SUBHARMONIC BIFURCATION IN MALARIA-LASSA FEVER CO-INFECTION EPIDEMIC MODEL WITH OPTIMAL CONTROL APPLICATION

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Certification

I certify that this work was carried out by Mr Akindele Akano ONIFADE with matriculation number 159290 in the Department of Mathematics, Faculty of Science, University of Ibadan under my supervision

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Dedication

This thesis is dedicated to the glory of Almighty God, THE FATHER, THE SON and THE HOLY SPIRIT, who has made this programme a success.

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Except the Lord builds the house, they labour in vain that build it..." Indeed without the involvement of the Almighty God - Omnipotent, Omniscient, Omnipresent, this work would not have been a success. Great is thy faithfulness O Lord! I sincerely thank my supervisor, Dr. O.S Obabiyi for his counsel, advice, instructions, free access and all the encouragement given to make this work a success. May the Lord guide, support, keep and promote him and his family.

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Abstract

Co-infection with malaria often complicate and increase the severity of disease pathogenesis. The co-infection of malaria and Lassa fever has not been fully understood. Many researcher have worked on mathematical models describing the features involved in the transmission of mono-infection of malaria and Lassa fever. However, models on co-infection that incorporate seasonal variation of vectors needed for a full understanding and management of the co-infection in human with plasmodium falciparum and Lassa virus are sparse. Therefore, this study was designed to develop a mathematical model that incorporates seasonal variation of vectors and investigate the effect of endemic malaria mortality rate of Lassa fever patients.

A co-infection mathematical model governed by a system of ordinary differential equations that incorporates seasonal variation of vectors, ξ_m, diagnostic factor for treatment, η_v, treatment rate, σ, biting rate, b, contact rate, w_1, proportion of effective treatment, γ_v and force of infection, ϕ_0 was formulated using law of mass action. The state variables N_{es}, N_{is} and N_{rs} denoted the number of human population that were exposed, infected and recovered from Lassa fever, respectively, but susceptible to malaria. Moreover, N_{se}, N_{si} and N_{sr} represented those exposed, infected and recovered from malaria, respectively, but susceptible to Lassa fever. The rodent population (obtained from the literature) were classified as S_d, E_d and I_d represented those susceptible, exposed and infected, respectively. Furthermore, the mosquito population were classified as S_m, E_m and I_m denoted those susceptible, exposed and infected, respectively. Using next generation matrix method, the basic reproduction number, $R_0(a,t)$ of the co-infection model was computed, where a is the age and t is the time. Applying perturbation method, stable subharmonic bifurcation solutions were determined. With the aid of suitable Lyapunov function, the stability of the equilibra were explored. Using Pontryagin maximum principle,

necessary condition for the optimal control were derived. Numerical analyses of the model were carried out to investigate the parameters most responsible for disease transmission using data obtained from World Health Organization database.

The established mathematical model gives a system of fourteen ordinary differential equations with the first four as:

$$\begin{aligned} N'_{rs}(t) &= \alpha\gamma_v N_{es} + \eta_v \sigma N_{is} - \mu N_{rs} + bw_1\phi_0 N_{es}, \\ S'_m(t) &= \xi_m - \lambda_m S_m(t) N_{is} - \mu_m S_m, \\ E'_m(t) &= \lambda_m S_m(t) N_{is} - \mu_m E_m, \\ I'_m(t) &= -\mu_m I_m, \end{aligned}$$

where, μ and μ_m are human and mosquito death rate respectively;λ_m is the transmission rate. The $R_0(a,t)$ was computed as $R_0(a,t) = \sqrt{R_{hm}R_{mm}}$, where R_{mm} and R_{hm} are the vector and human threshold parameters, respectively. An infinite number (n) of stable subharmonic solutions was obtained as $N_{ss}(t,a_i) = N_{ss_n}(t+\alpha)$, where α is the treatment rate of infected human with malaria. The disease-free and endemic equilibria were found to be globally and asymptotically stable since $R_0(a,t) = 0.496$ and $R_0(a,t) = 2.684$, respectively. Conditions for existence and uniqueness of optimality system, $u_1u_2u_3$ were established, were $u_1u_2u_3$ are the control functions. Vectors biting rate b and contact rate w_1 among eleven positive sensitivity index parameter values: $\mu = 0.000038$, $b = 1.58$, $w_1 = 1.38$,$\mu_m = 0.054$, $\gamma_v = 0.00027$, $\sigma = 0.012$, $\alpha = 0.50$, $\eta_v 0.0053$, $\lambda_m = 0.26$, $\xi_m = 0.50$ and $\phi_0 = 0.24$ contributed majorly to the transmission of the diseases.

The formulated model captured seasonal variation of vectors and also showed that co-infection of malaria and Lassa fever increased mortality rate in infected patients.

