beta_H = 0.1$, $\beta_r = 0.005$, $\beta_{vv} = 0.07$, $\beta_{r1} = 0.1$, $\gamma = 0.1$, $\epsilon = 0.04$, $\delta = 0.003$, $\nu = 0.008$, $\mu_H = 0.000046$, $\Pi_H = 500$, $\Pi_{vv} = 250000$.

β_r against μ_{vv} for changing values of R_{r^*}. We note that an increase in β_r results in an increase in R_{r^*}. However as depicted earlier in FIG. 4.7, an increase in μ_{vv} leads to a decrease in R_{r^*}. As far as malaria eradication is concerned, the emphasis should be on increasing vector control and reducing contact rate. However β_r has more impact on R_{r^*} and hence any intervention that focuses on reducing contact between infected mosquitoes and human will have a greater impact.

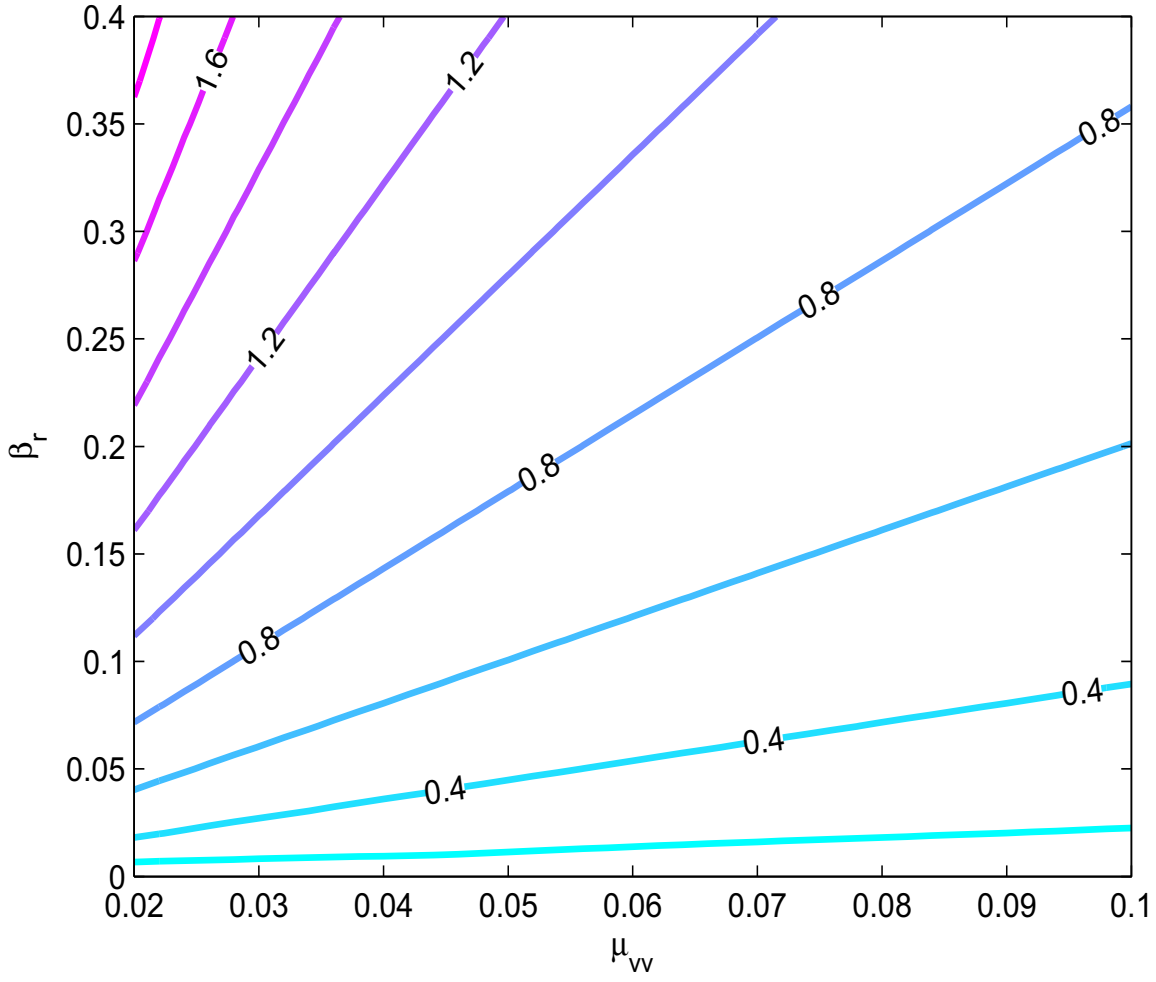


FIG. 4.8. Shows the contour plot of R_{r^*} as a function of the contact rates β_r and μ_{vv} (with resistance strain). Parameter values: $\beta_{r1} = 0.02$; $\beta_{vv} = 0.1$; $\beta_H = 0.04$; $\Pi_{vv} = 250000$; $\Pi_H = 500$; $\mu_H = 0.000046$; $\epsilon = 0.001$; $\delta = 0.001$; $\nu = 0.004$; $\gamma = 0.0078$.

