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MATHEMATICAL MODELING OF THE IMPORTED MALARIA IN THE UNITED ARAB EMIRATES

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This thesis is submitted in partial fulfillment of the requirements for the degree of Master of Science in Mathematics

Under the Supervision of Dr. Abdessamad Tridane

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Declaration of Original Work

I, Fatima Hassan Ali AlAwadhi, the undersigned, a graduate student at the United Arab Emirates University (UAEU), and the author of this thesis entitled *"Mathematical Modeling of the Imported Malaria in the United Arab Emirates"*, hereby, solemnly declare that this thesis is an original research work that has been done and prepared by me under the supervision of Dr. Abdessamad Tridane, in the College of Science at UAEU. This work has not been previously formed as the basis for the award of any academic degree, diploma or a similar title at this or any other university. The materials borrowed from other sources and included in my thesis have been properly cited and acknowledged.

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Abstract (in English)

Although the UAE was certified to be free of local malaria transmission cases in 2007, the increased number of imported malaria cases in recent years required the attention of the public health professionals. The aim of this work is to study, via mathematical modeling, the impact of imported malaria cases on the population of the UAE. The nature of the health policies in the UAE imposes on us a model that classifies the living population of the UAE in two categories. The *local* population, who represent the permanent residents that do not have any health requirement for their residency, and the *non-local* population, which are required to have certain health conditions to maintain their residency status in the country. Basic reproduction number was computed and stability analysis and local sensitivity analysis were performed to understand the epidemiological features of imported malaria in the UAE. The simulation showed that when an infection is established in the country, it will not be affected by reducing the burden of the endemic on the locals. Also, the local sensitivity presented the most influential parameter for the infected compartments which will assist in the control measures. My model helped to show the possible outcomes of such epidemic on both human subpopulation and the control strategy to maintain lower epidemic size in the UAE.

Keywords: malaria infection in the UAE, basic reproduction number, stability analysis, local sensitivity analysis.

Title and Abstract (in Arabic)

النمذجة الرياضية لمرض الملاريا المستورد في دولة الإمارات العربية المتحدة

الملخص

على الرغم من أن دولة الإمارات العربية المتحدة حصلت على شهادة معتمدة من منظمة الصحة العالمية تؤكد خلوها من حالات الملاريا المكتسبة محلياً في عام ٢٠٠٧، إلا أن الزيادة الملحوظة في عدد حالات الملاريا المستوردة في السنوات الأخيرة استدعى اهتمام العاملين في مجال الصحة العامة. الهدف من هذا العمل هو استخدام نموذج رياضي لدراسة تأثير حالات الملاريا المستوردة على سكان دولة الإمارات العربية المتحدة. طبيعة السياسات الصحية في دولة الإمارات العربية المتحدة تفرض علينا تصنيف سكان دولة الإمارات العربية المتحدة لفئتين في النموذج الرياضي المدروس. الفئتان تشملان السكان المحليين المقيمين في الدولة الذين لا يتطلب إقامتهم إلى فحوصات صحية دورية و السكان الغير المحليين الذين يتطلب وجودهم في الدولة إلى إجراءات طبية دورية. تم من خلال هذه الدراسة حساب عدد الاستنساخ الأساسي و تنفيذ تحليل الاستقرار و تحليل الحساسية المحلية للنموذج الرياضي من أجل فهم السمات الوبائية لمرض الملاريا المستوردة في الإمارات العربية المتحدة. أظهرت المحاكاة للنموذج الرياضي أن تقليل عدوى الملاريا عند السكان المحليين لن يؤثر على استمرارية و انتشار الملاريا في الدولة. قدم تحليل الحساسية المحلية توضيح عن قيم المتغيرات الأكثر تأثيرا على الفئات المصابة والتي تساعد على تفعيل تدابير الرقابة. ساعد النموذج الرياضي على إظهار النتائج المحتملة لهذا الوباء على فئتي السكان المقيمين و اقتراح استراتيجية مكافحة الملاريا و الحفاظ على انخفاض حجم الوباء في الإمارات العربية المتحدة.

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I sincerely give my deepest gratitude to my advisor, Dr. Abdessamad Tridane, for his enormous efforts, patience, professionalism, and understanding for the past 2 years. His guidance helped me to be a better person, enhance my mathematical skills, and learn new practical programming. Also, I would like to thank Dr. Mohamed Ali Hajji and Dr. Mohammad Tufail Malik for their valuable comments and remarks on my thesis.

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I express my deepest thanks to my friends who were in different degree levels from different departments. Their advices and support helped me finish the journey of the masters degree. A spacial thanks to my friend Arwa Abdulla for her tremendous assistance in the thesis formatting.

I dedicate my achievements to my first supporters; my parents, sisters, and brothers without whom I could not start my graduate degree.

Dedication

To my beloved parents and teachers

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Chapter 1: Introduction

The United Arab Emirates (UAE) was certified local malaria free in 2007 by the World Health Organization (WHO). Since then, the UAE government has made an exceptional effort to protect the country from any possible malaria outbreak. This effort includes the establishment of different institutions that monitor the isolated malaria cases in the country. Moreover, the health authorities implemented health regulations that required each coming immigrant to be screened for communicable diseases before guaranteeing the residency. This screening is also required for residency renewal every three years.

All this effort paid off to keep the country malaria free, except some reported cases of malaria imported by immigrants from high risk epidemic areas every year. But, the fight against malaria in the UAE in not over. There are so many environmental, economical, and demographical factors that are imposed on us not to rule out the possibility of having malaria again in the UAE.Therefore, it is important to study the impact of a possibly imported malaria on the population living in the UAE.

This thesis is a contribution to this effort by presenting an analytical study, via a mathematical modeling of malaria in the UAE. This model can be described as policy based because it takes to consideration the nature of the population in the UAE, as local and non-local, and the nature of the health policy of the country. By doing that, the aim is to make outcomes of this work accessible to the decision makers and as well as healthcare policy makers.

This thesis is organized in the following way:

First, in Chapter 2, I will present malaria as a disease and review the historical facts about malaria in the UAE by looking at all existing data of malaria in the country. This data is either of the previous local infections or the recent imported cases from epidemic areas. The goal is to give a clear motivation for this study.

Second, in Chapter 3, I will give a complete literature review of the different mathematical approaches to model malaria, starting from the first model by Sir Ronald Ross in 1911 to the most developed model, that includes different levels of complexity of the dynamic of the disease. The mathematical approaches are either single strain or multi-strain, with drug impact or immunity factor, age dependent (age structure) or spatial dependent, with environment factor or human factor, and deterministic or stochastic.

In chapter 4, I will introduce the threshold that had made the mathematical model in epidemiology a science that quantify the virulence of an infection in a population. This threshold is called **the basic reproduction number**, $\mathscr{R}_0$. I will introduce the idea behind the basic reproduction number. I will present the probabilistic approach to calculate $\mathscr{R}_0$ using the survival function equation. I will also introduce the next generation method approach to calculate $\mathscr{R}_0$. For illustration, I will use this method to calculate the basic reproduction number for a classic mathematical model of malaria.

The main result of this thesis will be presented in Chapter 5, where I will introduce my model that takes in consideration the nature of the health policies in the UAE. In this model I have three sets of populations. Local population (nationals), non-local population (immigrant) and vector-borne population (mosquitoes). I will present my well posed basic mathematical model by proving boundedness and positivity. I next calculate the basic reproduction number $\mathscr{R}_0$ using the next generation method. I also calculate the basic reproduction number related to sub-population: locals $\mathscr{R}_0^L$ and non-locals $\mathscr{R}_0^N$. Hence I will find the relationship between three thresholds. Next, I will use very well-known results of the next generation method to give the stability results. Finally, I will also find the conditions of existence of possible endemic equilibrium with respect to $\mathscr{R}_0$.

To illustrate the outcomes of my analytical study, I will give, in Chapter 6, time series simulations of my model using existent parameters estimation. The simulation will confirm the mathematical finding by showing the results of a possible malaria epidemic in the UAE, depending of the level of the infection in each sub-population. These findings are discussed in this chapter in detail. Moreover, I will also introduce the sensitivity analysis of parameters of my model and investigate the impact these sensitivity on my

variables; particularly on the burden of infection. All the simulations were done with **R** software [78] with different open source packages [18, 89].

I will finish this work by a conclusion in which I will try to cover all aspects of my work. I will also present some possible extension of this work.

All the definitions which will be used in my model will be presented in Appendix 1. All the codes used in this thesis will presented for the reader in Appendix 2.

Chapter 2: Introduction to Malaria and Malaria in the United Arab Emirates

2.1 Malaria Disease

All over the globe specialists of infectious diseases including epidemiologists, public health professionals and ecologists are always concerned about the spread and the impacts of diseases on human life and ecosystems. Malaria is one of these infectious diseases with estimated annual mortality rate ranging from 700,000 to 2.7 million people, with more than 75% children and pregnant women with low immunity [59]. The word malaria is originally an Italian word which means bad air. It was described as symptoms in ancient writing, including Chinese, Indian, Greek, and Roman [14]. In 2008, 109 countries, in the tropical and subtropical regions, were declared malaria endemic areas, whereas some counties like the United Arab Emirates was certified as malaria free since 2007 [30, 59].

Malaria as a vector borne disease needs two hosts to complete the life cycle of the causing parasite which are the vector (mosquitoes) and the humans [14]. Protozoan parasite of genus *Plasmodium* is the main cause for malaria disease which is transmitted between humans through the bite of mosquitoes [14, 53]. There are four species of this parasite that cause malaria in humans which are *P. falciparum*, *P. vivax*, *P. malariae* and *P. ovale* and other species that cause malaria in animals [14]. *P. falciparum* which is responsible for nearly 80% of all recorded malaria cases all over the world and 90% of deaths is very common in the tropical areas of Africa and South East Asia [59].

Plasmodium species that infect humans with malaria have three main stages in their life cycle: one is in the mosquito host and the other two are in the human body specifically in the liver and blood [14]. The completion of *Plasmodium* parasite life cycle depends on environmental factors such as temperature and humidity with optimal temperature between $20°C$ and $300°C$ and relative humidity exceeding 60% [14]. As for

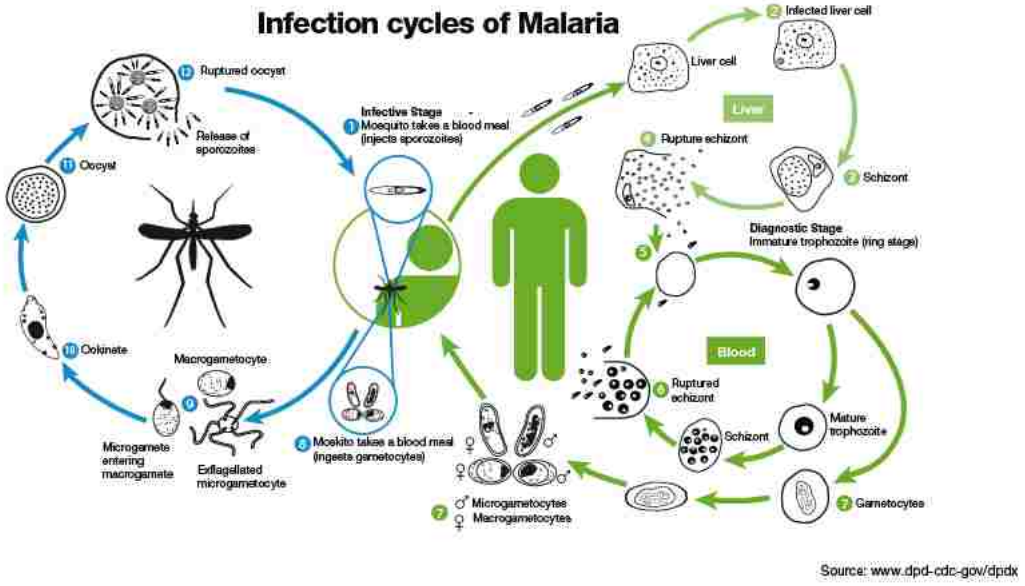


Figure 2.1: Malaria Parasite Life Cycle

the mosquito life cycle, it develops through four main stages which are egg, larva, pupa and adult and these stages are temperature and water dependent [14]. The increase in the mosquito population is the result of warmer temperature and rainfall where the first speeds up the development of mosquito from egg to adult and the second increases the breeding sites of mosquitoes [14].

The transmission of malaria to humans is usually by the bite of infected female *Anopheles* mosquitoes [14]. However, it can be transmitted directly from humans to humans in several ways such as blood transfusions, needle sharing and vertically from mother to child, but these types of transmission are considerably lower than those through mosquitoes [14]. The malaria disease is divided into two types: uncomplicated malaria and severe malaria [14]. The symptoms for the uncomplicated malaria include periodic temperature with headache, shivering, muscle pains, diarrhea and vomiting with attacks appearing in 2 to 3 days depending on the *Plasmodium* specie or even after number of years for some cases [14]. On the other hand, severe malaria can be associated with severe organ failure which happen to people with low or no immunity and the symptoms are severe anemia with 30% of red blood cells being infected and can be lethal without transfusion, cerebral malaria which is characterized by abnormal behavior and coma and can cause 20% mortality even if treated and also kidney failure [14]. Diagnosing patients

with malaria could be difficult task, since the symptoms of uncomplicated malaria are similar to other diseases. Hence it is easy to have fault first hand diagnosis. Therefore several blood smears are needed to confirm the presence of the parasite [14]. The microscopic diagnosis is the main method to diagnosis the disease. Other methods, including antigen detection and molecular diagnosis, are available but they are expensive and not very commonly used in the endemic malaria regions [14].

Early diagnosis and efficient treatment of malaria would result in cure or increase the survival chances for the malaria patients [14]. There is a variety of drugs that eliminate the blood-borne parasites, for example: chloroquine, sulfadoxine-pyrimethamine, mefloquine. Due to higher prices and serious side-effects of the other drugs; chloroquine is the prime medication for the malaria disease in the endemic regions [14]. The extensive use this particular drug in these endemic regions led development of drug resistance [14].

The control measure to reduce the burden of malaria can be summarized in the destruction of mosquitoes breeding site by regular inspection, indoor residual spraying to increase the chance of killing infected mosquitoes, using insecticide-treated bed nets which has succeeded in decreasing the number of bites and the transmission of the disease and other methods as producing drugs and vaccine to eliminate the parasite [14, 53]. These control strategies are faced with different types of problems such as lack of resources in the endemic regions affecting the productivity and the poor economy of these countries due to spending a large proportion of the annual income on the public health system to cure malaria cases [14, 59]. In addition, there is a continuous increase of the number of drug-resistant strains of *Plasmodium* and insecticide-resistant mosquitoes, which represent other obstacles facing the control of malaria [14]. Human activities, overpopulation, urbanization and specially climate change are other serious problems related to the spread of malaria [14, 59].

2.2 Malaria in the UAE

The UAE was one of the endemic areas of malaria disease; however, this small country battled strongly and came up with different strategies and plans, with the help of

the citizens, to be the first country to be certified local malaria free in 2007. Singapore and Australia in the 1980s become certified by the World Health Organization (WHO) and became the example for other countries [30, 87]. Prior to the early 1970s, the areas of Ras Al Khaimah, Sharjah, Fujairah, the east along the Omani border and the central plateau were highly endemic with main *Plasmodium* parasites being *P. falciparum*, *P. vivax* and *P. malariae*. However, the other parts of the country, on the coastal line, starting from Abu Dhabi to Umm Al Quwain and Ajman and including the oasis areas of Al Ain had a low rate of malaria transmission [30, 87]. As for the mosquitoes vector hosts, two particular species existed: *Anopheles stephensi* and *Anopheles culicifacies* that breed mainly in deep wells, shallow wells, basins, drums and irrigation channels [30, 87].

Throughout 30 years of applying many antimalarial plans and strategies, the UAE was able to accomplish the goals of being local malaria transmission free. These strategies included annual spraying of DDT at the densely populated areas and near the breeding sites before it was banned in 1975 and reintroduced again as DDT indoor residual spraying (IRS) [87]. Also, distributing chloroquine as part of mass drug administration by the school health department and other types of drugs and vaccines was one of methods used to reduce the transmission of malaria disease in the country especially for children [87]. Establishment of the Central Malaria Department (CMD) in the late 1970s in Sharjah with clinics and laboratories across the country the most important factor that contributed in the early detection of malaria by understanding the nature of the disease in the UAE and deciding on the the best approach for controlling malaria transmission [30, 87]. In addition, having the national health budget support for controlling malaria disease in the country increased yearly made huge difference [30, 87]. Moreover, the introduction of larvivorous fish (A. *dispar* and *Tilapia*) assisted the elimination and reduction of the mosquito population from early stages [87]. Other plans were also put in action until the full eradication of local malaria where the last reported local malaria case was in Masfout in July 1997 [30].

The battle with malaria in the UAE did not end due to the increased number of yearly reported imported malaria cases. The number of imported malaria cases in recent

years was between 2000 to 3000 cases yearly due to several reasons or factors [2]. These reasons include the trade movements, tourism and importing workers from other endemic counties especially from the Indian subcontinent countries [30]. Another major factor to consider, is the global climate change, fluctuation in temperatures, change of rainfall patterns and melting ice that rise the sea level annually, as well as other environmental factors that may negatively influence the world map of malaria [87]. The UAE government is currently concerned with the environmental impacts of continuous development and destroying the natural habitats in the UAE due to the fact that the UAE has one of the highest ecological footprints in the world. Therefore, the UAE is continuously alert to avoid any type of epidemic specially malaria [30].

In order to have a better perspective of the malaria disease history in the UAE, several data and figures were collected from the literature and available data and discussed chronologically. World Health organization (WHO) does an annual assessment of various diseases for different countries to understand the actual situation and give suitable suggestions and recommendations about certain diseases. One of these studies was done in 1983 to evaluate the burden of the malaria disease in the UAE. The report [24] contained a detailed information about malaria epidemiological data, the used detection methods, following procedures, and the difficulties faced in different areas in the UAE. From this report, two figures were plotted to represent the number of reported malaria cases in 1982 in different areas of the UAE, figure 2.2, and the *P. falciparum* malaria cases in the same areas, figure 2.3, since *P. falciparum* is the parasite causing malaria. Al Ain area had the largest number of reported malaria cases with highest *P. falciparum* cases of all other regions. A main reason for the high number in Al Ain is due to open borders with Oman and easy mobility. On the other hand, Abu Dhabi had the lowest number of malaria cases in the UAE. As noticed in the figures 2.2 and 2.3, there are two main peaks in May and November where the numbers of malaria cases increase rapidly.

Dar et al. [20] showed several data, figures, and tables that described malaria cases in Al Ain region specifically. It was reported in [20] that the last local transmission case of malaria in Al Ain district was in 1981. All the UAE nationals' cases were caused

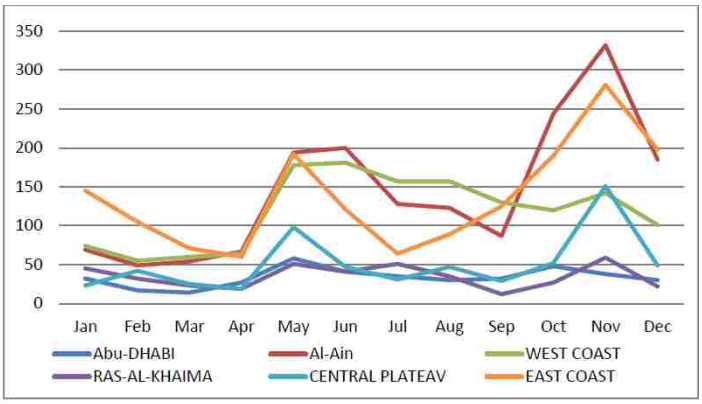


Figure 2.2: UAE Reported Malaria Cases in 1982

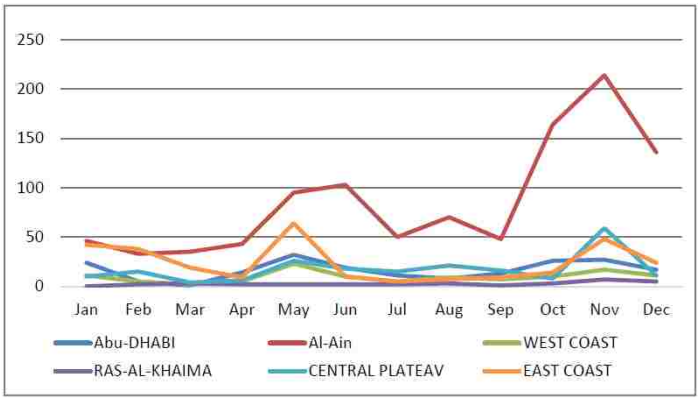


Figure 2.3: 1982 *P. falciparum* UAE Malaria Cases

by other means, either by traveling to malaria endemic countries or by getting infected by infectious mosquitoes. Figure 2.4 shows the steady increase in the number of imported malaria cases who tested positively in Al Ain between 1988 and 1991. As for table 2.5, it gives the number and percentage of imported malaria cases with their nationalities. The Pakistani nationals had the highest percentage of imported malaria cases followed by Omani and the UAE infected people. However, this does not mean that the origin of the malaria infection is the same as their nationalities; this needs more investigation to be determine. For more details see table 3 in [20].

Since there are several parasites responsible for transmitting malaria, figure 2.6 shows the number of imported malaria cases in Al Ain by causing parasite among different nationalities. It is noticeable that the leading parasite causing malaria in Al Ain is *P. falciparum* and then *P. vivax* among all nationalities except Indians where the second parasite is contributing more in the transmission of malaria.

Due to the extensive use of the drug (chloroquine) as a treatment for the malaria

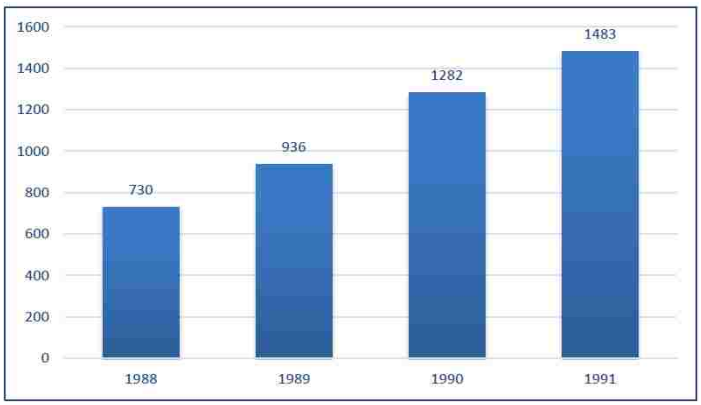


Figure 2.4: Number of Cases Tested Positively for Imported Malaria in Al Ain From 1988 to 1991

	Number of Infected			
Nationality	1988	1989	1990	1991
UAE	205 (21.9%)	171 (20.2%)	239 (18.6%)	190 (12.8%)
Omani	160 (17.1%)	215 (25.3%)	291 (22.7%)	233 (15.7%)
Sudanese	57 (6.1%)	37 (4.4%)	21 (1.6%)	18 (1.2%)
Other Arab	8 (0.9%)	14 (1.7%)	17 (1.3%)	20[a] (1.4%)
Pakistani	340 (36.3%)	310 (36.5%)	509 (39.7%)	839 (56.6%)
Indian	13 (1.4%)	11 (1.3%)	15 (1.2%)	11 (0.7%)
Others	16 (1.7%)	11 (1.3%)	32 (2.5%)	26 (1.8%)
Unrecorded	137 (14.6%)	79 (9.3%)	158 (12.4%)	146 (9.8%)
Total	936 (100%)	848 (100%)	1282 (100%)	1483 (100%)

[a] 7 Egyptians, 4 Somalis, 3 Jordanians, 3 Mauritanians, 2 Yemenis, and 1 Tunisian

Figure 2.5: Imported Malaria Cases of Various Nationalities in Al Ain From 1988 to 1991

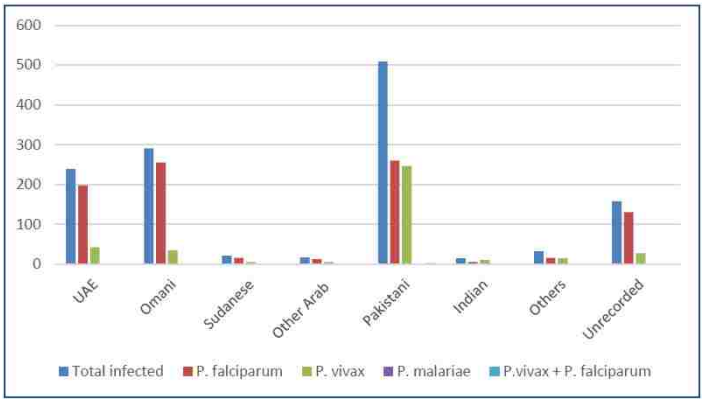


Figure 2.6: Display of 1990 *Plasmodium* Species Diagnosed Amongst the Various Nationalities in Al Ain

disease, *P. falciparum* developed resistance towards it. In 1984, the cases of drug-resistance started to show up in Al Ain region and the number is on the rise as shown in figure 2.7.

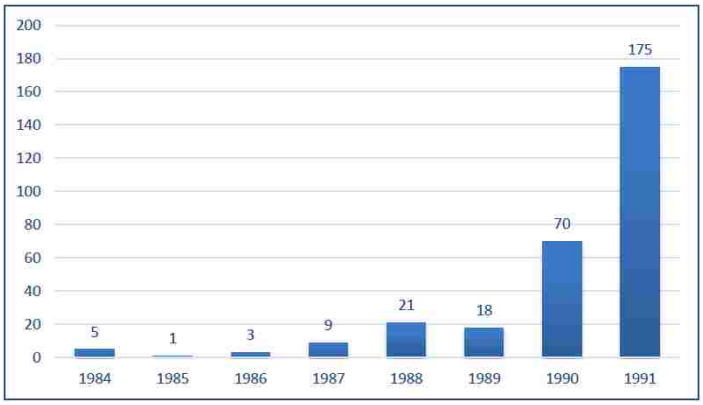


Figure 2.7: Chloroquine-resistant *P. falciparum* Malaria Cases in Al Ain, UAE From 1984 to 1991

A study was conducted in Rashid Hospital in Dubai from January 2008 to December 2010. This study examined the epidemiological and clinical characteristics of imported malaria [67]. The results of this study showed that most malaria cases were caused by *P. vivax* mainly coming from the subcontinent countries of Pakistan and India (90.1%) and 7% from sub-Saharan Africa. The other causing parasites were *P. falciparum* and mixed *P. falciparum / P. vivax*. It stated that clinicians should be aware of *P. vivax* since it causes severe malaria and may not be detected for several months. Figure 2.8 displays the number of imported malaria cases in Rashid Hospital from 2008 to 2010 where most imported cases were detected in September of each year.

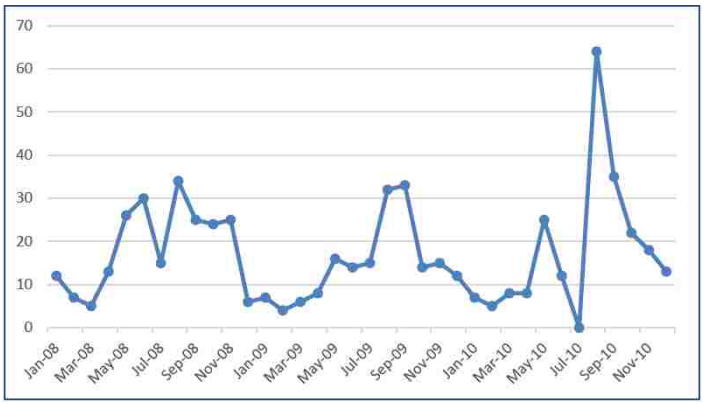


Figure 2.8: Imported Malaria Cases in Rashid Hospital From 2008 to 2010

The following data is on the imported malaria cases in the UAE [101]. These data were gathered by (WHO), and they clearly show the increase in the number of yearly

imported malaria cases as in figures 2.9 and 2.11. Top ten countries of imported malaria cases are shown in figure2.10 where most cases are from the subcontinental countries.

