CLIMATE DEPENDENT MALARIA DISEASE TRANSMISSION MODEL AND ITS ANALYSIS

By

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Abstract

The impact of climate change on human health, particularly through the potential increase in vector- and water-borne diseases, has received increasing attention in recent years. Environmental variables are known to affect significantly the population dynamics and abundance of insects major catalysts of vector-borne diseases, but the exact extent and consequences of this sensitivity are not yet well-established. Malaria infection continues to be a major problem in many parts of the world including Africa. We focus here on mathematical model that describes the impact of climate variation on the malaria dynamics. To study this relation, a non-autonomous deterministic model is designed by incorporating the effect of both temperature and rainfall to the dispersion and mortality rate of adult mosquitoes and this is used to assess the impact of the variability in temperature and rainfall on the transmission dynamics of malaria in a population. In the model, the periodic variation of seasonal variables as well as the non-periodic variation due to the long term climate variation has been incorporated and analysed. In both cases, it has been shown that the disease-free solution of the model is globally asymptotically stable when the basic reproduction ratio is less than unity in the periodic system and when the threshold function is less than unity in the non-periodic system. The disease is uniformly persistent when the basic reproduction ratio is greater than unity in the periodic system and when the threshold function is greater than unity with some additional conditions in the non-periodic system. The model has been validated using epidemiological data collected from western region of Ethiopia, by considering the trends for monthly number of microscopically confirmed cases of malaria during the years 2000-2012 and the climate variation in the region. Then time dependent optimal control theory in the non periodic environment is applied to investigate optimal strategies for controlling the spread of malaria disease using insecticide treated bed nets, spray of mosquito insecticide and treatment as the system time dependent control variables. The possible impact of using combinations of two controls or one at a time on the spread of the disease is also examined.

Keywords: Asymptotic stability; Periodic and non-periodic climate dependent growth rates; validation using epidemiological data, time dependent optimal control

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.

This thesis is dedicated to my family

Chapter 1

Introduction

Malaria is caused by a parasite called *Plasmodium falciparum* and is transmitted by *Anopheles* mosquitoes. Mosquito abundance is basically dependent on rainfall patterns and also dependent on temperature by influencing the mosquito population dynamics as well as the parasite development within the mosquito [27]. The vector that spreads malaria and the parasite that causes the disease are sensitive to rainfall and temperature change and they widely expected to significantly affect the global spread, intensity, and distribution of malaria [58, 51]. Although changes in temperature and rainfall, influences the dynamics of malaria and other VBDs, this influence may be affected by non-climatic factors, such as epidemiological, environmental, socio-economic and demographic factors (see [61] and some of the references therein).

Future malaria transmission rates worldwide may not be the consequence of the strong connection between malaria and climate mainly because there are many other factors that affect the spread of the disease including socioeconomic development, drug resistance, and immunity [94].

Climate variables, such as temperature, humidity, rainfall and wind, significantly affect the life-cycle and, consequently, the abundance of mosquitoes in populations and a number of mathematical models have been designed and used to assess the impact of climate change and seasonality on the transmission dynamics of malaria (see [1] and the references therein). According to the IPCC Fourth Assessment Report, climate change has already altered the distribution of some vectors that transmit disease. The climate scenarios in East Africa can be taken as indicator for longer malaria transmission seasons and geographic expansion of the disease into highland areas. According to published literature [30, 68, 63, 62] the earliest malaria-climate connection in the East African highlands was identified in the 1980s when there was a series of malaria epidemics connected to increases and anomalies in mean monthly maximum temperatures and increase in rainfall in the highlands. Since then, the frequency and size of epidemics increased with serious outbreaks in 1995, 1998 and 2002, corresponding to climate variations such as a significant increase ($\geqslant 3^{\circ}$C) in mean temperatures, high rainfall, drought and El Nino events (see [22], and the references therein).

The impact of climate change on regional and global malaria cases and deaths is even less understood. Some studies have shown that an increase in temperature has allowed the introduction of malaria into higher altitude areas in Colombia, Ethiopia and Kenya, where it was previously too cold for the disease to thrive [20].

Vector-borne diseases are transmitted typically by the bite of an infected arthropod. The arthropod could be something rather familiar like a mosquito, tick, or black fly. Or it might be a less familiar species such as an African Tsetse fly or copepod. These arthropods that carry and transmit diseases are known as vectors. Other non-arthropod vectors can include rodents such as rats, certain bats, a species of aquatic snail, and several species of wild birds. Different vectors carry different diseases such as malaria, dengue, encephalitis, African sleeping sickness, and yellow fever. Ticks have extended their range north in Sweden and Canada and into higher altitudes in the Czech Republic (see [94]). Malaria, the diseases transmitted by mosquito vectors and the potential impacts of climate change on it is described below.

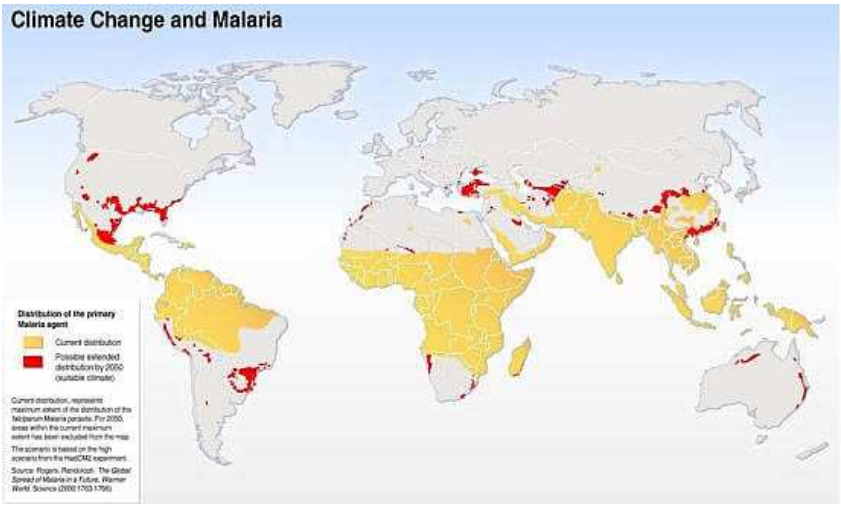


Figure 1.1. Climate change will allow malaria to spread into new areas. This map shows the new areas where the Malaria parasite *Plasmodium falciparum*, will likely be able to spread by 2050 based on the Hadley Center model's high scenario. Areas shown in yellow indicate the current distribution of malaria. Areas shown in red indicate areas where climate will be suitable for malaria by 2050. Other areas may become free of malaria as climate changes. $Courtesy of Hugo Ahlenius, UNEP/GRID - Arendal$ [94]

When an *Anopheles* mosquito bites a person infected with the malaria parasite, the mosquito becomes a carrier of the disease. When that mosquito bites another person, that person becomes infected with the parasite too. Malaria causes the infected person to develop a fever and flu-like symptoms. While most infected individuals recover from malaria, it can cause death, especially in children. Each year there are between 350 million and 500 million cases of malaria worldwide. Over one million of those people die

from the disease. Most of the people who die from malaria are children in Sub-Saharan Africa.

In Ethiopia, for example, malaria transmission is largely determined by altitude and climate as affected by Indian Ocean conditions and global weather patterns, including El Nino and La Nina. The malaria transmission occurs between September and December, after the main rainy season from June to August. Certain areas, largely in the western and eastern parts of the country experience a second minor malaria transmission period from April to May, following a short rainy season from February to March [70]. The incidence of the disease has been significantly increased since the 1980s. Specific data on the number of malaria cases in Ethiopia is available only since the end of 1980s ([76],[55],[54]) as presented in Figure 1.2. There has been a noticeable increase in the number of cases in the country over time, except for 1999/00 and 2000/01 years [78]. This change has to be investigated whether it is the impact of climate change besides other factors or not that mainly causes the prevalence of the disease.

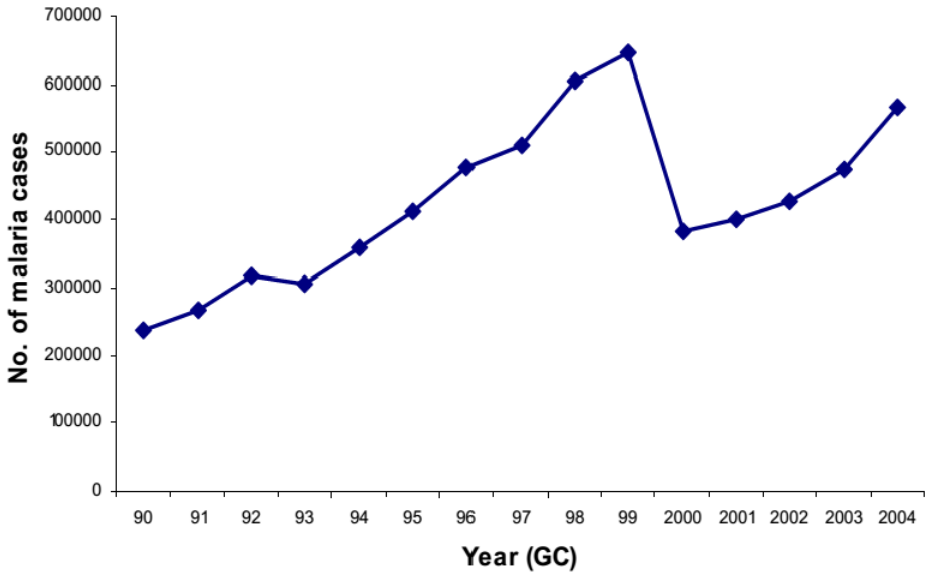


Figure 1.2. Trends for annual number of microscopically confirmed cases of malaria in Ethiopia (1990-2004). Reporting is from July to June annual cycle. The year 90, for example, represents from July 1989 to June 1990, and so on.

According to [23] and the references therein, approximately 60% of Ethiopia's population lives in malarious areas, and 68% of the country's landmass is favorable for malaria transmission, with malaria primarily associated with altitude and rainfall. In general, the peak of malaria incidence follows the main rainfall season (July to August) each year. However, many areas in the south and west of the country have a rainfall season beginning earlier in April and May or have no clearly defined rainfall season. Consequently, malaria transmission tends to be highly heterogeneous geo-spatially within

each year as well as between years. Additionally, malaria in Ethiopia is characterized by widespread epidemics occurring every five to eight years, with the most recent epidemic occurring in 2003/2004.

In 2014/2015, the total number of laboratory-confirmed plus clinical malaria cases were 2,174,707. Of those cases, 1,867,059 (85.9%) were confirmed by either microscopy or rapid diagnostic tests (RDTs) out of which 1,188,627 (63.7%) were *Plasmodium falciparum* and 678,432 (36.3%) were *P.vivax*.

Overall, the malaria transmission pattern in the country is seasonal and unstable, often characterized by focal and large-scale cyclic epidemics. A relatively long transmission season exists in the western lowland areas, river basins, valleys, and irrigations schemes. Due to the unstable and seasonal transmission of malaria, protective immunity is generally low and all age groups of the population are at risk of the disease. The central highlands, which are >2,500m ASL(Above sea level), are generally free of malaria. The rest of the country, however, has a varied pattern of malaria transmission (see Figure 1.3), with the transmission season ranging from less than three months to greater than six months.

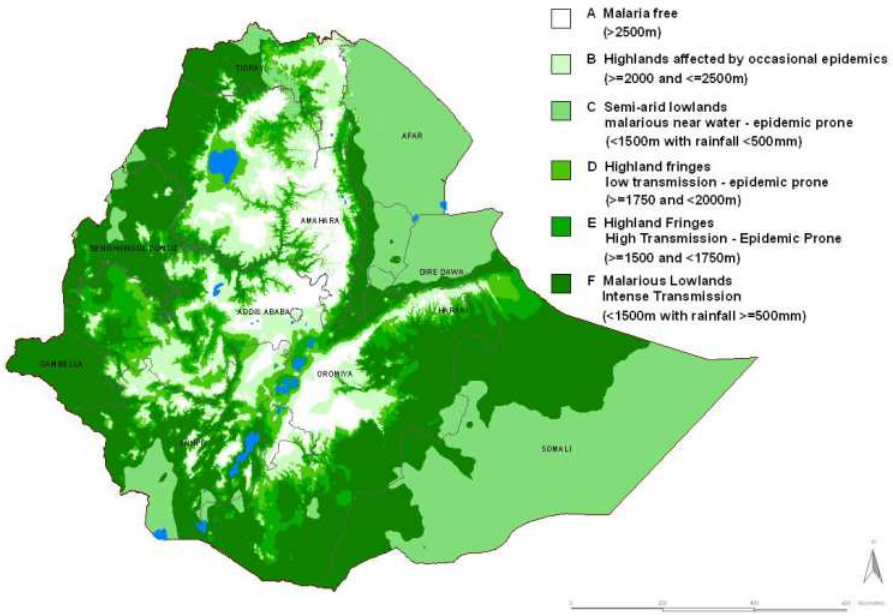


Figure 1.3. Malaria risk stratification, Ethiopia (adopted from the Malaria NSP 2014-2020) [23]

Malaria risk stratification was revised in 2014 using annual parasite incidence per 1,000 population (per the World Health Organization [WHO] recommendation) plus altitude and expert opinions from different malaria stakeholders. According to the new stratification, malaria risk in Ethiopia by annual parasite incidence is classified into high,

medium, low and malaria-free as shown in Figure 1.4 and Table 1.1. For the purposes

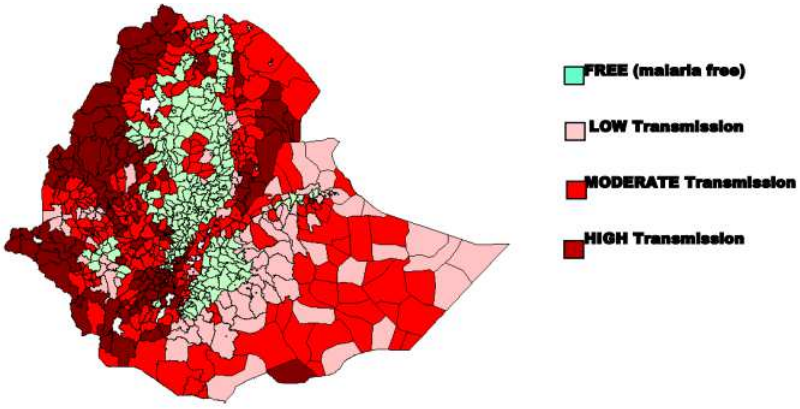


Figure 1.4. Malaria risk stratification, Ethiopia (adopted from the Malaria NSP(National Strategic Plan for Malaria Prevention, Control, and Elimination) 2014-2020) [23]

Table 1.1. Malaria stratification and proposed intervention per stratum [23]

Malaria strata	API*	Elevation (m)	Population (2013)	Percent population	No. of woredas	Percentage of woredas	Interventions					
							LLIN	IRS	Larval Control	Case Mx	Surveillance	IEC/ BCC*
FREE	0	>= 2,000 ASL	33,639,639	40 percent	290	35 percent	-	-	-	X	X	X
LOW	>0 &<5	< 2,000 ASL*	11,153,499	13 percent	101	12 percent	X	X*	WA*	X	X	X
MODERATE	>=5 &<100		28,410,564	34 percent	287	34 percent	X	-	WA	X	X	X
HIGH	>=100		11,023,284	13 percent	157	19 percent	X	X	WA	X	X	X
Total			**84,226,986**	**100 percent**	**835**	**100 percent**						

*Only 32 percent of at risk population in highland fringe/epidemic-prone areas will be covered by IRS
API: Annual parasite index; ASL: above sea level; IEC/BCC: information, education, and communication/behavior change communication; WA: where applicable

of the Ethiopia National Malaria Indicator Survey (MIS), areas below 2,000m ASL were considered as a target for malaria interventions, while those between 2,000m and 2,500m ASL were included to assess potential intervention and transmission, as these areas are historically prone to malaria transmission.

Malaria control is a big challenge due to many factors [50].There is the complexity of disease control process; the complexity of the vectors; expensiveness of the control program. There is a variation of disease patterns and transmission dynamics from place

to place, by season and according to climate and environmental circumstances. Since malaria varies from season to season and from place to place within the country, approaches will also differ in the planning and implementation of vector control. Each region's circumstances will influence the organization of practical programs to identify local problems and priorities, and the design and implementation of appropriate interventions. Therefore, selection of suitable, sustainable and cost-effective interventions must be based on local analysis and this, therefore, calls for careful consideration and appropriate decisions on what control measures to be applied, for a maximum cost-effectiveness. A number of control measures are available which differ in their levels of effectiveness. Thus selection of a method should consider the magnitude of the malaria problem, the major vectors involved, levels of transmission and risk groups, available resources, technical and operational realities. Sustainability of selected interventions must be assured. In most cases these measures should be used in an integrated manner to maximize effectiveness [50].

During the past decade, several interventions have been used to reduce malaria transmission. These include insecticide-treated nets (ITNs), indoor residual spraying (IRS), intermittent preventive treatment in pregnant women and infants, larval control, and other vector control interventions. ITNs are bed-nets treated with pyrethroid, an insecticide that kills and repels mosquitoes, and thus provide a barrier around people sleeping under them. Since malaria typically affects rural and poor populations, ITNs have proven to be one of the most effective interventions in reducing morbidity and mortality due to their low cost and ease in implementation [12].

1.1 Malaria transmission

Malaria parasites are transmitted by female mosquitoes belonging to the genus Anopheles. The development of malaria parasites in the vector, called sporogony, includes a number of stages in different organs of the insect. Male and female gametocytes mate after being ingested by an anopheline mosquito during blood-feeding. The zygotes develop as ookinetes, which move across the mosquito stomach to form oocycsts, within which asexual multiplication leads to the production of up to thousands of sporozoites. The sporozoites migrate and accumulate in the salivary glands, from which they are injected when the infective mosquito bites a human or animal host for a blood-meal. The speed of development of sporozoites depends on temperature and the parasite species. At the optimal temperature, 28°C, the duration of sporogony is 9-10 days for P. falciparum and 8-10 days for P. vivax . The time from ingestion of gametocytes to release of sporozoites is the extrinsic incubation period (or duration of sporogony). Sporozoites injected by a mosquito enter the hosts blood circulation; when they reach the liver, they invade hepatocytes. All P. falciparum sporozoites then undergo exo-erythrocytic

schizogony, in which the parasite nucleus divides repeatedly over several days; at the end, the schizont bursts, giving rise to thousands of merozoites, which are released into the bloodstream. The duration of exo-erythrocytic schizogony is 5.5-7 days for P. falciparum and 6-8 days for P. vivax. In P. vivax malaria, some sporozoites, after invading hepatocytes, become dormant as hypnozoites for periods lasting from 3 to 18 months and very rarely up to 5 years. The merozoites invade erythrocytes, where the great majority multiply asexually, undergoing repeated cycles of growth, rupture, release and re invasion of fresh red cells. All clinical manifestations of malaria are due to this erythrocytic schizogony. The duration of each cycle of erythrocytic schizogony is about 48 h for both P. falciparum and P. vivax . Some merozoites grow and develop into male or female gametocytes within erythrocytes. When mature, they do not develop further, unless they are ingested by a mosquito vector. The immature gametocytes (stages 1-4) of P. falciparum are sequestered in the bone marrow and other deep tissues; only mature gametocytes (stage 5) circulate in the blood. In contrast, all stages of gametocytes of the three other species are present in the peripheral circulation [86].

1.1.1 Model and analysis of climate driven malaria dynamics so far

Ahmed Abdelrazec, Abba B. Gumel, [1] qualitatively assessed the impact of temperature and rainfall on the population dynamics of female mosquitoes in a certain region by designing a non-autonomous mathematical model, which incorporates variability in temperature and rainfall. They studied the dynamics of the aquatic and adult stages of female mosquitoes in the given region. Their study focused only on the vector population and they did not consider the rainfall dependence on the mortality rate of adult mosquitoes. For the non-autonomous model (with temperature and rainfall effects), they have shown that the local and global asymptotic dynamics, with respect to the trivial solution, matches that of the associated autonomous model (with a different, but similar, threshold condition) and derived conditions for the existence, uniqueness and global asymptotic stability of the non trivial periodic solution of the model (in the absence of density-dependent mortality rate for larvae). They validated their model result in the given region.

Agusto et al. [3] developed temperature-dependent deterministic model to gain qualitative insight into the effects of temperature variability only on malaria transmission dynamics. They incorporated a gradual increase in infection-acquired immunity via repeated exposure to malaria infection. The focus of their study was on analyzing the impact of changing temperature and temperature variability on short-term malaria dynamics (due, for instance, to seasonality), and not on long-term malaria dynamics (due to climate change).

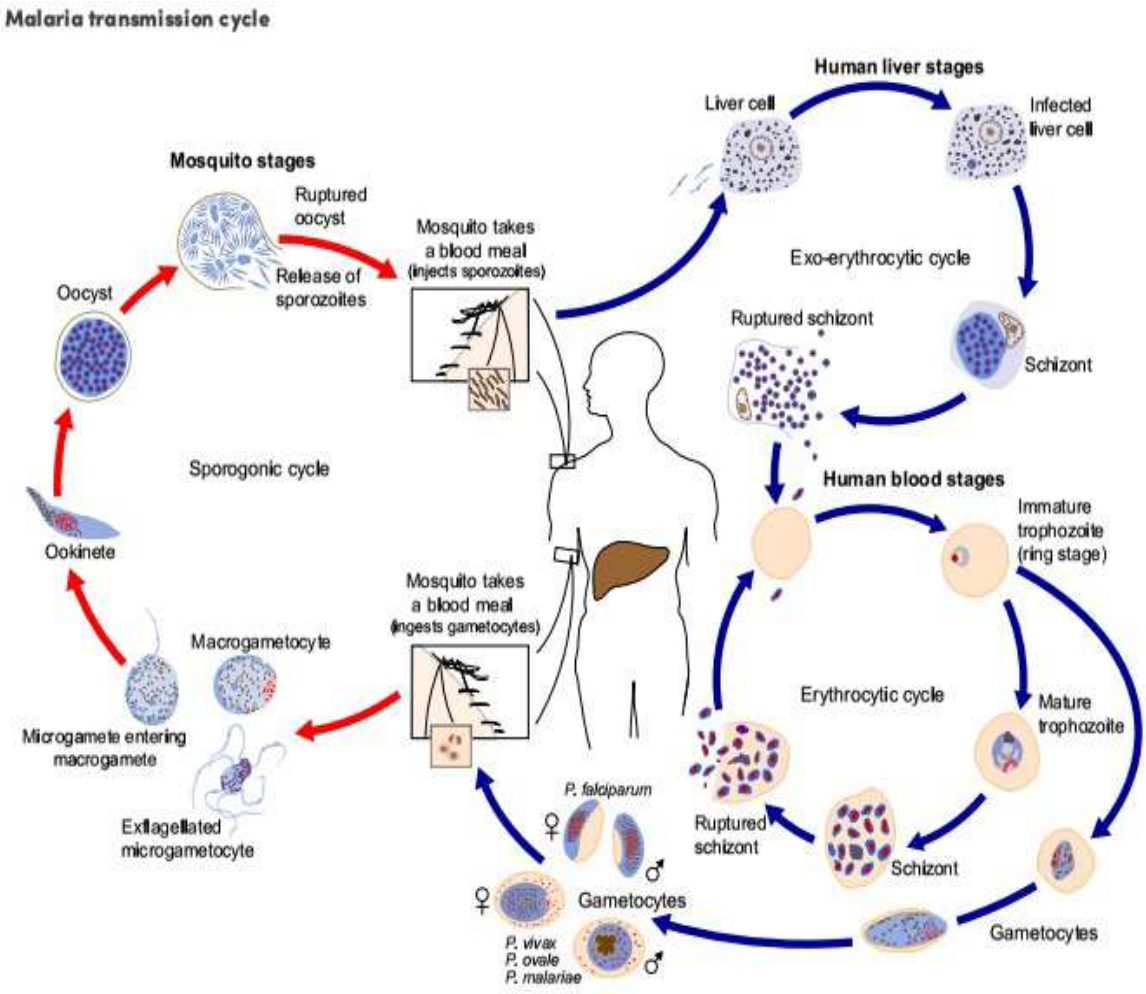


Figure 1.5. The malaria transmission cycle

Parham et al. [67] have shown the impact of environmental factors (temperature and rainfall) in the transmission dynamics by defining the adult mosquito birth rate as a function of temperature and rainfall while other parameters are dependent only on either temperature or rainfall alone. They validated also their results by considering the mosquito population in Tanzania where malaria is highly-endemic, expressing the temperature and rainfall by the cosine function thinking that the conclusions drawn about the effects of seasonality in environmental factors are general. This may ignore the actual variations in the environmental factors and has to be extended and consolidated by setting up a model that incorporates the effects of both temperature and rainfall in the birth and death rates of the vector population. Moreover, the climate (temperature and rainfall) driven model in the periodic and non-periodic environments are research gaps suggested to be studied further. Specially a climate driven model with parameters dependent on both climate variables (temperature and rainfall) in a non-periodic

environment is not yet developed as far as the knowledge of the authors go and this work gives much emphasis on this issue and attempts to introduce an optimal control analysis to support the malaria disease eradication intervention mechanism efficiently with minimal cost.