Keyword: Seasonal variation, Co-infection mathematical model, Stable subharmonic solution

Word count: 491

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CHAPTER ONE

INTRODUCTION

Human beings are at constant risk of infectious diseases. No human can be exempted from the menace of epidemic disease (Ademola and Odeniran 2016) . The continuous reports from emerging and re-emerging infectious diseases remain a global concern. Transmission mechanisms of epidemic disease can only be properly understood by developing potent prophylactic tools for existing and emerging organisms (CDC 2019). Micro-organisms are usually the main causes of infectious diseases, depending on their virulence and pathogenic state. The major causal organisms causing infectious diseases are those of parasites, viruses and bacteria. The infectious attribute of pathogens connotes "transmission of organism from an infected individual to a non-infected individual". At this juncture, our discussion is limited to malaria, Lassa fever and malaria-Lassa fever co-infection diseases which are the main focus of this study.

Malaria, a common parasitic disease in some parts of sub-Saharan Africa, Asia and Latin America, is caused by the genus *Plasmodium*. There are several known species, however, humans are often affected through the bite of the female Anopheles mosquito vector. Global estimates of malaria show 80 percent cases from Africa, and malaria is responsible for more than a million annual death in affected developing countries(WHO, 2012; CDC, 2019). Among children under five years of age, malaria seems to be the leading cause of mortality, with similar incidence among pregnant women (WHO, 2012). In pregnant women, severe malaria cases have been reported to cause maternal death, still birth, severe anaemia, congenital malformations and low birth weights (WHO, 2012; Olaniyi et al 2018). The problem of chemotherapeutic drug resistance against the *Plasmodium* organism and insecticidal resistance on the mosquito vector has been widely reported and also linked to the growing incidence rate of malaria disease in endemic communities (CDC, 2019). Therefore, the transmission dynamics can only be better understood by developing

cogent parameters in the disease transmission coupled with strategically analysing the control measures to stem its spread.

Lassa fever is a viral disease caused by an Arenavirus popularly called Lassa virus. It is zoonotic and acute in nature, responsible for severe haemorrhagic fever with symptomatic conditions such as sore throat, chest and abdominal pain, fever, nausea, muscle cramps, vomiting and ocular discharges (CDC, 2015). Although, there is no clinical manifestation of the virus in Mastomys natalensis, the virus has been observed to be excreted at higher doses in the urine (Keenlyside et al, 1983). Infection are often observed across the year, however, peak periods have been observed between January and May during the dry season in tropical regions (Tomori et al, 1998). Rodents with the virus remain carriers and serve as reservoir host. The virus are excreted in respiratory secretions, urine, wound sites from trauma and saliva (Keenlyside et al, 1983). Human-human Lassa fever transmission could occur through formites (equipment etc) (Fisher-Hoch et al, 1995).

1.1 History of malaria and Lassa fever

Here, we give a brief account of the origin, causes and transmission of malaria and Lassa fever diseases. However, a full account of the discovery of malaria and Lassa fever diseases can be seen in Nadezhda and David (2012) and Cox (2010) .

1.1.1 Malaria history

In 1880, a French physician, Charles Louis A. Laveran, while working in Algeria, made a landmark discovery of the main cause of the malaria disease that has been affecting human lives for a long period. He discovered the presence of a parasitic protozoan *Plasmodium* in the blood of humans infected with malaria and was as a result awarded the Nobel prize in 1907. In other discovery, an experiment was conducted in 1897 by a British Physician, Ronald Ross, who showed for the first time that mosquito is responsible for transmission of the *Plasmodium* parasite that causes malaria in human population.

Not less than half of the world's population, distributed across 104 countries are at risk of malaria disease (Olaniyi et al 2018; WHO, 2019). Meanwhile, an initial report of 300 - 500 million persons have been observed to be infected annually, of which 1.5 - 2.7 million annual deaths have been estimated (Magombedze et al, 2011; WHO, 2019). Malaria is widely spread in tropical and subtropical regions,

including Africa, Asia, Latin America, the middle East and some parts of Europe. However the most cases and deaths occur in sub-Saharan countries of Africa which account for 80 percent of the world's malaria cases and 90 percent of the global malaria deaths (WHO, 2012; CDC, 2019).

Death of an African child occurs in every 30 seconds, while global report of deaths from malaria exceeds 2000 among the youth. (Tumwiine et al, 2007; Okosun and Makinde, 2011; CDC 2019). For example, in Nigeria, malaria accounts for 60 percent of outpatient visits and 30 percent of hospitalization with children under five years of age most severely affected (USE, 2011).

1.1.2 Malaria parasites and cycle

Malaria is a disease characterized by fever, pain, paroxysms of chills, headache and vomitting. The disease is caused by protozoan parasite, known as *Plasmodium*. The commonest species that infect humans are; *Plasmodium vivax, P. ovale, P. falciparum, P. malariae* and *P. knowlesi*. The socioeconomic burden of malaria disease and its clinical signs include multi-organ failures such as lung, brain, liver and kidney (Tumwiine et al., 2007).