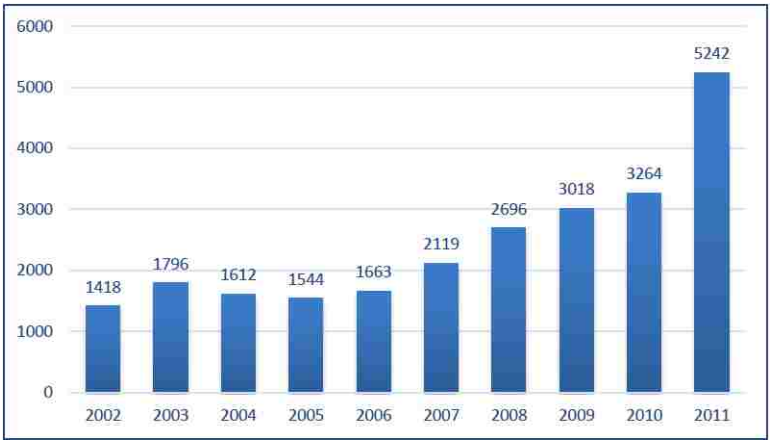


Figure 2.9: Total Imported Malaria Cases in the UAE

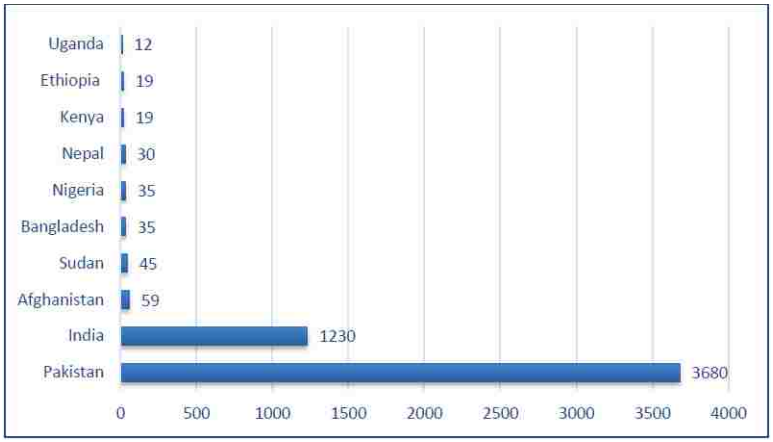


Figure 2.10: Imported Malaria Cases (Top 10 contries)

This issue needs to be taken seriously and studied properly; otherwise, there might be factors that lead to the reintroduction of local malaria transmission or malaria epidemic due to imported malaria cases.

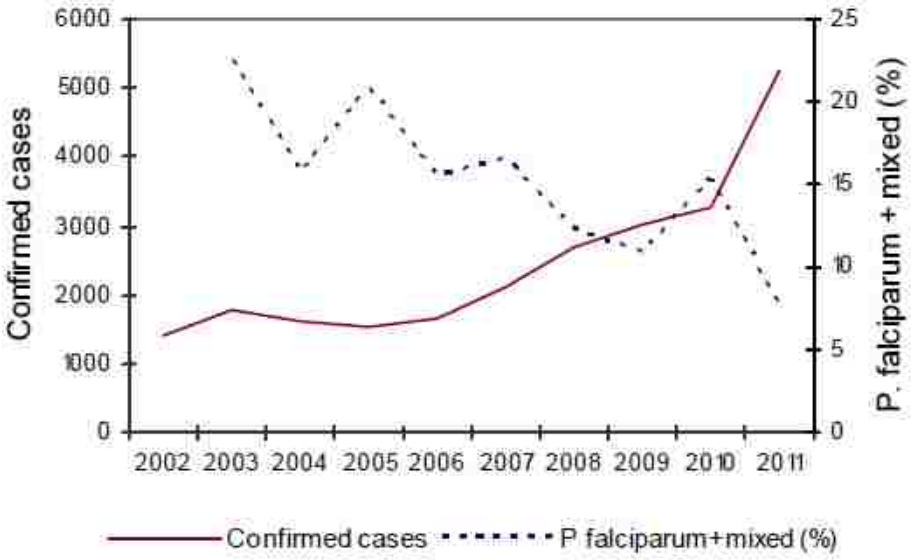


Figure 2.11: Total Confirmed Cases and % of *P. falciparum*+ Mixed Cases

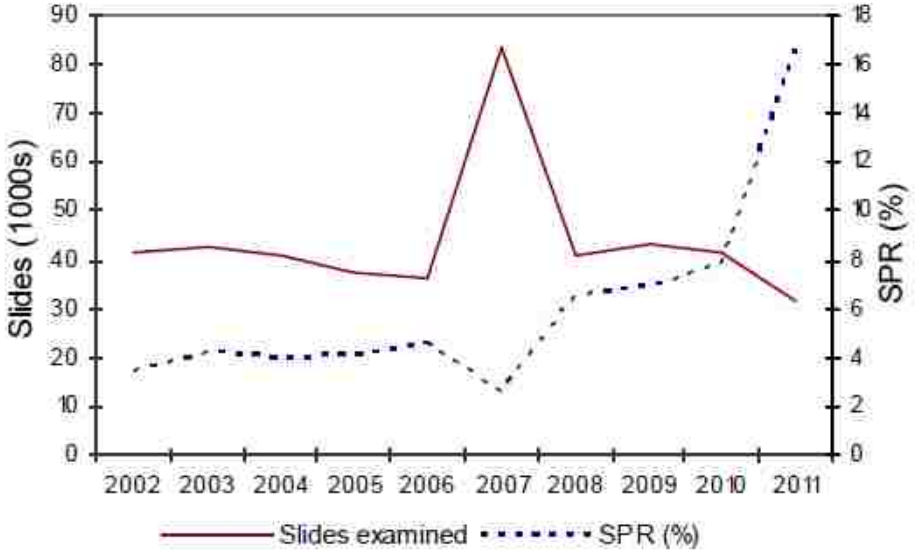


Figure 2.12: Total Slides Examined and Slide Positivity Rate (SPR)

Chapter 3: Literature Review

Malaria is an ancient disease that scientists have tried to understand its dynamics for hundreds of years because of its burden on human population all over the world. The break through happened when the mosquito role in the malaria transmission cycle was discovered by Grassi and Ross in 1897[53]. Ross was the first to publish a series of papers including a simple mathematical model that gave a better picture of interactive factors and their role in the eradication of malaria disease. Since then mathematical epidemiologists have realized the important of mathematical models in infectious diseases and, a lot of models have been built to understand the dynamics of malaria disease. Prediction of the prevalence of infectious diseases epidemic and guidance for malaria eradication and control research at the present time are the two main reasons for using mathematical models in epidemiology [53]. This chapter is an attempt to chronologically display a brief review of the history of malaria mathematical models. It is not a trivial task to describe and cover a hundred years of malaria models in one chapter, but the focus would be on the epidemiological compartment models. The basic methodology for this approach is based on deterministic differential equations mainly. There are other methodologies such as the "within hosts" models, parasite and immune cells interaction in an individual host, and population genetics models where the spread and the growth of parasite is studied with complex varying factors of human immunity and death, drugs and mosquito availability. Despite that there were recent modeling papers discussed using these methodologies and others including individual-based models, habitat-based models but the infection transmission in human and mosquito population epidemiological compartmental models remain the most used method. This chapter consists of two main parts. The first part presents the three fundamental malaria models of Ross, Macdonald and Anderson and May used as a basis for better understanding malaria as a disease. On the other hand, the second part presents the different approaches or factors used in compartmental malaria modeling based on the three fundamental malaria models mentioned in the first

part. Some of these factors include age, immunity and environmental factors that will be introduced in the second part of this chapter.

3.1 Ross Malaria Model

The first foundation of malaria models started in 1911 when Sir Ronald Ross was working on malaria cases in India [80]. He introduced the first deterministic differential equation malaria model in which the human population was structured as susceptible - infected - susceptible (*SIS*) compartmental model and the mosquito population as susceptible-infected (*SI*) model. Ross represented his model, known as the classical Ross model, as the following [53, 81]:

$$\begin{aligned} \frac{dI_h}{dt} &= abmI_m(1-I_h) - rI_h \\ \frac{dI_m}{dt} &= acI_h(1-I_m) - \mu_2 I_m \end{aligned} \tag{3.1}$$

The two differential equations are a presentation of the malaria disease compartments in Ross Model. The subscripts h and m are indicators for the human and mosquito populations, respectively. Different parameters are described in this model that include a as human biting rate, b is human infection produced by a proportion of bites, m is the ratio of female mosquitoes number to that of humans and r is human average recovery rate in the differential equation describing the infected humans. Other parameters contained in the infected mosquito compartment are c as a proportion of bites that infect mosquito and μ_2 is the per-capita mosquito mortality rate [53]. The basic features of malaria disease transmission were studied through the simple model of Ross. It concluded that reducing the number of mosquitoes to a certain level (transmission threshold) would decrease malaria transmission. This led to first thoughts of mosquitoes control programs. An important factor which is the survival and the latency period (defined as infection period up to the starting of infectious state where the parasite is in the exposed compartment) of the parasite in the mosquito was not considered in Ross model [53].

3.2 Macdonald Malaria Model

In 1950's George Macdonald reemphasized the importance of mathematical epidemiology and extended Ross model to a model that considered mosquito latency by adding the exposed compartment in the mosquito population. The human population remained as in the Ross model with susceptible-infected-susceptible (*SIS*) structure while the mosquito population was modified as susceptible-exposed-infected (*SEI*) model. The disease compartments included three variables that were I_h: infected humans, E_m exposed mosquito and I_m infected mosquito. All the parameters described in the Macdonald model are exactly the same as in Ross model with the addition of τ_m as the mosquito latent period. This model provided a better understanding of malaria cycle and proposed that the survival of adult mosquito is the weakest link in the cycle. This led to a massive malaria eradication campaign by the World Health Organization (WHO) by concentrating on the use of DDT as an insecticide to eliminate mosquito in Africa [49, 53, 71]. Macdonald model is represented in the following differential equations [48, 49, 50, 53]:

$$\begin{aligned}
\frac{dI_h}{dt} &= abmI_m(1-I_h) - rI_h \\
\frac{dE_m}{dt} &= acI_h(1-E_m-I_m) - acI_h(t-\tau_m)[1-E_m(t-\tau_m)-I_m(t-\tau_m)]e^{-\mu_2\tau_m} - \mu_2 E_m \\
\frac{dI_m}{dt} &= acI_h(t-\tau_m)[1-E_m(t-\tau_m)-I_m(t-\tau_m)]e^{-\mu_2\tau_m} - \mu_2 I_m
\end{aligned} \tag{3.2}$$

3.3 Derivation of the Basic Reproduction Number $\mathscr{R}_0$ as a Transmission Threshold

In 1982, Aron and May [7] described the Ross model and its properties. Also, they calculated the value of the basic reproduction number, $\mathscr{R}_0$, using the simple definition of Anderson and May of $\mathscr{R}_0$ described in chapter 4:

$$\mathscr{R}_0 = \frac{ma^2bc}{r\mu_2}.$$

where am is the number of contacts of one human with mosquitoes per unit time, assuming that the probability of transmission to be c from infectious human to susceptible mosquito and $1/r$ is the average duration of human infectious period. Thus, the number of infected

mosquitoes due to one infectious human over the entire infectious period is (mac/r). Likewise, a represent the number of contacts of one mosquito with humans per unit time; b is the transmission probability of infectious mosquito to susceptible human and $1/\mu_2$ the average duration of female mosquito infectious period. Therefore, (ab/c) is the number of infected humans due to one infectious mosquito over its infectious lifetime. $ma^2bc/r\mu_2$ is a product describing the number of infected humans caused by one infectious human, through a generation of infectious mosquitoes [14].

For Macdonald's model, the value of $\mathscr{R}_0$ is

$$\mathscr{R}_0 = \frac{ma^2bc}{r\mu_2}e^{-\mu_2\tau_m}$$

It is noticeable that if the value of τ_m is zero, then the reproduction number of Macdonald's model is $\mathscr{R}_0$ of Ross's Model.

3.4 Anderson and May Malaria Model

In 1991, Anderson and May also extended Macdonald malaria model naturally by including infection latency rate of humans that is represented by adding the exposed compartment to human population [4, 53]. The model divided both human and mosquito population into three compartments: susceptible S, exposed E and infected I compartments. $SEIS$ is the model structure for the human population while the mosquito population is represented in SEI compartmental model. The disease compartments for Anderson and May malaria model are exposed humans E_h, infected humans I_h, exposed mosquitoes E_m and infected mosquitoes I_m. Two parameters; μ_1 as a per-capita human mortality rate and τ_h as parasite latent period in human; were added to the model with the other parameters as in the previous models. The representation of Anderson and May model and its basic reproduction number $\mathscr{R}_0$ as follows:

$$\begin{aligned}
&\frac{dE_h}{dt} = abmI_m(1-E_h-I_h) - abmI_m(t-\tau_h)[1-E_h(t-\tau_h)-I_h(t-\tau_h)]e^{-(r+\mu_1)\tau_h} \\
&-rE_h - \mu_1 E_h \\
&\frac{dI_h}{dt} = abmI_m(t-\tau_h)[1-E_h(t-\tau_h)-I_h(t-\tau_h)]e^{-(r+\mu_1)\tau_h} - rI_h - \mu_1 I_h \\
&\frac{dE_m}{dt} = acI_h(1-E_m-I_m) - acI_h(t-\tau_m)[1-E_m(t-\tau_m)-I_m(t-\tau_m)]e^{-\mu_2\tau_m} - \mu_2 E_m \\
&\frac{dI_m}{dt} = acI_h(t-\tau_m)[1-E_m(t-\tau_m)-I_m(t-\tau_m)]e^{-\mu_2\tau_m} - \mu_2 I_m
\end{aligned} \tag{3.3}$$

$$\mathscr{R}_0 = \frac{ma^2bc}{r\mu_2}e^{-\mu_2\tau_m}e^{-\mu_1\tau_h}$$

3.5 Extensions of Malaria Mathematical Models

The three models (3.1),(3.2) and (3.3) are considered the foundation models for malaria transmission where more detailed models originated from them; see figure 2 in [53] or figure (3.1). There was a number of mathematicians and epidemiologists who were interested in modeling malaria disease from different point of views and various factors. Some of the studied factors were age, immunity, environment, social-economical factors, host-pathogen variability, resistant strains, migration and visitation factors [53]. These models used different approaches to answer their questions. Some of these models were designed as deterministic models while other models used stochastic or data based statistical models depending on the questions asked. The next paragraphs will mention some papers and their contributions to mathematical modeling of malaria disease.

3.5.1 Age Structure Models

Age and gender play essential roles in the malaria transmission burden. From early malaria surveys and papers, it was noticeable that most reported mortality cases were under the age of 5 in malaria endemic regions and the contentious exposure of the disease, gave the adults some kind of immunity to the disease. On the other hand, humans

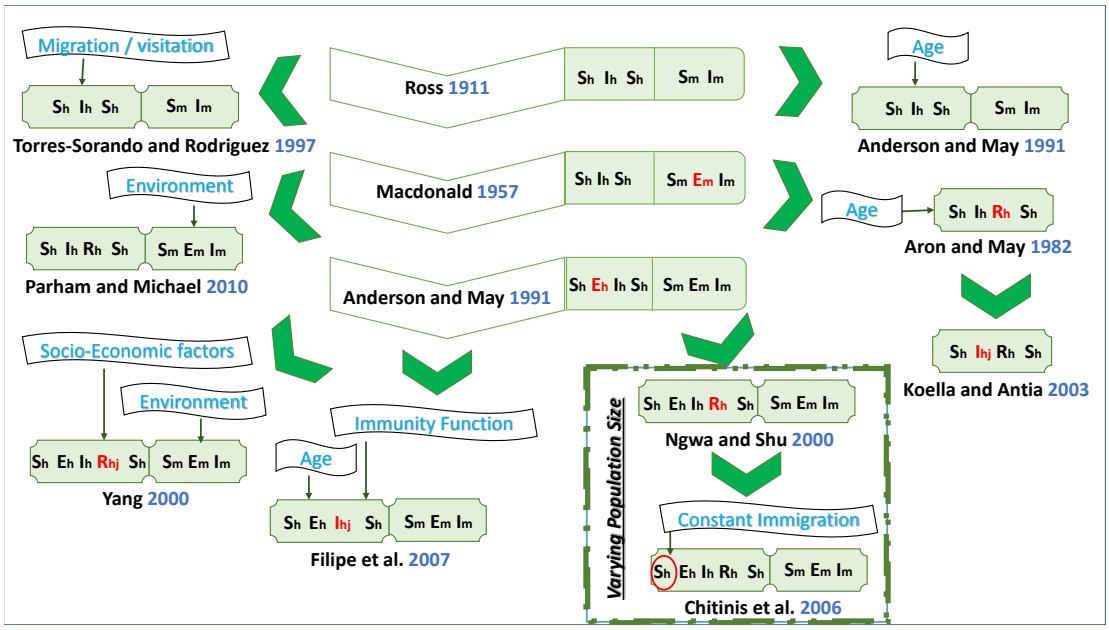


Figure 3.1: Malaria Models History

of different ages were susceptible to malaria in non-endemic areas due to non-continuous exposure to the malaria disease which led to the increase of malaria burden. This was studied in several papers such as Aron and May, 1982 [7]; Anderson and May, 1991 [4] and Tumwiine et al.,2008 [91, 96]. Based on Macdonald model, Aron and May in 1982 were the first to study the influence of human age on the spread of malaria. The model consisted of three compartments; susceptible humans S_h, infected humans I_h, and introduced the recovered compartment R_h with model structure as *SIRS* model. The vertical capacity of infection defined as:"the number of potentially infective contacts an individual person makes, through the vector population, per unit time" illustrated the effect of the vector in the model [53]. The partial differential equations variables depend on both time and age. The number of parasites and immunity level in average human is measured in this model instead of calculating the number of infected humans and mosquitoes. This is considered very useful since the difference of parasitemia load in various humans is ignored in the Macdonald model [14]. The effect of including age structure in basic Ross model was studied by Anderson and May in 1991 by looking at different control strategies, considering the effect of vaccine and decreasing malaria rate of transmission [14]. Their model is represented below 3.4 where the human population density in I_h is consisted of age and time dependent function. Parameters $N(\alpha)$ and $\hat{N}$ are denoted as

human population density at age α and mosquito density, respectively; whereas the definition of the other parameters is the same as in the basic models. The infection in this model differs depending on time and age, and the inclusion of force of infection that is defined as "per capita rate of infection acquisition" based on N, $\hat{N}$, a and b improved the basic models such that infection is age dependent in human population. This result did not match the observed trend of malaria prevalence with age and the need of models that give more explicit interaction between age and immunity is a must [53].

$$\begin{aligned} &\frac{\partial I_h(\alpha,t)}{\partial t} + \frac{\partial I_h(\alpha,t)}{\partial \alpha} = abmI_m(t)[N(\alpha) - I_h(\alpha,t)] - (r+\mu_1)I_h(\alpha,t) \\ &\frac{dI_m(t)}{dt} = ac\tilde{I}_h(t)[\hat{N} - I_m(t)] - \mu_2 I_m(t) \end{aligned} \tag{3.4}$$

3.5.2 Immune Class and Immunity Functions Models

The purpose of including immunity in malaria models was specified by Koella in [45] by two main reasons. The first reason is to increase the realism of malaria models; the effects of without the immunity factor, it will be less representative of the disease. Verifying malaria vaccines to predict the findings of vaccination programs is the second propose of the inclusion of immunity in malaria models [53]. There are two approaches to include immunity in malaria models which are either adding separate immune humans class R_h or incorporating an immunity function in malaria models. Many papers included immunity as a separate R_h class such as [6, 11, 14, 22, 62, 65, 102, 103] while other models used complex immunity functions to describe immunity like the following: [9, 25, 29, 31, 69]. More derails are mentioned in the next subsections.

- Immune Class Malaria Models: Two papers by Ngwa and Shu in 2000 [65] and Ngwa in 2004 [62] described malaria compartmental model which classify human population in *SEIRS* susceptible-exposed-infected-recovered-susceptible structure while mosquito population is put in *SEI* susceptible-exposed-infected compartments. A stable threshold below disease-free equilibrium was established and another above disease-free equilibrium where the disease can persist. Note that population size in [65] varies, and it is not constant in comparison to most models. After that, an extension for the model viewed in [65] and [62] was made by Chitnis et al. [11] and Chitnis et al. [12]. They modified the model in several ways such as

generalizing the rate of mosquito bite, including constant human immigration, and eliminating the direct infectious-to- susceptible human recovery. Paper [11] showed a bifurcation analysis for the model, calculated the basic reproduction number and proved the existence and stability of the disease-free and endemic equilibria. On the other hand, a sensitivity analysis for the reproduction number and the endemic equilibrium was found in [12] to indicate the importance of parameters in disease transmission model and prevalence. The representation of both Ngwa-Shu model (3.5) and Chitnis model (3.6) and their parameters are as follows:

$$\begin{aligned}
\frac{dS_h}{dt} &= g_h N_h + \gamma R_h + r I_h - (\mu_1' + \mu_1 N_h) S_h - \left(\frac{C_{mh} a I_m}{N_h}\right) S_h \\
\frac{dE_h}{dt} &= \left(\frac{C_{mh} a I_m}{N_h}\right) S_h - (\nu_h + \mu_1' + \mu_1 N_h) E_h \\
\frac{dI_h}{dt} &= \nu_h E_h - (r + q + \mu_d + \mu_1' + \mu_1 N_h) I_h \\
\frac{dR_h}{dt} &= q I_h - (\gamma + \mu_1' + \mu_1 N_h) R_h \\
\frac{dS_m}{dt} &= g_m N_m - (\mu_2' + \mu_2 N_m) S_m - \left(\frac{C_{hm} a I_h}{N_h}\right) S_m - \left(\frac{\tilde{C}_{hm} a R_h}{N_h}\right) S_m \\
\frac{dE_m}{dt} &= \left(\frac{C_{hm} a I_h}{N_h}\right) S_m + \left(\frac{\tilde{C}_{hm} a R_h}{N_h}\right) S_m - (\nu_m + \mu_2' + \mu_2 N_m) E_m \\
\frac{dI_m}{dt} &= \nu_m E_m - (\mu_2' + \mu_2 N_m) I_m
\end{aligned} \tag{3.5}$$

Parameter	Parameter Description
g_h/g_m	birth rate of human/mosquito
γ	rate of loss of immunity
ν_h/ν_m	infectious rate from exposed class for human / mosquito
μ_1'/μ_1	density independent / dependent death rate of human
μ_d	disease induced death rate of human
μ_2'/μ_2	density independent /dependent death rate of mosquito
q	acquire immunity rate
C_{mh}	infectivity of mosquito
C_{hm}	infectivity of infected human (I_h)
$\tilde{C}_{hm}$	infectivity of immune human (R_h)
a	biting rate of mosquito on human
r	average recovery rate of human from infectious to susceptible class

N_h/N_m	total number of human/mosquito

Table 3.1: Parameters Description of Ngwa-Shu and Chitnis Models

$$\begin{aligned}
\frac{dS_h}{dt} &= \Lambda + g_h N_h + \gamma R_h + rI_h - (\mu_1' + \mu_1 N_h)S_h - \left(\frac{C_{mh} a I_m}{N_h}\right) S_h \\
\frac{dE_h}{dt} &= \left(\frac{C_{mh} a I_m}{N_h}\right) S_h - (\nu_h + \mu_1' + \mu_1 N_h)E_h \\
\frac{dI_h}{dt} &= \nu_h E_h - (q + \mu_d + \mu_1' + \mu_1 N_h)I_h \\
\frac{dR_h}{dt} &= qI_h - (\gamma + \mu_1' + \mu_1 N_h)R_h
\end{aligned} \tag{3.6}$$

Mosquito dynamics equations is the same as Ngwa model, Λ is the immigration rate of human and all other parameters are the same as in Ngwa-shu model.

- Immunity Functions Malaria Models: The earlier described models do not take into consideration the immunity acquisition processes, their types, and their role in disease transmission and progression. A model of *SEI* structure was introduced by Filipe et al. with three age specific "immunity-functions" for the infected human population. These three compartments are: infected with severe disease I_{h1}, asymptomatic patent infection I_{h2} and infected with undetectable parasite density I_{h3}. The force of infection h is imposing the effect of mosquito density. Immunity functions in this model decrease the susceptibility to clinical disease φ, accelerate the clearance of detectable parasites r_A and rise the tolerance to sub-patent infections r_{ij}. In addition, they depend on age disease transmission intensity (i.e. Rate of infectious bites per person is termed as Entomological inoculation rate). More details regarding these immunity functions and their analysis is available in the additional file 2 of [53]. The results of this model indicate that two distinct acquired immunity processes is needed for the above mentioned three reasons also for explaining the clinical and parasite immunity duration from the pattern of age prevalence [53].

$$\begin{aligned}
\frac{\partial S_h}{\partial t} + \frac{\partial S_h}{\partial \alpha} &= -h(\alpha)S_h + \phi R_D I_{h1} + r_U I_{h3} \\
\frac{\partial E_h}{\partial t} + \frac{\partial E_h}{\partial \alpha} &= h(\alpha)S_h - \tau_h^{-1} E_h \\
\frac{\partial I_{h1}}{\partial t} + \frac{\partial I_{h1}}{\partial \alpha} &= \phi \tau_h^{-1} E_h + \phi h(\alpha) I_{h2} - (R_D + \mu_d) I_{h1} \\
\frac{\partial I_{h2}}{\partial t} + \frac{\partial I_{h2}}{\partial \alpha} &= (1-\phi)\tau_h^{-1} E_h + (1-\phi) R_D I_{h1} - \phi h(\alpha) I_{h2} - r_A I_{h2} \\
\frac{\partial I_{h3}}{\partial t} + \frac{\partial I_{h3}}{\partial \alpha} &= r_A I_{h2} - r_U I_{h3}
\end{aligned} \tag{3.7}$$

with

$$R_D = fr_T + (1-f)r_D$$

and

$$h(\alpha) = (EIR)b(1-e^{-\frac{\alpha}{\alpha_0}}) = (maI_m)b(1-e^{-\frac{\alpha}{\alpha_0}})$$

Parameter	Parameter Description
$h(\alpha)$	force of infection experienced by a person of age
τ_h	latent period of human
ϕ	proportion that developed symptomatic disease
f	proportion of symptomatic cases who receive treatment
r_T	recovery rate with treatment
r_D	natural recovery rate without treatment
r_A	rate at which infectious became subpatent
r_U	rate of clearance of subpatent infection
μ_d	disease induced mortality
α_0	age at which half the total increase in exposure is achieved EIR-entomological inoculation rate
a	biting rate of mosquito on human
b	proportion of bites that produce infection on humans
m	number of female mosquitoes relative to human

Table 3.2: Parameters Description of Filipe et al. Model

3.5.3 Host-Pathogen Variability and Resistant Strain Models

Homogeneity in response to infection in the host and parasite populations is assumed in the basic malaria Model. Malaria related Populations were thought to have equal chances to developing disease, getting immunity and transmitting infection. However modern studies discovered the diversity reaction toward infection in hosts and parasite population. This was due to the extensive use of insecticide (DDT) and drugs (quinine and

chloroquine) which led to the appearance and the rise of resistance strains toward insecticides and drugs that impacted negatively on malaria control. Population heterogeneity and resistance is considered in within-host processes [53]. Parameters including variable antigenic response, immune selection, and pathogen strain structure were studied in pathogen population structure and heterogeneous host population models [33, 34, 79]. For better malaria control strategies, evolution of drug resistance were included with other factors in several models [5, 16, 23, 35, 43, 44, 51, 76]. Models of resistant-strain were studied based on the development of drug resistance through the immunity of the host [16, 44] and the inclusion of many countries adapted artemisionin combination therapy(ACT) drug policies [76]. Cost of resistance of population genetic Γ defined as "The reduction of a resistant parasite's fitness relative to that of a sensitive parasite, when neither parasite is exposed to the drug" is added to this type of models [8, 43]. The interaction between various environmental, pharmacological, and genetic factors were illustrated in model [5] to present the complex processes of drug resistance. This type of models is important to public health professionals since they address the malaria parasites evolution of drug resistance.