Motivated by the works of ([56],[48],[87]), Wang et al. [80] proposed a malaria transmission non-autonomous model with periodic environment with out incorporating the climate factors in their model. They computed a basic reproduction number and have shown that the disease-free periodic solution of their model is globally asymptotically stable when the basic reproduction number is less than unity, that is, the disease goes extinct when the basic reproduction number is less than unity, while the disease is uniformly persistent and there is at least one positive periodic solution when the basic reproduction number is greater than unity. That is, they have shown that the basic reproduction number is the threshold value determining the extinction and the uniform persistence of the disease.

Kamaldeen Okuneye , Abba B. Gumel [61] extended the work in [66] by designing a new temperature and rainfall-dependent mechanistic malaria model that incorporates some more pertinent climatic and non-climatic features and factors not considered in [66] (such as host age-structure, dynamics of immature mosquitoes, reduced susceptibility due to prior malaria infection etc.) and analyzed the full non-autonomous model and carried out uncertainty and sensitivity analyzes on the parameters of the model with the mortality rate of juvenile and adult mosquitoes dependent only on temperature.

1.2 Aim and Objectives of the study

1.2.1 Aim

The main aim of this study is to investigate the impact of the variation in climate variables (temperature and rainfall) on the malaria diseases transmission dynamics and design a cost-effective malaria control intervention mechanisms under climate change.

1.2.2 Objectives

i. Develop a mathematical model for malaria disease transmission that accounts for variations in climate.

ii. Estimate model's climate dependent parameters (using relevant data).

iii. Investigating the impact of the embedded climate dependent parameters on the dynamics of the disease with particular focus on the model's stability behavior.

iv. Setting up a time-dependent control efforts and investigate the optimal control strategies and cost-effectiveness analysis of the malaria model in the non-periodic environment.

v. Validating the theoretical results using an epidemiological data collected from some part of a region in Ethiopia.

The purpose of this study is to investigate a climate driven malaria disease transmission model incorporating the effect of temperature in the biting rate and the effects of both temperature and rainfall in the birth rate and death rate of the vector population in both periodic and non-periodic environments by using the standard model considering the dynamics of the adult mosquito population only and referring the works of ([67, 61]). The study assesses the potential change in malaria risk caused by seasonal variations in temperature and rainfall which is important to investigate the dynamics of the disease in a short term basis and as climate impact upon the distribution of the malaria transmission in space and time is not always periodical, we need to investigate the potential change in malaria risk caused by the variations in temperature in the general case to investigate the dynamics of the disease in a long term basis and the information provided here might serve as an important contribution for strategic planning of malaria control in a long period of time in the future. The study also attempts to introduce an optimal control strategy in the non-periodic environment to support the malaria disease eradication intervention mechanism efficiently with minimal cost.

The thesis is organized as follows, in Chapter 2 we formulated a model consisting of ordinary differential equations (ODE) that describe the interactions between humans and mosquitoes populations and the underlying assumptions and a positively invariant set with respect to the system will be identified and shown to be a global attractor of all positive solutions of the system to confirm the biological well posedness of the model system. In Chapter 3, the non-autonomous periodic system is reviewed and analyzed while the non-autonomous non-periodic system is discussed and analyzed in Chapter 4 and we show the simulation results to illustrate the population dynamics in both environments at the end of the latter two chapters.The optimal control strategy is analyzed in Chapter 5. Our conclusions are discussed in Chapter 6.

Chapter 2

Malaria Disease Transmission Mathematical Model

Following the works in ([67, 61]), in developing a framework for understanding the impact of climate on malaria dynamics, we use the standard deterministic malaria disease transmission model with an SIR structure for humans and an SI structure for mosquitoes. Parameters that are assumed to be climate sensitive will be identified and defined as functions of the time dependent climate variables. Positivity of solutions is discussed and the invariant regions is identified.

2.1 Parameter Description

Malaria is a major cause of morbidity and mortality, and it is climate sensitive. Incorporating climate effects into models of disease dynamics is now very crucial as the evidence for climate impacts on disease transmission and potential vector distribution increases. Climate change is known to affect several parameters in the epidemiology of malaria and hence predicting climate change effects on disease transmission requires a framework that specifically incorporates the role of each climate sensitive parameter. Some models examining the contribution of climate change have been explored ([6, 17, 35, 52, 65]).

While we know that climate can affect malaria transmission, the impact of climate change on regional and global malaria cases and deaths is even less understood. Some studies have shown that an increase in temperature has allowed the introduction of malaria into higher altitude areas in Colombia, Ethiopia and Kenya, where it was previously too cold for the disease to thrive. This has put millions of people at risk for the disease [20].
Climate plays an important role in the dynamics and distribution of malaria. Although rainfall is critical in providing suitable habitats for mosquitoes to breed, temperature is a key driver of several of the essential mosquito and parasite life history traits that determines transmission intensity, including mosquito development rate, biting rate,

and development rate and survival of the parasite within the mosquito. Accordingly, a number of studies have used temperature (sometimes together with rainfall and/or humidity) to develop maps representing spatial and/or temporal variation in malaria transmission risk [10].

2.1.1 Temperature Dependence

Understanding the role of temperature in malaria transmission is of particular importance in light of climate change. The global mean temperature has increased by 0.7°C during the past 100 years and is predicted to increase by an additional 1.1-6.4°C during the twenty-first century unless some measures are employed.This additional warming is likely to affect malaria transmission because temperature changes can alter vector development rates, shift their geographical distribution and alter transmission dynamics of the disease [57].
Temperature affects how long mosquitoes live, how quickly they mature to adulthood, how often they bite, and ultimately how many mosquitoes are around. It also affects how quickly the malaria parasite inside of a mosquito becomes mature enough to infect humans. That is, it is known to play a major role in the life cycle of the malaria vector. The development of the three aquatic stages and their emergence to adulthood are strongly dependent on temperature. It takes 1, 3 and 10 days for eggs of some mosquitoes to hatch at temperatures of 30°C, 20°C and 10°C, respectively and water temperature regulates the speed of mosquito breeding [46].

2.1.2 Rainfall Dependence

Rainfall creates pools of water which are essential to mosquito breeding as mosquito eggs must be laid in water and mosquito larva mature in water. In places where the burden of malaria is the greatest, the rainy season is also known as the malaria season. Humidity, which is related to rainfall, increases the lifespan of mosquitoes, giving them more opportunities to carry malaria infections from one person to another. Rainfall has two principal influences on the mosquito life cycle:

- the increased near-surface humidity associated with rainfall enhances mosquito flight activity and host-seeking behavior, and
- rainfall can alter the abundance and type of aquatic habitats available to the mosquito for the deposition of eggs (oviposition) and the subsequent development of the immature stages [73].

In the semi-arid or arid lowlands, heavy rain or floods can cause a major outbreak of malaria, especially in areas in the vicinity of large rivers. Such an outbreak has affected the low-lying semi-arid areas in north-eastern Kenya in 1998 following a major rainfall

and floods [11]. Abnormal rainfall events have been shown to precipitate malaria epidemics even in wetter areas as evidenced by epidemics in Ethiopia, Kenya and Uganda [16].

While we know that climate can affect malaria transmission, the impact of climate change on regional and global malaria cases and deaths is even less understood. Some studies have shown that an increase in temperature has allowed the introduction of malaria into higher altitude areas in Colombia, Ethiopia and Kenya, where it was previously too cold for the disease to thrive. This has put millions of people at risk for the disease [20].
Climate plays an important role in the dynamics and distribution of malaria. Although rainfall is critical in providing suitable habitats for mosquitoes to breed, temperature is a key driver of several of the essential mosquito and parasite life history traits that determines transmission intensity, including mosquito development rate, biting rate, and development rate and survival of the parasite within the mosquito. Accordingly, a number of studies have used temperature (sometimes together with rainfall and/or humidity) to develop maps representing spatial and/or temporal variation in malaria transmission risk [10].

2.2 Model Formulation

Based on the transmission mechanism of malaria, we consider host population and vector population are human population and mosquito population, respectively. The proposed model with the population under study is divided into compartments. The total human population (N_h) is divided into three classes: susceptible (S_h), infectious (I_h) and recovered (R_h). People enter the susceptible class either through birth (at a constant per capita rate) or through immigration (at a constant rate) or after recovering from the disease. When an infectious mosquito bites a susceptible human, there is some finite probability that the parasite (in the form of sporozoites) will be passed on to the human. The parasite then travels to the liver of the person where it develops into its next life stage. After a certain period of time, the parasite (in the form of merozoites) enters the bloodstream, usually signaling the clinical onset of malaria.
The rate of infection of a susceptible individual is dependent on the mosquito biting rate ϕ (daily feeding rate of a vector on a host) defined using the exponential function of the temperature variable (Figure 2.1) as

$$\begin{aligned}\phi(T) =& 0.48\exp(0.14(T-23))/(\exp(-0.14(T-23))+\exp(0.14(T-23)))\\ &+(-0.48)\exp(0.32(T-40))/(\exp(-0.32(T-40))+\exp(0.32(T-40)))\end{aligned} \tag{2.1}$$

with standard incidence rate of $\frac{\beta_{vh}\phi I_v S_h}{N_h}$, where β_{vh} is the probability that the bites by an infectious mosquitoes on susceptible humans produce infection. Infected humans

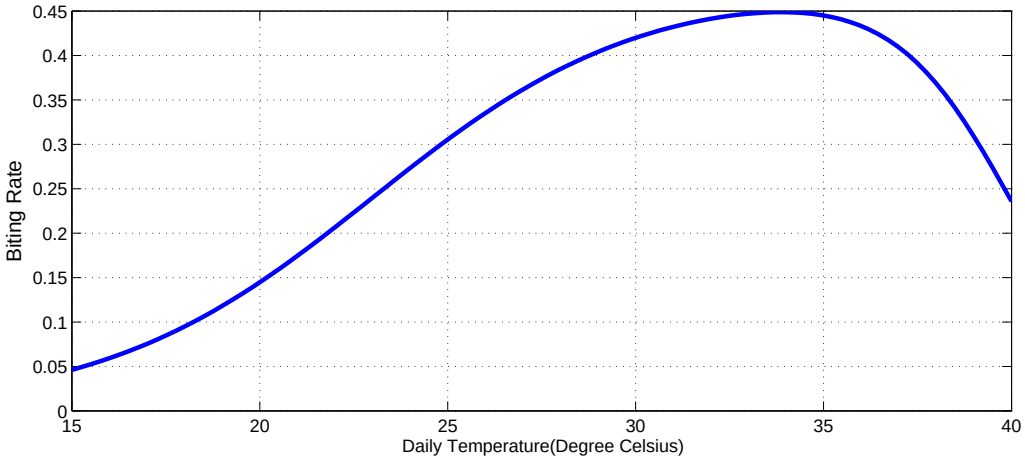


Figure 2.1. The mosquito biting rate (daily feeding rate of a vector on a host) $\phi(T)$.

recover at a constant rate r_h for some period of time and move to the recovered class R_h. The recovered humans may develop some immunity to the disease and do not get clinically ill, but they may still harbour low levels of parasite in their blood streams. However, since the rate of infections from this group of individuals is assumed to be very small, we omitted its impact in our model. After some period of time, recovered humans loose their immunity and return to the susceptible class at a constant rate σ. Infected individuals who do not get treatment may die from infection at a constant rate μ_d. Humans die naturally at a non-disease related per capita natural mortality constant rate μ_h.

Anopheles mosquitoes lay their eggs in the moist soil at the base of glasswort and of rush plants [71]. Eggs can resist desiccation until the flooding of breeding sites that triggers egg hatching and onset of aquatic stages [9]. Aquatic stages involve four successive larva stages plus a pupa with the duration of aquatic immature development, which clearly depends on temperature [14]. Following the aquatic phase, adults emerge and mate, and females start cycles of host-seeking, egg maturation and oviposition. Adults disappear from the area under observation because of both mortality and dispersion. As only females take blood-meals, the model considers only the female mosquito population. Instead of detailing the dynamics of all aquatic stages, we rather used an emergence rate $\Lambda_v(T, R)$ of adult female anopheles mosquitoes which is assumed to be a function of rainfall R and temperature T that recasts all the historical dynamics from egg hatching to emergence.

It is often difficult to establish significant and stationary relationships between the amount of precipitation and mosquito abundance or malaria disease transmission patterns. Rainfall can alter the abundance and type of aquatic habitats available to the mosquito for the deposition of eggs (oviposition) and the subsequent development of

the immature stages [73]. We assume that at any time t, the time variation of the emergence rate of adult female anopheles mosquitoes $\Lambda_v(T, R)$ is defined by Equation (2) in [67],(Figure 2.2):

$$\Lambda_v(T,R) = \frac{0.8438(4R(50-R))^3 \exp(-0.00554T + 0.06737)}{50^6(2 + (0.00554T - 0.06737)^{-1})} \tag{2.2}$$

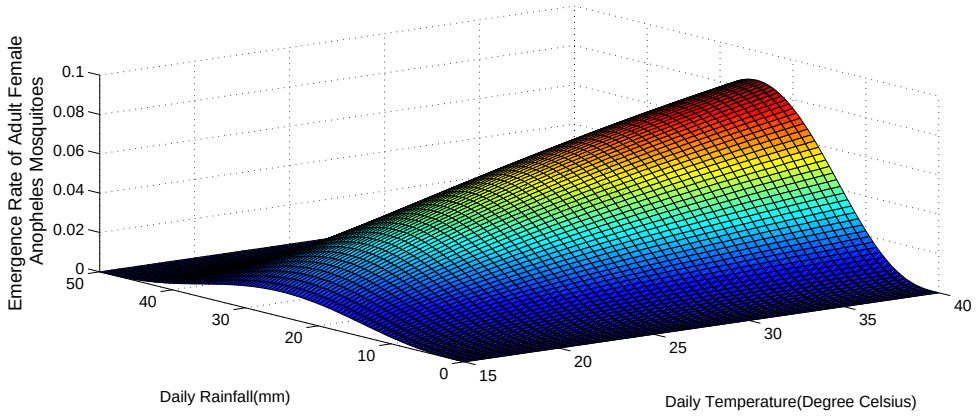


Figure 2.2. The emergence rate of adult female anopheles mosquitoes $\Lambda_v(T, R)$.

The adult female anopheles mosquitoes population is subdivided into two classes: susceptible (S_v) and infectious (I_v). Susceptible adult mosquitoes are recruited at a rate $\Lambda_v(T, R)$. The rate of infection for a susceptible mosquito depends on the mosquito's biting rate in which the transmission rate from infectious host to susceptible vector is given by $\frac{\beta_{hv}\phi I_h S_v}{N_h}$ where β_{hv} represents the probability that a susceptible mosquito get infected when biting an infected human. Although the rainfall effect on the survival of adult mosquitoes is not significantly high, its influence can not be ignored as the increased near-surface humidity associated with rainfall enhances mosquito flight activity and host-seeking behavior [73]. Mosquitoes leave the population through a per capita climate-dependent(temperature and rainfall) natural death rate given by (Figure2.3):

$$\mu_v(T,R) = 0.0886 \exp\left(\left(\frac{-0.01R + 1.01T - 21.211}{14.852}\right)^2\right) \tag{2.3}$$

which is assumed to follow the exponential distribution in temperature and rainfall [8].

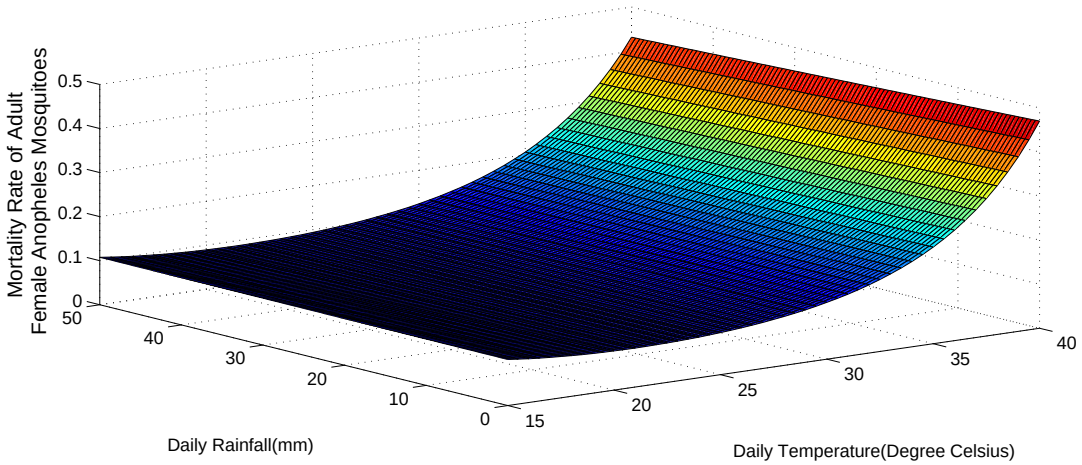


Figure 2.3. Mortality rate of adult mosquitoes $\mu_v(T, R)$.

A coupled mosquito-human compartmental model of malaria dynamics is presented in the figure below. The interaction between host and vector can be described by the

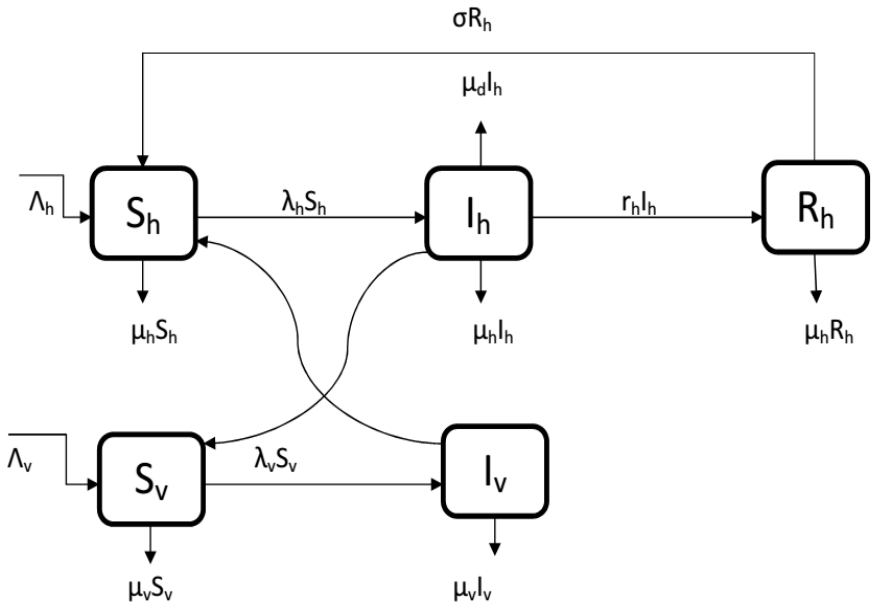


Figure 2.4. Mosquito-human model of malaria dynamics

system of nonlinear differential equations. The following system of differential equations describe the model. The system has time dependent coefficients as climate variables

could be expressed as a function of time.

$$\begin{aligned}
\frac{dS_v}{dt} &= \Lambda_v(T,R) - \lambda_v(T)S_v - \mu_v(T,R)S_v,\\
\frac{dI_v}{dt} &= \lambda_v(T)S_v - \mu_v(T,R)I_v,\\
\frac{dS_h}{dt} &= \Lambda_h - \lambda_h(T)S_h + \sigma R_h - \mu_h S_h,\\
\frac{dI_h}{dt} &= \lambda_h(T)S_h - (\mu_h + r_h + \mu_d)I_h,\\
\frac{dR_h}{dt} &= r_h I_h - (\mu_h + \sigma)R_h,
\end{aligned} \tag{2.4}$$

where $\lambda_h(T) = \frac{\beta_{vh}\phi(T)I_v}{N_h}$ and $\lambda_v(T) = \frac{\beta_{hv}\phi(T)I_h}{N_h}$ represent the force of infection of humans and mosquitoes, respectively.

$$N_h = S_h + I_h + R_h, \tag{2.5}$$

$$N_v = S_v + I_v \tag{2.6}$$

are the total human and mosquito population, respectively.

The reason for taking a simplistic model is to simplify the difficulty of the mathematical analysis for the general non-autonomous dynamical systems.

Table 2.1. Parameters of the basic malaria model in (2.4)

Symbol	Description
$\phi(T)$	The biting rate function of mosquitoes
β_{vh}	Probability of human getting infected per enough contact with infected mosquito
β_{hv}	Probability of mosquito getting infected per each enough contact with infected human
Λ_h	Recruitment rate of susceptible humans
μ_h	*Per capita* natural death rate for humans
r_h	human recovery rate
$\Lambda_v(T,R)$	Emergence rate function of female mosquitoes
σ	*Per capita* rate of loss of immunity
μ_d	*Per capita* disease induced death rate
$\mu_v(T,R)$	Mosquito per capita death rate function

2.3 Positivity of Solutions and the Invariant Region

Lemma 2.3.1. *Suppose f is a positive continuous function on $[t_0, \infty)$ for some $t_0 > 0$. Then for all $t \geqslant t_0$,*

$$\frac{\int_{t_0}^{t} e^{\int_{t_0}^{s} f(z)dz} ds}{e^{\int_{t_0}^{t} f(z)dz}} \leqslant \frac{1}{\inf\limits_{t \geqslant t_0} \{f(t)\}}. \tag{2.7}$$

proof: Suppose f is a positive continuous function on $[t_0, t]$ for an arbitrary real number t and let $m = \inf\limits_{t \geqslant t_0} \{f(t)\}$. Then for $s \in [t_0, t]$,

$$m(t-s) \leqslant \int_{s}^{t} f(z)dz,$$

and hence we have

$$e^{m(t-s)} \leqslant e^{\int_{s}^{t} f(z)dz}.$$

Inverting both sides we get,

$$\frac{1}{e^{\int_{s}^{t} f(z)dz}} \leqslant \frac{1}{e^{m(t-s)}},$$

which implies that

$$\int_{t_0}^{t} \frac{1}{e^{\int_{s}^{t} f(z)dz}} ds \leqslant \int_{t_0}^{t} e^{m(s-t)} ds = \frac{1}{m}\left[1 - e^{-m(t-t_0)}\right] \leqslant \frac{1}{m}.$$

But

$$\frac{\int_{t_0}^{t} e^{\int_{t_0}^{s} f(z)dz} ds}{e^{\int_{t_0}^{t} f(z)dz}} = \int_{t_0}^{t} \left(\frac{e^{\int_{t_0}^{s} f(z)dz}}{e^{\int_{t_0}^{t} f(z)dz}} \right) ds = \int_{t_0}^{t} \frac{1}{\left(e^{\int_{t_0}^{t} f(z)dz} e^{-\int_{t_0}^{s} f(z)dz} \right)} ds = \int_{t_0}^{t} \frac{1}{e^{\int_{s}^{t} f(z)dz}} ds.$$

Thus

$$\frac{\int_{t_0}^{t} e^{\int_{t_0}^{s} f(z)dz} ds}{e^{\int_{t_0}^{t} f(z)dz}} \leqslant \frac{1}{m}.$$

Since t is arbitrary, the proof is completed. ■

Theorem 2.3.1. *Let $(S_v(t), I_v(t), S_h(t), I_h(t), R_h(t))$ be the solution of system (2.4) with initial conditions $S_v(0) \geqslant 0, I_v(0) \geqslant 0, S_h(0) \geqslant 0, I_h(0) \geqslant 0, R_h(0) \geqslant 0$. Then, we have*

(a) $(S_v(t), I_v(t), S_h(t), I_h(t), R_h(t))$ is nonnegative for all $t \geqslant 0$ and ultimately bounded.