The life cycle of the *plasmodium* parasite can be divided into two phases: sexual and asexual phases, with the sexual phase taking place in the female *anopheles* mosquito and asexual phase in the human host (Ibezim). The infection subtly begins when an infectious mosquito pierces the human skin with its proboscis and injects parasite in the form of sporozoites into the human's bloodstream for blood circulation. In the process, the sporozoites enter the liver where each sporozoites undergoes asexual multiplication stage to produce cells called merozoites. This first asexual multiplication stage in human host is known as exoerythrocytic schizogony (Cox, 2010).

Following the rupture of the hepatocytes, merozites escape into circulatory system for asexual reproduction in the red cells, a stage called erythrocytic schizogony develops (Cox, 2010). At this stage, more merozoites are produced until the red blood cells burst and new merozoites are released to further infect other red blood cells while some merozoites developed into gametocytes (Cox, 2010). These geametocytes in the human's bloodstream can be taken up by a naive mosquito in the blood meal gametocytes and mature into male and female gametes in the mosquito's gut. Consequently, microgamete and macrogamete representing male and female gametes respectively, fuse salivary gland of the mosquito vector where they can be injected when the mosquito bites another human host to continue the cycle.

1.1.3 Lassa fever history

In Nigeria, Lassa fever was first identified in Lassa Town in 1969. The early description of the disease was identified as a new viral species without a name from a man in West Africa (Fisher-Hoch et al., 1995). A renouned scientist known as Dr John Frame of Columbia University was interested in nature of the fever among

Africans and needed blood samples to confirm the aetiological agent in the United States of America. It's discovery in Nigeria, occurred shortly after the death of two missionary nurses were reported with symptoms of dramatic fever. Incidentally, a third nurse (Penny Pinneo) got infected with similar symptoms and was quickly transferred to the USA for treatment. On this patient, Dr. Frame collected samples to be analysed. Also, during early stages of researching, the death of a laboratory technician at the Yale Arbovirus Research Unit was reported, while an infected researcher survived the disease episode (WHO, 2012).

Annual deaths in West Africa from Lassa fever stands at 5,000 (CDC, 2015). In spite of laudable achievements made in recent years in the biology and epidemiology of Lassa virus, there are still several aspects that need to be unraveled to improve the understanding of the disease.

1.1.4 Lassa virus

The disease, Lassa fever is caused by Lassa virus. The symptoms observed are not pathognomonic, hence several common signs include general weakness, headache, sore throat, fever, abdominal pain, cough and other flu-like characteristics. Clinical manifestations include haemorrhagic conditions especially vascular permeability (Nadezhda and David, 2012)

The 1960 Nobel winner of Medicine and Physiology, Peter Medawar, gave an intriguing definition of a virus as being a piece of nucleic acid enveloped in bad news. Basically, viruses contain genetic material composed of nucleic acid (DNA/RNA) in different forms (segmented/nonsegmetnted) and a protein coat. The information produced from the nucliec acid determines the multiplication of viruses. Their multiplication and survival only takes place in the host cell (plants, animals, fungi, protozoa and bacteria). One of the most distinguishing features of viruses is the lack of cellular wall, hence they are obligatory, with dependency on the host cells.

1.1.5 Co-infection of Lassa fever and malaria

When the Lassa virus infects the central nervous system, it is extremely difficult to treat This makes a *Plasmodium* and Lassa virus coinfection so severe that therapy may be ineffective. Co-infection of parasite-viral or bacteria-virus interaction need to be considered, especially when bacteria septicaemia often results from vi-

ral haemorrhagic fever complications. Moreover, positive test results for malaria disease should not exclude the possibility of viral haemorrhagic fever. This is an important consideration especially in a non-responsive antimalaria treatment, since parasitaemia in some cases may be pre-existing and often common in holoendemic areas. The co-infection of Lassa fever and malaria in endemic countries could limit the detection of Lassa fever, especially in areas were both disease are endemic (Okokhere et al, 2010).

Clinical diagnosis with improved techniques have been reported using RT-PCR. The method was able to detect the presence of Lassa virus and malaria parasite in 27 patients with a subsequent malaria blood smear method. Although, 46 patients were observed to be positive of Lassa fever but negative to malaria. Patients show transient fever duration and low average temperature on admission(Okokhere et al, 2010).