Resistant-strain mathematical models generally divide the infected human population I_h into two compartments of infected by drug-sensitive strain and drug-resistant strain of the parasite. A further division of infected human population was introduced in Koella and Antia model 3.8 by subdividing the drug-sensitive strain into treated and untreated compartments. Thus, the five human compartments of Koella and Antia model are: susceptible S_h, sensitive, infected and treated I_{h1}, sensitive, infected and untreated I_{h2}, infected with resistant strain I_{h3} and recovered r_h. The mosquito vector role is included in the inoculation rate of sensitive and resistant parasites. The model is presentation and variables description as below:

$$
\begin{aligned}
\frac{dS_h}{dt} &= g_h - \mu_1 S_h - (h_s + h_r) S_h - \gamma R_h \\
\frac{dI_{h1}}{dt} &= f h_s S_h - (r_{st} + \mu_1) I_{h1} \\
\frac{dI_{h2}}{dt} &= (1-f) h_s S_h - (r_{su} + \mu_1) I_{h2} \\
\frac{dI_{h3}}{dt} &= h_r S_h - (r_r + \mu_1) I_{h3} \\
\frac{dR_h}{dt} &= r_{st} I_{h1} + r_{su} I_{h2} + r_r I_{h3} - (\gamma + \mu_1) R_h
\end{aligned} \tag{3.8}
$$

$$
h_s = m b_s a^2 e^{-\mu_2 \tau} \cdot \frac{I_{hs}}{\mu_2 + a(b_s I_{hs} + b_r I_{h3})}
$$

with

$$
h_r = m b_r a^2 e^{-\mu_2 \tau} \cdot \frac{I_{h3}}{\mu_2 + a(b_s I_{hs} + b_r I_{h3})}
$$

$$
I_{hs} = I_{h1} + I_{h2}
$$

Parameter	Parameter Description
g_h	birth rate of human
μ_1	natural mortality rate of human
h_S	inoculation rate for anti malarial sensitive
h_r	inoculation rate for drug resistant
r_{st}	recovery rate from infection for treated
r_{su}	recovery rate from infection for untreated
r_r	recovery rate from infection for resistant strain
γ	rate of loss of immunity
f	percentage treated
b_s	proportion of bites that produces sensitive strain on human
b_r	proportion of bites that produces resistant strain on human
a	biting rate of mosquito on human
m	number of female mosquitoes relative to human
μ_2	mosquito death rate
τ_m	latent period of mosquito

Table 3.3: Parameters Description of Koella and Antia Model

The basic analysis of the model indicated that there is a threshold proportion of people f_c among I_{h1} class, where the resistant cannot spread below it, and eventually it will be fixed in the population above the threshold. The level of threshold is expressed as:

$$f_c = \frac{1 - 1/\Gamma}{1 - 1/\in}$$

where the "treatment effectiveness, i.e. the ratio of infection duration for the untreated and treated parasites" is denoted as $\in$ and the "cost of resistance" is defined as Γ and these two parameters would determine the domination of the drug sensitive or resistant parasite in the population. Another result from this model is that in the absence of drug or treatment; with respect to sensitive parasite, there is a reduction in resistant parasite fitness; or on the other hand, both types of parasites share the same properties, so it is impossible for them to coexist [53].

3.5.4 Environmental Factors Models

One of the factors that influences the life cycle of host-vector-parasite malaria dynamics, is the environmental factor. It is known that factors such as temperature, humidity, rainfall, and wind patterns have huge impacts on malaria disease, specially on the mosquito population density. Temperature for example has a large influence on both mosquito breeding and parasite sporogony in the vector where an increase in temperature reduces the days required for their propagation. Also, the increased concern about climate change or global warming has made more mathematical modelers to include these factors in their models by modifying the dynamics of mosquito population. The impact of changes in temperature and humidity on the transformation rate of juveniles to adult susceptible mosquito class was studied by Li et al. in 2002 [47]. In addition, several mathematical models simulation were preformed to investigate the environmental variability effect in the mosquito populations abundance including colour noise form like random fluctuation in infected mosquito population of Ross Model [10] and periodic or noisy form of infection force [4, 7, 10]. Various environmental factors were connected to malaria disease and studied at different aspects to better identify the relationship be-

tween process of pathogen transmission and climate factors like in the following articles: [39, 55, 72, 102, 103, 104] and others more. A resent paper by Parham and Michael in 2010 [72] discussed the effect of rainfall and temperature on the mosquito population dynamic where human population is structured as ($S_hI_hR_h$) susceptible-infected-recovered human with constant latency duration whereas mosquito population is consisted of susceptible S_m, exposed E_m and infected I_m compartmental classes. various parameters representing environmental factors where related to mosquito. Description of the parameters are shown in table (3.4). Mosquito birth rate is described as a function of temperature and rainfall, but other factors like the mortality rate of mosquitoes, rate of biting, sporogonic cycle duration, and infected mosquito survival probability over the parasite incubation period temperature variation dependent. The model concluded that rainfall pattern changes influence vector abundance as well as on malaria endemicity, invasion and extension. Moreover, with the existences of sufficient rainfall for vector development and survival is sustained,and the pathogen life cycle is affected by temperature which influences the spread of the disease rate [53]

$$\begin{aligned}
\frac{dS_h}{dt} &= -a(T)bI_mS_h/N_h \\
\frac{dI_h}{dt} &= a(T)bI_m(t-\tau_h)S_h(t-\tau_h)/N_h - r_h \\
\frac{dS_m}{dt} &= \lambda(R,T) - a(T)cI_hS_m/N_h - \mu_2(T)S_m \\
\frac{dE_m}{dt} &= a(T)cI_hS_m/N_h - \mu_2(T)S_m - a(T)cI_h(t-\tau_m(T))S_m(t-\tau_m(T))l_m(T)/N_h \\
\frac{dT_m}{dt} &= a(T)cI_h(t-\tau_m(T))S_m(t-\tau_m(T))l_m(T)/N_h - \mu_2(T)I_m
\end{aligned} \tag{3.9}$$

with

$$N_h = S_h + I_h + R_h$$

and

$$\lambda(R,T) = BP_E(R)P_L(R)P_L(T)P_P(R)/(\tau_E + \tau_L(T) + \tau_P)$$

Parameter	Parameter Description
R	Rainfall
T	Temperature

$\lambda(R,T)$	Adult mosquito birth rate per day
$a(T)$	biting rate of mosquito on human
b	proportion of bites that produce infection on humans
c	proportion of bites that produce infection on mosquitoes
$\mu_2(T)$	mosquito death rate
r	average recovery rate of human from infectious to susceptible class
$\tau_m(T)$	latent period of mosquito
$\tau_m(T)$	latent period of human
l_m	Survival probability of infected mosquitoes over the incubation period of the parasite
P_E, P_L, P_P	daily survival probabilities of eggs, larvae and pupae
τ_E, τ_L, τ_P	duration of egg, larvae and pupae stages respectively

Table 3.4: Parameters Description of Parham and Michael Model

3.5.5 Social and Economical Factors Models

Social and economical conditions have had enormous effects on the spread of malaria disease. Observing the world malaria map, one can clearly see that most endemic malaria countries are among the poorest. Therefore improving social and economical conditions in human population would definitely lessen the burden of malaria. As a consequence to malaria, economy would be affected on individual and society levels. It has a direct effect on individual's monthly incomes, reduces the workforce, decreases the foreign investments, trade, and tourism in the endemic malaria countries [59]. Many authors studied different social and economical factors affecting the burden of malaria. Those studies [3, 100, 46] include fertility, population growth and misdiagnosis. Most of the papers incorporate these types of factors as case studies and there are only a few that are differential equation models [53]. Based on Anderson and May malaria model, Yany in 2000 [103] included both socio-economic factors and the effect of environment in where the human population was divided into seven compartments as the following:

$$
\begin{aligned}
\frac{dS_h}{dt} &= g_h - \theta E_{h1} + \gamma R_{h3} - [h' I_m + \mu_1] S_h \\
\frac{dE_{h1}}{dt} &= h' I_m S_h - (\theta + \nu_h + \mu_1 + \mu_d) E_{h1} \\
\frac{dI_h}{dt} &= \nu_h E_{h1} - (q + \mu_1) I_h \\
\frac{dR_{h1}}{dt} &= q I_h + h' I_m R_{h2} + \nu_h E_{h2} - (\pi_1 + \mu_1) R_{h1} \\
\frac{dR_{h2}}{dt} &= \pi_1 R_{h1} - [h' I_m + \pi_2 + \mu_1] R_{h2} \\
\frac{dR_{h3}}{dt} &= \pi_2 R_{h2} + \theta E_{h2} - [h' I_m + \gamma + \mu_1] R_{h3} \\
\frac{dE_{h2}}{dt} &= h' I_m R_{h3} - (\theta + \nu_h + \mu_1) E_{h2} \\
\frac{dS_m}{dt} &= \Phi \frac{\sigma_1(T)}{\sigma_1(T) + \mu_e(T)} - [f' I_h + \mu_2 + \mu'] S_m \\
\frac{dE_M}{dt} &= f' I_h S_m - [\sigma_2(T) + \mu_2 + \mu'] E_m \\
\frac{dI_m}{dt} &= \sigma_2(T) E_m - [\mu_2 + \mu'] I_m
\end{aligned}
\tag{3.10}
$$

The human compartments are: susceptible S_h, incubating or exposed E_h, infectious I_h, immune R_{h1}, partially immune R_{h2}, non-immune but with immunologic memory R_{h3}, and incubating after reinfection E_{h2}. As for the mosquito population, it is structured as an *SEI* susceptible-exposed-infected model. Yong model parameters are stated in 3.5. Several factors like immunity, endemicity, resistance, economic conditions and temperature dependence of mosquito are development included in the model with three economic conditions (good, intermediate and poor) with further division into three temperature zones leading to different $\mathscr{R}_0$. This implies that the global climate change and social and economical factors alter the value of the basic reproduction number $\mathscr{R}_0$. The results of the model indicate that social and economical factors have more influence on the malaria transmission in endemic populations than temperature fluctuation which requires a better environmental and health care management [53]. The effectiveness of insecticide-treated nets and indoor residual spraying as a malaria control strategies were studied in [13] to conclude that the first strategy is more protective from malaria infection.

Parameter	Parameter Description
g_h	Human birth rate
μ_1	Human natural mortality rate

μ_d	Human disease induced mortality rate
θ	Natural resistance rate against malaria
h'	Force of infection produced by each infected mosquito
π_1	rate of loss of protective immunity
π_2	rate of loss of partial immunity
γ	rate of loss of immunological memory
ν_h	rate of production of gametocytes
q	acquire immunity rate
Φ	rate of oviposition
$\sigma_1(T)$	rate of becoming adult from egg
$\sigma_2^{-1}(T)$	duration of sporogony in the mosquito
$\mu_e(T)$	rate at which eggs becoming nonviable
μ_2	mosquito natural mortality rate
μ'	mosquito induced mortality rate
f'	rate of transmission of susceptible to infectious mosquito

Table 3.5: Parameters Description of Yong Model

3.5.6 Migration / Visitation Factors Models

Malaria as a disease that differs regionally in three main aspects which are transmission vectors, disease causing species and malaria intensity level [26]. One of the factors affecting the failure of malaria eradication strategies is the negligence of the host mobility patterns. These movement patterns which are responsible for infection transmission consist mainly of migration (i.e., human movement from region to another with no return) and visitation (i.e, returning to the original region after vi malaria intensity but can be controlled if the effect of both visitation and migration are well studied and understood [53, 54, 90]. Torres-Soranando and Rodriguez in 1997 were of one the mathematicians who modified the classical Ross model to include the effect of both visitation and migration in their multipatch model. Two models were designed to study the effects of both migration as in the first set of differential equations and visitation as in the second one in

malaria transmission.

$$\begin{aligned}
\frac{dn_i}{dt} &= \sum_{j\neq i} e_{ij}n_j - \sum_{j\neq i} e_{ij}n_i \\
\frac{dI_{hi}}{dt} &= abmI_{mi}[n_i - I_{hi}] - rI_{hi} + \sum_{j\neq i} e_{ji}I_{hj} - \sum_{j\neq i} e_{ij}I_{hj} \\
\frac{dI_{mi}}{dt} &= acI_{hi}[\frac{M}{A} - I_{mi}] - \mu_2 I_{mi}
\end{aligned} \tag{3.11}$$

$$\begin{aligned}
\frac{dI_{hi}}{dt} &= abmI_{mi}[n_i - I_{hi}] - rI_{hi} + \sum_{j\neq i} abmT_{ij}[n_i - I_{hi}]I_{mj} \\
\frac{dI_{mi}}{dt} &= ac(I_{hi} + \sum_{j\neq i} I_{hj}T_{ji})[\frac{M}{A} - I_{mi}] - \mu_2 I_{mi}
\end{aligned} \tag{3.12}$$

It is assumed that only humans move between patches and the distribution of mosquitoes is even. The parameters included in these differential equations are as follows: a is mosquito biting rate on human, b is proportion of bites that produces infection on humans and c is proportion of bites that produces infection on mosquitoes. μ_2 and μ_1 are mosquito and human death rate, respectively. Human average recovery rate is denoted as r while M is the total mosquito density, and A is the number of fragmentation of the total area Migration intensity from i^{th} patch to j^{th} patch and visitation time is given by e_{ij} and T_{ij}. It resulted in the enhancement of the persistence of the disease by increasing the mobility without any changes in prevalence and faster reach to equilibrium with higher level of migration. In case of visitation, there is an increase in the equilibrium prevalence in time of increased visitation and a decrease in time reaching the equilibrium with the rise in the intensity of visitation [53, 95].

3.5.7 Stochastic Models

Despite the facts that most of malaria models are designed as deterministic models, some recent papers have used stochastic models in order to give different and more realistic aspects of the dynamics of malaria transmission. This type of models provides more information for the public health decision makers to illustrate more policies than deterministic models. Stochastic models approach solve several drawbacks of deterministic models by considering integer state values, whereas the fractional state valve is allowed in deterministic models. Deterministic models are considered as an unrealistic approach

because of the improbability of half a human. Also, in the deterministic models, the system behavior is smoothed such that jumps in state variables as in real life is impossible to detect as one person gets infected. Deterministic simulation with the same initial conditions will produce the same result every time which is mathematically correct but not the real representation of epidemic situation [41]. The studies done by Marine in 2008 [52] and Plucinski et al. in 2011 [75] showed, via stochastic models, that for a general *SIS* disease model, a population can enter a disease or poverty trap or exist from it with usage of suitable economical and health motivation. However, essential changes for the initial conditions and parameters are needed for the deterministic models to be out of the poverty trap [91]. These models can be used to study malaria transmission with minor modifications but in general are harder to handle than deterministic ones [91]. Due to natural complexity of the different factors, interaction in malaria disease cycle, the stochastic behavior is a more appropriate assumption. In some individual based models, stochasticity of individual variability was included while keeping the main structure similar to compartmental differential equation based models such as in [32, 85]. Also, other models included stochasticity or probability in various variables and parameters to study the transmission of the disease with different environmental factors [53]. Some of these models are in [17, 19, 28, 73, 83, 85, 86] discussed stochastic integration with other factors such as the structure of spatial contact, temporal forcing and presented interesting malaria transmission features.

3.5.8 Other Types of Malaria Models

The complexity of the malaria disease cycle and its dependency on two hosts: humans and mosquitoes, made mathematical epidemiologists look at malaria in different aspects, using different represented mathematical methods, including various factors and parameters and on different scales and areas. Some models were designed in continuous time such as in [11, 65, 92, 93] while others, in discrete time [77]. Also, statistical based malaria models and stochastic based models play an essential role in forecasting malaria epidemics and public health management as mentioned before. Two of the early malaria papers based on statistics are [84] and [27] whereas for the stochastic based models [61]

is considered as one of the earliest papers. Variable human and mosquito population was shown in some extended models such as [11, 65], while delay inclusion was demonstrated in [64]. With the rise of anti-malaria drug resistance in malaria endemic regions, this factor was modeled in several papers like: [16, 70, 76]. Some researchers were motivated to understand the parasite population dynamics within the human [15, 37, 38, 40, 56, 57, 58, 66]. Vector transmission with the exclusion of the disease was the interesting factor to be studied in both [63, 68] papers. At the end of reviewing the different types of malaria mathematical models, I can not say that there is A model that combines all of these factors and maybe new discovered factors in the future in one set due the complexity of malaria disease. However, these models have helped much in understanding the disease dynamics and suggested some successful eradication and control strategies.

Chapter 4: Basic Reproduction Number $\mathscr{R}_0$

The Basic Reproduction Number $\mathscr{R}_0$ is one of the most fundamental concepts in mathematical epidemiology. The origin of $\mathscr{R}_0$ concept was to study demographics (B*ö*ckh 1886, Sharp and Lotk 1911 and others) [36]. Ross 1911 and MacDonald 1952 began the study of vector-borne diseases specially malaria and used the concept of $\mathscr{R}_0$ with simple models to investigate the impact of different parameters and to find some control measures. As $\mathscr{R}_0$ concept is used in several other fields such as infectious diseases, ecology and in-host dynamics, the definition of $\mathscr{R}_0$ differs accordingly. A general definition of $\mathscr{R}_0$ is " the expected number of secondary individuals produced by an individual in its life time" [36]. My main field of interest is epidemiology, so the definition of $\mathscr{R}_0$ is as follows: " the expected number of secondary infection produced by an index case in a completely susceptible population".

There are arguments regarding the naming of $\mathscr{R}_0$; as some researchers use reproductive rate or ratio instead of reproduction number, but both are accepted [99]. As for differential equation models, $\mathscr{R}_0$ is dimensionless number [42]. The basic reproduction number can be calculated as Anderson and May illustrated in literature as the following:

$$\mathscr{R}_0 = \tau \cdot \bar{c} \cdot d \tag{4.1}$$

where τ is the transmission probability (i.e., probability of infection given contact between susceptible and infected individuals), $\bar{c}$ is the average rate of contact and $d = \frac{1}{b}$ is the infectiousness duration (b: infection rate) [42]. This equation is commonly used by biologists, but it can be applied where there are no background death rates.

$\mathscr{R}_0$ is a threshold parameter to determine the spread of the infection in the population. When $\mathscr{R}_0 < 1$ one infected individual will infect on average less than one susceptible individual, and the inclination will die out. On the other hand, if $\mathscr{R}_0 > 1$ the infection persists in the population and can cause epidemic.

There are several methods to derive $\mathscr{R}_0$ from deterministic models. The main two

methods are survival function and next generation method.

4.1 Survival Function

This method is described as the "gold standard" for determining the value of $\mathscr{R}_0$. It can be applied with different lifetime distributions even if non-constant transmission probabilities are assumed [36]. As the first principle definition of $\mathscr{R}_0$, the survival function has been extensively used in literature, and it is not restricted to ordinary differential equations systems (ODEs). Considering a large population, the survival function is descried as follows:

$$\mathscr{R}_0 = \int_0^\infty b(a)F(a)da \tag{4.2}$$

This formula (4.2) can be used in any model where $F(a)$ and $b(a)$ are definable for it. $F(a)$ is the survival probability (i.e. the probability that a new infected individual remains infectious for at least time a) and $b(a)$ is defined as the average number of new infected individuals which the infectious individual will produce per unit time when infected for total time a (i.e. infectivity as a time function) [36].

Taking the epidemic malaria model in account, the complete cycle should be considered where an infected human may infect mosquito that would transmit the infection to more humans. $F(a)$ in malaria model is the probability of an infected human at time 0 producing an infected mosquito that stays alive at least a time. Since the malaria model consists of two distinct infectious states - three or more states would become cumbersome - $F(a)$ can be represented as the integral of the following probabilities product:

$$\begin{aligned} F(a) = \textstyle\int_0^a & \text{ prob(infected human at time 0 exists at time } t) \\ & \times \text{ prob(infected human for total time } t \text{ infects mosquito)} \\ & \times \text{ prob(infected mosquito lives to be age } a-t)\ dt \end{aligned}$$

$b(a)$ in the malaria model represents the average number of new infected humans, by a mosquito which has been infected for time a. The derived $\mathscr{R}_0$ represents the total number of infected humans produced by one infected human, and it can be defined in

the same style for the mosquito. In general cases it is defined as:" the total number of infectives in the same class produced by a single infective in the class". This definition has frequently been used by Anderson and May 1991 and others and still is the standard in epidemiology and immunology. The $\mathscr{R}_0$ definition discussed in the survival function method differs from the definition of $\mathscr{R}_0$ in the next generation method that which be discussed next.

4.2 Next Generation Method

The next generation method is the most common one used in biomathematics. It is considered as an extension of survival function method where there are more than two infection classes. It was first introduced by Diekmann et al. (1990) [21].

The heterogeneous population is divided into different distinguishable homogeneous compartments, where these compartments can be classified by disease and disease-free compartments. The disease compartments include both asymptomatic and symptomatic stages of infection. Assume that there are n disease compartments and m disease-free compartments and let the subpopulation in each compartment be $x \in \mathbb{R}^n$ and $y \in \mathbb{R}^m$. Also, let $\mathscr{F}_i$ denote secondary infections rate increase in the ith disease compartment and $\mathscr{V}_i$ disease progression ,death and recovery rates decrease in the ith compartment. The compartmental model is formed as the following:

$$\begin{aligned} x_i^{'} &= \mathscr{F}_i(x,y) - \mathscr{V}_i(x,y), \quad i = 1,.....,n, \\ y_j^{'} &= g_j, \quad j = 1,.....,m \end{aligned}$$

The derivation of $\mathscr{R}_0$ in the next degeneration method is based on linearization at the disease-free equilibrium (DFE) for ODE models. In order to ensure that the model is well posed and the DFE exists, five assumptions were introduced by [99] which differ slightly from [98] as follows:

1. $\forall y \geq 0$ and $i = 1,.....,n$, assume $\mathscr{F}_i(0,y) = 0$ and $\mathscr{V}_i(0,y) = 0$.

   There is no immigration of individuals into the disease compartments since all new

infections are arising from infected hosts as secondary infections.

2. $\forall x \geq 0, y \geq 0$ and $i = 1, ..., n$, assume $\mathscr{F}_i(x,y) \geq 0$.

   The function $\mathscr{F}$ represents new infection therefore cannot be negative.

3. Whenever $x_i = 0, i = 1, ..., n$, assume $\mathscr{V}_i(x,y) \leq 0$.

   Each compartment, $\mathscr{V}_i$ is considered as a net outflow from compartment i and must be negative (inflow only) whenever the compartment is empty.

4. $\forall x \geq 0, y \geq 0$, assume $\sum_{i=1}^{n} \mathscr{V}_i(x,y) \geq 0$.

   The sum represents the total outflow from all infected compartments. Terms that lead to increases in $\sum_{i=1}^{n} x_i$ belong to $\mathscr{F}$ since it represents secondary infections.

5. let $y^{'} = g(0,y)$ be a disease free system that has a unique asymptotically stable equilibrium(i.e. as $t \to \infty$ all solutions of initial conditions $(0,y)$ goes to $(0,y_0)$. This point is called disease-free equilibrium.

Following the derivation of $\mathscr{R}_0$ as in [99], the matrix $K = FV^{-1}$ is defined as the next generation matrix for the system at DFE. The (i,j) entry of K is the expected number of secondary infections in compartment i produced by individuals initially in compartment j. $F = \frac{\partial \mathscr{F}_i}{\partial x_j}(0,y_0)$ where the (i,j) entry of F is the rate producing secondary infections in compartment i by index case in compartment j. $V = \frac{\partial \mathscr{V}_i}{\partial x_j}(0,y_0)$ where the (i,j) entry of V^{-1} represents the expected time when initial individual introduced into j disease compartment spends in i disease compartment. Then $\mathscr{R}_0 = \rho(FV^{-1})$ where ρ is the spectral radius of matrix k. For more examples on $\mathscr{R}_0$ see [98] and [99].

Definition 4.2.1. Generation in epidemic modes are waves of secondary infection which flow from each previous infection. In general, $\mathscr{R}_i$ is the reproduction number in the ith generation, $\mathscr{R}_0$ is the expected number of secondary infections produced by generation zero [42]. See the figure below.

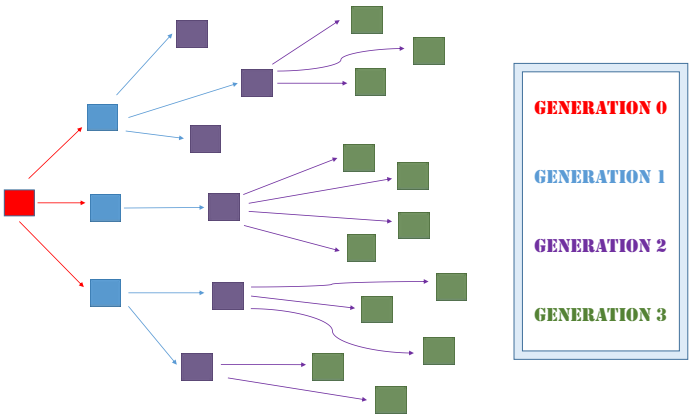


Figure 4.1: Graphical Description of Generation of an Epidemic

Example comparing the two methods for computing $\mathscr{R}_0$

As an example, consider the following malaria model is considered, where human population is considered as SIR model and mosquito population as SI model where S, I and R stand for susceptible, infected and recovered, respectivily.The malaria model of both human and mosquito populations is represented as below:

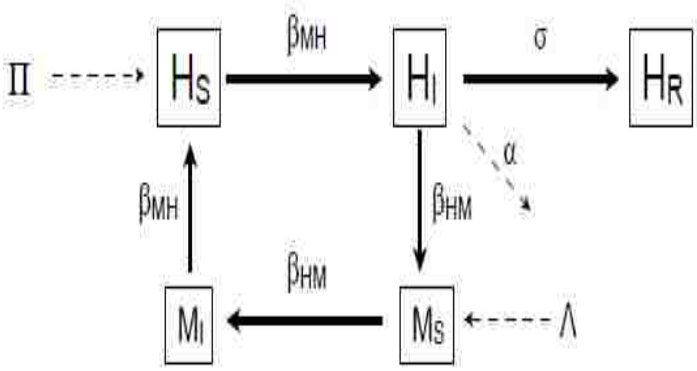


Figure 4.2: Example of Malaria Model

$$\begin{aligned} \dot{H}_S &= \Pi - \beta_{MH} M_I H_S - \mu_H H_S \\ \dot{H}_I &= \beta_{MH} M_I H_S - (\mu_H + \alpha + \sigma) H_I \\ \dot{H}_R &= \sigma H_I - \mu_H H_R \end{aligned} \tag{4.3}$$

$$\begin{aligned} \dot{M}_S &= \Lambda - \beta_{HM} M_S H_I - \mu_M M_S \\ \dot{M}_I &= \beta_{HM} M_S H_I - \mu_M M_I \end{aligned} \tag{4.4}$$

where H_I and M_I are the disease compartments, Π and Λ are recruitment rate for human and mosquito population, respectively. μ denotes natural death rate; whereas, σ is the death rate due to infection, β is the infection rate, and α is the recover rate. For this system at disease free equilibrium, using the next generation method, I have:

$$F = \begin{pmatrix} 0 & \beta_{MH} H_S(0) \\ \beta_{HM} M_S(0) & 0 \end{pmatrix}$$

and

$$V = \begin{pmatrix} \mu_H + \alpha + \sigma & 0 \\ 0 & \mu_M \end{pmatrix}$$

It is clear that V is nonsingular matrix so V^{-1} can be determined. Therefore, the value of $\mathscr{R}_{0,N}$ is

$$\mathscr{R}_{0,N} = \sqrt{\frac{\beta_{MH}\beta_{HM} H_S(0) M_S(0)}{(\mu_H + \alpha + \sigma)\mu_M}}$$

The basic reproduction number in the next generation matrix represents the mean number of new infection per infection in any class per generation. While computing the basic reproduction number for the survival function method I get:

$$\mathscr{R}_{0,S} = \frac{\beta_{MH}\beta_{HM} H_S(0) M_S(0)}{(\mu_H + \alpha + \sigma)\mu_M} = (\mathscr{R}_{0,N})^2$$

This reproduction number gives the total number of infections in the same class produced by a single infection in the class. It is important to note that the value of $\mathscr{R}_0$ is not unique and depends on both mathematical and biological interpretations.