The reduction of the contact rates between human beings and mosquitoes (and vice verse) has always been the primary object of malaria prevention. The use of mosquito nets, and repellents effectively reduces the contact rates. FIG. 4.9 (a) and (b) show the effects of varying contact rates on the human and vector populations. FIG. 4.9 (a) and (b) , shows the effect of varying β_H, β_r, β_{vv} and β_{r1} on the infected human and mosquito populations respectively, with the sensitive strain and resistance strain. Increasing values of contact rate can lead to endemicity of malaria. A comparison of the two figures shows that β_r and β_{r1} need not be larger to have a reproduction number above one as compared to β_H and β_{vv} for the sensitive strain.

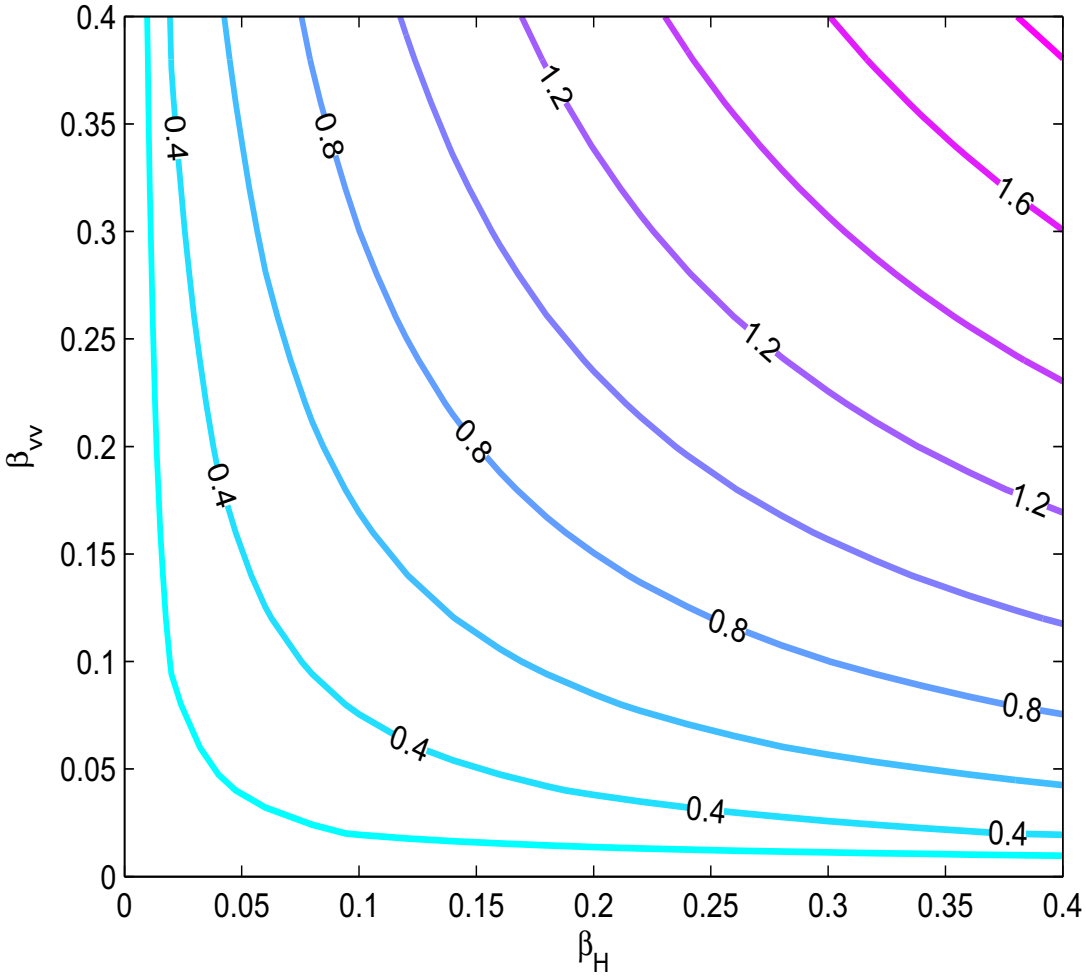


FIG. 4.9 (a)