1.1.6 Knowledge gap

Infectious disease is directly related to seasonal changes, which have now been observed in both tropical and temperate regions. However, seasonal variation of vectors that changes the transmission of malaria-Lassa fever co-infection and diagnostic factor for treatment have not been extensively studied using mathematical model. Humans in natural populations could be infected with multiple different parasites simultaneously (at a time). These parasites could interact with each other or act independently in the host, and this could result to different outcomes on individual health and survival. Therefore, this study was designed to develop a co-infection (malaria and Lassa fever) mathematical model to investigate the effect of endemic malaria mortality rate of Lassa fever patients and, to the best of our knowledge this has not been reported in the literature. The basic reproduction number R_0 for a non-seasonal infection is typically defined as the number of secondary infections that result from the introduction of a single infectious individual into an entirely susceptible population. This has been computed and used by many researchers in the area of mathematical biology to examine stability. However, the basic reproduction number, $R_0(a,t)$, for seasonal infection has not been examined on malaria-Lassa fever co-infection epidemic using mathematical model.

1.1.7 Motivation for the study

The motivation for this work is to study the qualitative and quantitative properties of solutions of subharmonic bifurcation in malaria-Lassa fever co-infection epidemic model with optimal control application by exploring periodic behaviour of the system in the sense of Ira and Smith 1983. Standard epidemiology theory such as basic reproduction number no longer enough to determine stability, and the implications for interventions that themselves may be periodic have not been formally examined. Therefore, this study established that for malaria-Lassa fever co-infection model that incorporate diagnostic factor for treatment and season variation of vectors (mosquito and rodent) there exists infinite number of subharmonic bifurcation.

1.1.8 Aims and objectives of the study

This study was designed to formulate and analyse mathematical model of malaria-Lassa fever co-infection dynamic that incorporates seasonal variation of vectors (mosquito and rodent) and diagnostic factor for treatment. These situation are critical to enhance predictive power for decision support. Furthermore, this study was also designed to investigate the effect of endemic malaria mortality rate of Lassa fever patients. To

In order to achieve the aforementioned aims, the following specific objectives are pertinent:

(1) Establish the feasible region where the formulated model is mathematically well posed in terms of seasonal incidence function.

(2) Obtain the equilibrium points of the model with respect to seasonal incidence function.

(3) Determine the basic reproduction number of the model in terms of seasonal incidence function.

(4) Investigate the nature of the system near the equilibrium point by local and global stability analysis with respect to seasonal incidence function.

(5) Determine the contributory effects of the model parameters in the transmission of malaria-Lassa fever co-infection through sensitivity analysis.

(6) Analyse the possibility of co-existence of the malaria-Lassa co-infection in terms of seasonal incidence function.

(7) Obtain the existence of subharmonic solutions of the model.

(8) Frame the disease management question of the model with respect to seasonal incidence function into an optimal control problem.

(9) Examine the significance of control strategies through numerical simulation.

CHAPTER TWO

LITERATURE REVIEW

Mathematical modelling of malaria began in 1911 with Ronald Ross who discovered the role of mosquito as an intermediate vector in the transmission of the pathogenic malaria parasite. He introduced the first deterministic model of the form

$$\begin{aligned} \frac{dI_h}{dt} &= b\beta_h m(1-I_h)I_m - rI_h \\ \frac{dI_m}{dt} &= b\beta_m(1-I_m)I_h - \mu I_m \end{aligned}$$

with variable I_h representing the fraction of infectious humans and I_m representing the fraction of infectious mosquitoes; b is the mosquito biting rate; β_h represents the proportion of bites that produce infection in human; m denotes the fraction of number of mosquitoes to that of humans; r represents human recovery rate; β_m represents the proportion of bites that produce infection in mosquito; and μ denotes per capita rate of mosquito mortality. This model revealed that eradication of malaria could be made possible by decreasing vector (mosquitoes) biting rate and increasing the mosquito death rate resulting to reduction of threshold parameter given

$$R_0 = \frac{mb^2\beta_h\beta_m}{r\mu}$$

The Ross model was modified by Macdonald (1957), his model incorporates the latency period of parasite in mosquitoes in which the exposed class was introduced. His findings showed that the basic reproduction number of the disease decreases with an increase in the latency period. A mathematical model was formulated by Ira and Smith (1983), the model stimulates permanent immunity and stability analysed. The findings of their study showed that environmental factor could perturb the dynamical state from one subharmonic to another.

Further extension was described by Chow and Shaw (1986), they came up with four dimensional piecewise linear second order ordinary differential equations. The behaviour of the periodic solutions of their model was examined. Their anal-

ysis concluded with the result that subharmonic motions with period n appear through saddle-node bifurcation for $n = 1, 2, 3, \ldots$. Macdonald's model was further extended by Anderson and May (1991) as they introduced new exposed class into the human population. This improvement has further decreased the long-term prevalence of both infected humans and mosquitoes.

Yu and Piccardi (1994) examined the bifurcation of the periodic solutions of models with sinusoidal varying contact rate. The research work which was an extension of Ira and smith demonstrated by numerical simulations that when there is a variation in latent period, the parameter portrait of the model undergoes significant structural changes.