Chapter 5: Mathematical Model of the Imported Malaria in the UAE

I am investigating a mathematical model of malaria infection with two patches of population. The local population, which will be represented with the standard *SEIRS* model, and the non-local (or immigrant), which will be represented with a simple *SEI* model. The *I* compartment in the *SI* model of mosquitoes population will be divided into two sub compartments of infected I_M^1 and infectious I_M^2.

5.1 Presentation of the Model

My model consists of two patches of human population, non-local N and local L, and the mosquitoes population M. The flowchart (5.1) represents the different compartments of my model. The local population is divided into susceptible S_L, infected but not infectious E_L, infectious I_L and recovered R_L, with $L = S_L + E_L + I_L + R_L$. The non-local population is divided into susceptible S_N, infected but not infectious E_N, and infectious I_N, with $N = S_N + E_N + I_N$. As I mentioned, I did not consider the recovery of the non-local population model, because once the immigrant is reported infected, she/he will be isolated from the population and deported from the country . The total human population is $\Sigma = L + N$. The mosquitoes population M is divided into susceptible S_M, infected I_M^1 and infectious I_M^2, with $M = S_M + I_M^1 + I_M^2$.

The local and non-local human populations are infected by the infectious mosquitoes bites. As a result the bitten person becomes infected and after an incubation period becomes infectious. The local population can recover and become susceptible again to possible infection of different mosquitoes strain. For this purpose and since I are studying imported malaria, which implies that the mosquitoes could have multi-strains, in my study, that the mosquitoes population is not strain specific. The infectious non-local individuals are removed after being screened. The susceptible mosquitoes population becomes infected after the mosquitoes bite an infectious human and that the mosquito becomes infectious. Hence, the equations below describe the dynamic of my policy-based malaria

model. Table 5.1 describes all the parameters used in this model with their units.

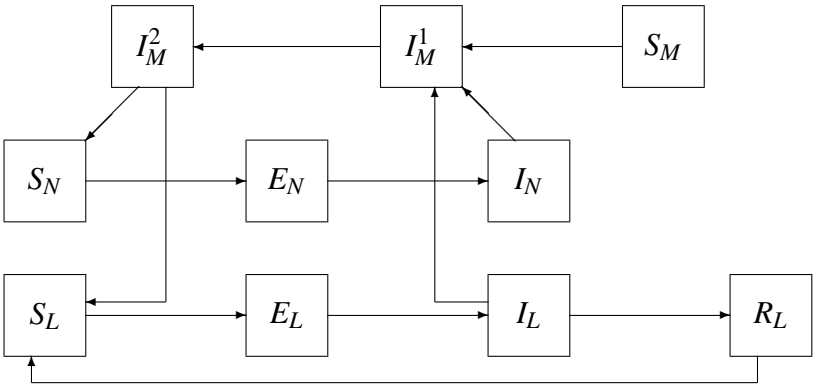


Figure 5.1: Flow Chart of the Different Compartments of my Model

The model for local population is as follows:

$$\begin{cases} \dot{S_L} &= \Lambda_L - d_L S_L - ac_1 \dfrac{S_L I_M^2}{\Sigma} + \beta_L R_L \\ \dot{E_L} &= ac_1 \dfrac{S_L I_M^2}{\Sigma} - (\nu_L + d_L) E_L \\ \dot{I_L} &= \nu_L E_L - (\gamma_L + d_L) I_L \\ \dot{R_L} &= \gamma_L I_L - (\beta_L + d_L) R_L \end{cases} \tag{5.1}$$

The non-local population model is

$$\begin{cases} \dot{S_N} &= \Lambda_N - d_N S_N - ac_2 \dfrac{S_N I_M^2}{\Sigma} \\ \dot{E_N} &= ac_2 \dfrac{S_N I_M^2}{\Sigma} - (\nu_N + d_N) E_N \\ \dot{I_N} &= \nu_N E_N - (\gamma_N + d_N) I_N \end{cases} \tag{5.2}$$

The mosquitoes population model is given by

$$\begin{cases} \dot{S_M} &= \Lambda_M - d_M S_M - ac_3 \dfrac{S_M I_L}{\Sigma} - ac_4 \dfrac{S_M I_N}{\Sigma} \\ \dot{I_M^1} &= ac_3 \dfrac{S_M I_L}{\Sigma} + ac_4 \dfrac{S_M I_N}{\Sigma} - (\nu_M + d_M^1) I_M^1 \\ \dot{I_M^2} &= \nu_M I_M^1 - d_M^2 I_M^2 \end{cases} \tag{5.3}$$

Where

$$\Sigma = L + N$$

Parameters Description and Dimension for the Core Model		
Λ_L	Birth Rate of Locals.	Human $\times$ Days^{-1}
Λ_N	Birth Rate of Non-Locals and New Immigration Rate.	Human $\times$ Days^{-1}
Λ_M	Birth and Recruitment Rate of Mosquitoes.	Mosquitoes $\times$ Days^{-1}
d_L	Death Rate of Locals.	Days^{-1}
d_N	Death Rate of Non-Locals and The Rate of Leaving Immigrants.	Days^{-1}
d_M	Death Rate of Susceptible Mosquitoes.	Days^{-1}
ac_1	Contact Rate of Susceptible Locals Contact With Infectious Mosquitoes.	Days^{-1}.
ac_2	Contact Rate of Susceptible Non-Locals Contact With Infectious Mosquitoes.	Days^{-1}
ac_3	Contact Rate of Susceptible Mosquitoes Contact With Infectious Locals.	Days^{-1}
ac_4	Contact Rate of Susceptible Mosquitoes Contact With Infectious Non-Locals.	Days^{-1}
β_L	Losing Immunity Rate of Locals.	Days^{-1}
ν_L	Rate of Exposed Locals Being Infected.	Days^{-1}
ν_N	Rate of Exposed Non-Locals Being Infected.	Days^{-1}
γ_L	Recovery Rate of Infected Locals.	Days^{-1}
γ_N	Isolation and Deportation Rate of Infected Non-Locals.	Days^{-1}
ν_M	Rate of Infected Mosquitoes Becoming Infectious.	Days^{-1}
d_M^1	Death Rate of Infected Mosquitoes.	Days^{-1}
d_M^2	Death Rate of Infectious Mosquitoes.	Days^{-1}.

Table 5.1: Parameters Description and Dimension for the Core Model

5.2 Basic Analysis

5.2.1 Boundedness and Positivity

I should first prove that all the variables of the model are non-negative, and they are biologically acceptable. To this end, I show that all of the solutions of (5.1)-(5.2)-(5.3), with initial condition in $\mathbb{R}^{10}_+$, are non-negative and bounded. For the non-negativity, following the standard argument in [94], I can prove the following:

Proposition 5.2.1.

Let $\mathbb{R}^{10}_+ = \{(s_1, s_2, ..., s_n) \in \mathbb{R}^{10} : s_i \geq 0, \forall i \in \{1, ..., n\}\}$. *Then* $\mathbb{R}^{10}_+$ *is positively invariant under the flow induced by model (5.1)-(5.2)-(5.3).*

Proof. For the boundedness, I have:

$$\dot{L} = \Lambda_L - d_L(S_L + E_L + I_L + R_L)$$

$$\dot{L} = \Lambda_L - d_L L$$

which leads to

$$\limsup_{t\to\infty} L \leq \frac{\Lambda_L}{d_L}$$

Similarly,

$$\dot{N} = \Lambda_N - \gamma_N I_N - d_N N \leq \Lambda_N - d_N N$$

Hence,

$$\limsup_{t\to\infty} N \leq \frac{\Lambda_N}{d_N}$$

Using the same process,

$$\dot{M} = \Lambda_M - d_M S_M - d_M^1 I_M^1 - d_M^2 I_M^2 = \Lambda_M - d_M^*(S_M + I_M^1 + I_M^2)$$

where

$$d_M^* = (d_M + d_M^1 + d_M^2)$$

Therefore,

$$\limsup_{t\to\infty} M \leq \frac{\Lambda_M}{d_M}$$

I conclude that my system is bounded. □

Proposition 5.2.2.

The variables of my system are bounded and I have

$$\limsup_{t\to\infty} L \leq \frac{\Lambda_L}{d_L},\ \limsup_{t\to\infty} N \leq \frac{\Lambda_N}{d_N} \textit{ and } \limsup_{t\to\infty} M \leq \frac{\Lambda_M}{d_M}$$

5.3 The Basic Reproductive Number

To determine the basic reproductive number $\mathscr{R}_0$ of the studied model, I use the next generation method approach developed in [99]. If fact I have:

$$\mathscr{F} = \begin{pmatrix} ac_1 \dfrac{S_L I_M^2}{\Sigma} \\ 0 \\ ac_2 \dfrac{S_N I_M^2}{\Sigma} \\ 0 \\ ac_3 \dfrac{S_M I_L}{\Sigma} + ac_4 \dfrac{S_M I_N}{\Sigma} \\ 0 \end{pmatrix}$$

and

$$\mathscr{V} = \begin{pmatrix} (\nu_L + d_L)E_L \\ -\nu_L E_L + (\gamma_L + d_L)I_L \\ (\nu_N + d_N)E_N \\ -\nu_N E_N + (\gamma_N + d_N)I_N \\ (\nu_M + d_M^1)I_M^1 \\ -\nu_M I_M^1 + d_M^2 I_M^2 \end{pmatrix}.$$

The Jacobian matrices of $\mathscr{F}$ and $\mathscr{V}$ are the following:

$$D\mathscr{F} = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & ac_1 \dfrac{S_L}{\Sigma} \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & ac_2 \dfrac{S_N}{\Sigma} \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & ac_3 \dfrac{S_M}{\Sigma} & 0 & ac_4 \dfrac{S_M}{\Sigma} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

then

$$D\mathscr{F}(x_0) = F = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & ac_1\dfrac{\Lambda_L}{d_L\Sigma} \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & ac_2\dfrac{\Lambda_N}{d_N\Sigma} \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & ac_3\dfrac{\Lambda_M}{d_M\Sigma} & 0 & ac_4\dfrac{\Lambda_M}{d_M\Sigma} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}.$$

Also

$$D\mathscr{V} = V = \begin{pmatrix} (\nu_L + d_L) & 0 & 0 & 0 & 0 & 0 \\ -\nu_L & (\gamma_L + d_L) & 0 & 0 & 0 & 0 \\ 0 & 0 & (\nu_N + d_N) & 0 & 0 & 0 \\ 0 & 0 & -\nu_N & (\gamma_N + d_N) & 0 & 0 \\ 0 & 0 & 0 & 0 & (\nu_M + d_M^1) & 0 \\ 0 & 0 & 0 & 0 & -\nu_M & d_M^2 \end{pmatrix}.$$

Then I have to find the inverse of V:

$$V^{-1} = \begin{pmatrix} \frac{1}{(\nu_L+d_L)} & 0 & 0 & 0 & 0 & 0 \\ \frac{\nu_L}{(\nu_L+d_L)(\gamma_L+d_L)} & \frac{1}{(\gamma_L+d_L)} & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{1}{(\nu_N+d_N)} & 0 & 0 & 0 \\ 0 & 0 & \frac{\nu_N}{(\nu_N+d_N)(\gamma_N+d_N)} & \frac{1}{(\gamma_N+d_N)} & 0 & 0 \\ 0 & 0 & 0 & 0 & \frac{1}{(\nu_M+d_M^1)} & 0 \\ 0 & 0 & 0 & 0 & \frac{\nu_M}{d_M^2\left(\nu_M+d_M^1\right)} & \frac{1}{d_M^2} \end{pmatrix}$$

$$F * V^{-1} = \begin{pmatrix} 0 & 0 & 0 & 0 & \frac{\nu_M \Theta}{(\nu_M + d_M^1)} & \Theta \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \frac{\nu_M \Phi}{(\nu_M + d_M^1)} & \Phi \\ 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{\nu_L \Upsilon}{(\nu_L + d_L)} & \Upsilon & \frac{\nu_N \Psi}{(\nu_N + d_N)} & \Psi & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

With

$$\Theta = \frac{ac_1 \Lambda_L}{d_L d_M^2 \Sigma};$$

$$\Phi = \frac{ac_2 \Lambda_N}{d_N d_M^2 \Sigma};$$

$$\Upsilon = \frac{ac_3 \Lambda_M}{d_M(\gamma_L + d_L)\Sigma};$$

and

$$\Psi = \frac{ac_4 \Lambda_M}{d_M(\gamma_N + d_N)\Sigma}$$

Now, I find the eigenvalues of $F * V^{-1}$ and then the value of

$$\mathscr{R}_0 = \sqrt{\frac{\nu_M \nu_L \Theta \Upsilon}{(\nu_M + d_M^1)(\nu_L + d_L)} + \frac{\Phi \Psi \nu_M \nu_N}{(\nu_M + d_M^1)(\nu_N + d_N)}}.$$

It is easy to see that (5.1)-(5.2)-(5.3) has unique disease free equilibrium E_0 defined by

$$E_0 = (\frac{\Lambda_L}{d_L}, 0, 0, 0, \frac{\Lambda_N}{d_N}, 0, 0, \frac{\Lambda_M}{d_M}, 0, 0)$$

Hence, using the result of [99], I have the following result:

Proposition 5.3.1. *The disease free equilibrium E_0 is locally asymptotically stable if and only if $\mathscr{R}_0 < 1$ and it is unstable if $\mathscr{R}_0 > 1$.*

5.3.1 The Value of $\mathscr{R}_0$ for the Sub-systems

- Local population with mosquitoes:

$$\mathscr{F} = \begin{pmatrix} ac_1 \dfrac{S_L I_M^2}{\Sigma} \\ 0 \\ ac_3 \dfrac{S_M I_L}{\Sigma} \\ 0; \end{pmatrix}$$

and

$$\mathscr{V} = \begin{pmatrix} (\nu_L + d_L)E_L \\ -\nu_L E_L + (\gamma_L + d_L)I_L \\ (\nu_M + d_M^1)I_M^1 \\ -\nu_M I_M^1 + d_M^2 I_M^2 \end{pmatrix}.$$

Hence

$$D\mathscr{F} = \begin{pmatrix} 0 & 0 & 0 & ac_1 \dfrac{S_L}{\Sigma} \\ 0 & 0 & 0 & 0 \\ 0 & ac_3 \dfrac{S_M}{\Sigma} & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

then

$$D\mathscr{F}(x_0) = F = \begin{pmatrix} 0 & 0 & 0 & ac_1 \dfrac{\Lambda_L}{d_L \Sigma} \\ 0 & 0 & 0 & 0 \\ 0 & ac_3 \dfrac{\Lambda_M}{d_M \Sigma} & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}.$$

Also

$$D\mathscr{V} = V = \begin{pmatrix} (\nu_L + d_L) & 0 & 0 & 0 \\ -\nu_L & (\gamma_L + d_L) & 0 & 0 \\ 0 & 0 & (\nu_M + d_M^1) & 0 \\ 0 & 0 & -\nu_M & d_M^2 \end{pmatrix}.$$

Then I have to find the inverse of V:

$$V^{-1} = \begin{pmatrix} \frac{1}{(\nu_L+d_L)} & 0 & 0 & 0 \\ \frac{\nu_L}{(\nu_L+d_L)((\gamma_L+d_L)} & \frac{1}{\gamma_L+d_L} & 0 & 0 \\ 0 & 0 & \frac{1}{(\nu_M+d_M^1)} & 0 \\ 0 & 0 & \frac{\nu_M}{d_M^2\left(\nu_M+d_M^1\right)} & \frac{1}{d_M^2} \end{pmatrix}.$$

$$F * V^{-1} = \begin{pmatrix} 0 & 0 & \frac{\nu_M\Theta}{\left(\nu_M+d_M^1\right)} & \Theta \\ 0 & 0 & 0 & 0 \\ \frac{\nu_L\Upsilon}{(\nu_L+d_L)} & \Upsilon & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}.$$

where the values of Θ and Υ as described in the main model. so the value of $\mathscr{R}_0^L$ is

$$\mathscr{R}_0^L = \sqrt{\frac{\nu_M\nu_L\Theta\Upsilon}{\left(\nu_M+d_M^1\right)\left(\nu_L+d_L\right)}}.$$

- Non local populations with mosquitoes:

$$\mathscr{F} = \begin{pmatrix} ac_2\frac{S_N I_M^2}{\Sigma} \\ 0 \\ ac_4\frac{S_M I_N}{\Sigma} \\ 0 \end{pmatrix}$$

and

$$\mathscr{V} = \begin{pmatrix} (\nu_N+d_N)E_N \\ -\nu_N E_N+(\gamma_N+d_N)I_N \\ (\nu_M+d_M^1)I_M^1 \\ -\nu_M I_M^1+d_M^2 I_M^2 \end{pmatrix}.$$

Hence

$$D\mathscr{F} = \begin{pmatrix} 0 & 0 & 0 & ac_2\dfrac{S_N}{\Sigma} \\ 0 & 0 & 0 & 0 \\ 0 & ac_4\dfrac{S_M}{\Sigma} & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}.$$

then,

$$D\mathscr{F}(x_0) = F = \begin{pmatrix} 0 & 0 & 0 & ac_2\dfrac{\Lambda_N}{d_N\Sigma} \\ 0 & 0 & 0 & 0 \\ 0 & ac_4\dfrac{\Lambda_M}{d_M\Sigma} & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}.$$

Also

$$D\mathscr{V} = V = \begin{pmatrix} (\nu_N + d_N) & 0 & 0 & 0 \\ -\nu_N & (\gamma_N + d_N) & 0 & 0 \\ 0 & 0 & (\nu_M + d_M^1) & 0 \\ 0 & 0 & -\nu_M & d_M^2 \end{pmatrix}.$$

Then I have to find the inverse of V:

$$V^{-1} = \begin{pmatrix} \frac{1}{(\nu_N+d_N)} & 0 & 0 & 0 \\ \frac{\nu_N}{(\nu_N+d_N)((\gamma_N+d_N)} & \frac{1}{\gamma_N+d_N} & 0 & 0 \\ 0 & 0 & \frac{1}{(\nu_M+d_M^1)} & 0 \\ 0 & 0 & \frac{\nu_M}{d_M^2\left(\nu_M+d_M^1\right)} & \frac{1}{d_M^2} \end{pmatrix}.$$

$$F * V^{-1} = \begin{pmatrix} 0 & 0 & \frac{\nu_M\Phi}{\left(\nu_M+d_M^1\right)} & \Phi \\ 0 & 0 & 0 & 0 \\ \frac{\nu_N\Psi}{(\nu_N+d_N)} & \Psi & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}.$$

where the values of Φ and Ψ are as noted in the core model.

$$\mathscr{R}_0^N = \sqrt{\frac{\nu_M \nu_N \Phi \Psi}{\left(\nu_M + d_M^1\right)\left(\nu_N + d_N\right)}}.$$

It is easy to conclude that

$$\mathscr{R}_0 = \sqrt{(\mathscr{R}_0^N)^2 + (\mathscr{R}_0^L)^2}.$$

Hence, the local stability of disease free equilibrium requires that $\mathscr{R}_0^N < 1$ and $\mathscr{R}_0^L < 1$, which means that the infection is not endemic in both local and non-local. On the other hand, I could have $\max(\mathscr{R}_0^N, \mathscr{R}_0^L) > 1$ to have unstable disease free equilibrium. Moreover, there is also possibility of having $\mathscr{R}_0^N < 1$ and $\mathscr{R}_0^L < 1$ but $(\mathscr{R}_0^N)^2 + (\mathscr{R}_0^L)^2 > 1$. which means the disease is not endemic per sub-population but it is endemic in whole the population.

5.4 Existence of Other Equilibrium Points

Now, I examine existence of possible equilibria point. As I mentioned previously, if there is no infection, I have a disease free equilibrium

$$E_0 = (\frac{\Lambda_L}{d_L}, 0, 0, 0, \frac{\Lambda_N}{d_N}, 0, 0, \frac{\Lambda_M}{d_M}, 0, 0)$$

If there is a malaria infection in the population, I have $I_L \neq 0$,$I_N \neq 0$ and $I_M \neq 0$. Then from the equation of local population I get:

$$R_L = \frac{\gamma_L}{\beta_L + d_L} I_L \tag{5.4}$$

$$E_L = \frac{\gamma_L + d_L}{\nu_L} I_L \tag{5.5}$$

$$ac_1 \frac{S_L I_M^2}{\Sigma} = (\nu_L + d_L) \frac{\gamma_L + d_L}{\nu_L} I_L \tag{5.6}$$

Then I use the previous equations (5.4),(5.5) and (5.6) the $\dot{S_L}$ equation, it yields:

$$d_L S_L = \Lambda_L - (\nu_L + d_L)\frac{\gamma_L + d_L}{\nu_L} I_L + \frac{\beta_L \gamma_L}{\beta_L + d_L} I_L \tag{5.7}$$

so,

$$S_L = \frac{\Lambda_L}{d_L} - [(\frac{(\nu_L + d_L)(\gamma_L + d_L)}{d_L \nu_L}) - \frac{\beta_L \gamma_L}{d_L(\beta_L + d_L)}] I_L \tag{5.8}$$

Now, from the non-local population:

$$E_N = \frac{\gamma_N + d_N}{\nu_N} I_N \tag{5.9}$$

$$ac_2 \frac{S_N I_M^2}{\Sigma} = (\nu_N + d_N)\frac{\gamma_N + d_N}{\nu_N} I_N \tag{5.10}$$

$$d_N S_N = \Lambda_N - (\nu_N + d_N)\frac{\gamma_N + d_N}{\nu_N} I_N \tag{5.11}$$

Then using the previous equations (5.9), (5.10) and (5.11) and $\dot{S_N}$ equation in my model:

$$S_N = \frac{\Lambda_N}{d_N} - (\frac{(\nu_N + d_N)(\gamma_N + d_N)}{\nu_N d_N})) I_N \tag{5.12}$$

Finally, from the mosquitoes population I get:

$$I_M^1 = \frac{d_M^2}{\nu_M} I_M^2 \tag{5.13}$$

$$ac_3 \frac{S_M I_L}{\Sigma} + ac_4 \frac{S_M I_N}{\Sigma} = \frac{d_M^2}{\nu_M}(\nu_M + d_M^1) I_M^2 \tag{5.14}$$

$$d_M S_M = \Lambda_M - \frac{d_M^2}{\nu_M}(\nu_M + d_M^1) I_M^2 \tag{5.15}$$

Therefore,

$$S_M = \frac{\Lambda_M}{d_M} - \frac{d_M^2}{\nu_M d_M}(\nu_M + d_M^1) I_M^2 \tag{5.16}$$

Considering (5.8), (5.12) and (5.16) equations and by substituting them in (5.6), (5.10) and (5.14), I get the following equations:

$$\begin{cases} \frac{ac_1}{d_L\Sigma}\{\Lambda_L - [\frac{(\nu_L+d_L)(\gamma_L+d_L)}{\nu_L} - \frac{\beta_L\gamma_L}{(\beta_L+d_L)}]I_L\}I_M^2 - \frac{(\nu_L+d_L)(\gamma_L+d_L)}{\nu_L} I_L = 0 \\ \frac{ac_2}{d_N\Sigma}\{\Lambda_N - [\frac{(\nu_N+d_N)(\gamma_N+d_N)}{\nu_N}]I_N\}I_M^2 - \frac{(\nu_N+d_N)(\gamma_N+d_N)}{\nu_N} I_N = 0 \\ \frac{a}{d_M\Sigma}(c_3 I_L + c_4 I_N)(\Lambda_M - \frac{d_M^2(\nu_M+d_M^1)}{\nu_M} I_M^2) - \frac{d_M^2(\nu_M+d_M^1)}{\nu_M} I_M^2 = 0 \end{cases} \tag{5.17}$$

Now, let $X = I_L$, $Y = I_N$ and $Z = I_M^2$, so substituting the previous system, this yields:

$$\begin{cases} \phi_1(\Lambda_L - (\alpha_1 - \beta_1)X)Z - \alpha_1 X = 0 \\ \phi_2(\Lambda_N - \alpha_2 Y)Z - \alpha_2 Y = 0 \\ (\phi_3 X + \phi_4 Y)(\Lambda_M - \alpha_3 Z) - \alpha_3 Z = 0 \end{cases} \tag{5.18}$$

With

$$\begin{gathered} \phi_1 = \frac{\Theta d_M^2}{\Lambda_L} = \frac{ac_1}{d_L\Sigma} \\ \alpha_1 = \frac{(\nu_L+d_L)(\gamma_L+d_L)}{\nu_L} \\ \beta_1 = \frac{\beta_L\gamma_L}{(\beta_L+d_L)} \\ \phi_2 = \frac{\Phi d_M^2}{\Lambda_N} = \frac{ac_2}{d_N\Sigma} \\ \alpha_2 = \frac{(\nu_N+d_N)(\gamma_N+d_N)}{\nu_N} \\ \phi_3 = \frac{\Upsilon(\gamma_L+d_L)}{\Lambda_M} = \frac{ac_3}{d_M\Sigma} \\ \phi_4 = \frac{\Psi(\gamma_N+d_N)}{\Lambda_M} = \frac{ac_4}{d_M\Sigma} \\ \alpha_3 = \frac{d_M^2(\nu_M+d_M^1)}{\nu_M} \end{gathered}$$

From the above system of polynomial equations, I can define both X and Y and then substitute them in the third polynomial in order to find the roots for the quadratic equation

$$X = \frac{\Lambda_L \phi_1 Z}{\phi_1(\alpha_1 - \beta_1)Z + \alpha_1}$$

and

$$Y = \frac{\Lambda_N \phi_2 Z}{\phi_2 \alpha_2 Z + \alpha_2}$$

so,

$$[\phi_3(\Lambda_L \phi_1 Z(\phi_2 \alpha_2 Z + \alpha_2)) + \phi_4((\Lambda_N \phi_2 Z)(\phi_1(\alpha_1 - \beta_1)Z + \alpha_1))](\Lambda_M - \alpha_3 Z)$$
$$-\alpha_3 Z[(\phi_1(\alpha_1 - \beta_1)Z + \alpha_1)(\phi_2 \alpha_2 Z + \alpha_2)] = 0$$

by factorizing the Z, I get

$$[\Lambda_L \phi_1 \phi_3(\phi_2 \alpha_2 Z + \alpha_2) + \Lambda_N \phi_2 \phi_4(\phi_1 \alpha_1 Z - \phi_1 \beta_1 Z + \alpha_1)](\Lambda_M - \alpha_3 Z)$$
$$= \alpha_3[(\phi_1 \alpha_1 Z - \phi_1 \beta_1 Z + \alpha_1)(\phi_2 \alpha_2 Z + \alpha_2)]$$