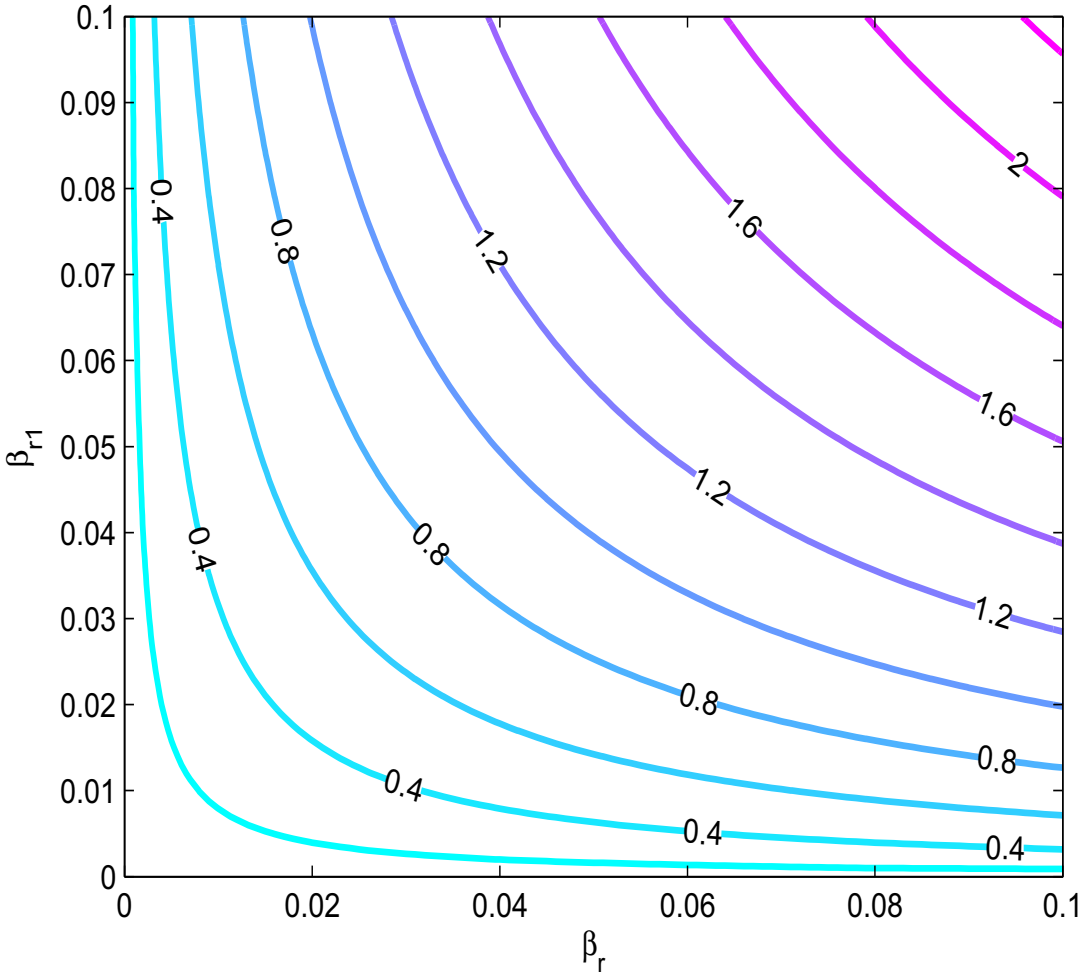
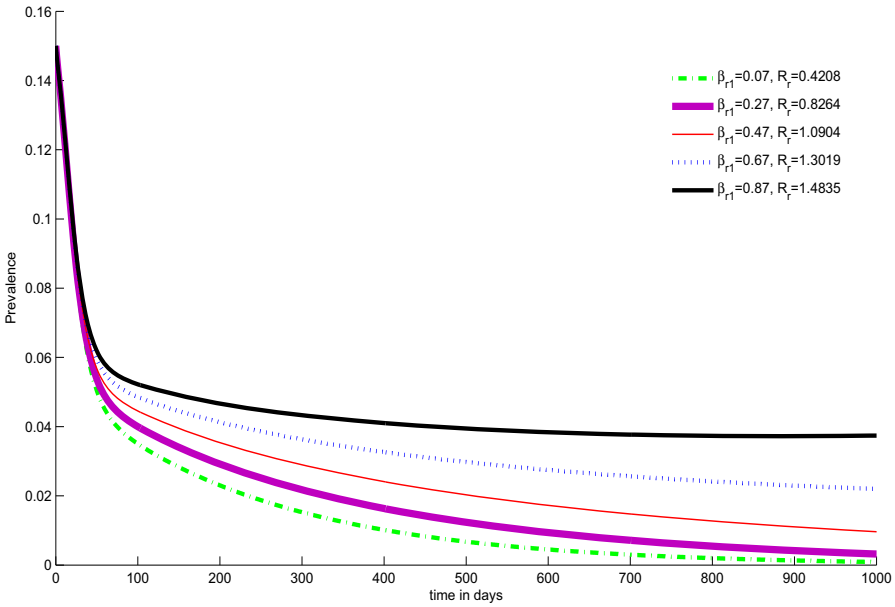