(b) If $S_v(0) > 0, I_v(0) > 0, S_h(0) > 0, I_h(0) > 0$ and $R_h(0) \geqslant 0$, then each component of $(S_v(t), I_v(t), S_h(t), I_h(t), R_h(t))$ also is positive for all $t > 0$.

proof: First we prove conclusion (b). Suppose that $(S_v(t), I_v(t), S_h(t), I_h(t), R_h(t))$ is defined for all $t \in [0, Q)$, where $Q > 0$. Integrating the first equation of system (2.4) from 0 to t, we have

$$S_v(t) \geqslant S_v(0) \exp\left(\int_{0}^{t} \left(-\frac{\beta_{hv} \phi(T(s))}{N_h} I_h - \mu_v(T(s), R(s)) \right) ds \right). \tag{2.8}$$

From $S_v(0) > 0$, we obtain that $S_v(t) > 0$ for all $t \in [0, Q)$.
Suppose that there exists a $t_1 \in (0, Q)$ such that

$$\min\{I_v(t_1), I_h(t_1)\} = 0.$$

Since $I_v(0) > 0$ and $I_h(0) > 0$, we can further assume $\min\{I_v(t), I_h(t)\} > 0$ for all $t \in [0, t_1)$. If $\min\{I_v(t_1), I_h(t_1)\} = I_v(t_1)$, then from $S_v(t) > 0$ for all $t \in [0, Q)$, we have

$$\dot{I}_v(t) \geqslant -\mu_v(T(t), R(t)))I_v(t) \quad \text{for all} \quad t \in [0, t_1].$$

Hence,

$$0 = I_v(t_1) \geqslant I_v(0)\exp\left(-\int_0^{t_1} \mu_v(T(s), R(s))ds\right) > 0,$$

which leads to a contradiction. If $\min\{I_v(t_1), I_h(t_1)\} = I_h(t_1)$, then since

$$\dot{R}_h(t) > -(\mu_h + \sigma)R_h(t) \quad \text{for all} \quad t \in [0, t_1),$$

we have

$$R_h(t) > R_h(0)\exp(-(\mu_h + \sigma)t) \geqslant 0 \quad \text{for all} \quad t \in (0, t_1].$$

From the fourth equation of system (2.4), we have

$$\dot{S}_h(t) \geqslant -\left(\frac{\beta_{vh}\phi(T(t))}{N_h} I_v(t) + \mu_h\right) S_h(t) \quad \text{for all} \quad t \in [0, t_1].$$

Hence,

$$S_h(t) \geqslant S_h(0)\exp\left(-\int_0^t \left(\frac{\beta_{vh}\phi(T(s))}{N_h} I_v(s) + \mu_h\right) ds\right) > 0 \quad \text{for all} \quad t \in [0, t_1].$$

From this, we further obtain

$$\dot{I}_h(t) \geqslant -(\mu_h + r_h + \mu_d)I_h(t) \quad \text{for all} \quad t \in [0, t_1].$$

Hence,

$$0 = I_h(t_1) \geqslant I_h(0)\exp(-(\mu_h + r_h + \mu_d)t_1) > 0,$$

which leads to a contradiction. This shows that $I_v(t) > 0$ and $I_h(t) > 0$ for all $t \in [0, Q)$. Furthermore, since

$$\dot{R}_h(t) > -(\mu_h + \sigma)R_h(t) \quad \text{for all} \quad t \in [0, Q),$$

we obtain

$$R_h(t) > R_h(0)e^{-(\mu_h+\sigma)t} \geqslant 0 \quad \text{for all} \quad t \in (0, Q).$$

Further from the third equation of (2.4) we have

$$\dot{S}_h(t) \geqslant -\left(\frac{\beta_{vh}\phi(T(t))}{N_h} I_v(t) + \mu_h\right) S_h(t) \quad \text{for all} \quad t \in [0, Q).$$

Hence,

$$S_h(t) \geqslant S_h(0)\exp\left(-\int_0^t \left(\frac{\beta_{vh}\phi(T(s))}{N_h} I_v(s) + \mu_h\right) ds\right) > 0 \quad \text{for all} \quad t \in [0, Q).$$

This shows that $(S_v(t), I_v(t), S_h(t), I_h(t), R_h(t))$ is positive on the interval of existence.This completes the proof of conclusion (b).

Next, we prove conclusion (a). From conclusion (b) and the continuous dependence of solutions of system (2.4) with respect to initial values, we immediately obtain that $(S_v(t), I_v(t), S_h(t), I_h(t), R_h(t))$ with initial condition $S_v(0) \geqslant 0, I_v(0) \geqslant 0, S_h(0) \geqslant 0, I_h(0) \geqslant 0, R_h(0) \geqslant 0$ is nonnegative on the interval of existence.

Now, we prove that the interval of existence of $(S_v(t), I_v(t), S_h(t), I_h(t), R_h(t))$ as a solution is $[0, \infty)$.

In fact, if the interval of existence of $(S_v(t), I_v(t), S_h(t), I_h(t), R_h(t))$ is a finite interval $[0, Q)$, then from the continuity and nonnegativity of $(S_v(t), I_v(t), S_h(t), I_h(t), R_h(t))$ on $[0, Q)$, it blows up when $t \to Q^-$ and hence it will not be bounded on $[0, Q)$. From

$$\dot{N}_v(t) \leqslant \Lambda_v(T(t), R(t)),$$

we obtain

$$N_v(t) \leqslant N_v(0) + \int_0^t \Lambda_v(T(s), R(s))ds \leqslant N_v(0) + \int_0^Q \Lambda_v(T(s), R(s))ds.$$

Hence, $N_v(t)$ is bounded on $[0, Q)$, which implies that $I_v(t)$ also is bounded on $[0, Q)$. This leads to a contradiction. Therefore, we finally have that $(S_v(t), I_v(t), S_h(t), I_h(t), R_h(t))$ is defined on $[0, \infty)$.

Adding equations one and two of system (2.4) we have

$$\dot{N}_v(t) = -\mu_v(T(t), R(t))N_v(t) + \Lambda_v(T(t), R(t)).$$

Integrating the above equation for any $t \geqslant 0$, we obtain

$$\begin{aligned} N_v(t) =& e^{-\int_0^t \mu_v(T(s),R(s))ds}\left\{N_v(0) + \int_0^t \Lambda_v(T(s), R(s))e^{\int_0^s \mu_v(T(\tau),R(\tau))d\tau} ds\right\} \\ =& e^{-\int_0^t \mu_v(T(s),R(s))ds} N_v(0) + e^{-\int_0^t \mu_v(T(s),R(s))ds}\int_0^t \Lambda_v(T(s), R(s))e^{\int_0^s \mu_v(T(\tau),R(\tau))d\tau} ds. \\ \leqslant& e^{-\int_0^t \mu_v(T(s),R(s))ds} N_v(0) + \frac{\sup\limits_{t>0}\{\Lambda_v(T(t), R(t))\}}{\inf\limits_{t>0}\{\mu_v(T(t), R(t))\}} \end{aligned}$$

by Lemma 2.3.1.

From this, we further obtain

$$\limsup_{t\to\infty} N_v(t) \leqslant \frac{\sup\limits_{t>0}\{\Lambda_v(T(t), R(t))\}}{\inf\limits_{t>0}\{\mu_v(T(t), R(t))\}} \tag{2.9}$$

Adding equations four, five and six of system (2.4) we have

$$\dot{N}_h(t) = \Lambda_h - \mu_h N_h(t) - \mu_d I_h(t) \leqslant \Lambda_h - \mu_h N_h(t)$$

and integrating this inequality for any $t \geqslant 0$, yields

$$\begin{aligned} N_h(t) \leqslant & e^{-\int_0^t \mu_h d\tau} \left\{ N_h(0) + \int_0^t \Lambda_h e^{\int_0^s \mu_h d\tau} ds \right\} \\ \leqslant & e^{-\mu_h t} N_h(0) + \Lambda_h e^{-\mu_h t} \int_0^t e^{\mu_h s} ds \\ \leqslant & e^{-\mu_h t} \left(N_h(0) - \frac{\Lambda_h}{\mu_h} \right) + \frac{\Lambda_h}{\mu_h}. \end{aligned}$$

Thus we obtain

$$\limsup_{t \to \infty} N_h(t) \leqslant \frac{\Lambda_h}{\mu_h} \tag{2.10}$$

Lastly, from (2.9) and (2.10), we finally obtain that all solutions of system (2.4) are ultimately bounded. This completes the proof of conclusion (a). ■

Remark. From (2.8) we obtain that $S_v(t) > 0$ for all $t \geqslant 0$ when $S_v(0) > 0$. Therefore, for any constant $\epsilon > 0$ small enough, we denote

$$\Omega_\epsilon = \{(S_v, I_v, S_h, I_h, R_h) : S_v > 0, I_v \geqslant 0, S_h \geqslant 0, I_h \geqslant 0, R_h \geqslant 0,$$

$$S_v + I_v \leqslant \Gamma_v + \epsilon, S_h + I_h + R_h \leqslant \frac{\Lambda_h}{\mu_h} + \epsilon\},$$

where $\Gamma_v = \frac{\sup_{t>0}\{\Lambda_v(T(t),R(t))\}}{\inf_{t>0}\{\mu_v(T(t),R(t))\}}$.
Then from Theorem (2.3.1), we see that Ω_ϵ is a positively invariant set with respect to system (2.4) and also a global attractor of all positive solutions of system (2.4).
Therefore, the model system is biologically well posed.

Chapter 3

Periodic System

3.1 Introduction

Malaria is a climate-sensitive tropical disease and hence climate exerts an impact upon the distribution of the malaria transmission in space and time. Climate variation can only be observed in long time horizon, at least 30 years is required. Instead of climate variation, we can call the variation, simply a "seasonal variation". In this chapter, it is assumed that for some shorter period of time, the variation in temperature and rainfall, and hence the corresponding parameters for malaria model, are to vary in seasonal manner. Assessment of the potential change in malaria risk caused by seasonal variations in temperature and rainfall is important to investigate the dynamics of the disease in a short term basis. The information provided here might serve as an important contribution for strategic planning of malaria control in a short period of time in the future.

For shorter period of study time the climatic values change seasonally and hence they are very much periodic in time. By considering periodicity in the climate variables and the corresponding parameters dependent on the periodic climate variables (temperature and rainfall), we analyze model 2.4 in the periodic environment. Thus the system will have time dependent periodic coefficients as climate variables could be expressed as a function of time.

$$\begin{aligned}
\frac{dS_v}{dt} &= \Lambda_v(T,R) - \lambda_v(T)S_v - \mu_v(T,R)S_v,\\
\frac{dI_v}{dt} &= \lambda_v(T)S_v - \mu_v(T,R)I_v,\\
\frac{dS_h}{dt} &= \Lambda_h - \lambda_h(T)S_h + \sigma R_h - \mu_h S_h,\\
\frac{dI_h}{dt} &= \lambda_h(T)S_h - (\mu_h + r_h + \mu_d)I_h,\\
\frac{dR_h}{dt} &= r_h I_h - (\mu_h + \sigma)R_h,
\end{aligned} \tag{3.1}$$

where $\lambda_h(T) = \frac{\beta_{vh}\phi(T)I_v}{N_h}$ and $\lambda_v(T) = \frac{\beta_{hv}\phi(T)I_h}{N_h}$ represent the force of infection of humans and mosquitoes, respectively.

3.2 Some Mathematical Preliminaries

3.2.1 The Basic Reproduction Ratio

In this subsection we will try to present briefly the mathematical results formulated in [81] for non-autonomous but periodic systems.We consider a heterogeneous population whose individuals can be grouped into n homogeneous compartments. Let $x = (x_1, ..., x_n)^T$, with each $x_i \geqslant 0$, be the state of individuals in each compartment. We assume that the compartments can be divided into two types: infected compartments, labeled by $i = 1, ..., m$, and uninfected compartments, labeled by $i = m+1, ..., n$. Define X_s to be the set of all disease-free states:

$$X_s := \{x \geqslant 0 : x_i = 0, \forall i = 1, ..., m\}.$$

Let $\mathcal{F}_i(t, x)$ be the input rate of newly infected individuals in the i^{th} compartment, $\mathcal{V}_i^+(t, x)$ be the input rate of individuals by other means (for example, births, immigrations), and $\mathcal{V}_i^-(t, x)$ be the rate of transfer of individuals out of compartment i (for example, deaths, recovery and emigrations). Thus, the disease transmission model is governed by a non-autonomous ordinary differential system:

$$\frac{dx_i}{dt} = \mathcal{F}_i(t, x) - \mathcal{V}_i(t, x) \triangleq f_i(t, x), i = 1, ..., n, \tag{3.2}$$

where $\mathcal{V}_i(t, x) = \mathcal{V}_i^-(t, x) - \mathcal{V}_i^+(t, x)$. Following the setting in [81] for non-autonomous compartmental epidemic models, we make the following assumptions:

(A1) For each $1 \leqslant i \leqslant n$, the functions $\mathcal{F}_i(t, x)$, $\mathcal{V}_i^+(t, x)$ and $\mathcal{V}_i^-(t, x)$ are nonnegative and continuous on $\mathbb{R} \times \mathbb{R}_+^n$ and continuously differentiable with respect to x.

(A2) There is a real number $\omega > 0$ such that for each $1 \leqslant i \leqslant n$, the functions $\mathcal{F}_i(t, x)$, $\mathcal{V}_i^+(t, x)$ and $\mathcal{V}_i^-(t, x)$ are ω-periodic in t.

(A3) If $x_i = 0$, then $\mathcal{V}_i^-(t, x) = 0$. In particular, if $x \in X_s$, then $\mathcal{V}_i^-(t, x) = 0$ for $i = 1, ..., m$.

(A4) $\mathcal{F}_i(t, x) = 0$ for $i > m$.

(A5) If $x \in X_s$, then $\mathcal{F}_i(t, x) = \mathcal{V}_i^+(t, x) = 0$ for $i = 1, ..., m$.

Note that (A1) arises from the simple fact that each function denotes a directed nonnegative transfer of individuals. Biologically, (A2) describes a periodic environment (e.g., due to seasonality); (A3) represents that if a compartment is empty, then there

is no transfer of individuals out of the compartment; (A4) means that the incidence of infection for uninfected compartments is zero; and (A5) implies that the population will remain free of disease if it is free of disease at the beginning and no infectious individual is introduced in the course of time..

We assume that the model (3.2) has a disease-free periodic solution $x^0(t) = (0, ..., 0, x^0_{m+1}(t), ..., x^0_n(t))^T$ with $x^0_i(t) > 0$, $m + 1 \leqslant i \leqslant n$ for all t. Let $f = (f_1, ..., f_n)^T$, and define an $(n - m) \times (n - m)$ matrix

$$M(t) := \left(\frac{\partial f_i(t, x^0(t))}{\partial x_j} \right)_{m+1 \leqslant i,j, \leqslant n}.$$

Let $\Phi_M(t)$ be the monodromy matrix of the linear ω-periodic system $\frac{dz}{dt} = M(t)z$. We further assume that $x^0(t)$ is linearly asymptotically stable in the disease-free subspace X_s, that is,

(A6) $\rho(\Phi_M(\omega)) < 1$, where $\rho(\Phi_M(\omega))$ is the spectral radius of $\Phi_M(\omega)$.

By the arguments similar to those in [[77], Lemma 1], it then follows that

$$D_x\mathcal{F}(t, x^0(t)) = \begin{pmatrix} F(t) & 0 \\ 0 & 0 \end{pmatrix}, \quad D_x\mathcal{V}(t, x^0(t)) = \begin{pmatrix} V(t) & 0 \\ J(t) & -M(t) \end{pmatrix},$$

where $F(t)$ and $V(t)$ are two $m \times m$ matrices defined by

$$F(t) = \left(\frac{\partial \mathcal{F}_i(t, x^0(t))}{\partial x_j} \right)_{1 \leqslant i,j, \leqslant m}, \quad V(t) = \left(\frac{\partial \mathcal{V}_i(t, x^0(t))}{\partial x_j} \right)_{1 \leqslant i,j, \leqslant m}, \tag{3.3}$$

respectively, and $J(t)$ is an $(n - m) \times n$ matrix. Furthermore, $F(t)$ is nonnegative, and $-V(t)$ is cooperative in the sense that the off-diagonal elements of $-V(t)$ are nonnegative.

Let $Y(t, s)$, $t \geqslant s$, be the evolution operator of the linear ω-periodic system

$$\frac{dy}{dt} = -V(t)y. \tag{3.4}$$

That is, for each $s \in \mathbb{R}$, the $m \times m$ matrix $Y(t, s)$ satisfies

$$\frac{d}{dt}Y(t, s) = -V(t)Y(t, s), \quad \forall t \geqslant s, \quad Y(s, s) = I,$$

where I is the $m \times m$ identity matrix. Thus, the monodromy matrix $\Phi_{-V}(t)$ of (3.4) equals $Y(t, 0)$, $t \geqslant 0$. Note that the internal evolution of individuals in the infectious compartments due to deaths and movements among the compartments is dissipative, and exponentially decays in many cases because of the loss of infective members from natural mortalities and disease-induced mortalities. Thus, we assume that

(A7) $\rho(\Phi_{-V}(t)) < 1$.

Based on the assumptions above, we are now able to analyze the reproduction ratios for the epidemic model (3.2). For this purpose, we always assume that the population is near the disease-free periodic state $x^0(t)$.
By the standard theory of linear periodic systems (see, e.g., [[32], Sect. III.7]), there exist $K > 0$ and $\alpha > 0$ such that

$$||Y(t,s)|| \leqslant Ke^{-\alpha(t-s)}, \quad \forall t \geqslant s, \quad s \in \mathbb{R}. \tag{3.5}$$

It follows that

$$||Y(t,t-a)F(t-a)|| \leqslant K||F(t-a)||e^{-\alpha a}, \quad \forall t \in \mathbb{R}, \quad a \in [0,\infty). \tag{3.6}$$

In view of the periodic environment, we suppose that $\varphi(s)$ is the initial distribution of infectious individuals, which is assumed to be ω-periodic in s. Then $F(s)\varphi(s)$ is the total distribution of new infections produced by the infected individuals who were introduced at time s. Given $t \geqslant s$, then $Y(t,s)F(s)\varphi(s)$ gives the distribution of those infected individuals who were newly infected at time s and remain in the infected compartments at time t. It follows that

$$\psi(t) := \int_{-\infty}^{0} Y(t,s)F(s)\varphi(s)ds = \int_{0}^{\infty} Y(t,t-a)F(t-a)\varphi(t-a)da$$

is the distribution of accumulative new infections at time t produced by all those infected individuals $\varphi(s)$ introduced at previous time to t.
Let C_ω be the ordered Banach space of all ω-periodic functions from $\mathbb{R} \to \mathbb{R}^m$, which is equipped with the maximum norm $||.||$ and the positive cone

$$C_\omega^+ := \{\varphi \in C_\omega : \varphi(t)) \geqslant 0 \text{ for all } t \in \mathbb{R}\}.$$

Then we can define a linear operator $L : C_\omega \to C_\omega$ by

$$(L\varphi)(t) = \int_{0}^{\infty} Y(t,t-a)F(t-a)\varphi(t-a)da \text{ for all } t \in \mathbb{R}, \quad \varphi \in C_\omega. \tag{3.7}$$

Motivated by the concept of next generation matrices introduced in ([18], [77]),we call L the next infection operator, and define the spectral radius of L as the basic reproduction ratio

$$R_0 := \rho(L) \tag{3.8}$$

for the periodic epidemic model (3.2).

Now let $A(t)$ be a continuous and ω-periodic $n \times n$ matrix function. We consider the following linear system

$$\dot{x} = A(t)x. \tag{3.9}$$

Following [81], let $\Phi_A(t)$ be the fundamental solution matrix of system (3.9) with initial condition $\Phi_A(0) = I$, where I is $n \times n$ identity matrix, and let $\rho(\Phi_A(\omega))$ be the

spectral radius of matrix $\Phi_A(\omega)$. Further, we assume that A(t) also is cooperative and irreducible, then by the Perron-Frobenius theorem, $\rho(\Phi_A(\omega))$ is the principal eigenvalue of $\Phi_A(\omega)$ in the sense that it is simple and admits an eigenvector $\nu^* \gg 0$.

In view of the biological background of system (3.1), in this chapter we only consider the solution of system (3.1) starting at $t = 0$ with initial values:

$$S_v(0) \geqslant 0, \quad I_v(0) \geqslant 0, \quad S_h(0) \geqslant 0, \quad I_h(0) \geqslant 0 \quad \text{and} \quad R_h(0) \geqslant 0. \tag{3.10}$$

In this chapter, for system (3.1) we introduce the following assumptions:

(H_1) $\Lambda_v(T(t), R(t))$, $\mu_v(T(t), R(t))$, $\lambda_h(T(t))$ and $\lambda_v(T(t))$ are continuous and ω-periodic functions.

(H_2) $\int_0^\omega \Lambda_v(T(t), R(t))dt > 0$.

The assumption H_1 is made to have a model with periodic coefficients and H_2 is taken to guarantee the existence and continuity of the emergence of the mosquito population.

When $I_h(t) \equiv 0, R_h(t) \equiv 0$ and $I_v(t) \equiv 0$, we can obtain the following two subsystem of system (3.1)

$$\dot{S}_h(t) = \Lambda_h - \mu_h S_h(t), \tag{3.11}$$

and

$$\dot{S}_v(t) = \Lambda_v(T(t), R(t)) - \mu_v(T(t), R(t))S_v(t). \tag{3.12}$$

We see that system (3.1) has a disease-free periodic solution (DFPS)

$$E_0^*(t) = (S_v^*(t), 0, \frac{\Lambda_h}{\mu_h}, 0, 0) \tag{3.13}$$

Lemma 3.2.1. *The function*

$$S_v^*(t) = S_v^0 e^{-\int_0^t \mu_v(\tau)d\tau} + \int_0^t \Lambda_v(s)\, e^{-\int_s^t \mu_v(\tau)d\tau} ds$$

where

$$S_v^0 = \frac{\int_0^\omega \Lambda_v(s)\, e^{-\int_s^\omega \mu_v(\tau)d\tau} ds}{1 - e^{-\int_0^\omega \mu_v(\tau)d\tau}}$$

is a ω-periodic disease free solution of equation (3.12).

proof: For any initial condition, S_v^0, equation (3.12) has a unique solution given by

$$S_v(t) = S_v^0 e^{-\int_0^t \mu_v(\tau)d\tau} + \int_0^t \Lambda_v(s)\, e^{-\int_s^t \mu_v(\tau)d\tau} ds.$$

In particular, we have

$$S_v(\omega) = S_v^0 e^{-\int_0^\omega \mu_v(\tau)d\tau} + \int_0^\omega \Lambda_v(s)\, e^{-\int_s^\omega \mu_v(\tau)d\tau} ds.$$

Hence we obtain $S_v(\omega) = S_v^0$.
Moreover,

$$\begin{aligned} S_v(t+\omega) &= S_v(\omega)\, e^{-\int_\omega^{t+\omega} \mu_v(\tau)d\tau} + \int_\omega^{t+\omega} \Lambda_v(s)\, e^{-\int_s^{t+\omega} \mu_v(\tau)d\tau} ds \\ &= S_v^0 e^{-\int_\omega^{t+\omega} \mu_v(\tau)d\tau} + \int_\omega^{t+\omega} \Lambda_v(s)\, e^{-\int_s^{t+\omega} \mu_v(\tau)d\tau} ds \end{aligned}$$

On the other hand, $e^{-\int_\omega^{t+\omega} \mu_v(\tau)d\tau} = e^{-\int_\omega^{t+\omega} \mu_v(\tau-\omega)d\tau}$ as μ_v is ω-periodic. By using the change of variable $s = \tau - \omega$, we obtain

$$e^{-\int_\omega^{t+\omega} \mu_v(\tau-\omega)d\tau} = e^{-\int_0^t \mu_v(s)ds}.$$

Furthermore, since Λ_v is also assumed to be ω-periodic, we have

$$\int_\omega^{t+\omega} \Lambda_v(\tau)\, e^{-\int_\tau^{t+\omega} \mu_v(s)ds} d\tau = \int_\omega^{t+\omega} \Lambda_v(\tau-\omega)\, e^{-\int_{\tau-\omega+\omega}^{t+\omega} \mu_v(s)ds} d\tau$$

By setting $x = \tau - \omega$, we obtain

$$\begin{aligned} &\int_\omega^{t+\omega} \Lambda_v(\tau-\omega)\, e^{-\int_{\tau-\omega+\omega}^{t+\omega} \mu_v(s)ds} d\tau \\ &= \int_0^t \Lambda_v(x)\, e^{-\int_{x+\omega}^{t+\omega} \mu_v(s)ds} dx \\ &= \int_0^t \Lambda_v(x)\, e^{-\int_x^t \mu_v(s)ds} dx \end{aligned}$$

Hence,

$$\int_\omega^{t+\omega} \Lambda_v(\tau)\, e^{-\int_\tau^{t+\omega} \mu_v(s)ds} d\tau = \int_0^t \Lambda_v(x)\, e^{-\int_x^t \mu_v(s)ds} dx.$$

This implies that

$$S_v(t+\omega) = S_v^0 e^{-\int_0^t \mu_v(\tau)d\tau} + \int_0^t \Lambda_v(x)\, e^{-\int_x^t \mu_v(s)ds} dx = S_v(t).$$

■

Now following [80], based on the assumptions H_1 and H_3, we compute the basic reproduction number of system (3.1) following the way given in ([77],[81]).
Let

$$\mathcal{F}(t,x) = \begin{pmatrix} \lambda_v(t)S_v \\ \lambda_h(t)S_h \\ 0 \\ 0 \\ 0 \end{pmatrix}, \qquad \mathcal{V}^-(t,x) = \begin{pmatrix} \mu_v(T(t),R(t))I_v \\ (\mu_h + r_h + \mu_d)I_h \\ \lambda_v(t)S_v + \mu_v(T(t),R(t))S_v \\ \lambda_h(t)S_h + \mu_h S_h \\ \mu_h R_h + \sigma R_h \end{pmatrix}$$

and

$$\mathcal{V}^+(t,x) = \begin{pmatrix} 0 \\ 0 \\ \Lambda_v(T(t),R(t)) \\ \Lambda_h + \sigma R_h \\ r_h I_h \end{pmatrix}$$

where $x = (S_v, I_v, S_h, I_h, R_h)^T$, then system (3.1) equals to the following form

$$\dot{x}(t) = \mathcal{F}(t,x) - \mathcal{V}(t,x) \triangleq f(t,x(t)), \tag{3.14}$$

where $\mathcal{V}(t,x) = \mathcal{V}^-(t,x) - \mathcal{V}^+(t,x)$.
In the following, we will check conditions (A1)-(A7) which are given above.