I can write this equation in the form of

$$f(Z) = g(Z), \tag{5.19}$$

with f and g defined as follows:

$$f(Z) = [\Lambda_L \phi_1 \phi_3(\phi_2 \alpha_2 Z + \alpha_2) + \Lambda_N \phi_2 \phi_4(\phi_1 \alpha_1 Z - \phi_1 \beta_1 Z + \alpha_1)](\Lambda_M - \alpha_3 Z)$$

and

$$g(Z) = \alpha_3[(\phi_1 \alpha_1 Z - \phi_1 \beta_1 Z + \alpha_1)(\phi_2 \alpha_2 Z + \alpha_2)]$$

The intersection of these two curves will be the solution of the equation (5.19). But first I need to investigate the zeros of the functions f and g and the y-intercept. The function f has two zeros which are

$$Z_1 = \frac{-\Lambda_L\phi_1\phi_3\alpha_2 - \Lambda_N\phi_2\phi_4\alpha_1}{\phi_1\phi_2(\Lambda_L\phi_3\alpha_2 + \Lambda_N\phi_4(\alpha_1 - \beta_1))} \text{ and } Z_2 = \frac{\Lambda_M}{\alpha_3}$$

The function g has also two zeros identified as:

$$Z_3 = \frac{\alpha_1}{\phi_1(\beta_1 - \alpha_1)} \text{ and } Z_4 = \frac{-1}{\phi_2}.$$

The position of these zeros will dictate the number of solutions of the equation (5.19). Notice that $C_2 = \alpha_1\alpha_2\alpha_3$ is the y-intercept and it is positive, and since Z_3 and Z_4 are negative, I conclude that g is a parabola concave up. On the other hand one zero of f, Z_2, is positive. Therefore, the position of the $C_1 = (\Lambda_L\phi_1\phi_3\alpha_2 + \Lambda_N\phi_2\phi_4\alpha_1)\Lambda_M$, the y-intercept of f, with respect to C_2 as well as the positivity of Z_1 is needed to be investigated. I notice that if $\alpha_1 > \beta_1$ then $Z_1 < 0$. In fact, according to the definition of α_1 and β_1, I have:

$$\alpha_1 = \frac{(\nu_L + d_L)(\gamma_L + d_L)}{\nu_L} \text{ and } \beta_1 = \frac{\beta_L\gamma_L}{(\beta_L + d_L)},$$

and I define

$$\frac{1}{\mathscr{R}_{LL}} = \frac{(\nu_L + d_L)(\gamma_L + d_L)(\beta_L + d_L)}{\nu_L\gamma_L\beta_L} > 1;$$

I can see that

$$\mathscr{R}_{LL} = \frac{\nu_L}{(\nu_L + d_L)} \times \frac{\gamma_L}{(\gamma_L + d_L)} \times \frac{\beta_L}{(\beta_L + d_L)} < 1$$

Hence $\alpha_1 > \beta_1$ and $Z_1 < 0$. This indicate that the only two possible cases as the following:

1. If $C_1 < C_2$, there is no feasible solution.

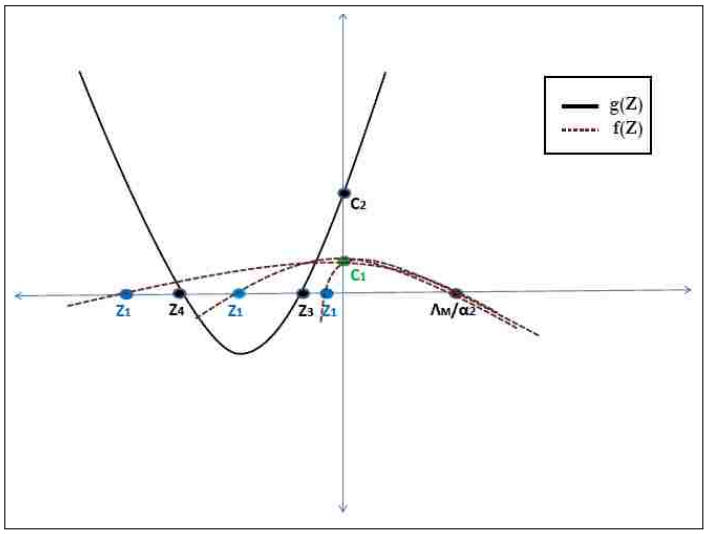


Figure 5.2: Case 1 with no Endemic Equilibrium

2. If $C_1 > C_2$, there is one solution.

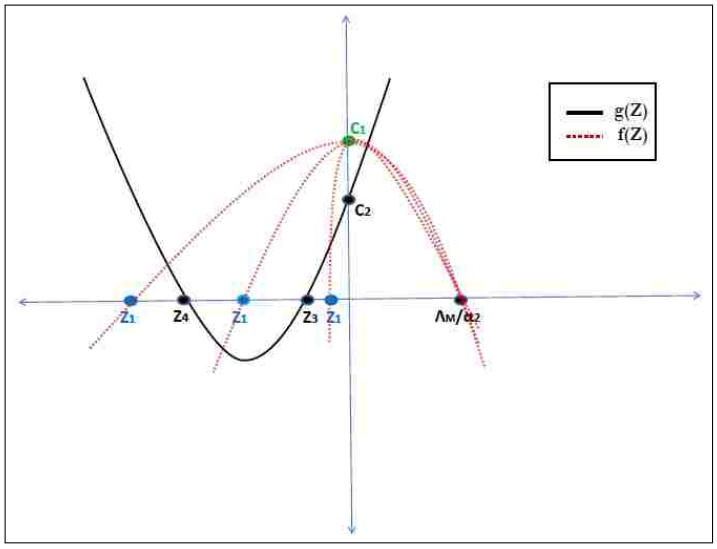


Figure 5.3: Case 2 with One Endemic Equilibrium

Computing the value of $\frac{C_1}{C_2} = \mathscr{R}_0^2$, I notice that there is one solution where $\mathscr{R}_0^2 > 1$ and no feasible solution in case where $\mathscr{R}_0^2 < 1$.

Theorem 5.4.1.

- *If $\mathscr{R}_0 < 1$, then there is no endemic equilibrium.*
- *If $\mathscr{R}_0 > 1$, then there is unique endemic equilibrium.*

Remark. 1. In case of $\mathscr{R}_0 = 1$ where $C_1 = C_2$, $z_1 = 0$. That is not the case here so it is not included.

5.5 Global Stability of the Disease Free Equilibrium

Following the method used in [99], consider that my model of malaria disease transmission can be written in the following form:

$$\begin{aligned} x' &= -Ax - \hat{f}(x,y), \\ y' &= g(x,y) \end{aligned} \tag{5.20}$$

Theorem 5.5.1. *If A is nonsingular M-matrix and $\hat{f} \geq 0$, then the disease free equilibrium of the model is globally asymptotically stable.*

Here I use the notation of M-Matrix (see Appendix 1). Using the above theorem 5.5.1, I need to show that:

1. A is nonsingular M-matrix.
2. $\hat{f} \geq 0$.

Proof. Consider that my model follows the assumptions mentioned in [99] which ensure the well posed definition of my model and the existence of disease free equilibrium. Define $A = (V - F)$ and

$$\hat{f}(x,y) = \begin{pmatrix} \frac{ac_1}{\Sigma}(S_L - S_{L0})I_M^2 \\ 0 \\ \frac{ac_2}{\Sigma}(S_N - S_{N0})I_M^2 \\ 0 \\ \frac{ac_3}{\Sigma}(S_M - S_{M0})I_L + \frac{ac_4}{\Sigma}(S_M - S_{M0})I_N \\ 0 \end{pmatrix}$$

Malaria transmission core model can be viewed as (5.20) as the following:

$$\begin{aligned}
\dot{x} &= -(V-F)x - \hat{f}(x,y) \\
\dot{S_L} &= \Lambda_L - d_L S_L - ac_1 \frac{S_L I_M^2}{\Sigma} + \beta_L R_L \\
\dot{R_L} &= \gamma_L I_L - (\beta_L + d_L) R_L \\
\dot{S_N} &= \Lambda_N - d_N S_N - ac_2 \frac{S_N I_M^2}{\Sigma} \\
\dot{S_M} &= \Lambda_M - d_M S_M - ac_3 \frac{S_M I_L}{\Sigma} - ac_4 \frac{S_M I_N}{\Sigma}
\end{aligned} \tag{5.21}$$

From Lemma 1 and Lemma 2 in [99], I know that $F \geq 0$ and V is a nonsingular M-matrix. Then $A = (V-F)$ is nonsingular M-matrix when $\mathscr{R}_0 < 1$ as it was proven in [99] . Thus, in order to satisfy the second condition; it is sufficient to prove that $S_L \leq S_{L0}$, $S_N \leq S_{N0}$ and $S_M \leq S_{M0}$. This was proven by the boundedness property of the model where:

$$\begin{aligned}
S_L &\leq \lim_{t\to\infty} sup N_L \leq \tfrac{\Lambda_L}{d_L} = S_{L0} \\
S_N &\leq \lim_{t\to\infty} sup N_N \leq \tfrac{\Lambda_N}{d_N} = S_{N0} \\
S_M &\leq \lim_{t\to\infty} sup N_M \leq \tfrac{\Lambda_M}{d_M} = S_{M0}
\end{aligned} \tag{5.22}$$

Therefore, the disease free equilibrium of the model is globally asymptotically stable when $\mathscr{R}_0 < 1$. □

Chapter 6: Numerical Simulation and Sensitivity Analysis

In this chapter, I will focus on the serial time simulation of my model as well as the numerical sensitivity of my parameters. All these simulations were done with **R** software [78, 82] and the open source packages [18, 88, 89]. The codes are available in the Appendix 2 of the this thesis.

6.1 Numerical Simulation of the Model

To illustrate the outcomes of my model and the analytical results, I will present, in the section, the simulation for different values of basic reproduction number $\mathscr{R}_0$. First, I simulate the case $\mathscr{R}_0 < 1$. Second, I will simulate the case $\mathscr{R}_0 > 1$ depending on the value of the sub-population basic reproduction numbers $\mathscr{R}_0^N$ and $\mathscr{R}_0^L$, since

$$\mathscr{R}_0 = \sqrt{(\mathscr{R}_0^N)^2 + (\mathscr{R}_0^L)^2}$$

I will choose my parameters in way to study mainly the epidemic equilibria which are:

1. $\mathscr{R}_0^L < 1$ and $\mathscr{R}_0^N > 1$ which is represented in plot by case 1.
2. $\mathscr{R}_0^L > 1$ and $\mathscr{R}_0^N < 1$ which is represented in plot by case 2.
3. $\mathscr{R}_0^L < 1$ and $\mathscr{R}_0^N < 1$ but $R_0 > 1$ which is represented in plot by case 3.
4. $\mathscr{R}_0^L > 1$ and $\mathscr{R}_0^N > 1$ which is represented in plot by case 4.

Some of the parameters were calculated in a way to fit the description of my model while the others were collected from [12]. Λ_L and Λ_N for human subpopulations were calculated in the same matter such that $\Lambda = BR + IR * \Sigma$ [12]. BR is the birth rate taken from [97] and IR is the immigration rate cited from [1]. The death rate for the human subpopulations is computed similarity where death rate and immigration rate are

taken in consideration [12]. As for the death rate of infected and infectious mosquitoes, both normal *NDR* and induced *IDR* death rate are included as the following:

$$d_M = NDR + IDR * \Sigma$$

6.1.1 Simulation of the Disease Free Equilibrium

The simulation below shows the outcomes of my model in the case of $\mathscr{R}_0 < 1$ for the following parameters. The parameters unit are presented before in table 5.1.

Parameter	Value	Reference
Λ_L	0.094	[12]
d_L	9×10^{-6},	[12]
ac_1	0.022	[12]
β_L	0.0027	[12]
ν_L	0.1	[12]
γ_L	0.0035	[12]
Λ_N	0.113	[12]
d_N	1.63×10^{-5}	[12]
ac_2	0.022	[12]
ν_N	0.1	[12]
γ_N	0.0035	[12]
Λ_M	0.13	[12]
d_M	0.033	[12]
ac_3	0.24	[12]
ac_4	0.48	[12]
ν_M	0.0833	[12]
d_M^1	0.1704	[12]
d_M^2	0.1704	[12]
Σ	1463	Assumed

Table 6.1: Parameters Used in the Simulation in the Case Disease Free Equilibrium

These time series simulation show that the disease pick around 1000 days (time) and the exposed compartment does not get to be established. Moreover the recovery of the population would take more time. The susceptible local population goes down in the begin of the time course, but gradually converges to the equilibrium point $\frac{\Lambda_L}{d_L}$.

For the non-local population, it follow the same patterns as in the local population.

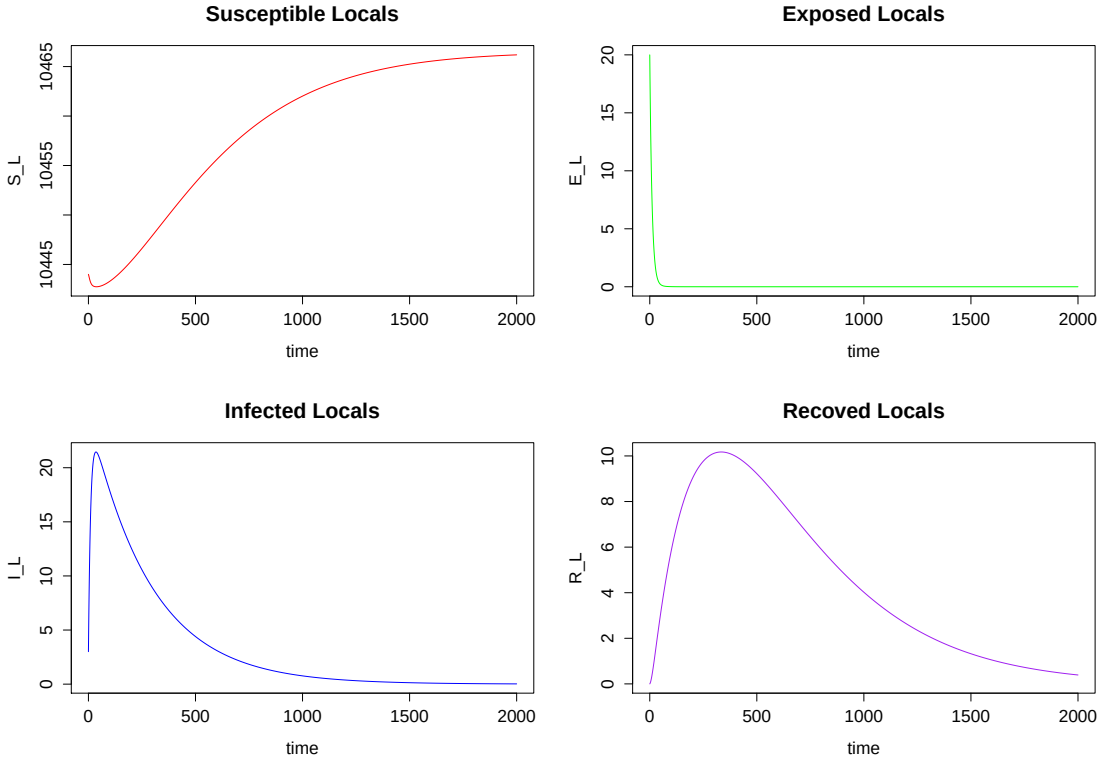


Figure 6.1: Local Compartments at the Disease Free Equilibrium

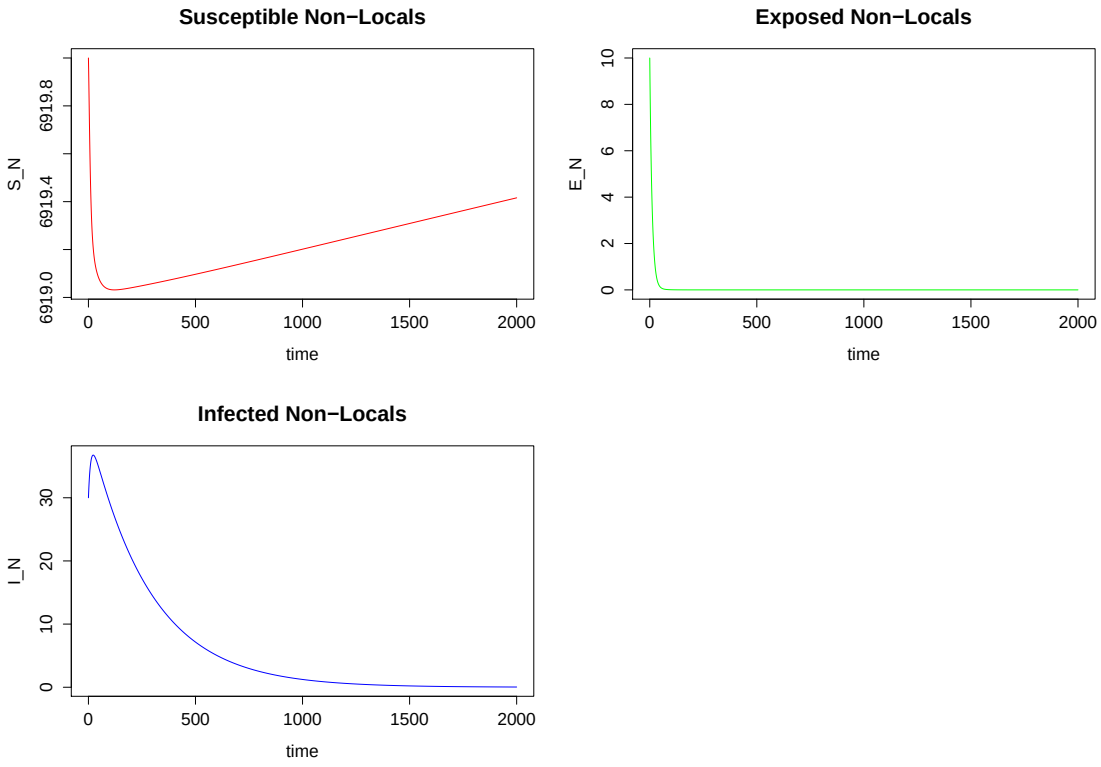


Figure 6.2: Non-locals Compartments at the Disease Free Equilibrium

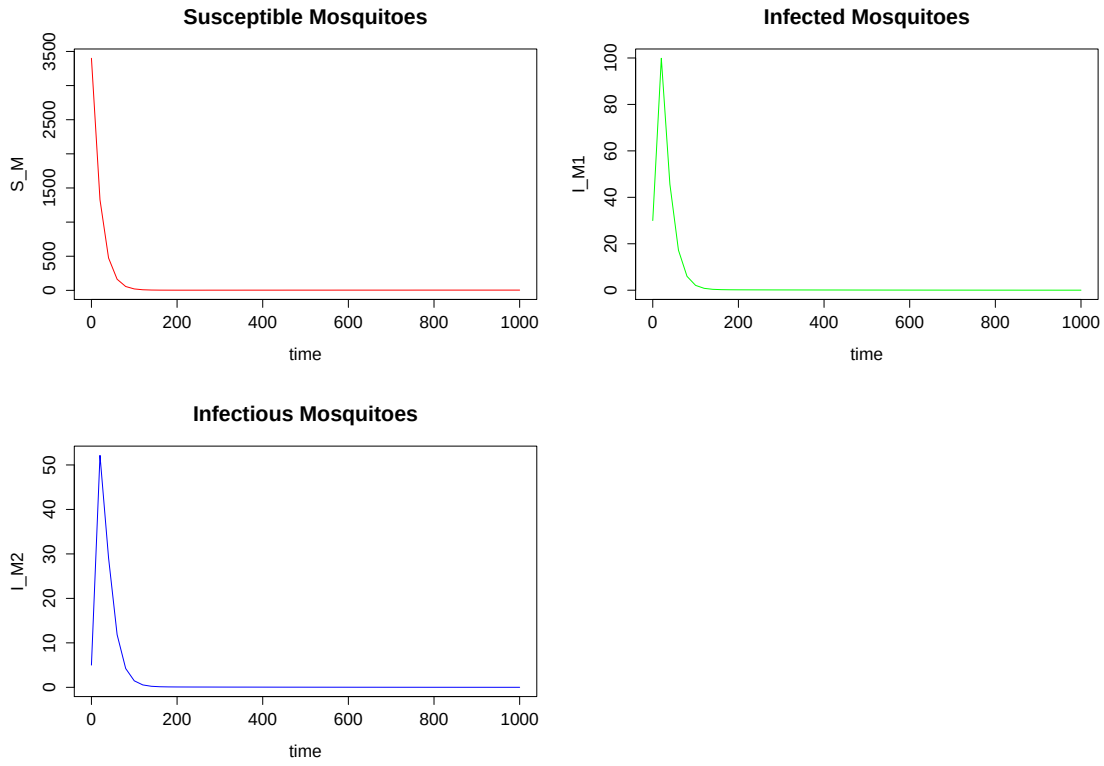


Figure 6.3: Mosquito Compartments at the Disease Free Equilibrium

The simulation of the mosquitoes population shows fast increase of this infected (infectious and non-infectious) population and fast decrease. Compared to the human dynamic this peak occurs before the human peak.

6.1.2 Simulation of the Endemic Equilibrium

To have better understanding of my model in the case of epidemic equilibria, I plot each figure the four cases per each population as I mentioned previously. They cases are as follow:

1. $\mathscr{R}_0^L < 1$ and $\mathscr{R}_0^N > 1$ which is represented in plot by case 1.
2. $\mathscr{R}_0^L > 1$ and $\mathscr{R}_0^N < 1$ which is represented in plot by case 2.
3. $\mathscr{R}_0^L < 1$ and $\mathscr{R}_0^N < 1$ but $R_0 > 1$ which is represented in plot by case 3.
4. $\mathscr{R}_0^L > 1$ and $\mathscr{R}_0^N > 1$ which is represented in plot by case 4.

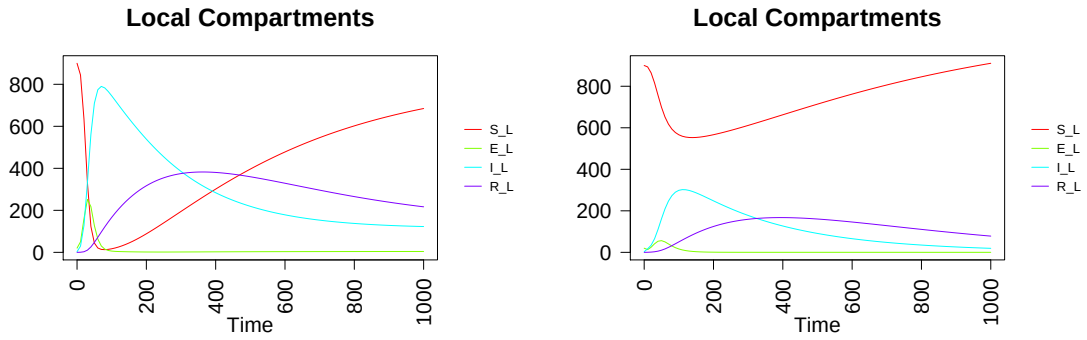
For simplicity, I will give all the parameters without unit since the same parameters were given in the previous table with units.

In the case 1 I choose the following parameters: $\Lambda_L = 0.3,\ d_L = 1.99 \times 10^{-4},\ ac_1 = 0.27,\ \beta_L = 0.0027, \nu_L = 0.1,\ \gamma_L = 0.0035,\ \Lambda_N = 0.11, d_N = 2 \times 10^{-4},\ ac_2 = 0.022,\ \nu_N = 0.1,\ \gamma_N = 0.0035,\ \Lambda_M = 0.27,\ d_M = 0.033,\ ac_3 = 0.48,\ ac_4 = 0.24,\ \nu_M = 0.0833,\ d_M^1 = 0.033,\ d_M^2 = 0.033,\ \Sigma = 1463$

For the case 2, I used these parameters : $\Lambda_L = 0.094,\ d_L = 9 \times 10^{-6},\ ac_1 = 0.022,\ \beta_L = 0.0027,\ \nu_L = 0.1,\ \gamma_L = 0.0035,\ \Lambda_N = 0.2,\ d_N = 1.63 \times 10^{-5},\ ac_2 = 0.1,\ \nu_N = 0.1,\ \gamma_N = 0.0035,\ \Lambda_M = 0.13,\ d_M = 0.033,\ ac_3 = 0.24,\ ac_4 = 0.64,\ \nu_M = 0.0833,\ d_M^1 = 0.033,\ d_M^2 = 0.033,\ \Sigma = 1463$

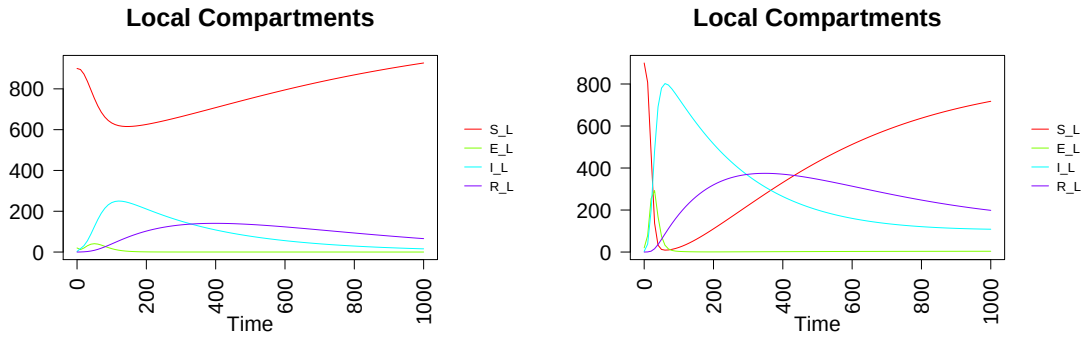
For the case 3, I have the following parameters: $\Lambda_L = 0.094,\ d_L = 9 \times 10^{-6},\ ac_1 = 0.022,\ \beta_L = 0.0027,\ \nu_L = 0.1,\ \gamma_L = 0.0035,\ \Lambda_N = 0.113,\ d_N = 1.63 \times 10^{-5},\ ac_2 = 0.022,\ \nu_N = 0.1,\ \gamma_N = 0.0035,\ \Lambda_M = 0.13,\ d_M = 0.033,\ ac_3 = 0.24,\ ac_4 = 0.48,\ \nu_M = 0.0833,\ d_M^1 = 0.033,\ d_M^2 = 0.033,\ \Sigma = 1463$

Finally, for the case 4 I have: $\Lambda_L = 0.3, d_L = 1.99 * 10^{-4},\ ac_1 = 0.27, \beta_L = 0.0027, \nu_L = 0.1,\ \gamma_L = 0.0035, \Lambda_N = 0.45,\ d_N = 2 \times 10^{-4},\ ac_2 = 0.27, \nu_N = 0.1, \gamma_N = 0.0035,\ \Lambda_M = 0.27, d_M = 0.01, ac_3 = 0.48,\ ac_4 = 0.64, \nu_M = 0.0833, d_M^1 = 0.05,\ d_M^2 = 0.05, \Sigma = 1463$



(a) Case 1: $\mathscr{R}_0^L < 1$ and $\mathscr{R}_0^N > 1$

(b) Case 2: $\mathscr{R}_0^L > 1$ and $\mathscr{R}_0^N < 1$



(c) Case 3: $\mathscr{R}_0^L < 1$ and $\mathscr{R}_0^N < 1$ but $R_0 > 1$

(d) Case 4: $\mathscr{R}_0^L > 1$ and $\mathscr{R}_0^N > 1$

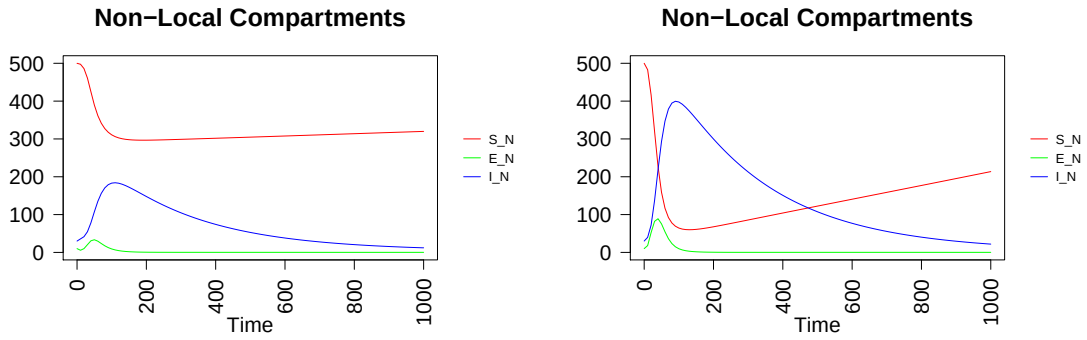
Figure 6.4: Local Population Compartments for the 4 Cases of $\mathscr{R}_0 > 1$

For the local population when $\mathscr{R}_0 > 1$:

The simulation of the model shows similar dynamic if $\mathscr{R}_0^N > 1$ regardless if $\mathscr{R}_0^L > 1$ or $\mathscr{R}_0^L < 1$ (see cases (6.4a) and (6.4d) in Figure 6.4), which means that if the infection is very well established in non-local population it will not be affected by the level of the infection in the local population.