The basic models discussed above are the building-ground for literature on malaria models. Since then, different factors have been incorporated in order to make the models epidemiologically more realistic. One such factor is the inclusion of recovered class into the human population on the idea that continuous exposure to reinfection could lead to acquired immunity in human. A deterministic model that incorporated human and mosquito populations with standard incidence function was developed by Nwga and shu (2000). Their model made an exploration of the structure in which an infectious human recovers with temporary immunity to become a recovered human before entering the susceptible compartment again. The result of their analysis revealed that there is persistence in the disease whenever the threshold parameter R_0 exceeds one and that the disease-free equilibrium is globally asymptotically stable when R_0 is below one.

Factors such as: environmental effects, mosquitoes resistance to insecticides, resistance of some parasite strains to anti-malaria drugs and the use of optimal control methods have been integrated into the models so as to gain more insight on the behaviour of the disease. Yang and Ferreira (2000) used bilinear incidence function to study malaria transmission model by incorporating socio-economic structure. Through the model analysis, they showed how the basic reproduction number changes with global warming and local social and economic conditions.

In addition, Iddi et al (2002) used deterministic model with standard incidence function to study the impact of infectious immigrants on vector-borne disease with direct transmission. The research work was analyzed qualitatively, the computation of the basic reproduction number using the next generation matrix method and

the conditions for the stability of the equilibra were determined. It was revealed through numerical simulation that hike in the number of immigrants tends to result to an increment in the number of infected population which leads to the persistence of the disease in the population.

Koella and Anita (2003) developed a model in order to understand the epidemiology of anti-malaria resistance and to assess approaches to decrease resistance spread. Their analyses showed that resistance to treatment does not spread if the fraction of infected individuals treated is less than a threshold value and if the drug treatment exceeds this value, then resistance to drug eventually becomes fixed in the population.

Chitnis et al (2006) presented a malaria model that incorporated human immigration and disease-induced death rates. This model was based on Nwga and Shu model. The basic reproduction number was obtained to investigate the stability of disease-free equilibrium point using the next generation operator approach. It was further depicted through numerical examples that backward bifurcation is possible for some positive values of disease-induced death rate.

In another development, Tumwiine et al (2007) developed a five dimensional model with standard incidence function for the dynamics of malaria in the human hosts and vectors. In this model, the reservoir of the susceptible human was refilled by immunity loss to the disease and newborns. The stability of the system was analysed for the existence of disease-free and endemic equilibra. However, it was shown that the basic reproduction number is independent of the rate of loss of immunity.

Schaffer and Bronnikova (2007), from another perspective, discussed the bifurcation structure of epidemic model subject to seasonality. The combination of phenomenological equation (Regression analysis in Statistical model) which admits to mathematical analysis and detailed simulation was suggested in their result as a proof and recipe for progress.

In addition, Chitnis et al (2008) carried out a sensitivity analysis of malaria model with human immigration factor and disease-induced death rate in order to determine the relative importance of model parameters to the disease transmission and prevalence. A computation of sensitivity indices of the basic reproduction number to parameters at the baseline values was done. It was found out that the

basic reproduction number is most sensitive to the mosquito biting rate.

Labadin et al (2009) formulated and analysed a deterministic model with standard incidence function. In this model, a consideration of the recovered population with and without immunity and the impact of the different values of the average duration to build effective immunity on infectious humans were investigated numerically. The findings of their research showed that if the ability to build an effective immunity is fast for those who recovered from the disease, then the number of cases could be reduced.

One of the contributory factors to the spread of malaria is proven to be the movement of human from one environment to another. In the light of this, Arino et al (2011) came up with a metapopulation model for malaria where interaction between humans in rural and urban area was investigated. They brought to the light that the basic reproduction number governed the stability of the disease-free steady state. Also, the unrestricted movement of infected humans could lead to the persistence of the disease in the population. Again, the class of infectious individuals with drug resistance symptoms was incorporated in the standard incidence function deterministic model that was formulated and analysed by Okosun and Makinde (2011). The model was shown to exhibit backward bifurcation and by the basic reproduction number, the existence and stability of equilibria were established. Pontryagin maximum principle was used to obtain conditions for optimal control of the disease and their numerical results showed that effective control of the proportion of individuals with drug resistance has a positive impact in reducing the spread of the disease.

Magombedze et al (2011) developed an intra-host mathematical model of malaria that described the interaction of immune system with the blood stage malaria merozoites. Optimal control strategy was used to analysis their model. This led to a suggestion in their result that a malarial therapy that seeks to minimize merozoites population was beneficial to patients as this will lead to the reduction of infected red blood cells. Also, a seven-dimensional compartmental model of malaria that incorporated three control functions such as: the prevention of host-vector contacts, treatment of hosts and reduction of mosquito population was studied by Lashari et al (2012). In the analyses by the model, necessary conditions for optimal control of malaria were obtained. The numerical simulation of

the model revealed that the combination of the control efforts has a very desirable effect on the population in reducing the number of infected individuals.