By the expressions of $\mathcal{F}(t,x)$ and $\mathcal{V}^+(t,x)$, we see that conditions (A1)-(A5) are satisfied. Now, we define

$$N(t) = \left(\frac{\partial f_i(t,x^*(t))}{\partial x_j}\right)_{3\leqslant i,j,\leqslant 5}$$

where $f_i(t,x^*(t))$ and x_i are the i^{th} component of $f(t,x(t))$ and x, respectively. By simple computations, we can obtain

$$N(t) = \begin{pmatrix} -\mu_v(T(t),R(t))) & 0 & 0 \\ 0 & -\mu_h & \sigma \\ 0 & 0 & -(\mu_h+\sigma) \end{pmatrix}.$$

and we finally get $\rho(\Phi_N(\omega)) < 1$. Thus, condition (A6) also holds.
Next, we set two 2×2 matrices as follows

$$F(t) = \left(\tfrac{\partial \mathcal{F}_i(t,x^*(t))}{\partial x_j}\right)_{1\leqslant i,j\leqslant 2} \text{ and } V(t) = \left(\tfrac{\partial \mathcal{V}_i(t,x^*(t))}{\partial x_j}\right)_{1\leqslant i,j\leqslant 2},$$

where $\mathcal{F}_i(t,x(t))$ and $\mathcal{V}_i(t,x(t))$ are the i^{th} component of $\mathcal{F}(t,x(t))$ and $\mathcal{V}(t,x(t))$, respectively. Then, by simple computations, it follows that

$$F(t) = \begin{pmatrix} 0 & \frac{\beta_{hv}\phi(T(t))}{N_h(t)} S_v^*(t) \\ \frac{\beta_{vh}\phi(T(t))\Lambda_h}{N_h(t)\mu_h} & 0 \end{pmatrix}, \quad V(t) = \begin{pmatrix} \mu_v(T(t),R(t)) & 0 \\ 0 & \mu_h + r_h + \mu_d \end{pmatrix}$$

Therefore, from assumption H_1, we obtain that $\rho(\Phi_{-V}(\omega)) < 1$. Thus, condition (A7) also holds.
For the periodic system (3.1), a stability analysis similar to the works of [80] is done using the basic reproduction ratio (3.8).

Lemma 3.2.2. *(Lemma 4 in [80]) Assume that (A1)-(A7) hold. Then the following statements are valid:*

(i) $R_0 = 1$ *if and only if* $\rho(\Phi_{F-V}(\omega)) = 1$*;*

(ii) $R_0 > 1$ *if and only if* $\rho(\Phi_{F-V}(\omega)) > 1$*;*

(iii) $R_0 < 1$ *if and only if* $\rho(\Phi_{F-V}(\omega)) < 1$*.*

Thus, $E^*(t)$ *is asymptotically stable if* $R_0 < 1$*, and unstable if* $R_0 > 1$*.*

Theorem 3.2.1. *If* $R_0 < 1$*, then the disease-free periodic solution* $E_0^*(t)$ *of system* (3.1) *is globally asymptotically stable.*

proof: From Lemma 3.2.2, we obtain that if $R_0 < 1$, $E_0^*(t)$ is locally asymptotically stable. Now, we will only prove the global attractivity of $E_0^*(t)$ for the case $R_0 < 1$. From $R_0 < 1$ and conclusion (iii) of Lemma 3.2.2, we have $\rho(\Phi_{F-V}(\omega)) < 1$, then we can choose a small enough constant $\epsilon_2 > 0$ such that $\rho(\Phi_{F-V+\epsilon_2 M}(\omega)) < 1$, where

$$M(t) = \begin{pmatrix} 0 & \frac{\beta_{hv}\phi(T(t))}{N_h} \\ \frac{\beta_{vh}\phi(T(t))}{N_h} & 0 \end{pmatrix}.$$

From (2.9) and (2.10), we obtain that for above given constant ϵ_2 there exists a $t_1 > 0$ such that for all $t > t_1$

$$S_h \leqslant \frac{\Lambda_h}{\mu_h} + \epsilon_2 \quad \text{and} \quad S_v \leqslant S_v^* + \epsilon_2.$$

From the second and fourth equations of system (3.1), we obtain that for all $t > t_1$

$$\begin{cases} \dot{I}_v \leqslant \frac{\beta_{hv}\phi(T(t))}{N_h}(S_v^*(t) + \epsilon_2)I_h - \mu_v(T(t), R(t))I_v, \\ \dot{I}_h \leqslant \frac{\beta_{vh}\phi(T(t))}{N_h}(\frac{\Lambda_h}{\mu_h} + \epsilon_2)I_v - (\mu_h + r_h + \mu_d)I_h. \end{cases} \tag{3.15}$$

Considering the following auxiliary system:

$$\begin{cases} \dot{\tilde{I}}_v = \frac{\beta_{hv}\phi(T(t))}{N_h}(S_v^*(t) + \epsilon_2)\tilde{I}_h - \mu_v(T(t), R(t))\tilde{I}_v, \\ \dot{\tilde{I}}_h = \frac{\beta_{vh}\phi(T(t))}{N_h}(\frac{\Lambda_h}{\mu_h} + \epsilon_2)\tilde{I}_v - (\mu_h + r_h + \mu_d)\tilde{I}_h. \end{cases}$$

For the convenience, we will rewrite it as follows

$$\frac{d}{dt}\begin{pmatrix} \tilde{I}_v \\ \tilde{I}_h \end{pmatrix} = (F(t) - V(t) + \epsilon_2 M(t))\begin{pmatrix} \tilde{I}_v \\ \tilde{I}_h \end{pmatrix} \tag{3.16}$$

From Lemma 2 in [80], it follows that there exists a positive ω-periodic function $q(t) = (q_1(t), q_2(t))^T$ such that $(\tilde{I}_v(t), \tilde{I}_h(t))^T = e^{\mu_1 t}q(t)$ is a solution of system (3.16), where

$\mu_1 = \frac{1}{\omega}\ln\left(\rho(\Phi_{F-V+\epsilon_2 M}(\omega))\right)$.

Denote $G(t) = (I_v(t), I_h(t))^T$.
We can choose a small constant $\xi > 0$ such that $G(t_1) \leqslant \xi q(t_1)$. Then, from (3.15) the comparison principle implies that

$$G(t) \leqslant \xi e^{\mu_1 t} q(t) \quad \text{for all} \quad t > t_1.$$

By $\rho(\Phi_{F-V+\epsilon_2 M}(\omega)) < 1$, it follows that $\mu_1 < 0$, then $\lim_{t\to\infty} G(t) = 0$, that is,

$$\lim_{t\to\infty} I_v(t) = 0, \quad \lim_{t\to\infty} I_h(t) = 0.$$

Moreover, from the equations of S_v,S_h and R_h in system (3.1), we can get

$$\lim_{t\to\infty} S_v(t) = S_v^*(t), \quad \lim_{t\to\infty} S_h(t) = \frac{\Lambda_h}{\mu_h}, \quad \lim_{t\to\infty} R_h(t) = 0.$$

Hence, disease-free periodic solution $E_0^*(t)$ of system (3.1) is globally attractive. This completes the proof. ■

Theorem 3.2.2. *If $R_0 > 1$, then system (3.1) is uniformly persistent. That is, there exists a positive constant ε, such that any solution $(S_v(t), I_v(t), S_h(t), I_h(t), R_h(t))$ of system (3.1) with initial conditions $S_v(0) \geqslant 0, I_v(0) \geqslant 0, S_h(0) \geqslant 0, I_h(0) \geqslant 0$ and $R_h(0) \geqslant 0$ satisfies*

$$\liminf_{t\to\infty}(S_v(t), I_v(t), S_h(t), I_h(t), R_h(t)) \geqslant (\varepsilon, \varepsilon, \varepsilon, \varepsilon, \varepsilon).$$

proof: From $R_0 > 1$ and conclusion (ii) of Lemma 3.2.2, we have $\rho(\Phi_{F-V}(\omega)) > 1$. Then, we can choose a small constant $\xi > 0$ such that $\rho(\Phi_{F-V-\xi M}(\omega)) > 1$, where $M(t)$ is defined in Theorem (3.2.1).
From H_2 and H_3, we obtain for any small enough $\varepsilon > 0$

$$\int_0^\omega [\Lambda_v(T(t), R(t)) - \frac{\beta_{hv}\lambda\phi(T(t))}{N_h}\varepsilon]dt > 0. \tag{3.17}$$

For this ε, we consider the following two perturbed equations

$$\dot{U}_\varepsilon(t) = \Lambda_v(T(t), R(t)) - \varepsilon\frac{\beta_{hv}\phi(T(t))}{N_h}U_\varepsilon(t) - \mu_v(T(t), R(t)))U_\varepsilon(t), \tag{3.18}$$

and

$$\dot{V}_\varepsilon(t) = \Lambda_h - \varepsilon\frac{\beta_{vh}\phi(T(t))}{N_h}V_\varepsilon(t) - \mu_h V_\varepsilon(t). \tag{3.19}$$

Using Theorem 3 in [80] and the references there in, from assumption (H_2) and (3.17), we can get that systems (3.18) and (3.19) admit globally uniformly attractive positive ω-periodic solutions $U_\varepsilon^*(t)$ and $V_\varepsilon^*(t)$, respectively. By the continuity of solutions with

respect to the parameter ε, for constant $\xi > 0$ given in above, there exists a constant $\varepsilon_1 > 0$ such that for all $0 < \varepsilon_1 < \varepsilon$ and $t \in [0, \omega]$

$$U^*_{\varepsilon_1}(t) > S^*_v(t) - \frac{\xi}{2}, \quad V^*_{\varepsilon_1}(t) > \frac{\Lambda_h}{\mu_h} - \frac{\xi}{2}. \tag{3.20}$$

Define

$$X = \{(S_v, I_v, S_h, I_h, R_h) : S_v > 0, I_v \geqslant 0, S_h \geqslant 0, I_h \geqslant 0, R_h \geqslant 0\}$$

and

$$X_0 = \{(S_v, I_v, S_h, I_h, R_h) \in X : I_v > 0, I_h > 0\}.$$

We have

$$\partial X_0 = X \backslash X_0 = \{(S_v, I_v, S_h, I_h, R_h) \in X : I_v I_h = 0\}$$

From system (3.1), it is easy to see that X and X_0 are positively invariant, and ∂X_0 is also a relatively closed set in X. Let $P : X \to X$ be the Poincar $\acute{e}$ map associated with system (3.1), that is

$$P(x_0) = u(\omega, x_0) \quad \text{for all} \quad x_0 \in X,$$

where $u(t, x_0)$ is the unique solution of system (3.1) satisfying initial condition $u(0, x_0) = x_0$. From the continuity of solutions of system (3.1) with respect to initial value x_0, we can obtain that P is compact. Moreover, by Theorem 2.3.1, we obtain that P is point dissipative on X.
Further, we define

$$M_\partial = \{(S_v(0), I_v(0), S_h(0), I_h(0), R_h(0)) \in \partial X_0 :$$

$$P^m(S_v(0), I_v(0), S_h(0), I_h(0), R_h(0)) \in \partial X_0 \quad \text{for all} \quad m > 0\},$$

where $P^m = P(P^{m-1})$ for all $m > 1$ and $P^1 = P$.
Now, we claim that

$$M_\partial = \{(S_v, 0, S_h, 0, 0) : S_v > 0, S_h \geqslant 0\}. \tag{3.21}$$

First, for any point $(S_v(0), 0, S_h(0), 0, 0)$, where $S_v(0) > 0$ and $S_h(0) \geqslant 0$, according to the existence and uniqueness of solutions of system (3.1), we can obtain that $(S_v(t), I_v(t), S_h(t), I_h(t), R_h(t))$ with $I_v(t) \equiv 0, I_h(t) \equiv 0$ and $R_h(t) \equiv 0$ is the unique solution of system (3.1) satisfying initial condition

$$(S_v(0), I_v(0), S_h(0), I_h(0), R_h(0)) = (S_v(0), 0, S_h(0), 0, 0).$$

Therefore, we obtain for any integer $m > 0$

$$P^m(S_v(0), 0, S_h(0), 0, 0) \in \{(S_v, 0, S_h, 0, 0) : S_v > 0, S_h \geqslant 0\} \subseteq \partial X_0.$$

This shows $(S_v, 0, S_h, 0, 0) \in M_\partial$. Consequently,

$$\{(S_v, 0, S_h, 0, 0) : S_v > 0, S_h \geqslant 0\} \subseteq M_\partial.$$

On the other hand, if $M_\partial \backslash \{(S_v, 0, S_h, 0, 0) : S_v > 0, S_h \geqslant 0\} \neq \varnothing$, then there exists at least a point $(S_v(0), I_v(0), S_h(0), I_h(0), R_h(0)) \in M_\partial$ satisfying $I_h(0) > 0$ or $I_v(0) > 0$. If $I_v(0) = 0$ and $I_h(0) > 0$, then it is clear that from system (3.1)

$$I_h(t) \geqslant I_h(0)e^{-(\mu_h + r_h + \mu_d)t} > 0 \quad \text{for all} \quad t > 0.$$

From $S_v(0) > 0$ we can obtain from the first equation of system (3.1) that $S_v(t) > 0$ for all $t > 0$. Hence,

$$I_v(t) = \left[I_v(0) + \int_0^t \frac{\beta_{hv}\phi(T(s))}{N_h} S_v(s) I_h(s) e^{\int_0^s \mu_v(T(u),R(u))du} ds \right] e^{-\int_0^t \mu_v(T(u),R(u))du} > 0$$

for all $t > 0$. If $I_v(0) > 0$ and $I_h(0) = 0$, then we have

$$I_v(t) = \left[I_v(0) + \int_0^t \frac{\beta_{hv}\phi(T(s))}{N_h} S_v(s) I_h(s) e^{\int_0^s \mu_v(T(u),R(u))du} ds \right] e^{-\int_0^t \mu_v(T(u),R(u))du} > 0$$

for all $t > 0$. From the third equation of system (3.1) we have

$$\dot{S}_h(t) > -\left(\frac{\beta\phi(T(t))}{N_h} I_v(t) + \mu_h \right) S_h(t) \quad \text{for all} \quad t \geqslant 0.$$

Hence, we further have $S_h(t) > 0$ for all $t > 0$. Consequently, by the fourth equation of system (3.1) we have

$$\dot{I}_h(t) > -(\mu_h + r_h + \mu_d) I_h(t) \quad \text{for all} \quad t \geqslant 0$$

and hence $I_h(t) > 0$ for all $t > 0$. This shows that $(S_v(t), I_v(t), S_h(t), I_h(t), R_h(t)) \notin \partial X_0$. Hence, $(S_v(0), I_v(0), S_h(0), I_h(0), R_h(0)) \notin M_\partial$ which leads to a contradiction. It indicates that $M_\partial \subseteq \{(S_v, 0, S_h, 0, 0) : S_v > 0, S_h \geqslant 0\}$. Therefore, we finally obtain that claim (3.21) holds.

It is clear that there is a fixed point of P in M_∂ , which is $M_1 = (S_v^*(0), 0, \frac{\Lambda_h}{\mu_h}, 0, 0)$. Denote $x_0 = (S_v(0), I_v(0), S_h(0), I_h(0), R_h(0)) \in X_0$. By the continuity of solutions with respect to the initial value, for above given constant $\varepsilon_1 > 0$, there exists $\delta_0 > 0$ such that for all $x_0 \in X_0$ with $||x_0 - M_1|| \leqslant \delta_0$, it follows that

$$||u(t, x_0) - u(t, M_1)|| < \varepsilon_1 \quad \text{for all} \quad t \in [0, \omega]. \tag{3.22}$$

Now, we prove

$$\limsup_{m \to \infty} d(P^m(x_0), M_1) \geqslant \delta_0. \tag{3.23}$$

Suppose the conclusion is not true, then

$$\limsup_{m \to \infty} d(P^m(x_0), M_1) < \delta_0.$$

for some $x_0 \in X_0$. Without loss of generality, we can assume that

$$d(P^m(x_0), M_1) < \delta_0 \quad \text{for all} \quad m \geqslant 0$$

Further, from (3.22) we have

$$||u(t, P^m(x_0)) - u(t, M_1)|| < \varepsilon_1 \quad \text{for all} \quad m \geqslant 0, \quad t \in [0, \omega].$$

For any $t \geqslant 0$, let $t = m\omega + t'$,where $t' \in [0, \omega)$ and $m = [\frac{t}{\omega}]$ is the greatest integer less than or equal to $\frac{t}{\omega}$, then we can get

$$||u(t, x_0) - u(t, M_1)|| = ||u(t', P^m(x_0)) - u(t', M_1)|| < \varepsilon_1 \quad \text{for all} \quad t \geqslant 0. \tag{3.24}$$

Since $u(t, x_0) = (S_v(t), I_v(t), S_h(t), I_h(t), R_h(t))$ and $u(t, M_1) = (S_v^*(t), 0, \frac{\Lambda_h}{\mu_h}, 0, 0)$, it follows from (3.24) that $0 \leqslant I_v(t) \leqslant \varepsilon_1$ and $0 \leqslant I_h(t) \leqslant \varepsilon_1$ for all $t \geqslant 0$. Then, by the first and third equation of system (3.1) we get for any $t \geqslant 0$

$$\dot{S}_v(t) \geqslant \Lambda_v(T(t), R(t)) - \varepsilon_1 \frac{\beta_{hv}\phi(T(t))}{N_h} S_v(t) - \mu_v(T(t), R(t)) S_v(t),$$

and

$$\dot{S}_h(t) \geqslant \Lambda_h - \varepsilon_1 \frac{\beta_{vh}\phi(T(t))}{N_h} S_h(t) - \mu_h S_h(t).$$

By the comparison principle, we obtain for any $t \geqslant 0$

$$S_v(t) \geqslant U_{\varepsilon_1}(t), \quad S_h(t) \geqslant V_{\varepsilon_1}(t),$$

where $U_{\varepsilon_1}(t)$ and $V_{\varepsilon_1}(t)$ are the solutions of systems (3.18) and (3.19) with parameter ε_1 satisfying initial conditions $U_{\varepsilon_1}(0) = S_v(0)$ and $V_{\varepsilon_1}(0) = S_h(0)$, respectively. Since systems (3.18) and (3.19) with parameter ε_1 have globally uniformly attractive positive ω-periodic solutions $U_{\varepsilon_1}^*(t)$ and $V_{\varepsilon_1}^*(t)$, respectively, there exists a $t_1 > 0$ such that

$$U_{\varepsilon_1}(t) > U_{\varepsilon_1}^*(t) - \frac{\xi}{2}, \quad V_{\varepsilon_1}(t) > V_{\varepsilon_1}^*(t) - \frac{\xi}{2} \quad \text{for all} \quad t \geqslant t_1. \tag{3.25}$$

Combining (3.20) and (3.25), we have

$$U_{\varepsilon_1}(t) > S_v^*(t) - \xi, \quad V_{\varepsilon_1}(t) > \frac{\Lambda_h}{\mu_h} - \xi \quad \text{for all} \quad t \geqslant t_1.$$

Thus, we finally obtain that for all $t \geqslant t_1$

$$\begin{cases} \dot{I}_v \geqslant \frac{\beta_{hv}\phi(T(t))}{N_h}(S_v^*(t) - \xi) I_h - \mu_v(T(t), R(t)) I_v, \\ \dot{I}_h \geqslant \frac{\beta_{vh}\phi(T(t))}{N_h}(\frac{\Lambda_h}{\mu_h} - \xi) I_v - (\mu_h + r_h + \mu_d) I_h. \end{cases} \tag{3.26}$$

Consider the following auxiliary system

$$\begin{cases} \dot{\hat{I}}_v = \frac{\beta_{hv}\phi(T(t))}{N_h}(S_v^*(t) - \xi) \hat{I}_h - \mu_v(T(t), R(t)) \hat{I}_v, \\ \dot{\hat{I}}_h = \frac{\beta_{vh}\phi(T(t))}{N_h}(\frac{\Lambda_h}{\mu_h} - \xi) \hat{I}_v - (\mu_h + r_h + \mu_d) \hat{I}_h. \end{cases}$$

For the convenience, we will rewrite it as follows

$$\frac{d}{dt}\begin{pmatrix}\hat{I}_v\\ \hat{I}_h\end{pmatrix} = (F(t) - V(t) - \xi M(t))\begin{pmatrix}\hat{I}_v\\ \hat{I}_h\end{pmatrix} \tag{3.27}$$

From Lemma 2 in [80], it follows that there exists a positive ω-periodic function $p(t) = (p_1(t), p_2(t))^T$ such that $(\hat{I}_v(t), \hat{I}_h(t))^T = e^{\mu_2 t}p(t)$ is a solution of system (3.27), where $\mu_2 = \frac{1}{\omega}\ln(\rho(\Phi_{F-V-\xi M}(\omega)))$.

Since $G(t) \in \text{int}\mathbb{R}^2_+$ where $G(t) = (I_v(t), I_h(t))^T$,we can select a small constant $\alpha > 0$ such that $G(t_1) > \alpha p(t_1)$. Then, by (3.26) and the comparison principle, we can obtain that

$$G(t) \geqslant \alpha e^{\mu_2 t}p(t) \quad \text{for all} \quad t > t_1.$$

By $\rho(\Phi_{F-V-\xi M}(\omega)) > 1$, it follows that $\mu_2 > 0$, then $\lim_{t\to\infty} G(t) = \infty$, that is,

$$\lim_{t\to\infty} I_v(t) = \infty, \quad \lim_{t\to\infty} I_h(t) = \infty.$$

which is a contradiction with $0 \leqslant I_v(t) \leqslant \varepsilon_1$ and $0 \leqslant I_h(t) \leqslant \varepsilon_1$.
Therefore, claim (3.23) holds. This shows $W^s(M_1)\bigcap X_0 = \varnothing$. From Lemma 1 in [80], we can obtain that $\{M_1\}$ is globally attractive in M_∂, that is, each orbit in M_∂ converges to $\{M_1\}$. Hence, $\{M_1\}$ is isolated in M_∂ , and hence in X. Furthermore, $\{M_1\}$ also is invariant and $\{M_1\}$ does not form a cycle in M_∂ , and hence in ∂X_0. Therefore, by Lemma 3 in [80], we finally obtain that P is uniformly persistent with respect to $(X_0, \partial X_0)$.
Finally, from Theorem 3.1.1 given in [88] we further obtain that all solutions of system (3.1) is uniformly persistent with respect to $(X_0, \partial X_0)$.
Furthermore, from the last equation of system (3.1) we can directly obtain that R_h in system (3.1) also is uniformly persistent. This completes the proof. ■

Remark. The influence of climate variables on malaria disease can be determined by the basic reproduction ratio (R_0), which defines the number of cases of a disease that arise from one case of the disease introduced into a population of susceptible hosts. By Lemma (3.2.2), we can see that in the realistic applications, if we want to verify R_0 is greater or less than unity, it suffices to verify that $\rho(\Phi_{F-V}(\omega))$ is greater or less than unity. It has been shown that the disease-free solution of the model is globally asymptotically stable when the basic reproduction ratio is less than unity and the disease is uniformly persistent when the basic reproduction ratio is greater than unity.