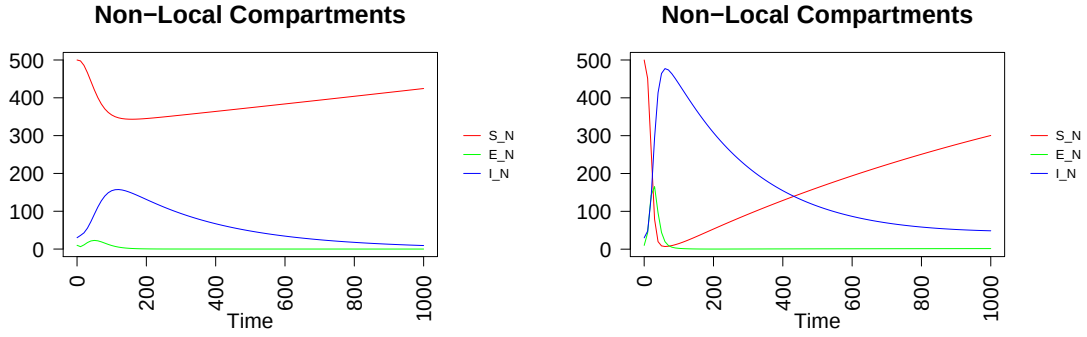
On the other hand, if $\mathscr{R}_0^N < 1$ regardless if $\mathscr{R}_0^L > 1$ or $\mathscr{R}_0^L < 1$ (see cases (6.4b) and (6.4c) in Figure 6.4), I can see that, again, the dynamics of model are similar in both cases with low endemic equilibrium compare to the previous two cases.

I conclude that the non-local population has more impact on the size of the malaria epidemic in the case of the UAE. More precisely, when there is an endemic equilibrium ($\mathscr{R}_0 > 1$), then, if the basic reproduction number of transmission of malaria infection in non-local population $\mathscr{R}_0^N > 1$, then I have higher endemic equilibria regardless the level of the infection in the local population. If $\mathscr{R}_0^N < 1$, then I have lower endemic equilibria regardless the level of the infection in the local population.



(a) Case 1: $\mathscr{R}_0^L < 1$ and $\mathscr{R}_0^N > 1$

(b) Case 2: $\mathscr{R}_0^L > 1$ and $\mathscr{R}_0^N < 1$



(c) Case 3: $\mathscr{R}_0^L < 1$ and $\mathscr{R}_0^N < 1$ but $R_0 > 1$

(d) Case 4: $\mathscr{R}_0^L > 1$ and $\mathscr{R}_0^N > 1$

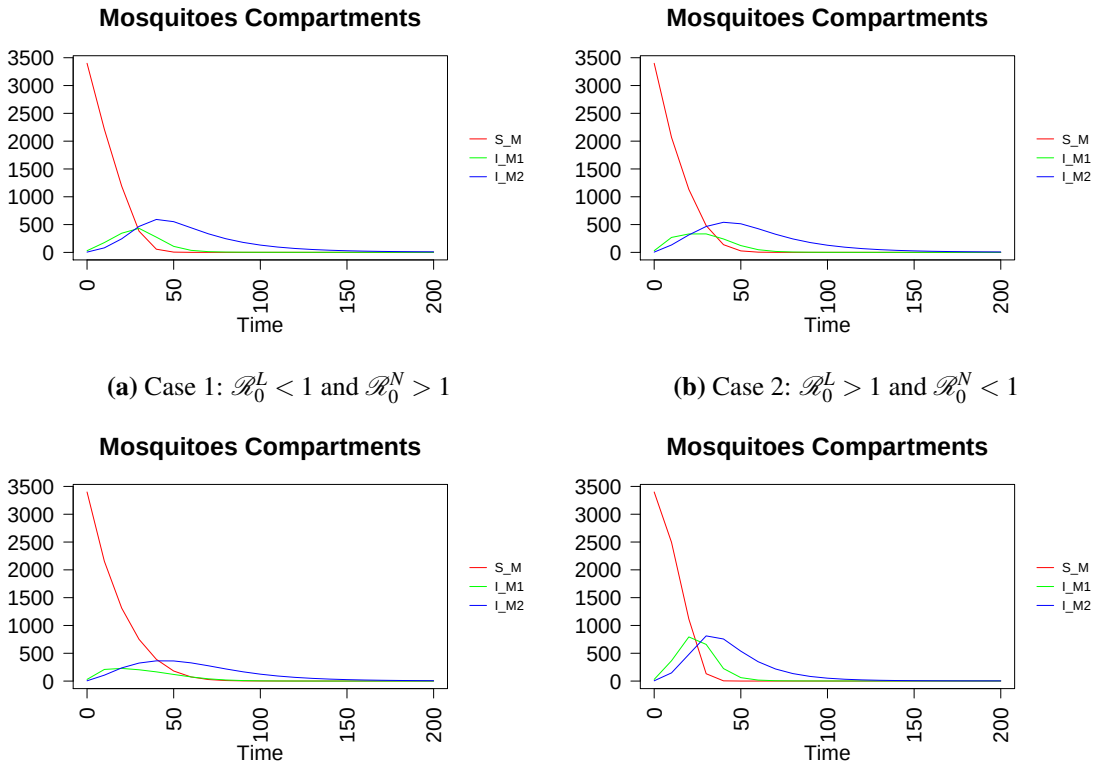
Figure 6.5: Non-Local Population Compartments for the 4 Cases of $\mathscr{R}_0 > 1$

For the non-local population when $\mathscr{R}_0 > 1$:

By analyzing the four figure corresponding to this case, I see similarity between the two cases where $\mathscr{R}_0^L < 1$. More precisely, the time series of the variables in the case $\mathscr{R}_0^N < 1$ is similar to the case $\mathscr{R}_0^N > 1$ (see cases (6.5a) and (6.5c) in figure (6.5) respectively when $\mathscr{R}_0^L < 1$), but with high endemic equilibrium when the disease is endemic in non-local sub-population (i.e, $\mathscr{R}_0^N > 1$). That shows that if the level of the infection of local is low then reduce the size of the epidemic on the non-local.

For the case where $\mathscr{R}_0^L > 1$, again, the dynamic of these two cases are similar, (see cases (6.5b) and (6.5d) in figure (6.5) respectively), with even higher endemic equilibrium and higher big when the disease is endemic in non-local sub-population ($\mathscr{R}_0^N > 1$).

This analysis shows that the infection in local population has positive impact infection of the non-local population. In fact when $\mathscr{R}_0^L < 1$ the endemic equilibria lower in the non-local population compared to when $\mathscr{R}_0^L > 1$. That shows the protecting the local population from possible malaria infection is beneficial to the overall infection in



(a) Case 1: $\mathscr{R}_0^L < 1$ and $\mathscr{R}_0^N > 1$

(b) Case 2: $\mathscr{R}_0^L > 1$ and $\mathscr{R}_0^N < 1$

(c) Case 3: $\mathscr{R}_0^L < 1$ and $\mathscr{R}_0^N < 1$ but $R_0 > 1$

(d) Case 4:$\mathscr{R}_0^L > 1$ and $\mathscr{R}_0^N > 1$

Figure 6.6: Mosquitoes Population Compartments for the 4 Cases of $\mathscr{R}_0 > 1$

the UAE.

The analysis of the time series of the 4 cases of endemic equilibrium for the mosquitoes compartments display similar dynamics where it is the highest in the fourth case when $\mathscr{R}_0^L > 1$ and $\mathscr{R}_0^N > 1$

6.2 Sensitivity Analysis of the Model

In [12] two types of sensitivity analysis indices were preformed. The first one is the sensitivity indices of $\mathscr{R}_0$ which is related directly to initial malaria disease transmission and the other one is sensitivity indices of x_{ee} - endemic equilibrium point - which is connected to the malaria disease prevalence. It discussed the most sensitive parameters of the model and the possible control strategies of these parameters. Also, the sensitivity indices of both $\mathscr{R}_0$ and x_{ee} were examined at two areas: one with low malaria transmission and the other one with high malaria transmission and found out that different parameters are sensitive at different transmission areas. Mosquito biting rate was the most sensitive

parameter to reproduction number and endemic equilibrium point of infectious human in areas with low malaria transmission. On the other hand, high malaria transmission areas' infectious humans were most sensitive to mosquito biting rate with respect to $\mathscr{R}_0$ sensitivity indices while is was human recovery rate of infectious humans, the most sensitive parameter at endemic equilibrium point.

The next 3 subsections will include a detailed discussion of local sensitivity analysis of infected population compartments of both humans and mosquitoes. The followed procedure of results is based on the local sensitivity analysis done in [88, 89]. The global sensitivity analysis is not preformed in this thesis. All the **R** commands of the local sensitivity are available in Appendix 2. Each subsection will begin with two figures representing the local sensitivity of the compartment or variables at two sequence of time which are from 0 to 1000 and 1 to 100. The second part would be the univariate sensitivity summary table that include the following:

- L1-norm: $\sum \left|S_{ij}\right| /n$.
- L2-norm: $\sqrt{\sum (S_{ij}^2)/n}$.
- Mean: The mean value of sensitivity functions.
- Min: The minimal value of sensitivity functions.
- Max: The maximal value of sensitivity functions.

The positive and negative sign of the sensitivity index indicate the dependence of the variable or compartment quantity on each parameter. Moreover, the absolute value of the sensitivity index (L1) shows the strength of the parameters affecting the variable where the larger the value, the more effect on the final size of compartments population. Bivariate sensitivity is discussed thirdly be calculating the pairwise sensitivity correlation of parameters and representing them as pairwise plot during the 100 days when most changes occur . The sensitivity functions pairs are considered to have strong relationship if $r^2 > 0.85$ and it is important to note that the correlation coefficients is not exactly 1 or -1 where the largest value of $|r| = 0.995$[89]. The correlation table of the parameters is not included but can be produced using the cor command in the Appendix 2. In addition,

for the infected locals, infected non-locals and infectious mosquitoes compartments, one more figure was added that described the mean value of the local sensitivity of these compartments.

6.2.1 I_L Local Sensitivity Analysis

By looking at the sensitivity analysis of all parameters of my model with respect to local infected variable in figures 6.7 and 6.8, I find certain parameters have more impact on local infection population than others. This impact could be either positive or negative. The figure 6.7 give long time series of these sensitivity while 6.8 zooms in one ten of the previous one to better understand these sensitivity. I took another step to determine the statistical summary of the sensitivity of each parameters in table 6.2.1 by give the mean, max, min and I plot the mean of these variables in figure 6.9. In this figure, I see that variables $\nu_N, ac_2, d_N, \Lambda_N$ have almost no effect on I_L. The variables $\nu_L, \gamma_N, ac_3, ac_4, d_M$ have slight effect on I_L. More precisely, γ_L, d_M have the same negative sign which means the increase of the parameter will result a decrease of I_L. On the other hand, γ_L, ac_3, ac_4 are affecting in positive way I_L. That means the increase of theses variables will slightly increase I_L. The remain of the variables are of significance to I_L; particularly γ_L. This variables has high impact on I_L. These effects are described as follows: The variables $\Sigma, d_L, d_M^1, d_M^2$ have opposite sign to I_L. These are normal because as the death rate increase in each population, I will not have an infected population. The only surprise fact is that Σ will effect negatively I_L. The parameters that have positive effect on I_L are $\Lambda_L, ac_1, \beta_L, \gamma_N, \nu_M$. The first three parameters are the birth rates of local population, infection rate by mosquitoes and lost of immunity of local population. For these parameters it make sense that the increase will result more infection. For γ_N, which is isolation of non-local infected population, I can explain that by the following. As the isolation rate increase, the mosquitoes will only have the local population to bite and infect which will increase the infected local population. This explain also the positive effect of ν_M on I_L since this parameter represent the rate of infected mosquitoes becoming infectious. The parameter γ_L has negative effect on I_L where it represent the recovery rate of the local population. Hence this means the more population recover, the less infected pile of local

will be. This also show that the sensitivity of this variables is very significant. I also look at the pairwise sensitivity analysis of the parameters as it is given in figure 6.10. I find that γ_L has no correlation with any parameter which means emphasize the highest sensitivity.

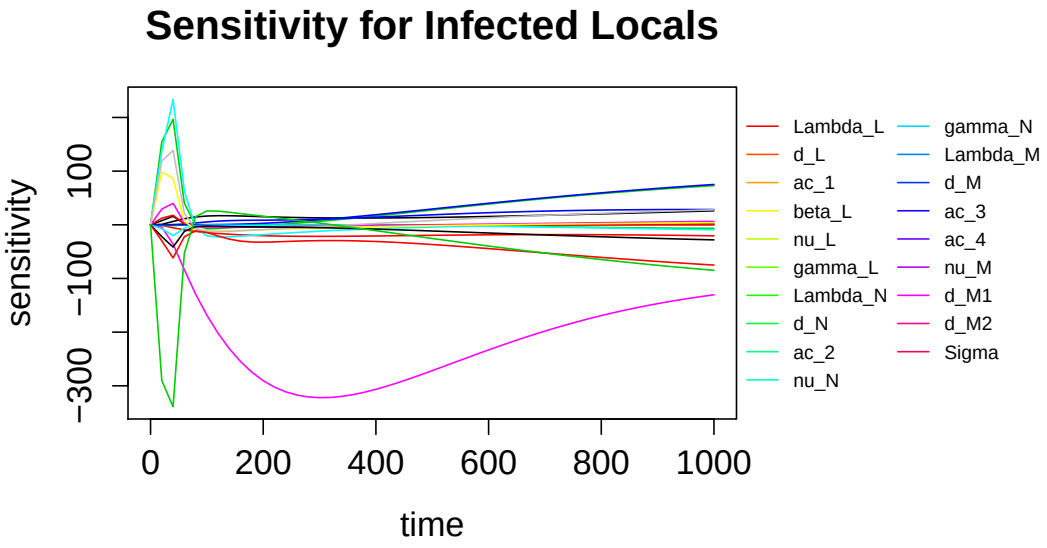


Figure 6.7: I_L Local Sensitivity for 1000 Days

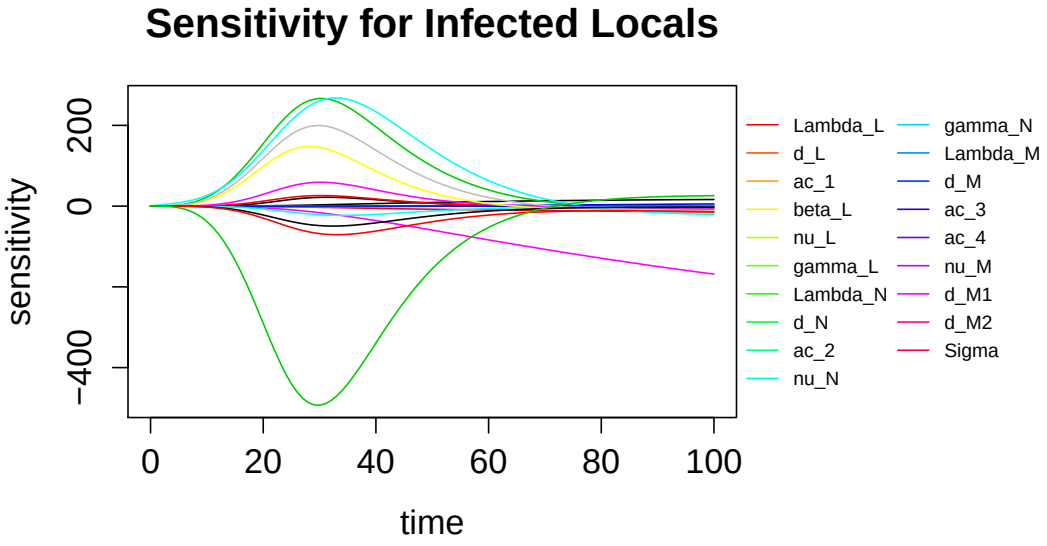


Figure 6.8: I_L Local Sensitivity for 100 Days

parameter	value	scale	L1	L2	Mean	Min	Max	N
Λ_L	0.30	0.30	16.00	2.36	16.00	0.00	26.02	51.00
d_L	0.00	0.00	18.07	2.61	-18.07	-21.53	0.00	51.00
ac_1	0.27	0.27	38.13	7.42	37.02	-7.59	196.38	51.00
β_L	0.00	0.00	17.43	2.76	17.43	0.00	28.47	51.00
ν_L	0.10	0.10	14.41	5.61	2.77	-22.81	233.67	51.00
γ_L	0.00	0.00	214.08	32.14	-214.08	-322.11	0.00	51.00
Λ_N	0.45	0.45	0.50	0.12	0.50	-0.02	2.29	51.00
d_N	0.00	0.00	0.16	0.03	-0.15	-0.52	0.02	51.00
ac_2	0.27	0.27	1.29	0.37	0.30	-1.87	15.85	51.00
ν_N	0.10	0.10	1.29	0.45	-0.04	-2.18	17.72	51.00
γ_N	0.00	0.00	2.28	0.45	-2.23	-6.65	0.19	51.00
Λ_M	0.27	0.27	31.67	5.70	31.67	0.00	75.13	51.00
d_M	0.01	0.01	3.71	0.73	-3.71	-20.38	0.00	51.00
ac_3	0.48	0.48	4.20	1.08	1.96	-4.98	39.96	51.00
ac_4	0.64	0.64	7.52	2.67	1.70	-11.70	98.42	51.00
ν_M	0.08	0.08	17.70	4.17	13.56	-12.68	138.50	51.00
d_M^1	0.05	0.05	14.23	2.37	-14.23	-41.50	0.00	51.00
d_M^2	0.05	0.05	42.84	6.49	-42.84	-75.10	0.00	51.00
Σ	1463.00	1463.00	48.32	10.76	-40.97	-338.92	25.82	51.00

Table 6.2: I_L Local Sensitivity Summary

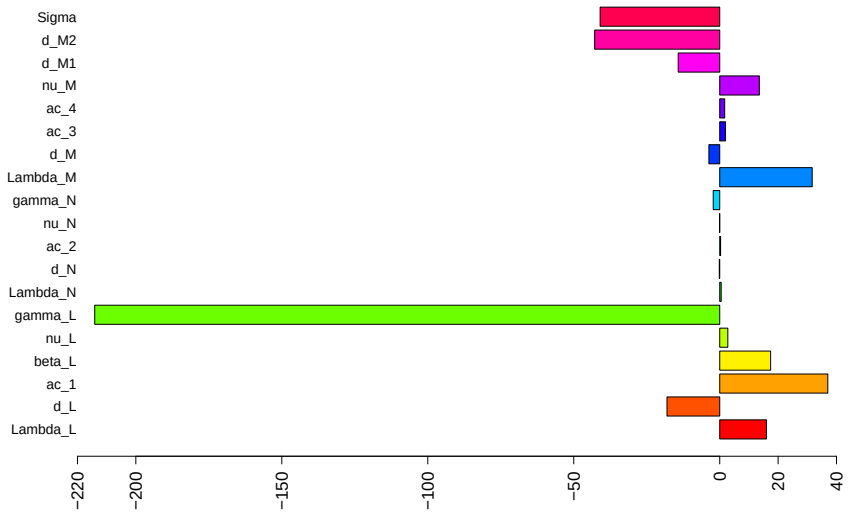


Figure 6.9: Mean of Local Sensitivity of I_L

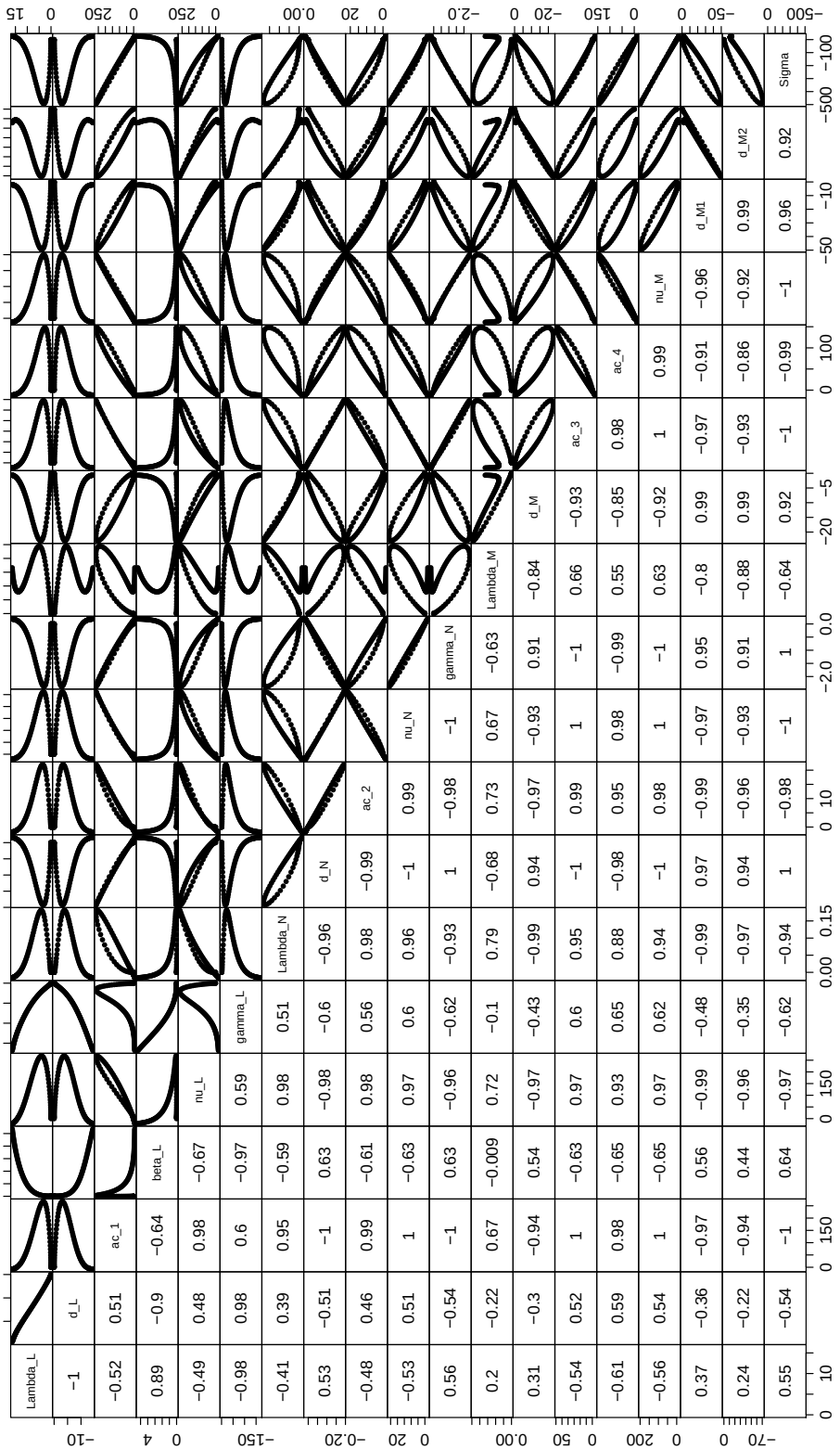


Figure 6.10: I_L Local Pairs Analysis

6.2.2 I_N Local Sensitivity Analysis

Following the approach used for the local sensitivity analysis of infected local compartment, the analysis of the infected non-local population included figures 6.11 and 6.12. The first figure 6.11 illustrated the local sensitivity of parameters with respect to infected non-local population in time series of 1000 days while the second figure 6.12 take a closer look on the parameters sensitivity for the first 100 days. Table 6.2.2 shows the statistical analysis for the local sensitivity of I_N which included L1, L2, mean, max, and min. From this table 6.2.2 I plotted the mean value of parameters local sensitivity to I_N which is shown in 6.13. I can see from this figure that the parameters sensitivity to I_N varies in magnitude and sign where they may have positive or negative effect. Parameters $\Lambda_L, d_L, \beta_L, \gamma_L$ are not sensitive at all to infected non-local population. Furthermore, parameters ac_1, ν_N, ac_3, ac_4 have slight positive effect on I_N and Λ_N, d_M have slight negative effect on I_N. All these parameters are not sufficient to change the non-local population size. This differs for the rest of the parameters where an increase or decrease will effect the infected non-local population. The four parameters $\Lambda_N, ac_2, \Lambda_M, \nu_M$ are positively sensitive to I_N in descending order where an increase in one of them would rise the number of infected non-local population. The most sensitive parameter to I_N is γ_N that has a high negative effect. This parameter represents the isolation and deportation of infected non-local population which means that increasing the isolation rate would definitely decrease the infected non-local population. The death rates of infected non-locals d_N, infected mosquitoes d_M^1 and infectious mosquitoes d_M^2 have normal negative effect on I_N since increasing these death rates would decrease the number if infected non-locals. The only surprising parameter is Σ since it is negatively affecting I_N. This can be explained due to the dynamic of my model. I can conclude from the pairwise correlation plot 6.12 that $\gamma_N$has no correlation with other parameters. In addition, the pairwise correlation plot can be used to inspect the correlation between different parameters such that if the value is bigger than 0.85, it shows a strong correlation between the two parameters.