The influence of seasonal forcing system when the dynamical system which is unforced have either stable, monotonic or oscillatory cycle was examined by Rachel et al (2012). Their results revealed that the degree of oscillation in the unforced system has a larger effect on the range of behaviour when the system is seasonally forced.

Moreover, Gouhei and Kazuyuki (2013) investigated the influence of seasonal structure on disease transmission dynamics. In their result, it was suggested that accurately estimated seasonal fluctuation is necessary to have good knowledge on disease transmission.

Furthermore, Olaniyi and Obabiyi (2013) formulated a mathematical model that incorporated antibodies to curtail transmission of parasite that causes malaria in both human and mosquito; and stability analyzed through threshold parameter. The results of their analyses showed that the disease will not persist in the population whenever R_0 is below unity. However, the system become unstable whenever R_0 is above unity.

In a related work, a non- autonomous model that incorporated multiple control measures was developed by Olaniyi et al (2018) to investigate the dynamics of malaria transmission in both human and mosquito populations. With the aid of suitable Lyapunov functions, the stability of both disease-free and endemic equilibra was established. A suggestion was made in the result of their analysis that combination of multiple control at a time by human traveler will help to eliminate the spread of malaria in the population.

Okuonghae and Okuonghae (2006) pioneered research work on Lassa fever using Mathematical modelling. In their study, they derived the conditions for existence of disease-free and endemic equilibra and stability analyzed. The findings of their model revealed that to temporarily control the rodents with the virus, the policy of isolation of individuals infected with the virus is the best strategy against the spread and transmission of the disease.

The knowledge of parasite-host interactions is limited since most studies have focused on mono-parasite infections, and few have worked on co-infections while assessing the severity of infectious diseases. Ademola and Odeniran (2016) in-

vestigated the effect of co-infection of *T. brucei* with *Plasmodium berghei* on parasitaemia, haematological parameters, blood glucose level and survivability in a mice model. The results of their analyses showed that co-infection of mice with *P. berghei* and *T.brucei* resulted in rapid P. berghei and *T. brucei* development and increased parasitaemia. A suggestion was made in the result of their analysis that co-infection of mice with *P. berghei* and *T. brucei* could increase pathologic impact to the host by increasing parasitaemia.

In another development, Okosun and Makinde (2014) proposed a mathematical model for malaria-cholera co-infection in order to investigate their synergistic relationship in the presence of treatments. The results of their analyses revealed that malaria infection may be associated with an increased risk of cholera. However, cholera infection is not associated with an increased risk for malaria. A suggestion was made in the result of their analysis that to effectively control malaria, the malaria intervention strategies by policy makers must at the same time also include cholera control.

The ubiquity of malaria as a co-morbidity in human with Lassa fever and the effect on outcome was investigated by Okokhere et al (2010). In their study, it was revealed that there is high ubiquity of co-infection with malaria in human with Lassa fever, hence spotlighting a high index of suspicion for diagnosis and testing for Lassa fever in malaria endemic area.

Ogabi et al (2012) presented a mathematical model based on the outbreak of Lassa fever in the northern part of Edo State with high prevalence of Lassa fever on contact persons. In their model, the threshold parameter was computed to assess the stability of the model and numerical simulations of their model were discussed. Their analyses established the results that proper awareness need to be done, for people to have a sound knowledge about the disease. Furthermore, government at all level need to embark on a subsidised housing scheme project to reduce contact rate.

A mathematical model for Lassa fever transmission dynamics in two interacting population was formulated by Bawa et al (2013). The stability of the disease free equilibrium was established as well as computing the threshold parameter. Their work suggested the result that every effort must be put in place by all concerned to prevent the virus infection by reducing the threshold parameter

In another development, James et al (2015) formulated a mathematical model for Lassa fever transmission dynamics and stability analyzed. The study established local stability of the disease free equilibrium and computed the threshold parameter which can be used to control the transmission dynamics of the disease.

Onuorah et al (2016) formulated six dimensional system of nonlinear ordinary differential equation for Lassa fever. In their analyses, the effects of the control parameters on the various compartments of the model were revealed and they concluded that if the basic reproduction number is low the disease will still continue to spread. Suggestion for further studies was made on the endemic equilibrium and bifurcation analysis.

A mathematical model presented in this work differs but gains insight from that studied by Chow and Shaw (1986), Akinwande (2013) and Onuorah et al (2016) in conjunction with the previous studies surveyed so far as it incorporates seasonal variation of vectors and diagnostic factor for treatment of malaria-Lassa fever co-infection. Also, there is a need to further investigate the effect of endemic malaria mortality rate of Lassa fever patients.