3.3 Existence of backward bifurcation in the autonomous version of the model

In the autonomous version of (3.1), as $\bar{R}_0$ is defined as the spectral radius (dominant eigenvalue) of the next generation matrix FV^{-1}, we define

$$\bar{R}_0 = \sqrt{\frac{\beta_{vh}\beta_{hv}\phi^2\Lambda_v\mu_h}{\mu_v^2\gamma\Lambda_h}}$$

where $\gamma = \mu_h + r_h + \mu_d$.
The disease-free periodic solution (DFPS) of the autonomous version of (3.1) exists and is given by $E_0^* = (\frac{\Lambda_v}{\mu_v}, 0, \frac{\Lambda_h}{\mu_h}, 0, 0)$.
At the steady states of the autonomous version of (3.1) which is calculated by equating its right side to zero, the zero force of infection corresponds to the disease-free periodic solution (DFPS) of the autonomous version and the non zero force of infection $\lambda_h^* = \frac{\beta_{vh}\phi I_v^*}{N_h^*}$ satisfies the quadratic equation

$$A{\lambda^*}_h^2 + B\lambda_h^* + C = 0 \tag{3.28}$$

where

$$\begin{aligned}
\kappa &= \mu_h + \sigma \\
A &= (\kappa + r_h)\Lambda_h[\mu_v(\kappa + r_h) + \beta_{hv}\phi\kappa) \\
B &= \frac{\kappa(\kappa\gamma - r_h\sigma)\gamma\mu_v\Lambda_h}{\mu_h}(M_\lambda - R_0^2) \\
C &= \kappa^2\gamma^2\mu_v\Lambda_h(1 - R_0^2)
\end{aligned}$$

and

$$M_\lambda = \frac{\mu_h(\beta_{hv}\phi + 2(\kappa + r_h))}{(\kappa\gamma - r_h\sigma)\mu_v}.$$

which implies that

$$\alpha_h^* = \frac{-B \pm \sqrt{B^2 - 4AC}}{2A}$$

Note that $M_\lambda > 1$ if and only if

$$\beta_{hv} > \lambda_0 := \frac{(\kappa\gamma - r_h\sigma)\mu_v - 2(\kappa + r_h)\mu_h}{\phi\mu_h}$$

Proposition 3.3.1. *1. If $\beta_{hv} \geqslant \lambda_0$, the autonomous version of (3.1) exhibits transcritical bifurcation.*

2. If $\beta_{hv} < \lambda_0$, then the autonomous version of (3.1) exhibits backward bifurcation. That is, there exists R_c in (0,1) such that

i. *If* $1 \leqslant \bar{R}_0$ *then the autonomous version of* (3.1) *has one endemic equilibrium point.*

ii. *If* $R_c < \bar{R}_0 < 1$ *then the autonomous version of* (3.1) *has two endemic equilibrium points.*

iii. *If* $\bar{R}_0 = R_c$ *then the autonomous version of* (3.1) *has one endemic equilibrium point.*

iv. *If* $\bar{R}_0 < R_c$ *then the autonomous version of* (3.1) *has no endemic equilibrium points.*

proof:

1. If $\beta_{hv} \geqslant \lambda_0$ then $M_\lambda < 1$. In this case, we have the following.

   i. If $\bar{R}_0 > 1$, then $C < 0$. In this case (3.28) has a unique positive solution.

   ii. If $\bar{R}_0 \leqslant 1$, then $C \geqslant 0$ and $B \geqslant 0$ (because $\bar{R}_0 \leqslant 1 \leqslant \sqrt{M_\lambda}$). This together with $A > 0$ imply that (3.28) has no positive solution.

2. If $\beta_{hv} < \lambda_0$, then $M_\lambda < 1$. In this case we have

   i. If $\bar{R}_0 \geqslant 1$, then $C \leqslant 0$ which implies that (3.28) has a unique positive solution.

   ii. If $\bar{R}_0 \leqslant \sqrt{M_\lambda}$, then $B \geqslant 0$ and $C > 0$. This implies that 3.28 has no positive solution.

   iii. If $\sqrt{M_\lambda} < \bar{R}_0$, we consider the discriminant of (3.28) $\triangle(\bar{R}_0) := B^2 - 4AC$. One can see that $\triangle(\sqrt{M_\lambda}) := -4AC < 0$ and $\triangle(1) := B^2 > 0$. Therefore, there exists $R_c \in (\sqrt{M_\lambda}, 1)$ such that $\triangle(R_c) = 0$ and $\triangle < 0$ for $\bar{R}_0 \in (\sqrt{M_\lambda}, R_c)$ and $\triangle > 0$ for $\bar{R}_0 \in (R_c, 1)$. In this case we have

      a. If $\sqrt{M_\lambda} < \bar{R}_0 < R_c$ then (3.28) has no positive solution.

      b. If $\bar{R}_0 = R_c$ then $\triangle = 0$ and $B < 0$. This implies that (3.28) has one positive solution.

      c. If $R_c < \bar{R}_0 < 1$ then (3.28) has two real solutions which are positive since $C > 0$ and $B < 0$.

■

Proposition 3.3.1 establishes the existence of two endemic equilibria for $\bar{R}_0$ in $(R_c, 1)$.

When all the parameters are constant, that is when the model is reduced to its autonomous version, the fact that the model exhibit a backward bifurcation is well known in many of the literatures (see for example [59], [57], [26]) and our model also reduces to the same phenomena. However, when some of the parameters themselves are made to be time dependent, no such phenomenon (like backward bifurcation) is established yet. In the contrary, as can be mentioned in the next subsection, it has been asserted that the DFS is globally asymptotically stable for $\bar{R}_0$ less than unity.

3.4 Numerical Simulations

The numerical simulation of the non-autonomous model (3.1) is used to illustrate the impact of the seasonal variables (temperature and rainfall) on the malaria disease dynamics in a population and to validate the model results in the real situation on the ground.

In this section, we give numerical simulations to confirm the above theoretical analysis in the real situation in Ethiopia. For this purpose, the daily temperature and rainfall data is taken from the National Meteorological Agency of Ethiopia and the corresponding microscopically confirmed cases of malaria from 1984-2012 for Asendabo, a western region of Ethiopia, is obtained from Asendabo clinic.

For the simulation, the monthly average maximum temperature and the average monthly rainfall is used to show their impact on the incidence and prevalence of the malaria disease in the region. The temperature and rainfall raw data, respectively, are fitted (Figure 3.1 and 3.2) by the periodic functions

$$T(t) = 19.5932 + 1.2697\cos(0.5240t + 4.3391) - 0.6343\cos(2 * 0.5240t - 0.6963) \quad (3.29)$$

and

$$\begin{aligned} R(t) =& 99.4876 + 89.8581\cos(0.5232t + 15.4500) + 19.1069\sin(2 * 0.5232t) \\ & -8.5891\cos(3 * 0.5232t + 3.7723) + 6.4660\sin(5 * 0.5232t). \end{aligned} \quad (3.30)$$

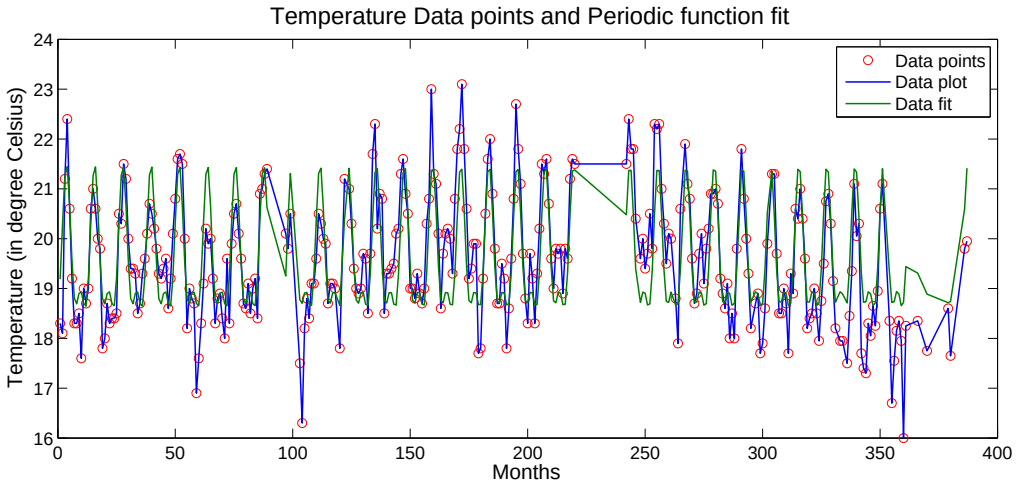


Figure 3.1. Monthly average maximum temperature raw data taken is fitted by a periodic function 37 that can possibly be best fit to data so that its functional value is used in the analysis of its impact on the disease dynamics in the periodic environment.

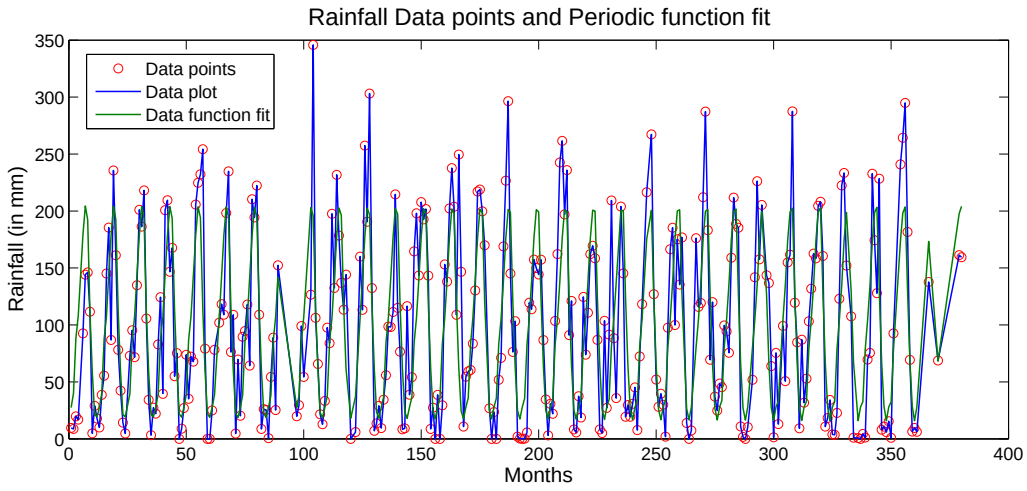
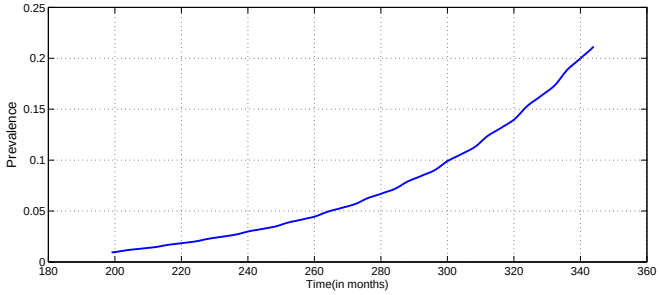


Figure 3.2. Monthly average rainfall raw data taken is fitted by a periodic function 37 that can possibly be best fit to data so that its functional value is used in the analysis of its impact on the disease dynamics in the periodic environment.

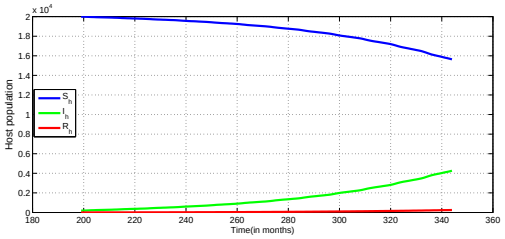
It is assumed that initially, the susceptible and infected adult mosquitoes are $S_v(0) = 800000$ are $I_v(0) = 700$, respectively. The corresponding initial host population distributions in the three compartments are assumed to be $S_h(0) = 20000$, $I_h(0) = 190$ and $R_h(0) = 5$, respectively, and the parameter values (per day) are $\Lambda_h = 0.415244, \sigma = 0.00137, \mu_h = 0.000024, \mu_d = 0.00047, \beta_{vh} = 0.24, \beta_{hv} = 0.022, r_h = 0.0028$.

Note here that there is no control intervention assumed to have been implemented in this period of time, and the model produces the dynamics of the disease if no intervention were employed.

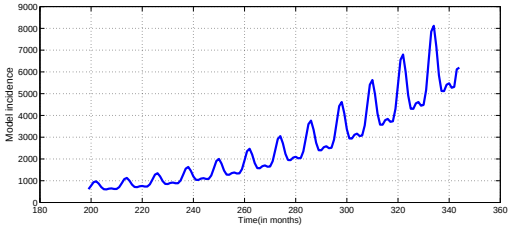
The actual malaria confirmed cases in the Asendabo region, collected in the years 2000-2012 is plotted against time in months (Figure 3.3d). In spite of all the expected data collection and recording errors, the data shows that the incidence pattern does not follow a periodic flow. So, it is more appealing to formulate and analyze a non-autonomous model system for the epidemic.



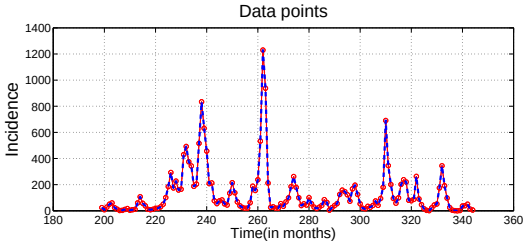
(a) A plot showing prevalence.



(b) A plot showing proportions of human population.



(c) A plot showing the model disease incidence.



(d) A plot showing the actual malaria confirmed cases in the Asendabo region, collected in the years 2000-2012.

Figure 3.3. Plots showing (a) prevalence, (b) proportions of human population, (c) model disease incidence and (d) the actual malaria cases (actual incidence).

Chapter 4

Nonperiodic System

4.1 Introduction

The climate impact upon the distribution of the malaria transmission in space and time is not always periodical and we need to investigate the potential change in malaria risk caused by the variations in temperature and rainfall in the general case.That is when these climate variables are any time dependent functions. This may help to investigate the dynamics of the disease in a long term basis and the information provided here might serve as an important contribution for strategic planning of malaria control in a long period of time in the future. As the variation of rainfall is too seasonal and hence nearly periodic, the non-periodic fit does not give a better fit than the periodic fit. For this reason, the present chapter is devoted to studying the dynamics of the disease with parameters dependent on the non-periodic climate variable (temperature) and the periodic climate variable (rainfall).

Even though the climate variables (temperature and rainfall) values change seasonally, they are not totally periodic and hence it is very important to investigate the dynamics in the non-periodic environment too. For the general case, that is, for the general climate variables values, we analyze model (2.4) by making the model parameters dependent on the general climate variables. Thus the system will have time dependent non-periodic coefficients as climate variables could be expressed as a function of time.

$$\begin{aligned}
\frac{dS_v}{dt} &= \Lambda_v(T,R) - \lambda_v(T)S_v - \mu_v(T,R)S_v,\\
\frac{dI_v}{dt} &= \lambda_v(T)S_v - \mu_v(T,R)I_v,\\
\frac{dS_h}{dt} &= \Lambda_h - \lambda_h(T)S_h + \sigma R_h - \mu_h S_h,\\
\frac{dI_h}{dt} &= \lambda_h(T)S_h - (\mu_h + r_h + \mu_d)I_h,\\
\frac{dR_h}{dt} &= r_h I_h - (\mu_h + \sigma)R_h,
\end{aligned} \tag{4.1}$$

where $\lambda_h(T) = \frac{\beta_{vh}\phi(T)I_v}{N_h}$ and $\lambda_v(T) = \frac{\beta_{hv}\phi(T)I_h}{N_h}$ represent the force of infection of humans and mosquitoes, respectively.

4.1.1 Mathematical Preliminaries for the general non-autonomous systems

Consider a definite linear non-autonomous system

$$\frac{dx}{dt} = A(t)x, \tag{4.2}$$

and an indefinite linear system

$$\frac{dx}{dt} = A(t)x + B(t)x, \tag{4.3}$$

where $x \in \mathbb{R}^n$, $A(t)$ is a known $n \times n$ continuous matrix function and $B(t)$ an unknown $n \times n$ continuous matrix function. Assume that one only knows some boundedness property of $B(t)$. We will discuss the equivalence in stability of systems (4.2) and (4.3), so that one can use the simple and definite system (4.2) to study the complex and indefinite system (4.3).

For the analysis we need to define what to mean by matrix norms in two different ways, which we will use them in our later discussion.

Definition 4.1.1. The *induced norm* of an $m \times n$ matrix A is defined to be

$$\|A\| = \max_{\|x\|=1} \|Ax\|.$$

We remark that the norm of A induced by the Euclidean norm above is equal to the nonnegative square root of the absolute value of the largest eigenvalue of the symmetric matrix A^TA. Thus, we define this norm next.

Definition 4.1.2. The *spectral norm* of an $m \times n$ matrix A is defined to be

$$\|A\| = \left[\max_{\|x\|=1} x^T A^T Ax\right]^{\frac{1}{2}}.$$

This will be the matrix norm that is used in the sequel and will be denoted by $\|.\|$.

Theorem 4.1.1. *(See [45]) If there exist constant $M > 0$ and $0 < r < 1$ such that the following estimation*

$$\int_{t_0}^{t} \|B(s)\|ds \leqslant r(t - t_0) + M \tag{4.4}$$

is valid, then the exponential stabilities of the zero solutions of (4.2) *and* (4.3) *are equivalent.*

proof: Assume that the zero solution of (4.2) is exponentially stable, then there exist constants $M_1 > 0$ and $\alpha_1 > 0$ such that the Cauchy matrix solution of (4.2), $K(t, t_0)$, admits the estimation:

$$\|K(t, t_0)\| \leqslant M_1 e^{-\alpha_1(t-t_0)}. \tag{4.5}$$

Let $r < \frac{\alpha_1}{M_1}$. Then, the general solution of (4.3) can be expressed as

$$x(t, t_0, x_0) = K(t, t_0)x_0 + \int_{t_0}^{t} K(t, s)B(s)x(s)ds.$$

Thus, we obtain

$$\begin{aligned}\|x(t, t_0, x_0)\| \leqslant & \|K(t, t_0)\|\|x_0\| + \int_{t_0}^{t} \|K(t, s)\|\|B(s)\|\|x(s)\|ds \\ \leqslant & M_1 e^{-\alpha_1(t-t_0)}\|x_0\| + \int_{t_0}^{t} M_1 e^{-\alpha_1(t-s)}\|B(s)\|\|x(s)\|ds.\end{aligned}$$

By using the Gronwall-Bellman inequality, we have the following estimation:

$$\begin{aligned}\|x(t)\|e^{\alpha_1 t} \leqslant & M_1 e^{\alpha_1 t_0}\|x_0\| e^{\int_{t_0}^{t} M_1\|B(s)\|ds} \\ \|x(t)\| \leqslant & M_1 e^{-\alpha_1(t-t_0)}\|x_0\| e^{M_1 r(t-t_0)+M_1 M} \\ = & M_1 e^{M_1 M}\|x_0\| e^{-(\alpha_1 - M_1 r)(t-t_0)}.\end{aligned}$$

This estimation shows that the zero solution of (4.3) is exponentially stable, where $r < \frac{\alpha_1}{M_1}$. On the other hand, system (4.2) can be rewritten as

$$\frac{dx}{dt} = A(t)x = (A(t) + B(t) - B(t))x := (\tilde{A}(t) + \tilde{B}(t))x,$$

where $\tilde{A}(t) = A(t) + B(t), \tilde{B}(t) = -B(t)$.
However,

$$\int_{t_0}^{t} \|\tilde{B}(s)\|ds = \int_{t_0}^{t} \|B(s)\|ds \leqslant r(t - t_0) + M.$$

From the above results, we know that the exponential stability of the zero solution of (4.3) implies the exponential stability of the zero solution of (4.2). ■

Theorem 4.1.2. *The zero solution of* (4.2) *is uniformly asymptotically stable if and only if it is exponentially stable.*

proof: One only needs to prove that the uniform asymptotic stability of the zero solution of (4.2) implies its exponential stability.

$$\forall \varepsilon > 0 (0 < \varepsilon < 1) \;\; \exists \delta(\varepsilon) > 0, \;\; \exists G(\varepsilon) > 0, \text{ when } t \geqslant t_0 + G, \; \|K(t, t_0)\| < \varepsilon \text{ holds.}$$

Owing to the uniform stability of the zero solution, there exists a constant $M > 0$ such that

$$\|K(t, t_0)\| < M, \qquad t_0 \leqslant t \leqslant t_1 + G.$$

Assume that

$$n\delta \leqslant t - t_0 \leqslant (n+1)\delta \qquad (n = 0, 1, 2, ...).$$

Then, from the property of the Cauchy matrix solution $K(t, t_0)$, we have

$$K(t, t_0) = K(t, t_1)K(t_1, t_0) \qquad (t_0 \leqslant t_1 \leqslant t).$$

Therefore,

$$K(t, t_0) = K(t, n\delta + t_0) \times K(n\delta + t_0, (n-1)\delta + t_0) \times \cdots \times K(\delta + t_0, t_0), \tag{4.6}$$

and thus

$$\begin{aligned} \|K(t, t_0)\| \leqslant & \|K(t, n\delta + t_0)\| \times \|K(n\delta + t_0, (n-1)\delta + t_0)\| \times \cdots \times \|K(\delta + t_0, t_0)\| \\ \leqslant & Me^{\lambda\delta}e^{-(n+1)\lambda\delta} \\ \leqslant & Ne^{-\lambda(t-t_0)}, \end{aligned} \tag{4.7}$$

where $N = Me^{\lambda\delta}$.
This implies that the zero solution of (4.2) is exponentially stable. ■

We state the Mean Value Theorem for integrals without proof to prove Lemma (4.1.1).

Theorem 4.1.3. *(The Mean Value Theorem) Let $f : [a, b] \to \mathbb{R}$ be a continuous function and*
$g : [a, b] \to \mathbb{R}$ be a nonnegative integrable function. Then there is $c \in [a, b]$ such that

$$\int_a^b f(x)g(x)dx = f(c)\int_a^b g(x)dx.$$

Lemma 4.1.1. *Suppose f and g are positive, bounded and continuous functions on $[t_0, \infty)$ for some $t_0 > 0$. Let*

$$U(t) = e^{-\int_{t_0}^{t} g(z)dz}\int_{t_0}^{t} e^{-\int_{t_0}^{s} f(z)dz}e^{\int_{t_0}^{s} g(z)dz}ds \tag{4.8}$$

for all $t \geqslant t_0$, then there exist $\alpha > 0$ and $M > 0$ such that

$$U(t) \leqslant Me^{-\alpha(t-t_0)}.$$

proof: By Theorem 4.1.3, there exists $c \in [t_0, t]$ such that

$$\begin{aligned} U(t) =& e^{-\int_{t_0}^{t} g(z)dz} \int_{t_0}^{t} e^{-\int_{t_0}^{s} f(z)dz} e^{\int_{t_0}^{s} g(z)dz} ds \\ =& e^{-\int_{t_0}^{t} g(z)dz} e^{-\int_{t_0}^{c} f(z)dz} \int_{t_0}^{t} e^{\int_{t_0}^{s} g(z)dz} ds \\ \leqslant& e^{-\int_{t_0}^{c} f(z)dz} \left(\frac{\int_{t_0}^{t} e^{\int_{t_0}^{s} g(z)dz} ds}{e^{\int_{t_0}^{t} g(z)dz}} \right) \\ \leqslant& \frac{1}{\inf\limits_{t \geqslant t_0} \{g(t)\}} e^{-\int_{t_0}^{c} f(z)dz} \qquad \text{by Lemma 2.3.1.} \end{aligned}$$

Now

$$\int_{t_0}^{t} e^{-\int_{t_0}^{s} f(z)dz} e^{\int_{t_0}^{s} g(z)dz} ds = e^{-\int_{t_0}^{c} f(z)dz} \int_{t_0}^{t} e^{\int_{t_0}^{s} g(z)dz} ds = \int_{t_0}^{t} e^{\int_{t_0}^{s} g(z)dz} e^{-\int_{t_0}^{c} f(z)dz} ds$$

if and only if

$$\int_{t_0}^{t} e^{\int_{t_0}^{s} g(z)dz} \left(e^{-\int_{t_0}^{s} f(z)dz} - e^{-\int_{t_0}^{c} f(z)dz} \right) ds = 0.$$

By the Fundamental Theorem of Calculus, (First Form), we get

$$\frac{d}{dt} \int_{t_0}^{t} e^{\int_{t_0}^{s} g(z)dz} \left(e^{-\int_{t_0}^{s} f(z)dz} - e^{-\int_{t_0}^{c} f(z)dz} \right) ds = e^{\int_{t_0}^{t} g(z)dz} \left(e^{-\int_{t_0}^{t} f(z)dz} - e^{-\int_{t_0}^{c} f(z)dz} \right) = 0.$$

Which implies

$$e^{-\int_{t_0}^{t} f(z)dz} = e^{-\int_{t_0}^{c} f(z)dz},$$

and hence

$$\int_{t_0}^{t} f(z)dz = \int_{t_0}^{c} f(z)dz,$$

that is

$$\int_{c}^{t} f(z)dz = 0,$$

and this happens only when $c = t$, since $f(z) > 0$ on $[t_0, t]$ for all $t > t_0$.