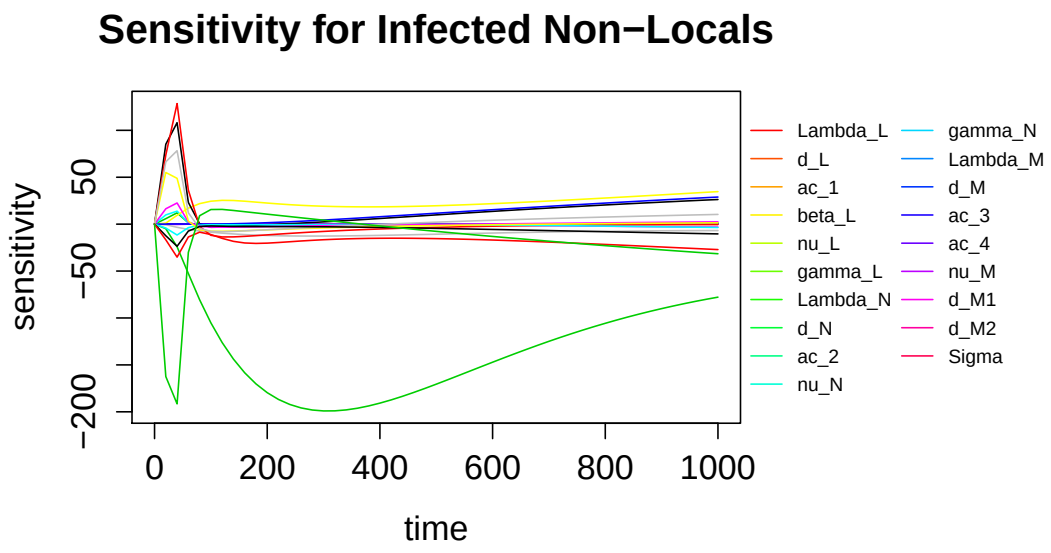


Figure 6.11: I_N Local Sensitivity for 1000 Days

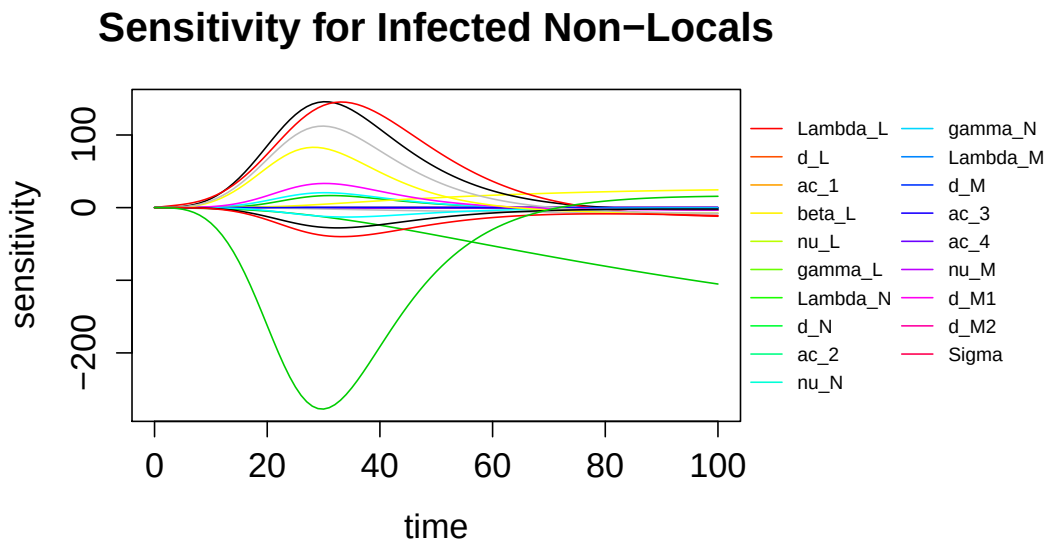


Figure 6.12: I_N Local Sensitivity for 100 Days

parameter	value	scale	L1	L2	Mean	Min	Max	N
Λ_L	0.30	0.30	0.11	0.02	0.10	-0.01	0.50	51.00
d_L	0.00	0.00	0.10	0.02	-0.10	-0.42	0.01	51.00
ac_1	0.27	0.27	1.06	0.29	0.17	-1.66	12.04	51.00
β_L	0.00	0.00	0.14	0.03	0.14	-0.00	0.60	51.00
ν_L	0.10	0.10	1.09	0.36	-0.11	-1.99	13.86	51.00
γ_L	0.00	0.00	1.03	0.21	-1.01	-3.12	0.05	51.00
Λ_N	0.45	0.45	22.63	3.31	22.63	0.00	34.67	51.00
d_N	0.00	0.00	9.12	1.34	-9.12	-12.72	0.00	51.00
ac_2	0.27	0.27	15.14	3.37	14.65	-3.35	108.11	51.00
ν_N	0.10	0.10	8.70	3.10	0.65	-13.64	128.47	51.00
γ_N	0.00	0.00	133.32	20.01	-133.32	-199.07	0.00	51.00
Λ_M	0.27	0.27	12.28	2.18	12.28	0.00	28.89	51.00
d_M	0.01	0.01	1.56	0.33	-1.56	-11.60	0.00	51.00
ac_3	0.48	0.48	2.17	0.60	0.59	-3.27	22.56	51.00
ac_4	0.64	0.64	4.37	1.51	0.32	-7.61	55.07	51.00
ν_M	0.08	0.08	7.98	2.18	5.04	-8.05	78.29	51.00
d_M^1	0.05	0.05	5.87	0.98	-5.87	-23.58	0.00	51.00
d_M^2	0.05	0.05	18.51	2.69	-18.51	-35.17	0.00	51.00
Σ	1463.00	1463.00	20.83	5.46	-15.73	-191.53	15.72	51.00

Table 6.3: I_N Local Sensitivity Summary

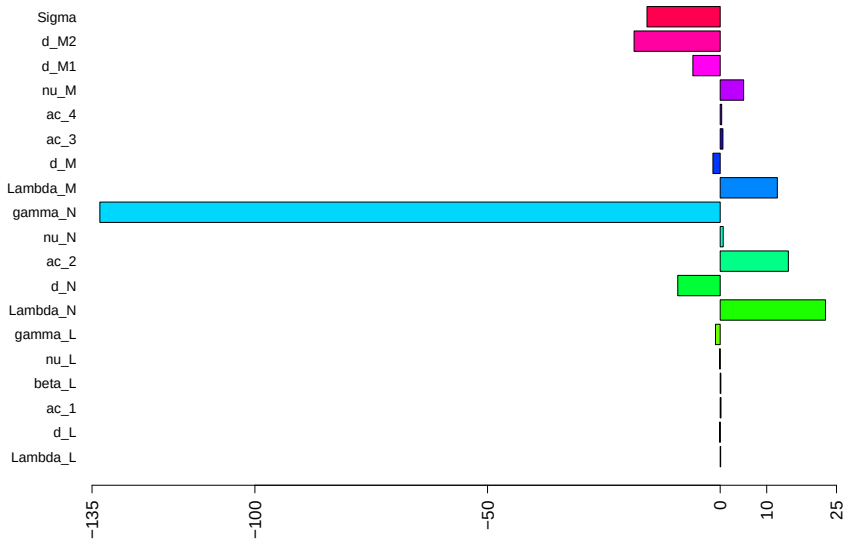


Figure 6.13: Mean Local Sensitivity of I_N

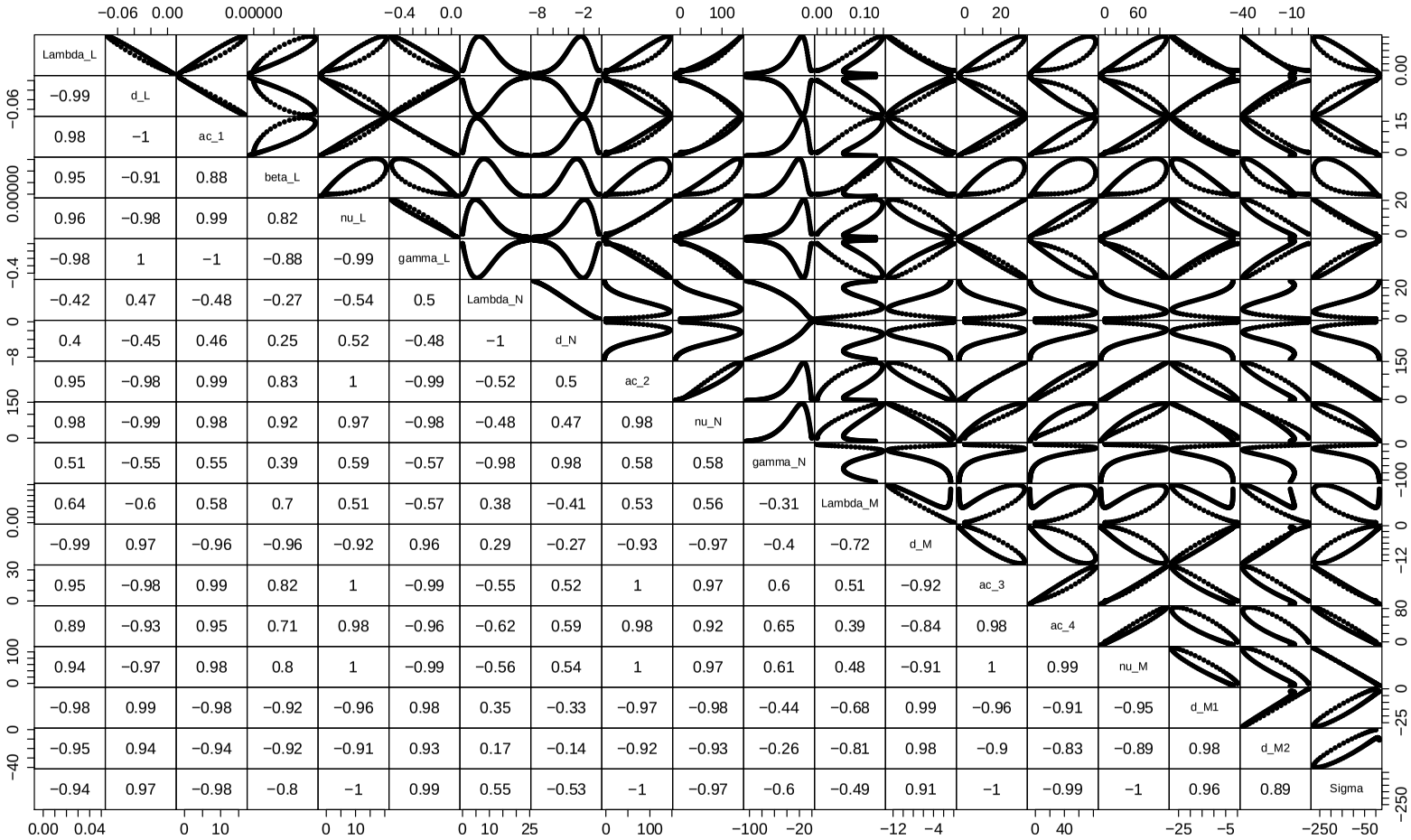


Figure 6.14: I_N Local Pairs Analysis

6.2.3 I_M^2 Local Sensitivity Analysis

The local sensitivity analysis for the infectious mosquitoes population was performed in the same style as for the infected locals and infectious non-locals populations. Figures 6.15 and 6.16 show a general look for the local sensitivity of parameter with respect to infectious mosquitoes population. The first figure 6.15 display the parameters sensitivity for time series of 1000 day and the second one 6.15 in time series of 100 days. After that, the table 6.2.3 present a statistical summary for the local sensitivity analysis of I_M^2 that include: L1, L2, mean, min, and max. Using the value of parameters mean from this table 6.2.3, it is illustrated in the figure 6.17. The figure shows the different effects of parameters on I_M^2 that may be positive or negative. It is noticeable that the parameter d_M^2 has the highest negative impact on infectious mosquitoes population such that an increase in the value of d_M^2 would decrease I_M^2. Parameters $\Lambda_L, d_L, \beta_L, \Lambda_N, d_N$ have no impact on I_M^2. Both γ_L and γ_N very small negative effect on I_M^2. Four of the parameters have slight positive effect on infectious mosquitoes population which are ac_1, ν_L, ac_2, ν_N. Also, parameters $\nu_M, \Lambda_M, \Lambda_N, ac_2$ have positive effect on I_M^2 but much higher than the previous ones. Similar to the infected non-local population, parameters $d_N, d_M^1, d_M^2, \Sigma$ have a negative effect on the infectious mosquitoes population. As for the pairwise correlation plot 6.18, I can see that d_M^2 has no strong correlation with all parameters except the parameter d_M^1 that has a strong correlation with value equal 0.85.

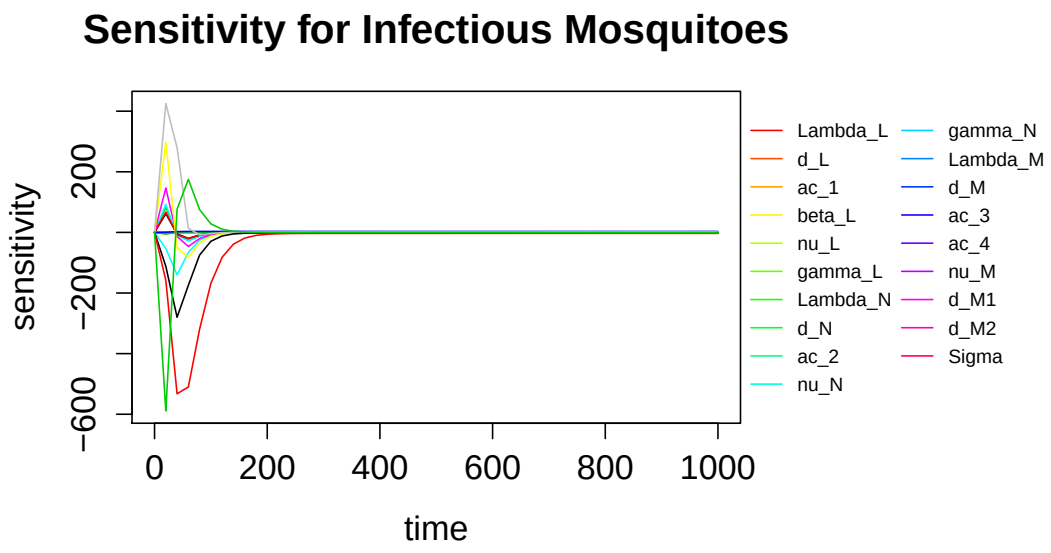


Figure 6.15: I_M^2 Local Sensitivity for 1000 Days

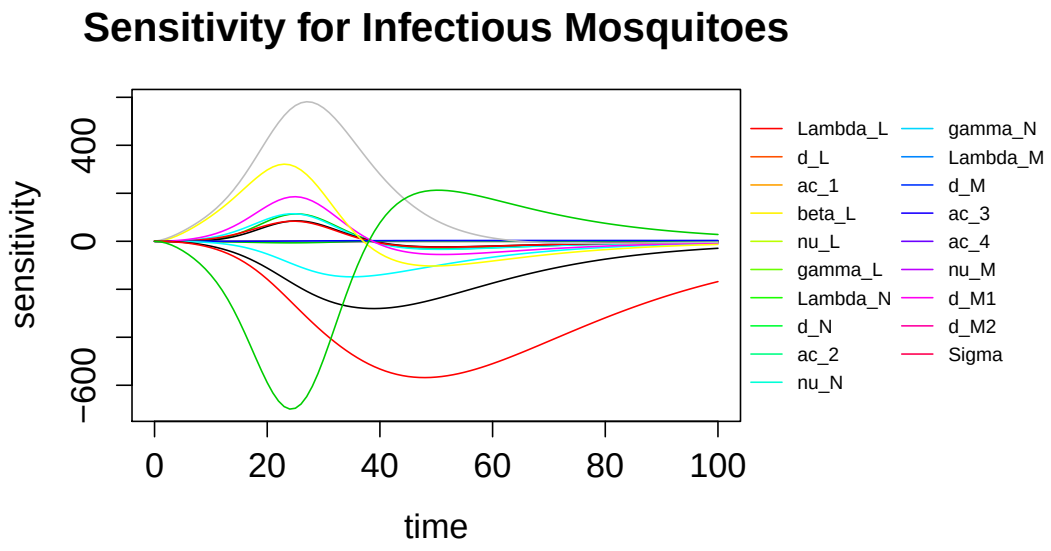


Figure 6.16: I_M^2 Local Sensitivity for 100 Days

Parameter	value	scale	L1	L2	Mean	Min	Max	N
Λ_L	0.30	0.30	0.03	0.01	0.02	-0.12	0.24	51.00
d_L	0.00	0.00	0.03	0.01	-0.02	-0.34	0.14	51.00
ac_1	0.27	0.27	2.72	1.74	0.67	-26.62	83.27	51.00
β_L	0.00	0.00	0.03	0.01	0.03	-0.00	0.08	51.00
ν_L	0.10	0.10	2.95	1.92	0.68	-27.91	92.57	51.00
γ_L	0.00	0.00	0.27	0.06	-0.22	-2.16	0.82	51.00
Λ_N	0.45	0.45	0.06	0.01	0.05	-0.24	0.48	51.00
d_N	0.00	0.00	0.03	0.01	-0.02	-0.48	0.16	51.00
ac_2	0.27	0.27	2.01	1.29	0.48	-19.84	61.96	51.00
ν_N	0.10	0.10	2.13	1.39	0.49	-20.32	66.91	51.00
γ_N	0.00	0.00	0.34	0.12	-0.21	-5.61	1.64	51.00
Λ_M	0.27	0.27	3.03	0.43	3.03	0.00	3.28	51.00
d_M	0.01	0.01	6.10	3.25	-6.10	-139.90	0.00	51.00
ac_3	0.48	0.48	4.82	3.06	1.23	-46.39	146.66	51.00
ac_4	0.64	0.64	9.63	6.17	2.22	-82.28	297.20	51.00
ν_M	0.08	0.08	15.32	9.98	14.81	-8.40	425.03	51.00
d_M^1	0.05	0.05	14.50	7.01	-14.50	-279.93	0.00	51.00
d_M^2	0.05	0.05	38.64	16.50	-38.64	-532.44	0.00	51.00
Σ	1463.00	1463.00	19.17	12.25	-4.61	-589.09	175.12	51.00

Table 6.4: I_M^2 Local Sensitivity Summary

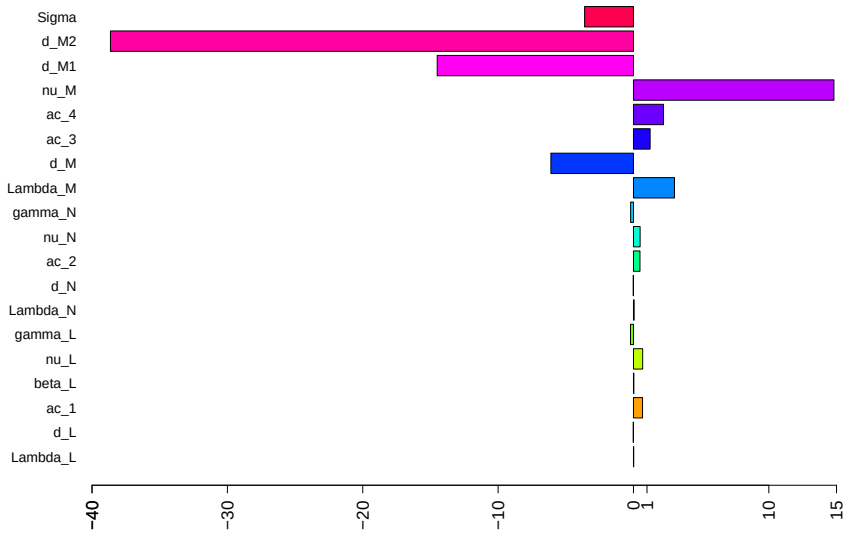


Figure 6.17: Mean Local Sensitivity of I_M^2

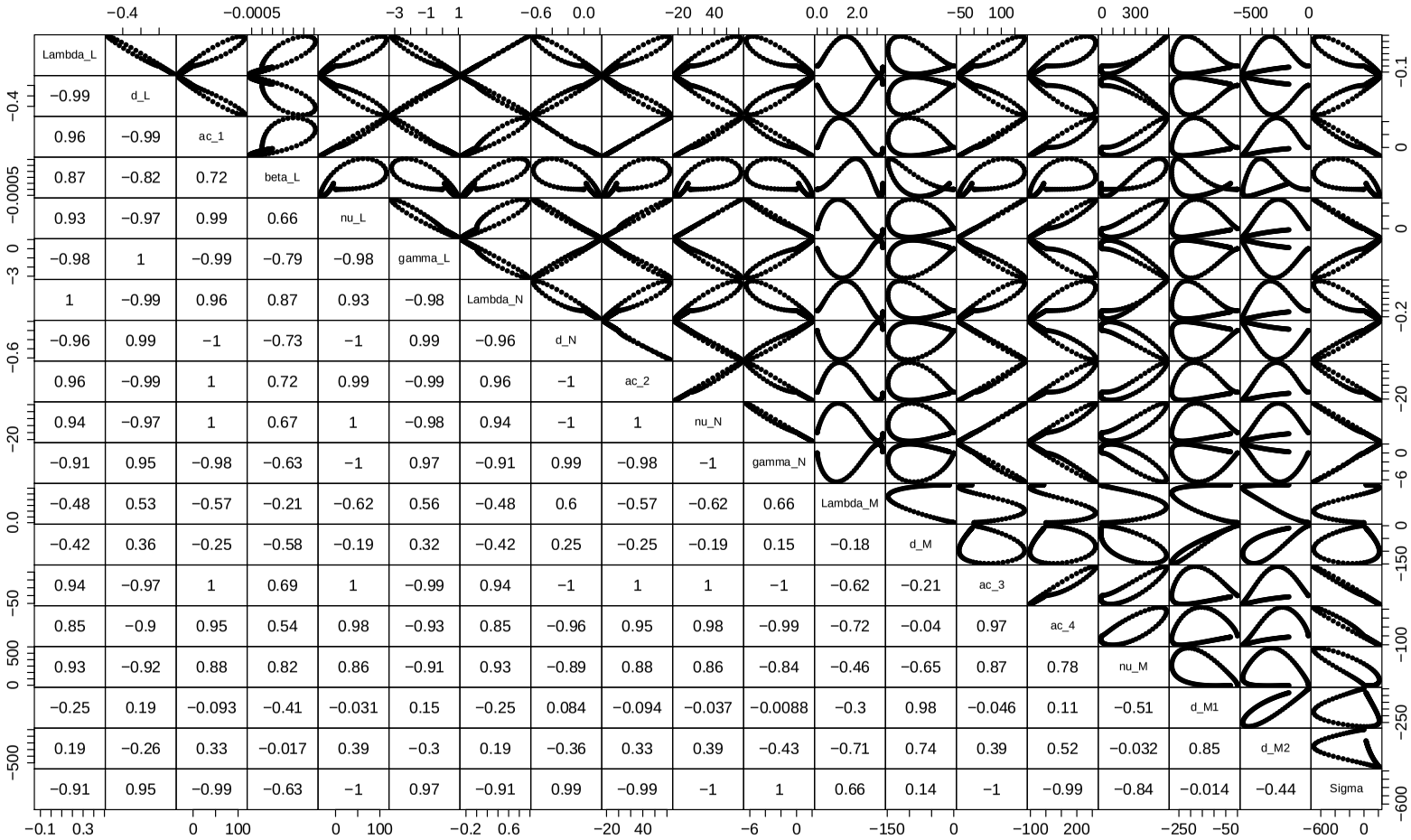


Figure 6.18: I_M^2 Local Pairs Analysis

Chapter 7: Conclusion

Malaria is an infectious disease with estimated annual mortality rates ranging from 700000 to 2.7 million people. It has intense effects on both societies and individuals. These effects include economical, environmental, and health aspects. Since the discovery of the causing parasite and its connection with the female *Anopheles* mosquitoes in transmitting malaria disease to human in late 19th century, epidemiologists, public health professionals, and even biomathematicians have made efforts the find the optimal control procedures to decrease and eliminate the transmission of malaria all over the globe.

The early attempts for mathematical models of malaria started with *SIR* simple Ross model where he concluded that the reduction of mosquito numbers to certain levels would decrease the number of malaria cases. After that, both Macdonald model and Anderson and May model were extensions of the Ross model. They included the mosquito and human latency period, respectively, which improved the general understanding of the substantial parameters influencing the transmission of malaria. These were the basic foundation models of malaria that were modified to include different factors and parameters. Age, immunity, environmental factors, social, and economical factors are some of the elements added to malaria models to study their effects on the malaria disease.

While some countries like Australia and Singapore succeeded in eliminating the local transmission of malaria, other countries especially in Africa and the Indian subcontinent suffer severely from the high transmission rate of malaria. Like most countries, the UAE was a malaria endemic region until it was certified free of local malaria in 2007. Despite this huge accomplishment for the UAE, the issue of malaria disease did not end in the UAE and even for the other countries. This is due to various factors such as the recruitment of workers from the endemic malaria countries, trade movements, and tourism. Environmental factors are also essential contributing factors in the transmission of malaria disease with the variation of temperatures and rainfall patterns. From the conducted malaria studies in the UAE, it is noticeable that there has been a rapid increase

in the number of imported malaria cases in the UAE in last few years. The number of imported malaria cases is expected to rise due to the need of more workers to fulfill the required duties for the preparation of Expo 2020.

The main goal of this thesis is to study the impact of malaria disease on the population of the UAE in non-pharmaceutical approach. The presented mathematical model is designed to fit the demography of the UAE. The human population is divided into two subpopulation which are locals and non-locals populations. The definition of locals and non-locals is based on the neediness of health check up to remain resident in the country. My model is deterministic model with *SEIR* structure for local population, *SEI* compartments for non-locals, and *SI* structure for mosquito population. The model is also policy based that takes into consideration the health policies in the UAE since the infected non-locals are isolated or returned to their countries. In order to study the epidemiological features of the model, mathematical analysis was conducted. The analysis included the proof of boundedness, and positivity of the system of ordinary differential equations that indicate that the model is well posed mathematically and epidemiologically.

The basic reproduction number is defined as the number of secondary infected individuals caused by infected individual during the infection period in completely susceptible population. $\mathscr{R}_0$ for the entire population was calculated and also the value of the basic reproduction number of the subpopulation locals $\mathscr{R}_0^L$ and non-locals $\mathscr{R}_0^N$. The next step was the evaluation and proof of local and global stability of the model. The disease free equilibrium is locally asymptotically stable if $\mathscr{R}_0 < 1$ and there is a stable endemic equilibrium if $\mathscr{R}_0 > 1$. As for the endemic equilibrium, it was studied in four different cases.

After that, the model's parameters were estimated from the literature reviews and assumptions. Moreover, the local sensitivity was studied to determine the effect of different parameters on the model dynamics. This was determined through the simulated figures using the free software **R** [78]. The simulation for the local and non-local compartments showed similar patterns when $\mathscr{R}_0 < 1$. The susceptible compartments showed a decrease in their numbers at first and then they converge to the equilibrium points $\frac{\Lambda_L}{d_L}$ and

$\frac{\Lambda_N}{d_N}$. Exposed compartments is not developed, while the infection reaches a peak around 100 days and then decrease. The recovery of locals take more time. On the other hand, the mosquito infected and infectious compartments displayed a rapid rise and then decline compared to the human population compartments.

From the preformed simulation for the 4 endemic cases where $\mathscr{R}_0 > 1$, I concluded the infection in non-local population has the most effect on the malaria transmission in the UAE regardless the value of $\mathscr{R}_0^L > 1$ or $\mathscr{R}_0^L < 1$. In cases of $\mathscr{R}_0^N < 1$, the country will be endemic with low transmission and endemic with high transmission in cases of $\mathscr{R}_0^N > 1$. Continuing the analysis for the non-local population, the positive effects of local population infection on the malaria transmission of non-locals were noticed such that protecting local population from malaria infection would definitely reduce the burden of the endemic in the UAE.

I also used the local sensitivity analysis to study the parameters that my model is sensitive to. My focus is the sensitivity with respect to the variables that measure impact of the disease on the population and more significant to the public health, which are the infected locals I_L and infected non-locals I_N. I considered also the sensitivity with respect to the infectious mosquitoes I_M^2 to know what parameter could be influential in mosquitoes dynamics. I found that the recovery rate of the infected locals γ_L is the most sensitive parameter for infected locals, hence it has the biggest negative influence on the size of the burden of the epidemic on the local populations. A similar way, the isolation and deportation rate of the infected non-locals γ_N has similar impact of the non-local population. By focusing only on the γ_L sensitivity, I realize the importance of having a good estimation of this parameter to validate the outcome of my model. In fact, the recovery rate of the infected population is parameter that depend on the nature of malaria strain and its virulence, the efficacy of the drug, the available health resources and personnel that can handle the possible imported disease. All of these inputs could make the estimation parameter a big challenge. For γ_N, it is also difficult to estimate this parameter, because it depends on the policy of the country on isolation and deportation of the patient and right diagnosis of these patients.