CHAPTER THREE

MATERIALS AND METHODS

3.1 STUDY ONE

Basic tools in mathematical modelling

3.1.1 Malaria-Lassa fever co-infection model seasonal functionality description based on feasible region

Deterministic mathematical models are those in which the values assumed by the variables, or the changes in the variables, can be predicted with certainty. They have no features that are intrinsically uncertain, unlike stochastic models, and thus no parameters in the models are characterized by probability distributions. Furthermore, deterministic models require fewer simulations for a given set of parameters, and they always produce the same results for a given set of starting values. Deterministic models use algebraic or differential equations to model real-world scenarios, whereas stochastic models use probability distributions.

Deterministic models are commonly used in mathematical epidemiology to explain the spread of infectious diseases in a population. Because the individuals in the population are divided into subgroups or compartments based on their status in relation to the infection under study, these models are often referred to as compartmental models (Ross, 1911). In general, compartmental models of infectious disease transmission dynamics are governed by an n^{th}-dimensional system of first order nonlinear continuous ordinary differential equations of the form:

$$\left.\begin{array}{rcl} \frac{dx_1}{dt} & = & f_1(x_1(t), x_2(t), ..., x_n(t)) \\ \frac{dx_2}{dt} & = & f_2(x_1(t), x_2(t), ..., x_n(t) \\ \vdots & & \\ \frac{dx_n}{dt} & = & f_n(x_1(t), x_2(t), ..., x_n(t) \end{array}\right\} \tag{3.1.1}$$

which can be expressed in matrix form as

$$\frac{d\mathbf{X}}{dt} = \mathbf{f}(\mathbf{X}(t)) \tag{3.1.2}$$

where

$$\mathbf{X} = \begin{pmatrix} x_1 \\ x_2 \\ \vdots \\ x_n \end{pmatrix} \quad \text{and} \quad \mathbf{f} = \begin{pmatrix} f_1 \\ f_2 \\ \vdots \\ f_n \end{pmatrix}.$$

The main point of interest in mathematical modelling is long-term behaviour of solutions to the equations involved.

3.1.2 Model description

At this stage, mathematical symbols are introduced to represent the important features of the problem. This usually involves writing the assumptions as mathematical equations by concentrating on the variables and parameters of the problem.

To study the transmission dynamics of malaria-Lassa fever co-infection in three interacting populations of humans (the host), mosquitoes (the vector) and rodents (the vector) that incorporate seasonal variation of vectors and diagnostic factor for treatment of malaria-Lassa fever co-infection, we formulated a model which subdivides the total human and rodent populations size at time t and discrete age a_i and e_j denoted by $N_h(t,a_i) = N_{ss}(t,a_i) + N_{es}(t,a_i) + N_{is}(t,a_i) + N_{rs}(t,a_i) + N_{se}(t,a_i) + N_{si}(t,a_i) + N_{sr}(t,a_i) + N_{rr}(t,a_i)$ and $N_d(t,e_j) = S_d(t,e_j) + E_d(t,e_j) + I_d(t,e_j)$ with $i = 0,1,2,...,L$ and $j = 0,1,2,...,T$. a_L and e_T are the maximum age of humans and rodents in the population. Similarly, the total mosquito population size at time t is denoted by $N_m(t) = S_m(t) + E_m(t) + I_m(t)$.

The state variables N_{es}, N_{is} and N_{rs} denote the number of human population that were exposed, infected and recovered from Lassa fever, respectively, but susceptible to malaria. Moreover, N_{se}, N_{si} and N_{sr} represents those exposed, infected and recovered from malaria, respectively, but susceptible to Lassa fever. However, N_{ss} represents those susceptible to both diseases. The rodent population were classified as S_d, E_d and I_d representing those susceptible, exposed and infected, respectively. Furthermore, the mosquito population were classified as S_m, E_m and I_m denoting those susceptible, exposed and infected, respectively. Let $\lambda_M(t) = c_0(a_i)(1 + b\cos(2\pi t + T))I_m$ be the malaria infection rate, where $c_0(a_i) = \frac{c_m(a_i)}{N_h(t,a_i)}$, $\frac{b}{N_h(t,a_i)}$ is the contact rate between human and mosquito and b is the rate at which human is being bitten by mosquito. Similarly, $\lambda_a(t) = \rho_0(a_i)(1 + w_2(e_j)\cos(2\pi t + T))I_d(t,e_j)$ and $\lambda_b(t) = \sigma_0(a_i)(1 + w_1(a_i)\cos(2\pi t + T))N_{is}(t,a_i)$ are the force of infection for

Lassa fever, where $\sigma_0 = \frac{d_1(a_i)}{N_h(t,a_i)}$ and $\rho_0 = \frac{d_2(a_i)}{N_h(t,a_i)}$. In the mosquito and rodent populations $\lambda_m(t) = \phi_0(1+b\cos(2\pi t+T))$ and $\lambda_d(t) = \beta_0(e_j)(1+w_2(e_j)\cos(2\pi t+T))$, where $\phi_0 = \frac{\sigma_m}{N_m}$ and $\beta_0(e_j) = \frac{\beta_d(e_j)}{N_d(t,e_j)}$

The subscripts d, m represent Lassa fever (rodent) and malaria (mosquito) respectively. Since ribavirin (anti-viral drug) is effective when it is administered early. It is assumed that both exposed and infectious human are treated at rate $\gamma_v(a_i)\alpha(a_i)N_{es}(t,a_i)$ and $\eta_v(a_i)\sigma(a_i)N_{is}(t,a_i)$ respectively. $N_{rr}(t,a_i)$ represents those who are infected with both diseases.