FIG. 4.9 (b)

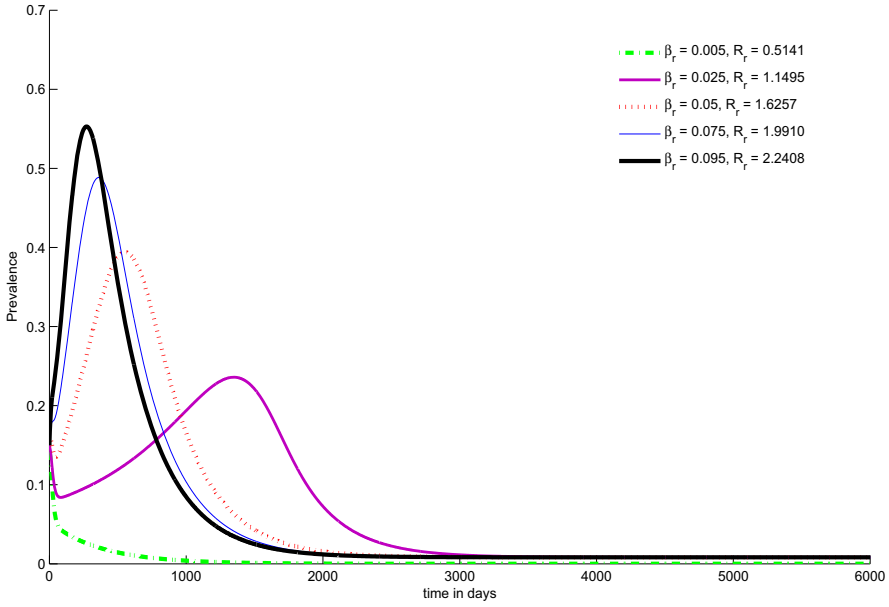
FIG. 4.9. (a) Shows the contour plot of R_{w^*} as a function of the contact rates β_H and β_{vv} (with sensitive strain). (b) Shows the contour plot of R_{r^*} as a function of the contact rates β_r and β_{r1} (with resistance strain). Parameter values: $\mu_{vv} = 0.1$, $\gamma = 0.1$, $\epsilon = 0.01$, $\delta = 0.0045$, $\nu = 0.008$, $\mu_H = 0.000046$, $\Pi_H = 500$, $\Pi_{vv} = 250000$.

What we have observed here is that the curves in FIG. 4.10 (a) decrease exponentially with time with the larger value of β_{r1} settling at a higher prevalence value.

While for FIG. 4.10 (b) the curves rise to a peak prevalence value with the curve for the largest β_r peaking first and then tending to zero faster than the smaller values of β_r. The smallest value of β_r on the other hand peaks a smaller prevalence value and its peak is delayed and tends to zero more slowly than the others.



(a)



(b)

FIG. 4.10. (a) Shows the infected mosquitoes (with resistance strain) as contact rate β_{r1} varies and (b) shows infected humans (with resistant strain), as the contact rate β_r varies. Parameter values: $\mu_{vv} = 0.1$, $\beta_{vv} = 0.1$, $\beta_H = 0.1$, $\gamma = 0.1$, $\epsilon = 0.04$, $\delta = 0.003$, $\nu = 0.008$, $\mu_H = 0.000046$, $\Pi_H = 500$, $\Pi_{vv} = 250000$.