For the infected mosquitoes, I focus on the most sensitive parameters d_{M^1} and d_{M^2}, which are the death rate of the two types of infected mosquitoes. No surprise, these parameters are the most influential because they represent the impact of the death of the mosquitoes, mainly by pesticides, on the size of the infectious and non infectious mosquitoes.

This thesis contained what I could call *core model for malaria disease in the UAE*. Which means that a lot of possible extensions of the model could be derived from this model. For example, I could consider the case of multi-malaria strains. In fact, since the UAE had its local malaria, it should be interesting to investigate the impact of possible re-emergence of the local malaria in the presence of an imported strain of the disease. The model could also be extended to consider the non-local population from epidemic malaria regions and non-epidemic regions. This will help to understand the impact of selective isolation of non-locals on reducing the size of possible epidemic in the UAE. Moreover, I can also study the impact of different control measures by considering the policy of the country in implementing these measures.

My work is an analytical investigation of a hypothetical scenario of imported malaria in the UAE. Learning form the experience that the country faced before 2007, I are addressing the impact of such possible disease on the country, via mathematical modeling, in order to understand how we can be prepare for it. The goal is to bring awareness and to increase the preparedness to deal with Malaria, if it happened in the UAE again, or any other vector-borne disease.

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Appendix A: Appendix 1

In this Appendix, I will introduce some definitions used in my mathematical analysis of the model [60].

Definition A.0.1. Let A be $n \times n$ matrix with eigenvalues $\lambda_i, i = 1, ..., n$, the maximum modulus of any eigenvalue λ_i is called the spectral radius ρ such that $\rho(A) = \max_{1 \leq i \leq n} (|\lambda_i|)$

Definition A.0.2. Let A be $n \times n$ matrix with eigenvalues $\lambda_i, i = 1, ..., n$, the maximum real part of the eigenvalues λ_i is called the spectral abscissa $s(A)$ such that

$$s(A) = \max_{1 \leq i \leq n} \{\Re(\lambda_i)\}$$

Definition A.0.3. A matrix (or vector) A is nonnegative, denoted as $A \geq 0$, if every element is nonnegative. If every element of A is strictly positive, it is denoted as $A > 0$.

Definition A.0.4. A nonnegative matrix A is said to be irreducible if it is not the 1×1 zero matrix and it can not be expressed as

$$PAP^{-1} = \begin{pmatrix} A_{11} & A_{12} \\ 0 & A_{22} \end{pmatrix}$$

, such that A_{11} and A_{22} are nontrivial square block matrices and P is a permutation matrix.

Definition A.0.5. If A is an $n \times n$ matrix such that $a_{ij} \leq 0, \forall i \neq j$, then A has the Z-sign pattern.

Definition A.0.6. If A is an $n \times n$ matrix such that $A = sI - B$ where $s > 0$, I is the $n \times n$ identity matrix, $B \geq 0$ entry-wise and $s \geq \rho(B)$, then A is an M-matrix. Moreover, if $s > \rho(B)$, then A is a nonsingular M-matrix. If $s = \rho(B)$, then A is a singular M-

matrix[60].

Note that there are more than 40 equivalent characteristics of nonsingular M-matrix that were mentioned in [74] and [60].

Appendix B: Appendix 2

R version 3.1.3 (2015-03-09) [78] was the basic software used to do the numerical simulations of the model, calculate the value of the Basic reproduction number $\mathscr{R}_0$ and analyze the local sensitivity of the malaria model. Also, RStudio [82] was building editor for the mentioned tasks with the package FME [89].

B.1 R Commands for the Basic Reproduction Number $\mathscr{R}_0$

- Disease free equilibrium $\mathscr{R}_0 < 1$, with $\mathscr{R}_0^L < 1$ and $\mathscr{R}_0^N < 1$.

```
> Lambda_L=0.094;d_L=9*10^(-6);ac_1=0.022;
> beta_L=0.0027;nu_L=0.1;gamma_L=0.0035;
> Lambda_N=0.113;d_N=1.63*10^(-5);ac_2=0.022;
> nu_N=0.1;gamma_N=0.0035;Lambda_M=0.13;
> d_M=0.033;ac_3=0.24;ac_4=0.48;nu_M=0.0833;
> d_M1=0.1704;d_M2=0.1704;Sigma=1463
> R0L <- sqrt((nu_M*nu_L*ac_1*Lambda_L*ac_3*
Lambda_M)/(d_L*d_M*d_M2*Sigma^2*(nu_M+d_M1)*
(nu_L+d_L)*(gamma_L+d_L)))
> R0L
0.236073
> R0N <- sqrt((nu_M*nu_N*ac_2*Lambda_N*ac_4*
Lambda_M)/(d_N*d_M*d_M2*Sigma^2*(nu_M+d_M1)*
(nu_N+d_N)*(gamma_N+d_N)))
> R0N
```

```
0.2717045
> R0 <- sqrt(R0L^2+R0N^2)
> R0
0.2717045
```

#Endemic equilibrium:

- $\mathscr{R}_{0L} > 1, \mathscr{R}_{0N} < 1$ and $\mathscr{R}_0 > 1$ (CASE 1).

```
> Lambda_L=0.3;d_L=1.99*10^(-4);ac_1=0.27;
> beta_L=0.0027;nu_L=0.1; gamma_L=0.0035;
> Lambda_N=0.11; d_N=2*10^(-4);ac_2=0.022;
> nu_N=0.1;gamma_N=0.0035; Lambda_M=0.27;
> d_M=0.033; ac_3=0.48;ac_4=0.24; nu_M=0.0833;
> d_M1=0.033; d_M2=0.033;Sigma=1463
> R0L <- sqrt((nu_M*nu_L*ac_1*Lambda_L*ac_3*
Lambda_M)/(d_L*d_M*d_M2*Sigma^2*(nu_M+d_M1)*
(nu_L+d_L)*(gamma_L+d_L)))
> R0L
2.091313
> R0N <- sqrt((nu_M*nu_N*ac_2*Lambda_N*ac_4*
Lambda_M)/(d_N*d_M*d_M2*Sigma^2*(nu_M+d_M1)*
(nu_N+d_N)*(gamma_N+d_N)))
> R0N
0.2549294
> R0 <- sqrt(R0L^2+R0N^2)
> R0
```

```
2.106793
```

- $\mathscr{R}_{0L} < 1, \mathscr{R}_{0N} > 1$ and $\mathscr{R}_0 > 1$ (CASE 2)

```
> Lambda_L=0.094;d_L=9*10^(-6);ac_1=0.022;
> beta_L=0.0027;nu_L=0.1; gamma_L=0.0035;
> Lambda_N=0.2;d_N=1.63*10^(-5);ac_2=0.1;
> nu_N=0.1;gamma_N=0.0035;Lambda_M=0.13;
> d_M=0.033;ac_3=0.24;ac_4=0.64;nu_M=0.0833;
> d_M1=0.033;d_M2=0.033; Sigma=1463
> R0L <- sqrt((nu_M*nu_L*ac_1*Lambda_L*ac_3*
Lambda_M)/(d_L*d_M*d_M2*Sigma^2*(nu_M+d_M1)*
(nu_L+d_L)*(gamma_L+d_L)))
> R0L
0.7923088
>R0N <- sqrt((nu_M*nu_N*ac_2*Lambda_N*ac_4*
Lambda_M)/(d_N*d_M*d_M2*Sigma^2*(nu_M+d_M1)*
(nu_N+d_N)*(gamma_N+d_N)))
> R0N
2.986613
> R0 <- sqrt(R0L^2+R0N^2)
> R0
3.08992
```

- $\mathscr{R}_{0L} < 1, \mathscr{R}_{0N} < 1$ but $\mathscr{R}_0 > 1$ (CASE 3)

```
>Lambda_L=0.094;d_L=9*10^(-6);ac_1=0.022;
> beta_L=0.0027;nu_L=0.1; gamma_L=0.0035;
```

```
> Lambda_N=0.113;d_N=1.63*10^(-5);ac_2=0.022;
> nu_N=0.1;gamma_N=0.0035;Lambda_M=0.13;
> d_M=0.033;ac_3=0.24; ac_4=0.48;nu_M=0.0833;
> d_M1=0.033;d_M2=0.033;Sigma=1463
> R0L <- sqrt((nu_M*nu_L*ac_1*Lambda_L*ac_3*
Lambda_M)/(d_L*d_M*d_M2*Sigma^2*(nu_M+d_M1)*
(nu_L+d_L)*(gamma_L+d_L)))
> R0L
0.7923088
> R0N <- sqrt((nu_M*nu_N*ac_2*Lambda_N*ac_4*
Lambda_M)/(d_N*d_M*d_M2*Sigma^2*(nu_M+d_M1)*
(nu_N+d_N)*(gamma_N+d_N)))
> R0N
0.9118955
> R0 <- sqrt(R0L^2+R0N^2)
> R0
1.208018
```

- $\mathscr{R}_{0L} > 1, \mathscr{R}_{0N} > 1$ and $\mathscr{R}_0 > 1$ (CASE 4)

```
> Lambda_L=0.3; d_L=1.99*10^(-4); ac_1=0.27;
> beta_L=0.0027; nu_L=0.1;gamma_L=0.0035;
> Lambda_N=0.45; d_N=2*10^(-4); ac_2=0.27;
> nu_N=0.1;gamma_N=0.0035; Lambda_M=0.27;
> d_M=0.01;  ac_3=0.48;ac_4=0.64;nu_M=0.0833;
> d_M1=0.05; d_M2=0.05; Sigma=1463
```

```
> R0L <- sqrt((nu_M*nu_L*ac_1*Lambda_L*ac_3*
Lambda_M)/(d_L*d_M*d_M2*Sigma^2*(nu_M+d_M1)*
(nu_L+d_L)*(gamma_L+d_L)))
> 0L
2.882854
> R0N <- sqrt((nu_M*nu_N*ac_2*Lambda_N*ac_4*
Lambda_M)/(d_N*d_M*d_M2*Sigma^2*(nu_M+d_M1)*
(nu_N+d_N)*(gamma_N+d_N)))
> R0N
4.066197
> R0 <- sqrt(R0L^2+R0N^2)
> R0
4.984456
```

B.2 R Commands for the Graphical Representation of the Model at Various $\mathscr{R}_0$

Using the same malaria function with different set of parameters to produce different compartments at various values of $\mathscr{R}_0$. The primary used package for the simulation and local sensitivity analysis is **FME** [89].

```
> install.packages("FME")
> require(FME)
> pars1 <- list(Lambda_L=0.094,d_L=9*10^(-6),
ac_1=0.022,beta_L=0.0027,nu_L=0.1,gamma_L=0.0035,
Lambda_N=0.113,d_N=1.63*10^(-5),ac_2=0.022,
nu_N=0.1,gamma_N=0.0035,Lambda_M=0.13,d_M=0.033,
ac_3=0.24,ac_4=0.48,nu_M=0.0833,d_M1=0.1704,
```

```
d_M2=0.1704,Sigma=1463)
> pars2 <- list(Lambda_L=0.3, d_L=1.99*10^(-4),
ac_1=0.27, beta_L=0.0027,nu_L=0.1,gamma_L=0.0035,
Lambda_N=0.11,d_N=2*10^(-4),ac_2=0.022,nu_N=0.1,
gamma_N=0.0035, Lambda_M=0.27,d_M=0.033,
ac_3=0.48,ac_4=0.24,nu_M=0.0833, d_M1=0.033,
d_M2=0.033,Sigma=1463)
> pars3 <- list(Lambda_L=0.094,d_L=9*10^(-6),
ac_1=0.022,beta_L=0.0027,nu_L=0.1,gamma_L=0.0035,
Lambda_N=0.2,d_N=1.63*10^(-5),ac_2=0.1,nu_N=0.1,
gamma_N=0.0035,Lambda_M=0.13,d_M=0.033,ac_3=0.24,
ac_4=0.64,nu_M=0.0833,d_M1=0.033,d_M2=0.033,
Sigma=1463)
> pars4 <- list(Lambda_L=0.094,d_L=9*10^(-6),
ac_1=0.022,beta_L=0.0027,nu_L=0.1,gamma_L=0.0035,
Lambda_N=0.113,d_N=1.63*10^(-5),ac_2=0.022,
nu_N=0.1,gamma_N=0.0035,Lambda_M=0.13,d_M=0.033,
ac_3=0.24,ac_4=0.48,nu_M=0.0833,d_M1=0.033,
d_M2=0.033,Sigma=1463)
> pars6 <- list(Lambda_L=0.3, d_L=1.99*10^(-4),
ac_1=0.27,beta_L=0.0027,nu_L=0.1,gamma_L=0.0035,
Lambda_N=0.45,d_N=2*10^(-4), ac_2=0.27,nu_N=0.1,
gamma_N=0.0035, Lambda_M=0.27,d_M=0.01, ac_3=0.48,
ac_4=0.64,nu_M=0.0833, d_M1=0.05, d_M2=0.05,
Sigma=1463)
```

```
> Malaria <-function(pars6,times=seq(0,10000,by=10)){
derivs<-function(t,state,pars6){
with(as.list(c(state,pars6)),{
dS_L<- Lambda_L - (d_L*S_L) - ac_1*((S_L*I_M2)/Sigma)
+ (beta_L*R_L)
dE_L<- ac_1*((S_L*I_M2)/Sigma) - (nu_L+d_L)*E_L
dI_L<- (nu_L*E_L) - (gamma_L+d_L)*I_L
dR_L<- (gamma_L*I_L) - (beta_L+d_L)*R_L
dS_N<- Lambda_N - (d_N*S_N) - ac_2*((S_N*I_M2)/Sigma)
dE_N<- ac_2*((S_N*I_M2)/Sigma) - (nu_N+d_N)*E_N
dI_N<- (nu_N*E_N) - (gamma_N+d_N)*I_N
dS_M<- Lambda_M - (d_M*S_M) - ac_3*((S_M*I_L)/Sigma)
- ac_4*((S_M*I_N)/Sigma)
dI_M1<- ac_3*((S_M*I_L)/Sigma) + ac_4*((S_M*I_N)/Sigma)
- (nu_M+d_M1)*I_M1
dI_M2<- (nu_M*I_M1) - (d_M2*I_M2)
return(list(c(dS_L,dE_L,dI_L,dR_L,dS_N,dE_N,dI_N,dS_M,
dI_M1,dI_M2)))
    })
  }
state<-c(S_L=900,E_L=20,I_L=3,R_L=0,S_N=500,E_N=10,
I_N=30,S_M=3400,I_M1=30,I_M2=5)
# ode solves the model by integration
return(ode(y=state,times=times,func=derivs,parms=pars6))
}
```

```
> out <- Malaria(pars6)
```

R commands used to plot the malaria model at $\mathscr{R}_0 = 0.27$

```
# locals compartments
> par(mfrow=c(2,2))
> plot(out[,1],out[,2],main="Susceptible Locals",
ylab="S_L", xlab="time",type="l",col="red")
> plot(out[,1],out[,3],main="Exposed Locals",
ylab="E_L", xlab="time",type="l",col="green")
> plot(out[,1],out[,4],main="Infected Locals",
ylab="I_L", xlab="time",type="l",col="blue")
> plot(out[,1],out[,5],main="Recoved Locals",
ylab="R_L", xlab="time",type="l",col="purple")
> par(mfrow=c(1,1))
# Non-locals compartments
> par(mfrow=c(2,2))
> plot(out[,1],out[,6],main="Susceptible Non-Locals",
ylab="S_N", xlab="time",type="l",col="red")
> plot(out[,1],out[,7],main="Exposed Non-Locals",
ylab="E_N", xlab="time",type="l",col="green")
> plot(out[,1],out[,8],main="Infected Non-Locals",
ylab="I_N", xlab="time",type="l",col="blue")
> par(mfrow=c(1,1))
# Mosquitoes compartments
> par(mfrow=c(2,2))
```

```
> plot(out[,1],out[,9],main="Susceptible Mosquitoes",
ylab="S_M",xlab="time",type="l",col="red")
> plot(out[,1],out[,10],main="Infected Mosquitoes",
ylab="I_M1", xlab="time",type="l",col="green")
> plot(out[,1],out[,11],main="Infectious Mosquitoes",
ylab="I_M2", xlab="time",type="l",col="blue")
> par(mfrow=c(1,1))
```

R commands for plotting the four cases of $\mathscr{R}_0 > 1$

1. Local population compartments plot.

```
> par(mar=c(5.1, 4.1, 4.1, 6.1), xpd=TRUE)
> SLC<- out[,2]
> ELC<- out[,3]
> ILC<- out[,4]
> RLC<- out[,5]
> COLORS <- rainbow(4)
> LC<- data.frame(SLC=SLC,ELC=ELC,ILC=ILC, RLC=RLC)
> matplot(out[,1],LC, type = "l", xlab="Time",
ylab="", main="Local Compartments",
col = COLORS,lty=1)
> legend("right",c("S_L", "E_L","I_L","R_L"),
bty = "n", col = COLORS,cex = 0.6,lty=1,
inset=c(-0.2,0))
# return the par to original
> par(mar=c(5, 4, 4, 2) + 0.1)
```

2. Non-Locals population compartments plot.

```
> par(mar=c(5.1, 4.1, 4.1, 6.1), xpd=TRUE)
> SNC<- out[,6]ENC<- out[,7]
> INC<- out[,8]
> COLORS <- rainbow(3)
> NC<- data.frame(SNC=SNC,ENC=ENC,INC=INC)
> matplot(out[,1],NC, type = "l", xlab="Time",
ylab="", main="Non-Local Compartments",
col = COLORS,lty=1)
> legend("right",c("S_N", "E_N","I_N"),bty ="n",
 col = COLORS,cex = 0.6,lty=1,inset=c(-0.2,0))
#return the par to original
> par(mar=c(5, 4, 4, 2) + 0.1)
```

3. Mosquito population compartments plot.

```
> par(mar=c(5.1, 4.1, 4.1, 6.1), xpd=TRUE)
> SMC<- out[,9]
> IM1C<- out[,10]
> IM2C<- out[,11]
> COLORS <- rainbow(3)
> NC<- data.frame(SMC=SMC,IM1C=IM1C,IM2C=IM2C)
> matplot(out[,1],NC, type = "l", xlab="Time",
ylab="",main="Mosquitoes Compartments",
col = COLORS,lty=1)
> legend("right",c("S_M", "I_M1","I_M2"),bty ="n",
```

```
    col = COLORS,cex = 0.6,lty=1,inset=c(-0.2,0))
    # return the par to original
    > par(mar=c(5, 4, 4, 2) + 0.1)
```

For better viewing of Mosquitoes compartments, the time in the Malaria function was changed to seq(0,200,by=10)

B.3 R Commands for Local Sensitivity Analysis of Malaria Model

Local sensitivity analysis of the model was conducted at value of $\mathscr{R}_0 = 4.98$.

```
> require(FME)
> pars6 <- list(Lambda_L=0.3, d_L=1.99*10^(-4),
ac_1=0.27, beta_L=0.0027, nu_L=0.1,gamma_L=0.0035,
Lambda_N=0.45, d_N=2*10^(-4), ac_2=0.27,nu_N=0.1,
gamma_N=0.0035,Lambda_M=0.27,d_M=0.01, ac_3=0.48,
ac_4=0.64,nu_M=0.0833,d_M1=0.05, d_M2=0.05,Sigma=1463)
> Malaria2 <-function(pars6,times=seq(0,1000,by=20)){
derivs<-function(t,state,pars6){
with(as.list(c(state,pars6)),{
dS_L<- Lambda_L - (d_L*S_L) - ac_1*((S_L*I_M2)/Sigma)
+ (beta_L*R_L)
dE_L<- ac_1*((S_L*I_M2)/Sigma) - (nu_L+d_L)*E_L
dI_L<- (nu_L*E_L) - (gamma_L+d_L)*I_L
dR_L<- (gamma_L*I_L) - (beta_L+d_L)*R_L
dS_N<- Lambda_N - (d_N*S_N) - ac_2*((S_N*I_M2)/Sigma)
dE_N<- ac_2*((S_N*I_M2)/Sigma) - (nu_N+d_N)*E_N
dI_N<- (nu_N*E_N) - (gamma_N+d_N)*I_N
```

```
dS_M<- Lambda_M - (d_M*S_M) - ac_3*((S_M*I_L)/Sigma)
- ac_4*((S_M*I_N)/Sigma)
dI_M1<- ac_3*((S_M*I_L)/Sigma) + ac_4*((S_M*I_N)/Sigma)
- (nu_M+d_M1)*I_M1
dI_M2<- (nu_M*I_M1) - (d_M2*I_M2)
return(list(c(dS_L,dE_L,dI_L,dR_L,dS_N,dE_N,dI_N,
dS_M,dI_M1,dI_M2)))
    })
  }
state<-c(S_L=900,E_L=20,I_L=3,R_L=0,S_N=500,E_N=10,
I_N=30,S_M=3400,I_M1=30,I_M2=5)
# ode solves the model by integration
return(ode(y=state,times=times,func=derivs,parms=pars6))
}
> out2 <- Malaria2(pars6)
# Local Sensitivity Analysis
# Local Sensitivity analysis on several variables
> summary(sensFun(Malaria2,pars6,varscale=1),var=TRUE)
# Local sensitivity functions for each variable in
the infected compartments :
# I_L
> SnsI_L<-sensFun(func=Malaria2,parms=pars6,
sensvar="I_L",varscale=1)
> SnsI_L
> par(mar=c(5.1, 4.1, 4.1, 10.1), xpd=TRUE)
```

```
> plot(SnsI_L,legpos="NULL",main="Sensitivity
for Infected Locals")
> legend("right",
legend=c("Lambda_L","d_L","ac_1","beta_L","nu_L",
"gamma_L","Lambda_N","d_N","ac_2","nu_N","gamma_N",
"Lambda_M", "d_M", "ac_3", "ac_4", "nu_M", "d_M1",
"d_M2", "Sigma"),bty = "n",col = rainbow(19),
cex = 0.55,lty=1,inset=c(-0.5,0), ncol=2)
#return the par to original
> par(mar=c(5, 4, 4, 2) + 0.1)
#Univariate Sensitivity
> summary(SnsI_L)
# Bivariate Sensitivity
> cor(SnsI_L[,-(1:2)])
> pairs(SnsI_L)
# I_N
> SnsI_N<-sensFun(func=Malaria2,parms=pars6,
sensvar="I_N",varscale=1)
> SnsI_N
> par(mar=c(5.1, 4.1, 4.1, 10.1), xpd=TRUE)
> plot(SnsI_N,legpos="NULL",main="Sensitivity
for Infected Non-Locals")
> legend("right",
legend=c("Lambda_L","d_L","ac_1","beta_L","nu_L",
"gamma_L","Lambda_N","d_N","ac_2","nu_N","gamma_N",
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"Lambda_M", "d_M", "ac_3", "ac_4", "nu_M", "d_M1",
"d_M2", "Sigma"),bty = "n",col = rainbow(19),
cex = 0.55,lty=1,inset=c(-0.5,0), ncol=2)
#return the par to original
> par(mar=c(5, 4, 4, 2) + 0.1)
#Univariate Sensitivity
> summary(SnsI_N)
# Bivariate Sensitivity
> cor(SnsI_N[,-(1:2)])
> pairs(SnsI_N)
# I_M2
> SnsI_M2<-sensFun(func=Malaria2,parms=pars6,
sensvar="I_M2", varscale=1)
> SnsI_M2
> par(mar=c(5.1, 4.1, 4.1, 10.1), xpd=TRUE)
> plot(SnsI_M2,legpos="NULL",main="Sensitivity
for Infectious Mosquitoes")
> legend("right",
legend=c("Lambda_L","d_L","ac_1","beta_L","nu_L",
"gamma_L","Lambda_N","d_N","ac_2","nu_N","gamma_N",
"Lambda_M", "d_M", "ac_3", "ac_4", "nu_M", "d_M1",
"d_M2", "Sigma"),bty = "n", col = rainbow(19),
cex = 0.55,lty=1,inset=c(-0.5,0), ncol=2)
#return the par to original
> par(mar=c(5, 4, 4, 2) + 0.1)
```

```
#Univariate Sensitivity
> summary(SnsI_M2)
# Bivariate Sensitivity
> cor(SnsI_M2[,-(1:2)])
> pairs(SnsI_M2)

# Mean of I_L.
> yL <- c(16.00,-18.07,37.02,17.43,2.77,-214.08,0.50,
-0.15, 0.30,-0.04,-2.23,31.67,-3.71,1.96,1.70,13.56,
-14.23,-42.84,-40.97)
> par(las=2) # make label text perpendicular to axis
> par(mar=c(5,8,4,2)) # increase y-axis margin.
> barplot(yL,names=c(" Lambda_L", "d_L", "ac_1",
"beta_L", "nu_L", "gamma_L", "Lambda_N","d_N",
"ac_2", "nu_N","gamma_N", "Lambda_M", "d_M",
"ac_3", "ac_4", "nu_M", "d_M1","d_M2", "Sigma"),
col=rainbow(19),xlim=c(-215,40),horiz=TRUE,
cex.names=0.8)
> axis(1, at = c(-220, 40, by = 20))
> #return the par to original
> par(mar=c(5, 4, 4, 2) + 0.1)

# Mean of I_N.
> yN <- c(0.10,-0.10,0.17,0.14,-0.11,-1.01,22.63,
-9.12,14.65,0.65,-133.32,12.28,-1.56, 0.59,0.32,
5.04,-5.87,-18.51,-15.73)
```

```
> par(las=2) # make label text perpendicular to axis
> par(mar=c(5,8,4,2)) # increase y-axis margin.
barplot(yN,names=c(" Lambda_L", "d_L", "ac_1",
"beta_L",  "nu_L", "gamma_L", "Lambda_N","d_N",
"ac_2", "nu_N" , "gamma_N", "Lambda_M", "d_M",
"ac_3", "ac_4", "nu_M", "d_M1","d_M2", "Sigma"),
col=rainbow(19),xlim=c(-135,25),horiz=TRUE,
cex.names=0.8)
> axis(1, at = c(-135,25, by = 10))
#return the par to original
> par(mar=c(5, 4, 4, 2) + 0.1)

# Mean of I_M2
> yM <- c(0.02,-0.02,0.67,0.03,0.68,-0.22,0.05,
-0.02,0.48,0.49,-0.21,3.03,-6.10,1.23,2.22,
14.81,-14.50,-38.64,-3.61)
> par(las=2) # make label text perpendicular to axis
> par(mar=c(5,8,4,2)) # increase y-axis margin.
> barplot(yM,names=c(" Lambda_L", "d_L", "ac_1",
"beta_L",  "nu_L", "gamma_L", "Lambda_N","d_N",
 "ac_2", "nu_N" , "gamma_N", "Lambda_M", "d_M",
 "ac_3", "ac_4", "nu_M", "d_M1","d_M2", "Sigma"),
col=rainbow(19),xlim=c(-40,15),horiz=TRUE,
 cex.names=0.8)
> axis(1, at = c(-40,15, by = 1))
#return the par to original
```

```
> par(mar=c(5, 4, 4, 2) + 0.1)
```

package (xtable) [18] was used to print R output into tex file.

```
> install.packages("xtable")

> library(xtable)

> result <-summary(SnsI_L)

> print(xtable(result), type="latex", file="output.tex")

#Note: You can control the number of digits using:

 > xtable(result, digits=-3)

# R output to csv file

result<- SnsI_L

write.csv(result, file = "output.csv")
```