We know that

$$\inf_{t \geqslant t_0} \{f(t)\} \leqslant f(t),$$

implies

$$-f(t) \leqslant -\inf_{t \geqslant t_0} \{f(t)\}.$$

Integrating the above inequality from t_0 to t, we obtain

$$-\int_{t_0}^{t} f(z)dz \leqslant -\int_{t_0}^{t} \inf_{t \geqslant t_0} \{f(t)\} dz$$

and

$$e^{-\int_{t_0}^{t} f(z)dz} \leqslant e^{-\int_{t_0}^{t} \inf\limits_{t\geqslant t_0}\{f(t)\}dz} = e^{-\inf\limits_{t\geqslant t_0}\{f(t)\}(t-t_0)}.$$

Then we have that

$$U(t) \leqslant \frac{1}{\inf\limits_{t\geqslant t_0}\{g(t)\}} e^{-\int_{t_0}^{c} f(z)dz} \leqslant \frac{1}{\inf\limits_{t\geqslant t_0}\{g(t)\}} e^{-\inf\limits_{t\geqslant t_0}\{f(t)\}(t-t_0)}.$$

Thus

$$U(t) \leqslant Me^{-\alpha(t-t_0)},$$

where $M = \frac{1}{\inf\limits_{t\geqslant t_0}\{g(t)\}}$ and $\alpha = \inf\limits_{t\geqslant t_0}\{f(t)\}$. ■

Theorem 4.1.4. *([33]) Let $x = 0$ be an equilibrium solution for the nonlinear system*

$$\dot{x} = f(t, x)$$

where $f : [0, \infty) \times D \to \mathbb{R}^n$ for $D = \{x \in \mathbb{R}^n : \|x\|_2 < r\}$ is continuously differentiable, the Jacobian matrix $\left[\frac{\partial f}{\partial x}\right]$ is bounded and Lipschitz on D, uniformly in t. Let

$$A(t) = \frac{\partial f}{\partial x}(t, x)|_{x=0}$$

Then, the origin is an exponentially stable equilibrium solution for the non-linear system if it is an exponentially stable equilibrium point for the linear system

$$\dot{x} = A(t)x.$$

We start the analysis of our model by linearising (4.1) about a solution of the system. For this we compute the Jacobian matrix of (4.1) as,

$$J(x) = \begin{pmatrix} -(\lambda_v(t) + \mu_v) & 0 & b_1 & -b_2 & b_1 \\ \lambda_v(t) & -\mu_v & -b_1 & b_2 & -b_1 \\ 0 & -b_3 & -(b_4 + \mu_h) & b_5 & \sigma + b_5 \\ 0 & b_3 & b_4 & -(b_5 + \gamma) & -b_5 \\ 0 & 0 & 0 & r_h & -(\mu_h + \sigma) \end{pmatrix} \tag{4.9}$$

where $x = (S_v, I_v, S_h, I_h, R_h)$,
$\mu_v(t) = \mu_v(T(t), R(t))$, $b_1 = \lambda_v(t)(\frac{S_v}{N_h})$, $\quad b_2 = \frac{\beta_{hv}\phi(T(t))S_v}{N_h}\left(1 - \frac{I_h}{N_h}\right)$, $\quad b_3 = \beta_{vh}\phi(T(t))\frac{S_h}{N_h}$,
$b_4 = \lambda_h(t)\left(1 - \frac{S_h}{N_h}\right)$, $\quad b_5 = \lambda_h(t)(\frac{S_h}{N_h})$, and $\gamma = \mu_h + r_h + \mu_d$.

Let $D = \{x \in R^n : \|x\|_2 < r\}$. For $x, y \in D$ defining $\Delta J := J(x) - J(y)$, we have

$$\Delta J = \begin{pmatrix} (-\lambda_v^x + \lambda_v^y) & 0 & (b_1^x - b_1^y) & (-b_2^x + b_2^y) & (b_1^x - b_1^y) \\ (\lambda_v^x - \lambda_v^y) & 0 & (-b_1^x + b_1^y) & (b_2^x - b_2^y) & (-b_1^x + b_1^y) \\ 0 & (-b_3^x + b_3^y) & (-b_4^x + b_4^y) & (b_5^x - b_2^y) & (b_5^x - b_5^y) \\ 0 & (b_3^x - b_3^y) & (b_4^x - b_4^y) & (-b_5^x + b_2^y) & (-b_5^x + b_5^y) \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix} \tag{4.10}$$

where $b_i^x,\ b_i^y$ and $\lambda_v^x,\ \lambda_v^y$ for each $i = 1, 2, 3, 4, 5$, represent the corresponding components of the Jacobian matrix evaluated at x and y, that is, $J(x)$ and $J(y)$ respectively.

Since $b_1 = (\frac{\lambda_v(t)}{N_h})S_v := d_1 S_v, \quad b_2 = \frac{\beta_{hv}\phi(T(t))}{N_h}\left(1 - \frac{I_h}{N_h}\right) S_v := d_2 S_v,$
$b_3 = \beta_{vh}\phi(T(t))\frac{S_h}{N_h} := d_3 S_h, \quad b_4 = \lambda_h(t)\left(1 - \frac{S_h}{N_h}\right) = \frac{\beta_{vh}\phi(T(t))I_v}{N_h}\left(1 - \frac{S_h}{N_h}\right) := d_4 I_v,$
$b_5 = \lambda_h(t)(\frac{S_h}{N_h}) = \frac{\beta_{vh}\phi(T(t))I_v}{N_h}(\frac{S_h}{N_h}) := d_5 I_v, \quad \lambda_v(t) = \frac{\beta_{hv}\phi(T(t))I_h}{N_h} := d_6 I_h,$
$\gamma = \mu_h + r_h + \mu_d, \quad \mu_v = \mu_v(T(t), R(t)).$
with $d_i \in [0, 1)$ for each $i = 1, 2, 3, 4, 5, 6$, the matrix in (4.10) is rewritten as

$$\Delta J = \begin{pmatrix} (-d_6^x I_h^x + d_6^y I_h^y) & 0 & (d_1^x S_v^x - d_1^y S_v^y) & (-d_2^x S_v^x + d_2^y S_v^y) & (d_1^x S_v^x - d_1^y S_v^y) \\ (d_6^x I_h^x - d_6^y I_h^y) & 0 & (-d_1^x S_v^x + d_1^y S_v^y) & (d_2^x S_v^x - d_2^y S_v^y) & (-d_1^x S_v^x + d_1^y S_v^y) \\ 0 & (-d_3^x S_h^x + d_3^y S_h^y) & (-d_4^x I_v^x + d_4^y I_v^y) & (d_5^x I_v^x - d_5^y I_v^y) & (d_5^x I_v^x - d_5^y I_v^y) \\ 0 & (d_3^x S_h^x - d_3^y S_h^y) & (d_4^x I_v^x - d_4^y I_v^y) & (-d_5^x I_v^x + d_5^y I_v^y) & (-d_5^x I_v^x + d_5^y I_v^y) \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

where again, $d_i^x I_v^x,\ d_i^x S_v^x,\ d_i^x I_h^x,\ d_i^x S_h^x$ and $d_i^y I_v^y,\ d_i^y S_v^y,\ d_i^y I_h^y,\ d_i^y S_h^y$ for each $i = 1, 2, 3, 4, 5, 6$, represent the corresponding components of the Jacobian matrix evaluated at x and y, that is, $J(x)$ and $J(y)$ respectively.

For simplicity of matrix norm calculation, let us write the above matrix as

$$\Delta J = \begin{pmatrix} J_{11} & 0 & J_{13} & J_{14} & J_{15} \\ J_{21} & 0 & J_{23} & J_{24} & J_{25} \\ 0 & J_{32} & J_{33} & J_{34} & J_{35} \\ 0 & J_{42} & J_{43} & J_{44} & J_{45} \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

Then

$$\begin{aligned} \|J(x) - J(y)\|^2 \leqslant\ & J_{11}^2 + J_{21}^2 + J_{32}^2 + J_{42}^2 + J_{13}^2 + J_{23}^2 + J_{33}^2 + J_{43}^2 + J_{14}^2 + J_{24}^2 + J_{34}^2 + J_{44}^2 \\ & + J_{15}^2 + J_{25}^2 + J_{35}^2 + J_{45}^2 + 2\{J_{11}J_{13} + J_{21}J_{23} + J_{11}J_{14} + J_{21}J_{24} + J_{11}J_{15} \\ & + J_{21}J_{25} + J_{32}J_{33} + J_{42}J_{43} + J_{32}J_{34} + J_{42}J_{44} + J_{32}J_{35} + J_{42}J_{45} + J_{13}J_{14} \\ & + J_{23}J_{24} + J_{33}J_{34} + J_{43}J_{44} + J_{13}J_{15} + J_{23}J_{25} + J_{33}J_{35} + J_{43}J_{45} + J_{14}J_{15} \\ & + J_{24}J_{25} + J_{34}J_{35} + J_{44}J_{45}\}. \end{aligned}$$

Each term to the right side in the above inequality is either of the form J_{ij}^2 or $J_{ij}J_{ik}$ for all $i, j, k \in \{1, 2, 3, 4, 5\}$.

Using the fact that for any two vectors $\mathbf{u}$ and $\mathbf{v}$ and for any $a, b \in [0, 1)$, there exists $\zeta \geqslant 0$ depending on a and b such that

$$\|a\mathbf{u} - b\mathbf{v}\| \leqslant \zeta\|\mathbf{u} - \mathbf{v}\|.$$

For each $i, j \in \{1, 2, 3, 4, 5\}$, from terms of the form J_{ij}^2 we obtain the relation

$$(d_i^x x_j - d_i^y y_j)^2 \leqslant (c_i(x_j - y_j))^2,$$

that is

$$|d_i^x x_j - d_i^y y_j| \leqslant |c_i||x_j - y_j| \tag{4.11}$$

and for the other terms of the form $J_{ij}J_{ik}$, we have

$$J_{ij}J_{ik} \leqslant |J_{ij}J_{ik}| \leqslant (\max\{J_{ij}, J_{ik}\})^2$$

which takes again the form J_{ij}^2. So an inequality of the form (4.11) can be obtained. We then conclude that

$$\|J(x) - J(y)\| \leqslant L\|x - y\|,$$

for some non negative number L. That is

$$\|J(t, x) - J(t, y)\| \leqslant L\|x - y\|, \quad \forall x, y \in D, \quad \forall t \geqslant 0.$$

Since every component of the Jacobian matrix of (4.1) is bounded, then the matrix is bounded. Thus the Jacobian matrix of (4.1) is bounded and Lipschitz on D, uniformly in t.

4.2 Disease Free Solution

In order to deduce the threshold condition for epidemic we replace the non-autonomous system (4.1) by an autonomous one, by regarding the time on the right side of the system (4.1) as a parameter and then carry out a stability analysis.

Consider the second and the fifth equations of (4.1):

$$\begin{aligned}
&\frac{dI_h}{dt} = \beta_{vh}\phi(T(t))\frac{S_h}{N_h}I_v - \gamma I_h \leqslant \beta_{vh}\phi(T(t))I_v - \gamma I_h,\\
&\frac{dI_v}{dt} \leqslant \beta_{hv}\phi(T(t))\frac{N_v}{N_h}I_h - \mu_v(T(t),R(t))I_v \leqslant \beta_{hv}\phi(T(t))\Gamma_v I_h - \mu_v(T(t),R(t))I_v.
\end{aligned} \tag{4.12}$$

We analyze the stability of the disease-free solution $I_v = I_h = 0$, that is, the solution representing the absence of the infection.

Linearizing the system (4.12) around a small amount of disease i_H and i_V as in [15], we get

$$\begin{aligned}
\frac{di_H}{dt} &= -\gamma i_H + \beta_{vh}\phi(T(t))i_V,\\
\frac{di_V}{dt} &= \beta_{hv}\phi(T(t))\Gamma_v i_H - \mu_v(T(t),R(t))i_V,
\end{aligned} \tag{4.13}$$

We then examine the stability of the disease-free solution of system (4.13), that is, $i_H = 0$ and $i_V = 0$ as if the system were autonomous [15]. For this we assume the solutions:

$$\begin{aligned}
i_H &= c_1 exp(\lambda_n s),\\
i_V &= c_2 exp(\lambda_n s)
\end{aligned} \tag{4.14}$$

and replace (4.14) into equation (4.13). The characteristic equation associated to system (4.13) is then obtained to be:

$$\begin{vmatrix} -(\lambda_n+\gamma) & \beta_{vh}\phi(T(t)) \\ \beta_{hv}\phi(T(t))\Gamma_v & -(\lambda_n+\mu_v(T(t),R(t))) \end{vmatrix} = 0 \tag{4.15}$$

that is,

$$\lambda_n(t) = \frac{1}{2}\left(-(\gamma+\mu_v) \pm \sqrt{(\gamma+\mu_v)^2 - 4(\gamma\mu_v - \beta_{hv}\beta_{vh}\phi^2(T(t))\Gamma_v)}\right)$$

where $\mu_v = \mu_v(T(t),R(t))$.
If all the roots of equation (4.15) have negative real parts, then the solution without disease is stable, that is, the origin is an attractor. We see that the first root that crosses the imaginary axis do so through the real axis and this happens when

$$\gamma\mu_v(T(t),R(t)) - \beta_{hv}\beta_{vh}\phi^2(T(t))\Gamma_v < 0$$

that is when

$$\tilde{\mathcal{R}}_{no}(t) := \frac{\beta_{hv}\beta_{vh}\phi^2(T(t))\Gamma_v}{\gamma\mu_v(T(t),R(t))} > 1.$$

Therefore, we can find the time t at which the disease-free solution of system (4.13), that is, $i_H = 0$ and $i_V = 0$ becomes unstable. The time t at which the disease-free solution (no-disease) of the autonomous system becomes unstable ($\tilde{\mathcal{R}}_{no} > 1$) corresponds approximately to the moment at which the epidemic takes off, that is, when the epidemic in system (4.1) begins to increase as a result of the introduction of a small amount of disease at time $t = 0$.

Theorem 4.2.1. *If $\tilde{\mathcal{R}}_{no}(t) < 1, \forall t \geqslant t_0$ then the disease-free solution (DFS) $E_0^*(t) = (S_v^*(t), 0, \frac{\Lambda_h}{\mu_h}, 0, 0)$ (3.13), is globally asymptotically stable.*

proof: From equation (4.12), we have that

$$dI_h/dt \leqslant \beta_{vh}\phi(T(t))I_v - \gamma I_h$$

and

$$dI_v/dt \leqslant \beta_{hv}\phi(T(t))\Gamma_v I_h - \mu_v(T(t),R(t))I_v.$$

Let $\mathrm{Y}=\binom{y_1}{y_2}$ be the solution of

$$\mathbf{Y}' = \begin{pmatrix} -\gamma+\varepsilon & \beta_{vh}\phi(T(t)) \\ \beta_{hv}\phi(T(t))\Gamma_v & -\mu_v(T(t),R(t))+\varepsilon \end{pmatrix} Y \tag{4.16}$$

with $y_1(0) = I_h(0) + \varepsilon, y_2(0) = I_v(0) + \varepsilon,\ \varepsilon > 0$.
From the argument above this Theorem 4.2.1, we see that the solutions of (4.16) are characterized by:

$$y_1(t) \longrightarrow 0 \ \text{ and } \ y_2(t) \longrightarrow 0 \ \text{ as } \ t \longrightarrow \infty. \tag{4.17}$$

We claim that

$$I_h(t) < y_1(t) \ \text{ and } \ I_v(t) < y_2(t) \ \ \forall t > 0. \tag{4.18}$$

Indeed, otherwise there exists a first point $t = t_0 > 0$ such that either $I_h(t_0) = y_1(t_0)$ or $I_v(t_0) = y_2(t_0)$. Suppose that the first case occurs. Then

$$\begin{aligned} \dot{y}_1(t_0) &= \beta_{vh}\phi(t_0)y_2(t_0) - \gamma y_1(t_0) + \varepsilon y_1(t_0) \\ &> \beta_{vh}\phi(t_0)\frac{S_h}{N_h}I_v(t_0) - \gamma I_h(t_0) \\ &= \dot{I}_h(t_0). \end{aligned}$$

On the other hand, since $y_1(t) - I_h(t) > 0$ for $t < t_0$ and $y_1(t_0) - I_h(t_0) = 0$, we obtain $\dot{y}_1(t_0) - \dot{I}_h(t_0) \leqslant 0$, which is a contradiction. The case $I_v(t_0) = y_2(t_0)$ can be handled in

the same way. Letting $t \to \infty$ in equation (4.18) and using equation (4.17), we conclude that

$$I_h(t) \to 0, \quad I_v(t) \to 0 \ \text{ if } \ t \to \infty. \tag{4.19}$$

It remains to show that $\lim_{t\to\infty} S_h(t) = N_h$.
From the system (4.1),

$$\frac{d(N_h - S_h)}{dt} + \kappa(N_h - S_h) = \rho(t),$$

where $\rho(t) = (\sigma - \mu_d)I_h + \beta_{vh}\phi(T(t))S_h\frac{I_v}{N_h}$ and $\kappa = \mu_h + \sigma$.

$$\begin{aligned} N_h(t) - S_h(t) &= exp\left(-\int_0^t \kappa d\tau\right)\left\{(N_h(0) - S_h(0)) + \int_0^t \rho(s)exp(\int_0^s \kappa d\sigma)ds\right\} \\ &= exp\,(-\kappa t)\left\{(N_h(0) - S_h(0)) + \int_0^t \rho(s)exp(\kappa s)ds\right\} \end{aligned}$$

Since $\rho(t) \to 0$ as $t \to \infty$, we can find $t_M > 0$ such that $\rho(t) \leqslant Me^{-\kappa t}$ for some constant M and $t > t_M$. Hence

$$\begin{aligned} \lim_{t\to\infty} exp(-\kappa t)\int_0^t \rho(s)exp(\kappa s)ds \leqslant & \lim_{t\to\infty} exp(-\kappa t)\left(\int_0^{t_M} \rho(s)exp(\kappa s)ds + \int_{t_M}^t Mds\right) \\ = & \lim_{t\to\infty} exp(-\kappa t)\left([\int_0^{t_M} \rho(s)exp(\kappa t)ds - Mt_M] + Mt\right) \\ = & \lim_{t\to\infty} exp(-\kappa t)(M_0 + Mt) = 0 \end{aligned}$$

letting the constant $\int_0^{t_M} \rho(s)exp(\kappa s)ds - Mt_M$ to be M_0 and by L'Hôpital's rule.
Thus $\lim_{t\to\infty}(N_h(t) - S_h(t)) = 0$. That is $S_h(t) \to N_h(t)$ as $t \to \infty$. ■

Let $\nu_1 = \frac{\gamma\mu_v(T(t),R(t))}{\beta_{hv}\beta_{vh}\Gamma_v}$ and $\nu_2 = \frac{1-r_h^2}{2\beta_{vh}^2+\beta_{hv}^2}$.

Theorem 4.2.2. *Suppose that $\sqrt{\nu_1} < \phi(T(t)) < \sqrt{\nu_2}$ for all $t \geqslant t_0$. Then the nonlinear system (4.1) is uniformly persistent, that is, there exists $c > 0$ (independent of initial conditions), such that $\liminf_{t\to\infty} I_h \geqslant c$ and $\liminf_{t\to\infty} I_v \geqslant c$.*

proof: Suppose $\sqrt{\nu_1} < \phi(T(t)) < \sqrt{\nu_2}$ for all $t \geqslant t_0$.
Then

$$\frac{\gamma\mu_v(T(t), R(t))}{\beta_{hv}\beta_{vh}\Gamma_v} < \phi^2(T(t))$$

and

$$\phi^2(T(t)) < \frac{1 - r_h^2}{2\beta_{vh}^2 + \beta_{hv}^2},$$

which implies that

$$\frac{\gamma\mu_v(T(t), R(t))}{\beta_{hv}\beta_{vh}\phi^2(T(t))\Gamma_v} < 1$$

and

$$1 < \frac{1 - r_h^2}{(2\beta_{vh}^2 + \beta_{hv}^2)\phi^2(T(t))}.$$

That is,

$$\frac{\beta_{hv}\beta_{vh}\phi^2(T(t))\Gamma_v}{\gamma\mu_v(T(t), R(t))} > 1$$

and

$$r_h^2 + (2\beta_{vh}^2 + \beta_{hv}^2)\phi^2(T(t)) < 1.$$

Thus

$$\tilde{\mathcal{R}}_{no} > 1$$

and

$$2\beta_{vh}^2\phi^2(T(t)) + r_h^2 < 1.$$

Let us now evaluate (4.9) at the disease free solution $E_0^*(t)$ and write it as $J(E_0^*(t)) = A(t) + B(t)$, where

$$A(t) = \begin{pmatrix} -\mu_v & 0 & 0 & -b_2 & 0 \\ 0 & -\mu_v & 0 & b_2 & 0 \\ 0 & 0 & -\mu_h & 0 & \sigma \\ 0 & 0 & 0 & -\gamma & 0 \\ 0 & 0 & 0 & 0 & -(\mu_h + \sigma) \end{pmatrix}$$

and

$$B(t) = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & -b_3 & 0 & 0 & 0 \\ 0 & b_3 & 0 & 0 & 0 \\ 0 & 0 & 0 & r_h & 0 \end{pmatrix}$$

The norm of the matrix $B(t)$ has the following relation.

$$\begin{aligned} \|B(t)\|^2 &\leqslant 2b_3^2 + r_h^2 \\ &= 2\beta_{vh}^2\phi^2(T(t))\left(\frac{S_h}{N_h}\right)^2 + r_h^2 \\ &\leqslant 2\beta_{vh}^2\phi^2(T(t)) + r_h^2 \\ &= 2\beta_{vh}^2\phi^2(T(t)) + r_h^2 \end{aligned}$$

Thus under the assumption

$$2\beta_{vh}^2\phi^2(T(t)) + r_h^2 < 1,$$

we have that $\|B(t)\| < 1$ and we can find some real number $r < 1$ such that $\|B(t)\| \leqslant r$. Then we get the estimation

$$\int_{t_0}^{t} \|B(s)\|ds \leqslant \int_{t_0}^{t} rdt = r(t-t_0) < r(t-t_0) + M.$$

for any $M > 0$.
Consider the system $\dot{x} = A(t)x$.

$$\begin{aligned}
\frac{dx_1}{dt} &= -\mu_v(T(t), R(t))x_1 - b_2x_4, \\
\frac{dx_2}{dt} &= -\mu_v(T(t), R(t))x_2 + b_2x_4, \\
\frac{dx_3}{dt} &= -\mu_h x_3 + \sigma x_5, \\
\frac{dx_4}{dt} &= -\gamma x_4, \\
\frac{dx_5}{dt} &= -(\mu_h + \sigma)x_5,
\end{aligned} \tag{4.20}$$

Then the Cauchy matrix solution of system (4.20) will be

$$K(t,t_0) = \begin{pmatrix} g_1 & 0 & 0 & h_{14} & 0 \\ 0 & g_2 & 0 & h_{24} & 0 \\ 0 & 0 & g_3 & 0 & h_{35} \\ 0 & 0 & 0 & g_4 & h_{45} \\ 0 & 0 & 0 & 0 & g_5 \end{pmatrix}, \qquad K(t_0,t_0) = I$$

Then

$$K(t,t_0)\|^2 \leqslant g_1^2 + g_2^2 + g_3^2 + g_4^2 + g_5^2 + h_{14}^2 + h_{24}^2 + h_{35}^2 + 2\{g_1h_{14} + g_2h_{24} + g_3h_{35}\}.$$

Each term to the right side in the above inequality is either of the form g_i^2, h_{ij}^2, or g_ih_{ij} for $i, j \in \{1,2,3,4,5\}$, where
$g_1(t) = g_2(t) = e^{-\int_{t_0}^{t}\mu_v(T(\tau),R(\tau))d\tau}$, $\quad g_3(t) = e^{-\mu_h(t-t_0)}$, $\quad g_4(t) = e^{-\gamma(t-t_0)}$,
$g_5(t) = e^{-(\mu_h+\sigma)(t-t_0)}$, $\quad h_{14}(t) = g_1\int_{t_0}^{t} -b_2g_4\frac{1}{g_1}d\tau$, $\quad h_{24}(t) = g_2\int_{t_0}^{t} b_2g_4\frac{1}{g_2}d\tau$,
$h_{35}(t) = g_3\int_{t_0}^{t}\sigma g_5\frac{1}{g_3}d\tau$.