4.6 Discussion

In this work we presented a mathematical model for the dynamics of malaria in the presence of drug resistance. We drew up an ordinary differential equation model with standard incidence to model the dynamics of malaria. The qualitative analysis of the model was presented in terms of the model reproduction number $\hat{R}_0 = \max(R_{w^*}, R_{r*})$, where R_{w^*} and R_{r^*} are the model reproduction numbers for the sensitive and resistant strain respectively. The reproduction number is important in determining the trend of an infectious disease [14]. The model has two unique equilibria, the disease free equilibrium point (DFEP) and the endemic equilibrium point (EEP). We noted that the DFEP is locally asymptotically stable for $\hat{R}_0 < 1$ and unstable for $R_0 > 1$.

Conditions for the existence of the endemic steady state were determined. The use of the center manifold theory enabled us to determine the stability of the EEP when $\hat{R}_0$ is close to unit. Numerical results show there is forward bifurcation when $R_{w^*} > R_{r^*}$, and that the EEP is locally asymptotically stable whenever $R_{w^*} > 1$. But when resistance strains dominate $R_{r^*} > R_{w^*}$, the model exhibits backward bifurcation. This results means that there are unstable sub-threshold endemic equilibria near DFEP. So that the disease may be still present in populations even of $R_{r^*} < 1$.

In simulations results, the drug resistant dominance show higher prevalence of disease while drug sensitive dominance show lower prevalence of disease. The graph of prevalence of malaria shows that the prevalence can approach zero percent by reducing both reproduction numbers to less than unit ($R_{r^*} < R_{w^*} < 1$) and the population remain free from disease. The effect of contact rate between human and mosquito population in both sensitive and resistant strain is shown by using the contour plot and prevalence curve. The results show that as we reduce the contact rates the reproduction number reduces to less than unit and prevalence of the disease in the population decreases. The effect of mortality rate of mosquitoes (μ_{vv}) is shown. The increase of mortality rate of mosquitoes decrease the prevalence of the disease.

We use the contour plot to see the effect of μ_{vv} and β_r with R_{r^*}. The results show that increasing mortality rate of mosquitoes with a decrease in contact rate can reduce the malaria disease. We emphasize that reducing contact rate and applying pesticides is

essential to eradicate the disease.

Considering the sensitive strain only leads to the same results obtained in the simple model in chapter 3.

Chapter 5

Conclusions

In this thesis we have discussed two models on malaria transmission, a simple malaria transmission model and a drug resistant model. The simple transmission model is considered in two parts. Firstly, we consider the model with a constant population. Secondly we consider the model with nonconstant population. The constant population model, does not take into account disease related deaths. This however, is an oversimplification of the model since malaria kills more than one million people annually [5]. The constant population model is mathematically tractable and can be used as a foundation to study more complex models, especially those with varying population. We have also developed a model on the transmission dynamics of malaria in the presence of sensitive and resistant strains. Such a model would be great help to public health programs on malaria and development of vaccines and drugs that can effectively control malaria.

Of particular importance in the dynamics of malaria is the model reproduction number. It measures the ability of malaria to spread in the population. In the presence of control measures, the model reproduction number can be used to provide the measure of the control efforts to eliminate the infections [7, 39].

We used the model reproduction number to determine the stability of the equilibrium points. We noted that each of the model reproduction number is the product of two reproduction numbers, one for the human population and other for the vector population. We noted that whenever the model reproduction number is less than unit malaria might not invade in population. While when the reproduction number is greater than unit the

disease might persists.

We however, noted that for the model with drug resistance, if the reproduction number due to resistant strains is greater than the reproduction number due to the sensitive strains then there is backward bifurcation even if both reproduction numbers are less than one.

For the simple model we drew up the following conclusions. Firstly, the spread of malaria can be controlled by eradication of mosquitoes. Secondly, a reduction in the contact rate between humans and mosquitoes can significantly reduce the spread of malaria. Similar conclusions we reached for the drug resistant model. A comparison of the contact rates between humans and mosquitoes for the drug sensitive and resistant strains showed that a decrease in the contact rates resulted in a decrease of the reproduction number. On the other hand reducing the time spent in the infected class reduces the model reproduction number. For the drug resistance model, strain dominance was found to affect the spread dynamics of malaria.

(i) If the resistant strains dominate, then the eradication of malaria could be difficult. Analytically this was shown by the presence of backward bifurcation in the model. On the other hand, if the sensitive strains dominate malaria controll could be achieved.

(ii) For the drug resistance model, eradication of the disease requires that both model reproduction numbers for the sensitive and resistant strains be less than unit, $R_{r^*} < R_{w^*}$.

(iii) For the control of malaria, we emphasize reducing contact rates together with pesticides to eradicate malaria.

From the prevalence curves we arrived at the following conclusions.

Effective malaria control can be achieved by the use of effective insecticides, treated mosquito nets and control of mosquito breeding places. Reducing the contact rate is also vital for malaria control and disease eradication. The use of mosquito nets and repellents can effectively reduce the contact rate.

Malaria has many factors, but from our study, we recommend some factors that the reader should take into account such as:

(i)The treatment of malaria in human.

(ii) Death of malaria due to sensitive strain.

(iii)Recovery rate due to resistant strain.

(iv)Using global stability for analyzing.

Appendix A

The next-generation method for determination of R_0

In this appendix we give a brief overview of how to calculate the basic reproduction number R_0, using the next generation method. Let $x = (x_1, \ldots, x_n)^t$ with $x_i \geq 0$, be the number of individuals in each compartment $(i = 1, \ldots, n)$ that can be grouped into n compartments. We will sort the compartments so that the first m compartments correspond to infected individuals. Then define all disease free equilibria (DFE) $x_0 = \{x \geq 0 \mid x_i = 0, i = 1, \ldots, m\}$.

For computation of R_0, it is important to distinguish new infections from all other changes in the population. We let $\mathcal{F}_i(x)$ be the rate of appearance of new infections in compartment i, $\mathcal{V}_i^+$ be the rate of transfer of individuals into compartment i and $\mathcal{V}_i^-(x)$ be the rate of transfer of individuals out of compartment i. See figure for illustration.

FIG. A.1. Representation of $\mathcal{F}$ and $\mathcal{V}$

$\mathcal{F}_\rangle(x), \mathcal{V}_i^+(x)$ and $\mathcal{V}_i^-(x)$ are continuous and at least twice differentiable in each variable. In general we can write a system of differential equation of the form $\dot{x} = f_i(x)$ in the form

$$\dot{x}(t) = \mathcal{F}_i(x) - \mathcal{V}_i(x), \qquad i = 1, ..., n$$
$$\mathcal{V}_i(x) = \mathcal{V}_i^-(x) - \mathcal{V}_i^+(x).$$

If $\mathcal{F}_i(x), \mathcal{V}_i^+(x), \mathcal{V}_i^-(x)$ satisfy the following assumptions.

(A1) : If $x \geq 0$ then $\mathcal{F}_i, \mathcal{V}_i^+, \mathcal{V}_i^- \geq 0$.

(A2) : If $x_i = 0$ then $\mathcal{V}_i^- = 0$. In particular, if $x \in x_0$, then $\mathcal{V}_i^- = 0$ for $i = 1, ..., m$.

(A3) : $\mathcal{F}_i = 0$, if $i > m$.

(A4) : If $x \in x_0$, then $\mathcal{F}_i(x) = 0$ and $\mathcal{V}_i^+(x) = 0$.

(A5) : If $f(x)$ is set to zero, then the eigenvalue of $Df(x_0)$ have negative real parts x_0 is DFE.

The condition listed above allow us to partition the matrix $\mathcal{DF}(x)$ as shown in the following remark,

Remark 1 *$\mathcal{DF}(x_0)$ is the derivative $\left[\frac{\partial f_i}{\partial x_j}\right]$ evaluated at DFE. The conditions $(A_1 - A_5)$ allow us to partition the matrix $\mathcal{DF}(x_0)$ and $\mathcal{DV}(x_0)$ as;*

$$\mathcal{DF}(x_0) = \begin{pmatrix} \mathcal{F} & 0 \\ 0 & 0 \end{pmatrix} \quad \textit{and} \quad \mathcal{DV}(x_0) = \begin{pmatrix} \mathcal{V} & 0 \\ J_3 & J_4 \end{pmatrix},$$

where $\mathcal{F}$ and $\mathcal{V}$ are $m \times m$ matrices defined by $\mathcal{F} = \left[\frac{\partial \mathcal{F}_i}{\partial x_j}(x_0)\right]$ and $\mathcal{V} = \left[\frac{\partial \mathcal{V}_i}{\partial x_j}(x_0)\right]$ Since $\mathcal{F}$ is non-negative, $\mathcal{V}$ is non-singular matrix and all eigenvalue of J_4 have positive real part.