We see that for each h_{ij} of the form $h_{ij}(t) = g_i\int_{t_0}^{t} q_i(\tau)g_j\frac{1}{g_i}d\tau$ where q_i is a bounded function of time, using Lemma 2.3.1, we have

$$h_{ij}(t) \leqslant Q_ig_i\int_{t_0}^{t} g_j\frac{1}{g_i}d\tau \leqslant M_ie^{-\sigma_i(t-t_0)},$$

for some constants $M_i > 0$ and $\sigma_i > 0$ where $Q_i = \sup_{t \geqslant t_0} \{q_i(t)\}$. We note also that such $h_{ij}'s$ are bounded functions of time.
Also, for each h_{ij} of the form $h_{ij}(t) = g_i \int_{t_0}^{t} q_i(\tau) h_{kj}(\tau) g_j \frac{1}{g_i} d\tau$ where q_i is a bounded function of time, by similar argument as above, we have that

$$h_{ij}(t) \leqslant L_i e^{-\zeta_i (t-t_0)},$$

for some constants L_i and ζ_i.
We see that

$$\|K(t,t_0)\|^2 \leqslant \sum_{i=1}^{N} M_i e^{-\alpha_i (t-t_0)}$$

for some natural number N. Let $\alpha = \min\{\alpha_1, \alpha_2, \cdots, \alpha_N\}$ and $M = M_1 + M_2 + \cdots + M_N$. Then

$$\|K(t,t_0)\|^2 \leqslant M e^{-\alpha (t-t_0)},$$

that is

$$\|K(t,t_0)\| \leqslant \sqrt{M} e^{-\frac{\alpha}{2}(t-t_0)}.$$

This shows that the zero solution of (4.20) is exponentially stable.
By Theorem 4.1.1, the zero solution of the system $\dot{x} = A(t)x + B(t)x$ is also exponentially stable. Hence by Theorem 4.1.2, the zero solution of the system $\dot{x} = A(t)x + B(t)x$ is uniformly asymptotically stable.
Thus by Theorem 4.1.4, the nonlinear system (4.1) is uniformly persistent, that is, there exists $c > 0$ (independent of initial conditions), such that $\liminf_{t\to\infty} I_h \geqslant c$ and $\liminf_{t\to\infty} I_v \geqslant c$ and hence the disease is endemic in the sense that the infected components of the model are uniformly persistent. ■

4.3 Numerical Simulations

In this section, we do some simulations similar to that of the periodic system. We use the daily temperature and daily rainfall data obtained from the National Meteorological Agency of Ethiopia from 1984-2012 for Asendabo region again. Here the temperature raw data is fitted by the general function

$$T(t) = 19.456 + 0.0006t + 1.2667\cos(0.524t + 4.3347) - 0.637\cos(2 * 0.524t - 0.7051) \quad (4.21)$$

the graph of which is drawn in Figure 4.1. We take the rainfall periodic function fit (3.30), again to study the non-periodic system as the raw rainfall data seems very much periodic. The initial data of the host and vector populations are taken to be

$$(S_v(0), I_v(0), S_h(0), I_h(0), R_h(0)) = (10000, 9, 20000, 190, 5),$$

the same value used in Section 3.4.

The model disease incidence is plotted in Figure 4.2c against time in months from the year 1984-2012 to compare it with the actual malaria incidence (cases) (Figure 4.2d) which is plotted against time in months too.

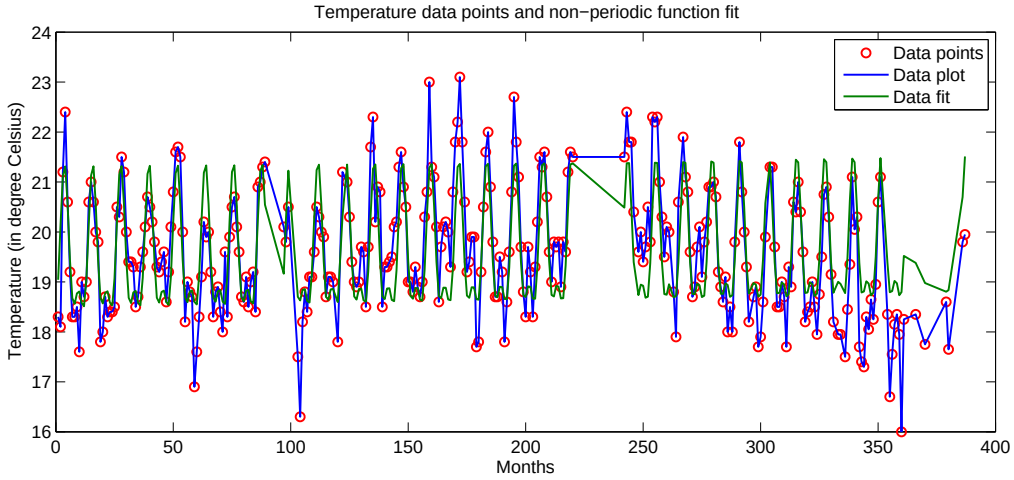
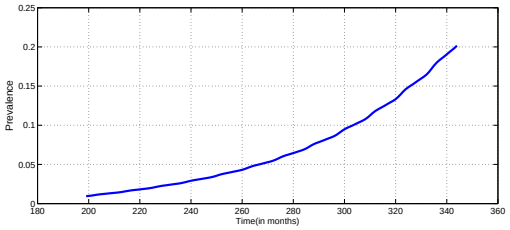
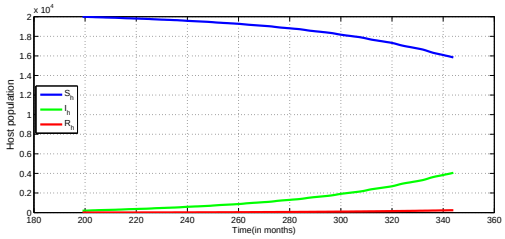


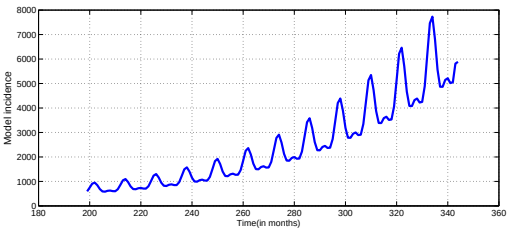
Figure 4.1. Non-periodic temperature curve fitted to the actual temperature data.



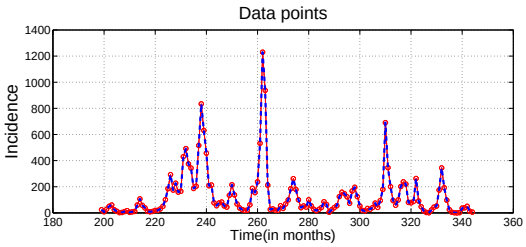
(a) A plot showing prevalence.



(b) A plot showing proportions of human population.



(c) A plot showing the model disease incidence.



(d) A plot showing the actual malaria confirmed cases in the Asendabo region, collected in the years 2000-2012.

In the non-periodic case, the simulation results of the prevalence, the host population

distribution and the model incidence have not shown an observable change in their behavior. This is due to the small additional non-periodic term $0.0006t$ in the temperature data fit (4.21) and the periodic rainfall data fit (3.30)used in the non-periodic system again besides the possible data collection and estimation errors.

Table 4.1. Parameter values used in all the simulations.

Parameter	Estimated value	Reference
Λ_h	0.415244 day^{-1}	[13]
σ	0.00137 day^{-1}	[39]
μ_h	0.0000388 day^{-1}	[13]
μ_d	0.00047 day^{-1}	[82]
β_{vh}	0.24 day^{-1}	[60]
β_{hv}	0.022 day^{-1}	[60]
r_h	0.0028 day^{-1}	[60]

Remark: Note here that there were no control interventions assumed to have been implemented in both periodic and non-periodic environments in the given period of time, and the model produces the dynamics of the disease if no intervention were employed.

Chapter 5

Optimal control strategies and cost-effectiveness analysis of the malaria model

5.1 Introduction

Malaria is a vector-borne disease that is prevalent over 100 countries worldwide with the highest incidence and mortality rates reported in sub-Saharan Africa. The World Health Organization (WHO) estimates that 660,000-971,000 people die every year from malaria and approximately 90% of the deaths occur in children under five years of age [83]. Several interventions have been used to reduce malaria transmission using insecticide-treated nets (ITNs), indoor residual spraying (IRS), intermittent preventive treatment in pregnant women and infants, larval control, and other vector control interventions. ITNs are bed-nets treated with pyrethroid, an insecticide that kills and repels mosquitoes, provides a barrier around people sleeping under them. Rural and poor populations are more often exposed to affected by malaria, ITNs have proven to be one of the most effective interventions in reducing morbidity and mortality due to their low cost and ease in implementation [12].

Malaria therefore incurs significant economic costs for endemic regions by incurring direct financial costs to the health system and costs associated with the reduced productivity of infected individuals and also caring the sick people is another burden of the disease on the society. Resources for malaria control are costly and limited.

The goal of this chapter is to incorporate time dependent control functions, in our model (2.4) and use the extended model to determine cost-effective strategies for best combating the spread of the malaria disease in a given population. In order to do this three control functions are used, one for vector-reduction strategies and other two for personal (human) protection and treatment, to reduce the exposed, infectious humans and the

total number of mosquitoes. Finally, we characterize the optimal control strategies and compute numerical solutions for the optimality system using an iterative method.

5.2 Formulation of the control model

We introduce into the model (4.1), time-dependent control efforts, namely, spray of insecticides u_2, Insecticide-Treated-Bed-Nets (ITBNs) b and treatment of infected individuals u_3 and derive optimal prevention and treatment strategies with minimal implementation cost. The control functions, b, u_2 and u_3, represent time dependent proportions of efforts for prevention and treatment, respectively and practiced on a time interval $[0, T_c]$.

The mosquitoes use favorable climatic conditions to flourish, particularly during hot and wet seasons. These effects are less visible during cold seasons. Therefore, we can use a time-dependent mosquito control, preferably applied in seasons favorable for mosquito outbreak.
According to [26], since ITBNs are treated with insecticide they can kill mosquitoes besides reducing the human-mosquito contact rate (or the biting rate). Due to insecticide treatment of bed-nets, female mosquitoes questing for blood meal could die when they become in contact with a treated bed-net. Therefore, we have the death rate of the mosquitoes as $\mu_v(b(t)) = \mu_v(T, R) + \mu_{max} b(t)$, $0 \leqslant b(t) \leqslant b_o$, taken as a linear function of $b(t)$ where $\mu_v(T, R)$ is the natural death rate, $\mu_{max} b(t)$ is the death rate due to pesticide on treated bed-nets and $b_o < 1$ is the maximum attainable range of using ITBN as mosquitoes can bite people having ITBN before they go to bed. On the other hand, susceptible mosquitoes move to the infected class by acquiring malaria through contacts with infected humans at a rate $(1 - b(t))\beta_{hv}\phi(T(t))\frac{I_h}{N_h}$, where β_{hv} is the probability for a vector to get infected by an infectious human.

The insecticides that are used for treating bed nets are lethal to the mosquitoes and other insects and also repels the mosquitoes, thus, reducing the number that attempt to feed on people in the sleeping areas with the nets. However, the mosquitoes can still feed on humans outside this protective areas, and so we have to include the spraying of insecticide. Consequently, we introduce $u_2(t)$ which is the control function representing spray of insecticide aimed at reducing the mosquitoes and $0 \leqslant u_2(t) \leqslant a_2$ where a_2 represents the maximum attainable rate due to cost and insecticide efficacy at reducing the mosquitoes population.

Susceptible host individuals move to the infected class by acquiring malaria through contact with infectious mosquitoes at a rate $(1 - b(t))\beta_{vh}\phi(T(t))\frac{I_v}{N_h}$, where β_{vh} is the transmission probability per bite.

Infectious individuals are assumed to recover at a rate $(r_h + \tau u_3(t))$, where r_h is the

rate of spontaneous recovery, $u_3(t)$ is the control on the rate/proportion of recruiting infected individuals for treatment and $\tau \in [0,1]$ is the efficacy of treatment. Infectious individuals who don't recover die at a rate $(\mu_h + \mu_d)$.

Putting the above formulations and assumptions together in to (4.1) gives the following vector-host model:

$$\begin{aligned}
\frac{dS_v}{dt} &= \Lambda_v(T(t),R(t)) - (1-b(t))\beta_{hv}\phi(T(t))\frac{I_h}{N_h}S_v - u_2(t)S_v - \mu_v(b(t))S_v,\\
\frac{dI_v}{dt} &= (1-b(t))\beta_{hv}\phi(T(t))\frac{I_h}{N_h}S_v - u_2(t)I_v - \mu_v(b(t))I_v,\\
\frac{dS_h}{dt} &= \Lambda_h - (1-b(t))\beta_{vh}\phi(T(t))\frac{I_v}{N_h}S_h + \sigma R_h - \mu_h S_h,\\
\frac{dI_h}{dt} &= (1-b(t))\beta_{vh}\phi(T(t))\frac{I_v}{N_h}S_h - (r_h + \tau u_3(t))I_h - (\mu_h+\mu_d)I_h,\\
\frac{dR_h}{dt} &= (r_h + \tau u_3(t))I_h - (\mu_h+\sigma)R_h,
\end{aligned} \tag{5.1}$$

where $\mu_v(b(t)) = \mu_v(T(t),R(t)) + \mu_{max}b(t)$.

5.3 Mathematical analysis of the controlled system

5.3.1 Disease Free Solution

In order to deduce the threshold condition for epidemic we use similar argument as in Section 4.2 and we replace the non-autonomous system (5.1) by an autonomous one, by regarding the time on the right side of the system (5.1) as a parameter and then carry out a local stability analysis.
Consider the second and the fifth equations of (5.1):

$$\begin{aligned}
\frac{dI_h}{dt} &= (1-b(t))\beta_{vh}\phi(T(t))\frac{I_v}{N_h}S_h - (\gamma + \tau u_3(t))I_h\\
&\leqslant (1-b(t))\beta_{vh}\phi(T(t))I_v - (\gamma+\tau u_3(t))I_h,\\
\frac{dI_v}{dt} &= (1-b(t))\beta_{hv}\phi(T(t))\frac{S_v}{N_h}I_h - (u_2(t)+\mu_v(b(t)))I_v\\
&\leqslant (1-b(t))\beta_{hv}\phi(T(t))\frac{N_v}{N_h}I_h - (u_2(t)+\mu_v(b(t)))I_v\\
&\leqslant (1-b(t))\beta_{hv}\phi(T(t))\Bbbk_v I_h - (u_2(t)+\mu_v(b(t)))I_v,
\end{aligned} \tag{5.2}$$

where $\gamma = \mu_h + r_h + \mu_d$ and $\Bbbk_v = N_v(0) + \frac{\sup_{t>0}\{\Lambda_v(T(t),R(t))\}}{\inf_{t>0}\{u_2(t)+\mu_v(T(t),R(t))\}}$.

we analyze the stability of the disease-free solution $I_v = I_h = 0$, that is, the solution representing the absence of the infection.

Linearizing the system around a small amount of disease i_H and i_V [15], we get

$$\begin{aligned}\frac{di_H}{dt} &= -(\gamma+\tau u_3(t))i_H + (1-b(t))\beta_{vh}\phi(T(t))i_V,\\ \frac{di_V}{dt} &= (1-b(t))\beta_{hv}\phi(T(t))\Bbbk_v i_H - (u_2(t)+\mu_v(b(t)))i_V,\end{aligned} \tag{5.3}$$

We then examine the stability of the disease-free solution of system (5.3), that is, $i_H = 0$ and $i_V = 0$ as if the system were autonomous [15]. For this we assume the solutions:

$$\begin{aligned}i_H &= c_1 exp(\lambda_c s),\\ i_V &= c_2 exp(\lambda_c s)\end{aligned} \tag{5.4}$$

and replace (5.4) into equation (5.3). The characteristic equation associated to system (5.3) is then obtained:

$$\begin{vmatrix} -(\lambda_c+\gamma+\tau u_3(t)) & (1-b(t))\beta_{vh}\phi(T(t)) \\ (1-b(t))\beta_{hv}\phi(T(t))\Bbbk_v & -(\lambda_c+u_2(t)+\mu_v(b(t))) \end{vmatrix} = 0 \tag{5.5}$$

that is,

$$\lambda_c(t) = -\frac{1}{2}(\gamma+\tau u_3(t)+u_2(t)+\mu_v(b(t))) \pm \frac{1}{2}\sqrt{(\gamma+\tau u_3(t)+u_2(t)+\mu_v(b(t)))^2 - 4\hat{c}}$$

where $\hat{c} = (\gamma+\tau u_3(t))(u_2(t)+\mu_v(b(t))) - (1-b(t))^2\beta_{hv}\beta_{vh}\phi^2(T(t))\Bbbk_v$.

If all the roots of equation (5.5) have negative real parts, then the equilibrium without disease is stable, that is, the origin is an attractor. We see that the first root that crosses the imaginary axis do so through the real axis and this happens when $\hat{c} < 0$, that is when

$$\tilde{\mathcal{R}}_{co}(t) := \frac{(1-b(t))^2\beta_{hv}\beta_{vh}\phi^2(T(t))\Bbbk_v}{(\gamma+\tau u_3(t))(u_2(t)+\mu_v(b(t)))} > 1.$$

Therefore, we can find the time t at which the stability of the trivial solution of system (5.3), that is, $i_H = 0$ and $i_V = 0$ becomes unstable. The time t at which the trivial solution (no-disease) of the autonomous system becomes unstable ($\tilde{\mathcal{R}}_{co} > 1$) corresponds approximately to the moment at which the epidemic takes off, that is, when the epidemic in system (5.1) begins to increase as a result of the introduction of a small amount of disease at time $t = 0$.

The stability analysis of the model (5.1) is similar to the analysis done in Section 4.2. We then investigate an optimal control strategy.

5.4 The impact of the control measures on the threshold function

The threshold function $\tilde{\mathcal{R}}_{co}(t)$ is dependent on the time dependent control variables b, u_2 and u_3. These control measures have their own impact on the disease dynamics and this is mainly manifested while influencing $\tilde{\mathcal{R}}_{co}(t)$. To see the impact of the control measures b, u_2 and u_3 on $\tilde{\mathcal{R}}_{co}(t)$, we differentiate $\tilde{\mathcal{R}}_{co}(t)$ with respect to these control variables.

$$\begin{aligned}
\frac{\partial\tilde{\mathcal{R}}_{co}}{\partial b} =& \frac{\partial}{\partial b}\left(\frac{(1-b(t))^2\beta_{hv}\beta_{vh}\phi^2(T(t))\mathbb{k}_v}{(\gamma+\tau u_3(t))(u_2(t)+\mu_v(T(t),R(t))+\mu_{max}b(t))}\right)\\
=& \left(\frac{\beta_{hv}\beta_{vh}\phi^2(T(t))\mathbb{k}_v}{(\gamma+\tau u_3(t))}\right)\frac{\partial}{\partial b}\left(\frac{(1-b(t))^2}{u_2(t)+\mu_v(T(t),R(t))+\mu_{max}b(t)}\right)\\
=& -(1-b(t))\left(\frac{\beta_{hv}\beta_{vh}\phi^2(T(t))\mathbb{k}_v}{(\gamma+\tau u_3(t))}\right)\left(\frac{2u_2(t)+2\mu_v(T(t),R(t))+\mu_{max}(1+b(t))}{(u_2(t)+\mu_v(b(t)))^2}\right)\\
=& -\Upsilon\left(\frac{2u_2(t)+2\mu_v(T(t),R(t))+\mu_{max}(1+b(t))}{u_2(t)+\mu_v(b(t))}\right),
\end{aligned}$$

$$\begin{aligned}
\frac{\partial\tilde{\mathcal{R}}_{co}}{\partial u_2} =& \frac{\partial}{\partial u_2}\left(\frac{(1-b(t))^2\beta_{hv}\beta_{vh}\phi^2(T(t))\mathbb{k}_v}{(\gamma+\tau u_3(t))(u_2(t)+\mu_v(b(t)))}\right)\\
=& \left(\frac{(1-b(t))^2\beta_{hv}\beta_{vh}\phi^2(T(t))\mathbb{k}_v}{(\gamma+\tau u_3(t))(u_2(t)+\mu_v(b(t)))}\right)\frac{\partial}{\partial u_2}\left(\frac{1}{u_2(t)+\mu_v(b(t))}\right)\\
=& -\left(\frac{(1-b(t))^2\beta_{hv}\beta_{vh}\phi^2(T(t))\mathbb{k}_v}{(\gamma+\tau u_3(t))}\right)\left(\frac{1}{u_2(t)+\mu_v(b(t))}\right)^2\\
=& -\Upsilon\left(\frac{1-b}{u_2(t)+\mu_v(b(t))}\right)
\end{aligned}$$

and

$$\begin{aligned}
\frac{\partial\tilde{\mathcal{R}}_{co}}{\partial u_3} =& \frac{\partial}{\partial u_3}\left(\frac{(1-b(t))^2\beta_{hv}\beta_{vh}\phi^2(T(t))\mathbb{k}_v}{(\gamma+\tau u_3(t))(u_2(t)+\mu_v(b(t)))}\right)\\
=& \left(\frac{(1-b(t))^2\beta_{hv}\beta_{vh}\phi^2(T(t))\mathbb{k}_v}{(u_2(t)+\mu_v(b(t)))}\right)\frac{\partial}{\partial u_3}\left(\frac{1}{\gamma+\tau u_3(t)}\right)\\
=& -\left(\frac{(1-b(t))^2\beta_{hv}\beta_{vh}\phi^2(T(t))\mathbb{k}_v}{(u_2(t)+\mu_v(b(t)))}\right)\left(\frac{\tau}{(\gamma+\tau u_3(t))^2}\right)\\
=& -\Upsilon\left(\frac{\tau(1-b)}{(\gamma+\tau u_3(t))}\right)
\end{aligned}$$

where

$$\Upsilon = \left(\frac{(1-b(t))\beta_{hv}\beta_{vh}\phi^2(T(t))\mathbb{k}_v}{(u_2(t)+\mu_v(b(t)))(\gamma+\tau u_3(t))}\right)$$

We see that

$$\frac{\partial\tilde{\mathcal{R}}_{co}}{\partial u_2} < 0 \quad \text{for all } t \geqslant 0,$$

$$\frac{\partial \tilde{\mathcal{R}}_{co}}{\partial b} < 0 \text{ for all } t \geqslant 0 \text{ and } 0 \leqslant b(t) < 1$$

and

$$\frac{\partial \tilde{\mathcal{R}}_{co}}{\partial u_3} < 0 \text{ for all } t \geqslant 0.$$

This shows that the control variables have an impact to decrease $\tilde{\mathcal{R}}_{co}(t)$ with time.

5.5 Optimal Control Analysis

We make an analysis based on the analysis done in [4]. We consider an optimal control problem with the objective function given by

$$J(b, u_2, u_3) = \int_0^{t_f} ([m + c_3 u_3] I_h + \frac{1}{2} cbN_h + c_2 u_2^2) dt \tag{5.6}$$

where t_f is the final time and the coefficients m, c, c_2, c_3 are positive weights to balance the factors.
The objective of our work is to minimize the infectious human population, the total number of vector population and the cost of implementing the control by using possible minimal control variables $b(t), u_2(t)$ and $u_3(t)$.

The objective functional includes the cost due to the number of infectious people and the cost of implementing the control measures that include quadratic costs related to the resources needed for, spraying of insecticides operations $c_2 u_2^2$. The weighting $(m + c_3 u_3)$ represents the cost per unit time of an infection burden I_h and the total costs $c_3 u_3 I_h$ and mI_h, respectively, correspond to factors such as the cost of treatment and the loss of productivity in the workplace caused by illness.

To use Insecticide-Treated-Bed-Nets, every individual buys one with unit price c. But one ITBN can be shared among people. We assume in our study that two individuals share one ITBN. The total cost will then be $\frac{1}{2} cbN_h$.

In effect we minimize the total number of infected humans $I_h(t)$, while minimizing the cost of controls $b(t), u_2(t), u_3(t)$. Thus, we seek an optimal control b^*, u_2^*, u_3^* such that

$$J(b^*, u_2^*, u_3^*) = \min_{b, u_2, u_3} \{J(b, u_2, u_3) | b, u_2, u_3 \in \mathcal{U}\} \tag{5.7}$$

subject to the system equations in 5.1, where the control set is given by

$$\mathcal{U} = \{(b, u_2, u_3) | u : [0, t_f] \to [0, 1], u \in \{b, u_2, u_3\} \text{ is Lebesgue measurable}\}.$$

The necessary conditions that an optimal control must satisfy come from the Pontryagins Maximum Principle [69]. This principle converts (5.1) and (5.6) into a problem of

minimizing pointwise a Hamiltonian H, with respect to (b, u_2, u_3)

$$\begin{aligned}
H =&(m + c_3u_3(t))I_h + cb(t)N_h + c_2u_2(t)^2 \\
&+\lambda_{S_v}\left\{\Lambda_v(T(t), R(t)) - (1 - b(t))\beta_{hv}\phi(T(t))\frac{I_h}{N_h}S_v - u_2(t)S_v - \mu_v(b(t))S_v\right\} \\
&+\lambda_{I_v}\left\{(1 - b(t))\beta_{hv}\phi(T(t))\frac{I_h}{N_h}S_v - u_2(t)I_v - \mu_v(b(t))I_v\right\} \\
&+\lambda_{S_h}\left\{\Lambda_h - (1 - b(t))\beta_{vh}\phi(T(t))\frac{I_v}{N_h}S_h + \sigma R_h - \mu_h S_h\right\} \\
&+\lambda_{I_h}\left\{(1 - b(t))\beta_{vh}\phi(T(t))\frac{I_v}{N_h}S_h - (r_h + \tau u_3(t))I_h - (\mu_h + \mu_d)I_h\right\} \\
&+\lambda_{R_h}\left\{(r_h + \tau u_3(t))I_h - (\mu_h + \sigma)R_h\right\}
\end{aligned} \tag{5.8}$$

where the $\lambda_{S_v}, \lambda_{I_v}, \lambda_{S_h}, \lambda_{I_h}$ and λ_{R_h} are the adjoint variables or co-state variables. [[25], Corollary 4.1] gives the existence of optimal control due to the convexity of the integrand of J with respect to b, u_2 and u_3 a priori boundedness of the state solutions, and the Lipschitz property of the state system with respect to the state variables. Applying Pontryagins Maximum Principle [69] and the existence result for the optimal control from [25], we obtain the following theorem.