If $f(x)$ satisfies $(A_1 - A_5)$, then R_0 is defined as $R_0 = \rho\left(\mathcal{F}\mathcal{V}^{-1}\right)$, where ρ is the spectral radius. [45]

Appendix B

Endemic equilibrium points for reduced constant population model

We are reducing our model equations to a system of three equations using the following transformations: $R_H = N_H - S_H - I_H$ and $S_{vv} = N_{vv} - I_{vv}$. The reduced system is given by:

$$\left.\begin{aligned} S_H &= \lambda_H N_H - \beta_H S_H I_{vv} + \epsilon(N_H - S_H - I_H) - \mu_H S_H + \nu I_H, \\ I_H &= \beta_H S_H I_{vv} - (\gamma + \mu_H + \nu) I_H, \\ I_{vv} &= \beta_{vv}(N_{vv} - I_{vv}) I_H - \mu_{vv} I_{vv}. \end{aligned}\right\} \tag{B.1}$$

At the stead state, the right hand side of system (B.1) will be equal to zero, so that;

$$0 = \lambda_H N_H - \beta_H S_H I_{vv} + \epsilon(N_H - S_H - I_H) - \mu_H S_H + \nu I_H, \tag{B.2}$$

$$0 = \beta_H S_H I_{vv} - (\gamma + \mu_H + \nu) I_H, \tag{B.3}$$

$$0 = \beta_{vv}(N_{vv} - I_{vv}) I_H - \mu_{vv} I_{vv}. \tag{B.4}$$

From equation (B.4) we have,

$$\beta_{vv}(N^*_{vv} - I^*_{vv}) I^*_H = \mu_{vv} I^*_{vv},$$

so that

$$I^*_{vv} = \frac{\beta_{vv} N^*_{vv} I^*_H}{\mu_{vv} + \beta_{vv} I^*_H} = \frac{R_{0v} I^*_H N^*_{vv}}{N^*_{vv} + R_{0v} I^*_H}, \tag{B.5}$$

where

$$R_{0v} = \frac{\beta_{vv} N^*_{vv}}{\mu_{vv}}.$$

We substitute I^*_{vv} in the equation (B.3) and obtain

$$\beta_H S^*_H \left(\frac{R_{0v} I^*_H N^*_{vv}}{N^*_{vv} + R_{0v} I^*_H} \right) - (\gamma + \mu_H + \nu) I^*_H = 0.$$

Either

$$S^*_H = \frac{(\gamma + \mu_H + \nu)(N^*_{vv} + R_{0v} I^*_H)}{N^*_H \beta_H R_{0v} N^*_{vv}},$$

or $I^*_H = 0$.

The case where $I^*_H = 0$ corresponds to the DFE point. We can write S^*_H in terms of R_0 as follows;

$$S^*_H = \frac{N_H(N^*_{vv} + R_{0v} I^*_H)}{R_0 N^*_{vv}}. \tag{B.6}$$

Substituting equation (B.6) and (B.5) into the equation (B.2) we have,

$$I^*_H = Q(R_0 - 1),$$

where

$$Q = \frac{N^*_H N^*_{vv}(\mu_H + \epsilon)}{(\mu_H + \gamma + \epsilon) R_0 N^*_{vv} + N^*_H (\mu_H + \epsilon) R_{0v}}.$$

Using back substitution we get the endemic equilibrium point as

$$E_1 = (S^*_H, I^*_H, I^*_{vv}),$$

where

$$\begin{aligned} S^*_H &= \frac{N_H[N^*_{vv} + R_{0v} Q(R_0 - 1)]}{R_0 N^*_{vv}}, \\ I^*_H &= Q(R_0 - 1), \\ I^*_{vv} &= \frac{R_{0v} N^*_{vv} Q(R_O - 1)}{N^*_{vv} + R_{0v} Q(R_0 - 1)}. \end{aligned} \tag{B.7}$$

We can now state a theorem on the existence of the endemic equilibrium point;

Theorem B.0.1 *The endemic point exist for* $R_0 > 1$.

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