Theorem 5.5.1. *Given an optimal control b^*, u_2^*, u_3^* and solutions $S_v^*, I_v^*, S_h^*, I_h^*, R_h^*$ of the corresponding state system (5.1) that minimizes $J(b, u_2, u_3)$ over $\mathcal{U}$. Then there exist adjoint functions $\lambda_{S_v}, \lambda_{I_v}, \lambda_{S_h}, \lambda_{I_h}, \lambda_{R_h}$ satisfying*

$$\begin{aligned}
-\frac{d\lambda_{S_v}}{dt} =&(1 - b(t))\beta_{hv}\phi(T(t))\left(\frac{I_h}{N_h}\right)(\lambda_{I_v} - \lambda_{S_v}) - (u_2(t) + \mu_v(b(t)))\lambda_{S_v} \\
-\frac{d\lambda_{I_v}}{dt} =& -(u_2(t) + \mu_v(b(t)))\lambda_{I_v} - (1 - b(t))\beta_{vh}\phi(T(t))\left(\frac{S_h}{N_h}\right)(\lambda_{S_h} - \lambda_{I_h}) \\
-\frac{d\lambda_{S_h}}{dt} =&cb(t) + (1 - b(t))\beta_{hv}\phi(T(t))I_hS_v\left(\frac{1}{N_h^2}\right)(\lambda_{S_v} - \lambda_{I_v}) \\
&+(1 - b(t))\beta_{vh}\phi(T(t))I_v\left(\frac{N_h - S_h}{N_h^2}\right)(\lambda_{I_h} - \lambda_{S_h}) + \mu_h\lambda_{S_h} \\
-\frac{d\lambda_{I_h}}{dt} =&m + c_3u_3(t) + cb(t) + (1 - b(t))\beta_{hv}\phi(T(t))S_v\left(\frac{N_h - I_h}{N_h^2}\right)(\lambda_{I_v} - \lambda_{S_v}) \\
&+(1 - b(t))\beta_{vh}\phi(T(t))I_vS_h\left(\frac{1}{N_h^2}\right)(\lambda_{S_h} - \lambda_{I_h}) \\
&-((r_h + \tau u_3(t)) + (\mu_h + \mu_d))\lambda_{I_h} + (r_h + \tau u_3(t))\lambda_{R_h} \\
-\frac{d\lambda_{R_h}}{dt} =&cb(t) + (1 - b(t))\beta_{hv}\phi(T(t))I_hS_v\left(\frac{1}{N_h^2}\right)(\lambda_{S_v} - \lambda_{I_v}) \\
&+(1 - b(t))\beta_{vh}\phi(T(t))I_vS_h\left(\frac{1}{N_h^2}\right)(\lambda_{S_h} - \lambda_{I_h}) + \sigma\lambda_{S_h} - (\mu_h + \sigma)\lambda_{R_h}
\end{aligned} \tag{5.9}$$

with transversality conditions

$$\lambda_{S_v}(t_f) = \lambda_{I_v}(t_f) = \lambda_{S_h}(t_f) = \lambda_{I_h}(t_f) = \lambda_{R_h}(t_f) = 0 \tag{5.10}$$

and the control u_2^* satisfies the optimality condition

$$u_2^* = max\left\{0, min\left(1, \frac{\lambda_{S_v} S_v^* + \lambda_{I_v} I_v^*}{2c_2}\right)\right\}. \tag{5.11}$$

For the linear controls b and u_3, the solutions are bang-bang and b^* and u_3^* satisfy the optimality condition

$$\begin{aligned} b^* &= \begin{cases} b_o & if\ b_1 > 0 \\ b_{singular} & if\ b_1 = 0 \\ 0 & if\ b_1 < 0 \end{cases} \\ u_3^* &= \begin{cases} 1 & if\ u_{31} > 0 \\ u_{3sinular} & if\ u_{31} = 0 \\ 0 & if\ u_{31} < 0 \end{cases} \end{aligned} \tag{5.12}$$

with switching functions for b^*

$$\begin{aligned} b_1 =& cN_h^* + (\lambda_{S_v} - \lambda_{I_v})\beta_{hv}\phi(T(t))\frac{I_h^*}{N_h^*}S_v^* - \mu_{max}(\lambda_{S_v} S_v^* + \lambda_{I_v} I_v^*) \\ &+(\lambda_{S_h} - \lambda_{I_h})\beta_{vh}\phi(T(t))\frac{I_v^*}{N_h^*}S_h^*, \end{aligned}$$

and for u_3^*

$$u_{31} = c_3 I_h^* - \tau\lambda_{I_h} I_h^* + \tau\lambda_{R_h} I_h^*.$$

proof: The differential equations governing the adjoint variables are obtained by differentiation of the Hamiltonian function, evaluated at the optimal control. Then the adjoint system can be written as

$$\begin{aligned} -\frac{d\lambda_{S_v}}{dt} = \frac{\partial H}{\partial S_v} =& (1 - b(t))\beta_{hv}\phi(T(t))\left(\frac{I_h}{N_h}\right)(\lambda_{I_v} - \lambda_{S_v}) - (u_2(t) + \mu_v(b(t)))\lambda_{S_v} \\ -\frac{d\lambda_{I_v}}{dt} = \frac{\partial H}{\partial I_v} =& -(u_2(t) + \mu_v(b(t)))\lambda_{I_v} - (1 - b(t))\beta_{vh}\phi(T(t))\left(\frac{S_h}{N_h}\right)(\lambda_{S_h} - \lambda_{I_h}) \\ -\frac{d\lambda_{S_h}}{dt} = \frac{\partial H}{\partial S_h} =& cb(t) + (1 - b(t))\beta_{hv}\phi(T(t))I_h S_v\left(\frac{1}{N_h^2}\right)(\lambda_{S_v} - \lambda_{I_v}) \\ &+(1 - b(t))\beta_{vh}\phi(T(t))I_v\left(\frac{N_h - S_h}{N_h^2}\right)(\lambda_{I_h} - \lambda_{S_h}) + \mu_h\lambda_{S_h} \end{aligned}$$

$$
\begin{aligned}
-\frac{d\lambda_{I_h}}{dt} = \frac{\partial H}{\partial I_h} =& m + c_3u_3(t) + cb(t) + (1-b(t))\beta_{hv}\phi(T(t))S_v\left(\frac{N_h - I_h}{N_h^2}\right)(\lambda_{I_v} - \lambda_{S_v}) \\
&+(1-b(t))\beta_{vh}\phi(T(t))I_vS_h\left(\frac{1}{N_h^2}\right)(\lambda_{S_h} - \lambda_{I_h}) \\
&+((r_h + \tau u_3(t)) + (\mu_h + \mu_d))\lambda_{I_h} + (r_h + \tau u_3(t))\lambda_{R_h} \\
-\frac{d\lambda_{R_h}}{dt} = \frac{\partial H}{\partial R_h} =& cb(t) + (1-b(t))\beta_{hv}\phi(T(t))I_hS_v\left(\frac{1}{N_h^2}\right)(\lambda_{S_v} - \lambda_{I_v}) \\
&+(1-b(t))\beta_{vh}\phi(T(t))I_vS_h\left(\frac{1}{N_h^2}\right)(\lambda_{S_h} - \lambda_{I_h}) + \sigma\lambda_{S_h} - (\mu_h + \sigma)\lambda_{R_h}
\end{aligned}
$$

with transversality conditions (5.10).

On the interior of the control set, where $0 < u_2 < 1$, we have

$$0 = \frac{\partial H}{\partial u_2} = 2c_2u_2^* - \lambda_{S_v}S_v^* - \lambda_{I_v}I_v^* \tag{5.13}$$

Hence, we obtain (see [43])

$$u_2^* = \frac{\lambda_{S_v}S_v^* + \lambda_{I_v}I_v^*}{2c_2}$$

Thus we have

$$u_2^* = max\left\{0, min\left(1, \frac{\lambda_{S_v}S_v^* + \lambda_{I_v}I_v^*}{2c_2}\right)\right\}.$$

Next we discuss the numerical solutions of the optimality system and the corresponding optimal control pairs, the parameter choices, and the interpretations from various cases. ■

5.6 Numerical Results

In this section, we study numerically the solution for the optimal control model (5.7). The optimal control is obtained by solving the optimality system, consisting of five ODEs from the state and five others from the adjoint equations. An iterative scheme is used for solving the optimality system. We start to solve the state equations with a guess for the controls over the simulated time using fourth order Runge-Kutta scheme. Because of the transversality conditions (5.10), the adjoint equations are solved by a backward fourth order Runge-Kutta scheme using the current iterations solutions of the state equation. Then the controls are updated by using a convex combination of the previous controls and the value from the characterizations (5.11). This process is repeated and iterations are stopped if the values of the unknowns at the previous iterations are very close to the ones at the present iterations as outlined in [43].

We explore the malaria model with preventive and treatment as control measures to

study the effects of control practices and the transmission of malaria. Using various combinations of the three controls, one control at a time, two controls at a time and all controls at the same time, we investigate and compare numerical results from simulations with the following scenarios:

i. using the control on the use of Insecticide-Treated-Bed-Nets (ITBNs) alone for personal protection (b) without insecticide spraying (u_2) and treatment of the symptomatic humans (u_3).

ii. using the control on the use of Insecticide-Treated-Bed-Nets (ITBNs) for personal protection (b) and insecticide spraying (u_2), without treatment of the symptomatic humans (u_3).

iii. using the control on the use of Insecticide-Treated-Bed-Nets (ITBNs) for personal protection (b) and treatment of the symptomatic humans (u_3), without insecticide spraying (u_2).

iv. using the control on the use of insecticide spraying (u_2) and treatment of the symptomatic humans (u_3) without Insecticide-Treated-Bed-Nets (ITBNs) for personal protection (b).

v. using all three control measures (b, u_2, u_3).

For the numerical simulation, we used the following weight factors, $c = 1.25$, $m = 32$, $c_2 = 300$, $c_3 = 3$ and the efficacy of treatment $\tau = 0.6$ which is 60%, with $\mu_{max} = 0.0951$. The assumption that the weight factor associated with control b is multiplied by half ($c = 0.5 * 2.5$) is based on the facts that one bed net can be shared with at least two people. The initial state variables used are $S_v(0) = 800000, I_v(0) = 700, S_h(0) = 5376, I_h(0) = 24, R_h(0) = 3$ and parameter values are $\Lambda_h = 0.415244, \sigma = 0.00137, \mu_h = 0.000024, \mu_d = 0.00047, \beta_{vh} = 0.24, \beta_{hv} = 0.022, r_h = 0.0028$, to illustrate the effect of different optimal control strategies on the spread of malaria in a population.

5.6.1 Insecticide-Treated-Bed-Net control

In this scenario, we activate only control on personal protection (b), while the controls on insecticide spraying (u_2) and treatment of the symptomatic humans (u_3) are set to zero. The profile of the optimal control (b) could be seen in Figure 5.1. Using the optimal control (b), the result shows a decrease in the prevalence of the disease with optimal strategy than without control. Specifically, we observed that the control strategy reduces the prevalence but still leads to an increase in the prevalence as against an increase in the uncontrolled case.

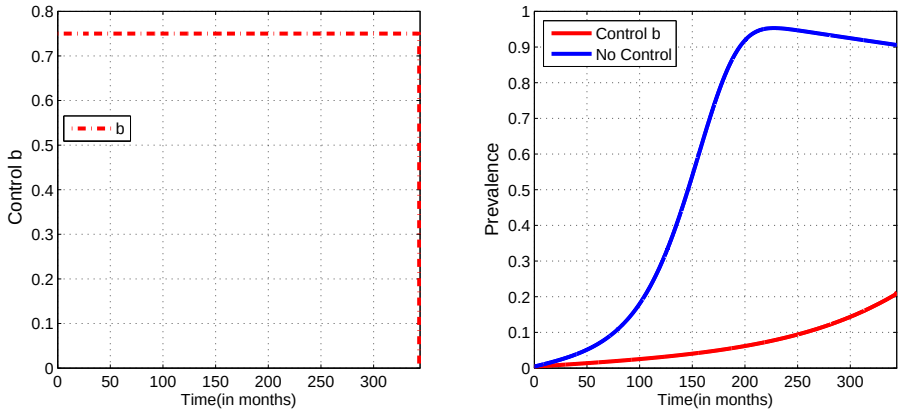


Figure 5.1. *Plots showing the effect of the control on personal protection* (b) *only on the prevalence while the control with insecticide spraying* (u_2) *and treatment of the symptomatic humans* (u_3) *are set to zero.*

5.6.2 Insecticide-Treated-Bed-Net and Insecticide Spraying controls

When the controls with Insecticide-Treated-Bed-Nets (ITBNs) for personal protection (b) and insecticide spraying (u_2) only are both activated setting the other controls to zero, a significant reduction in the prevalence than the effect of applying control (b) alone is achieved even though the result shows a slow increase in the prevalence of the disease. The profile of optimal controls (b) and (u_2) can be seen in Figure 5.2.

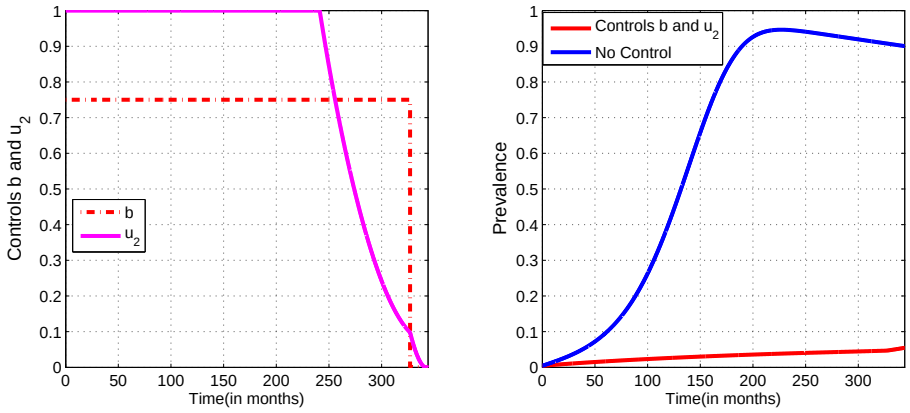


Figure 5.2. *Plots showing the effect of the controls with Insecticide-Treated-Bed-Nets (ITBNs) for personal protection* (b) *and insecticide spraying* (u_2) *on the prevalence while the control with treatment of the symptomatic humans* (u_3) *is set to zero.*

5.6.3 Insecticide-Treated-Bed-Net and Treatment controls

Again when the controls with Insecticide-Treated-Bed-Nets (ITBNs) for personal protection (b) and treatment of the symptomatic humans (u_3) are both applied setting the other control to zero, the controls profile in Figure 5.3 shows a better reduction in the prevalence than the effect of applying control (b) alone. Moreover, the reduction result shows a decrease in the prevalence as compared to the previous controls, Figures 5.1-5.2.

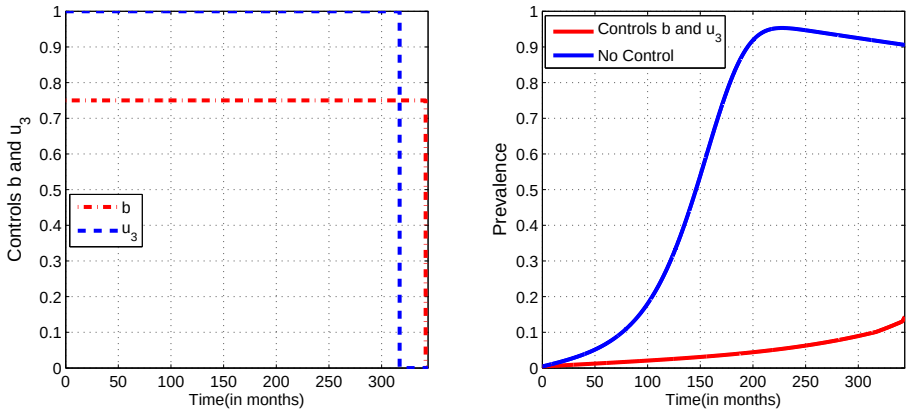


Figure 5.3. *Plots showing the effect of the controls with Insecticide-Treated-Bed-Nets (ITBNs) for personal protection* (b) *and treatment of the symptomatic humans* (u_3) *on the prevalence while the control with insecticide spraying* (u_2) *is set to zero.*

5.6.4 Insecticide Spraying and Treatment controls

The controls with insecticide spraying (u_2) and treatment of the symptomatic humans (u_3) are also activated by setting the other control to zero as before. In this scenario, the controls show a small reduction in the prevalence and their profile in Figure 5.4 shows a slow decrease in the disease prevalence.

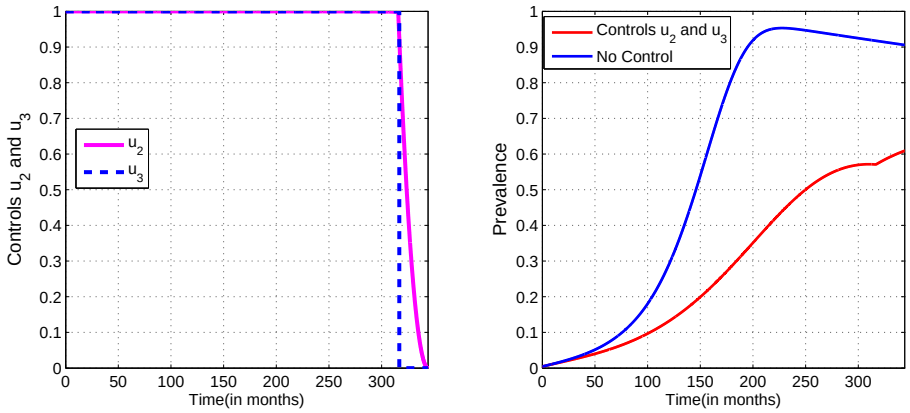


Figure 5.4. *Plots showing the effect of the controls with insecticide spraying* (u_2) *and treatment of the symptomatic humans* (u_3) *on the prevalence while the control with Insecticide-Treated-Bed-Nets (ITBNs) for personal protection* (b) *is set to zero.*

5.6.5 All controls

Lastly, the controls with Insecticide-Treated-Bed-Nets (ITBNs) for personal protection (b), insecticide spraying (u_2) and treatment of the symptomatic humans (u_3) are all activated together to optimize the objective function and their profile in Figure 5.5 show very significant decrease in the disease prevalence. In Figures 5.1-5.4, the results show

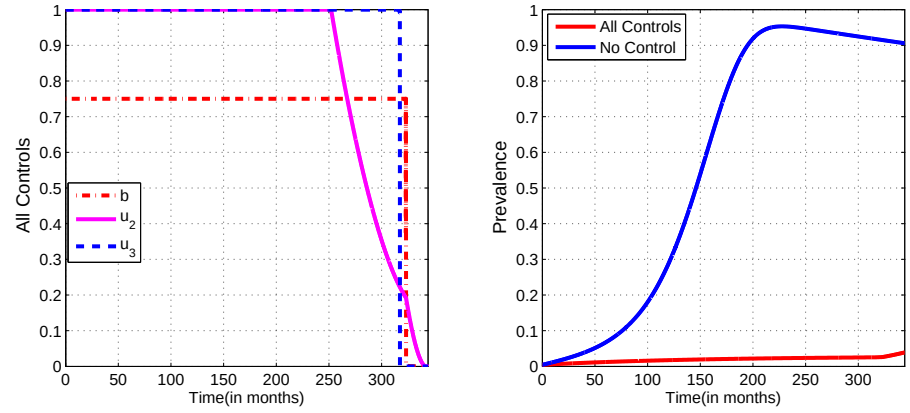


Figure 5.5. *Plots showing the effect of the controls with Insecticide-Treated-Bed-Nets (ITBNs) for personal protection* (b)*, insecticide spraying* (u_2) *and treatment of the symptomatic humans* (u_3) *on the prevalence.*

significant difference in the prevalence with optimal control strategy compared to prevalence without control. We observed that the control strategies resulted in a decrease in the prevalence as against an increase in the uncontrolled case.

The decrease is significantly very high when all the controls are applied together. From

Figure 5.5, we see that to achieve such a decrease in the prevalence of the disease in 344 months, Insecticide-Treated-Bed-Nets (ITBNs) for personal protection should be used intensively for almost 323 months and halted afterwards, insecticide spraying should be used intensively for almost 252 months but smoothly reduced afterwards, while the treatment of the symptomatic humans should be used intensively for almost 317 months and halted afterwards.

Chapter 6

Discussions and Conclusion

6.1 Discussions

In this study the climatic impacts on malaria prevalence in the periodic and non-periodic environments is analyzed. The climate variables which are mainly responsible for the malaria disease transmission in a population, namely, temperature and rainfall are given emphasis in this study. We used a mathematical model that describes the impact of climate variation on the malaria dynamics. To study this relation, a deterministic non-autonomous model is designed by incorporating the effect of both temperature and rainfall to the dispersion rate of adult mosquitoes, the mosquito biting rate and mortality rate of adult mosquitoes and this is used to assess the impact of the variability in temperature and rainfall on the transmission dynamics of malaria in a population. We analyzed our malaria disease transmission model with periodic coefficients using the analysis given in [81] and incorporating the periodic variation of seasonal variables due to climate variation. It has been shown that the disease-free solution of the model is globally asymptotically stable when the basic reproduction ratio is less than unity and the disease is uniformly persistent when the basic reproduction ratio is greater than unity.
To validate the model results in the real situation, we have used the annual number of microscopically confirmed cases of malaria in Ethiopia during the years 2000-2012 and the corresponding climate(temperature and rainfall) data from the National Meteorological Agency of Ethiopia. The temperature and rainfall data are fitted by periodic function curves and the model parameters are expressed as a function of these time dependent climate variables to study their impact on the malaria disease transmission dynamics. Finally the model has been validated using the epidemiological data collected from western region of Ethiopia, by considering the trends for monthly microscopically confirmed cases of malaria during the years 2000-2012 and the climate variation in the region.

The major finding of this study is the analysis of the model with non-periodic coefficients

incorporating non-periodic climate variables. The temperature data is fitted by a non-periodic function curve and expressed the model parameters as a function of these time dependent climate variables to study their impact on the malaria disease transmission dynamics on a long term basis. It has been shown also that the disease-free solution of the model is globally asymptotically stable when the threshold function is less than unity and the disease is uniformly persistent when the threshold function is greater than unity with some additional condition. The monthly microscopically confirmed cases and the corresponding climate(temperature and rainfall) data from the National Meteorological Agency of Ethiopia used in the periodic case have been used to validate the model results of the non-periodic case also.
In the non-periodic environment a time dependent optimal control strategy is introduced into the model (4.1) with three time dependent control variables, namely, spray of insecticides, bed net distribution and treatment of infected individuals and assess their impact on curtailing the spread of malaria. We applied and performed an optimal control analysis of the model (4.1) in the non-periodic environment. Applying optimal control, we could derive and analyze the conditions for optimal control of the disease with effective treatment regime and preventive measures. We tried to find an optimal and cost effective intervention mechanism that can have a strong impact on the disease control.

6.2 Conclusions

We derived and analyzed a deterministic non-autonomous model for the transmission of malaria disease in a periodic and non-periodic environments. We calculated the basic reproduction ratio and the threshold function respectively and investigated the existence and stability of the disease-free solutions in both environments. The dynamics of mosquito populations are driven by climatic factors, rainfall and temperature. The impact of these climatic variables, temperature and rainfall, in both environments is investigated and the corresponding model parameters are shown to be influenced by these climate variables. The model results have been validated using epidemiological data obtained from a western region of Ethiopia, by considering the trends for monthly microscopically confirmed cases of malaria during the years 2000-2012 and the corresponding climate variation in the region. In both environments, it has been shown that the model incidence result increases slowly until it reaches a point where it tends to stop rising in the absence of implementation of any kind of control measures and the actual incidence is a result of some control interventions implemented in the country in these years. This shows that the climate variables have significant impact on the disease dynamics and proper implementation of control measures is required to achieve a significant reduction of the malaria disease dynamics.

In addition to providing protection to individuals against the bites of infected mosquitoes

and treating infected individuals, vector control interventions can also have a substantial effect on mosquito population dynamics. Large reductions in mosquito numbers are frequently seen following the introduction of insecticide-treated bed nets or indoor residual spraying. Even greater reductions in mosquito numbers are possible by selecting combinations of interventions. Our investigation shows that the best malaria disease significant reduction is attained when all the controls are applied together.

When our model is reduced to its autonomous version, the fact that the model exhibit a backward bifurcation is well known in many of the literatures and our model also reduces to the same phenomena. However, when some of the parameters themselves are made to be time dependent, no such phenomenon (like backward bifurcation) is established yet. In the contrary it has been asserted that the DFS is globally asymptotically stable when the basic reproduction number $\bar{R}_0$ is less than unity.

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Declaration

This dissertation is my original work and has not been presented for a degree in any other university, and that all sources of the materials used for the dissertation have been duly acknowledged.

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