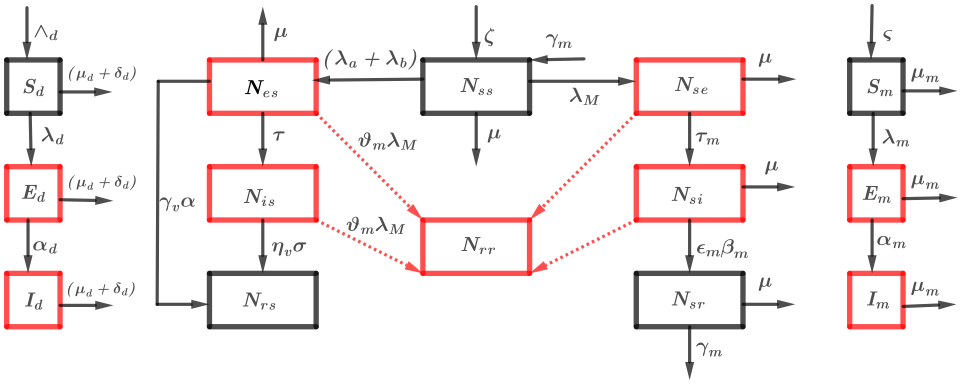

Figure 3.1: Compartmental model for the Malaria-Lassa fever co-infection transmission

In summary, the formulation of the compartmental model is based on the following assumptions:

1. That all humans are born susceptible to both Lassa fever and malaria. That is, humans are liable to contract the diseases.
2. That the susceptible humans, when infected, becomes exposed humans who are not yet infected.
3. That the exposed humans progress to become infectious only.
4. That the infectious humans may either die naturally or as a result of the disease, and if not, they become recovered humans due to treatment.
5. That humans can contract both Lassa fever and malaria simultaneously
6. That all rodents and mosquitoes are born susceptible.
7. That each class of rodents population may either die naturally or by hunting and use of pesticide
8. That the susceptible rodents, when infected, becomes exposed rodents which are not yet infectious.
9. That the exposed rodents and mosquitoes progress to become infectious only.
10. That the susceptible rodents become infected when they eat or drink water together with infected rodents.
11. That the infectious rodents and mosquitoes remain infectious for life. That is, there is no loss of infectiousness for both rodents and mosquitoes populations.

In what follows, we obtain a fourteen-dimensional system of ordinary differential equations which describes the disease transmission as:

$$\frac{dN_{ss}(t,a_i)}{dt} = \zeta(a_i) - \sum_{i=0}^{L}\sum_{j=0}^{T}(\lambda_a+\lambda_b)N_{ss}(t,a_i) - \sum_{i=0}^{L}\lambda_M N_{ss}(t,a_i)I_m$$
$$- \mu(a_i)N_{ss}(t,a_i) + \gamma_m(a_i)N_{sr}(t,a_i) \quad (3.1.3)$$

$$\frac{dN_{es}(t,a_i)}{dt} = \sum_{i=0}^{L}\sum_{j=0}^{T}(\lambda_a+\lambda_b)N_{ss}(t,a_i) - \sum_{i=0}^{L}\vartheta_m(a_i)\lambda_M N_{es}(t,a_i)I_m$$
$$- (\mu(a_i)+\gamma_v(a_i)\alpha(a_i)+\tau(a_i))N_{es}(t,a_i) \quad (3.1.4)$$

$$\frac{dN_{is}(t,a_i)}{dt} = \sum_{i=0}^{L}\tau(a_i)N_{es}(t,a_i) - \sum_{i=0}^{L}\vartheta_m(a_i)\lambda_M N_{is}(t,a_i)I_m$$
$$- (\mu(a_i)+\eta_v(a_i)\sigma(a_i))N_{is}(t,a_i) \quad (3.1.5)$$

$$\frac{dN_{rs}(t,a_i)}{dt} = \sum_{i=0}^{L}\gamma_v(a_i)\alpha(a_i)N_{es}(t,a_i) + \eta_v(a_i)\sigma(a_i)N_{is}(t,a_i) - \mu(a_i)N_{rs}(t,a_i) \quad (3.1.6)$$

$$\frac{dN_{se}(t,a_i)}{dt} = \sum_{i=0}^{L}\lambda_M N_{ss}(t,a_i)I_m - \sum_{i=0}^{L}\sum_{j=0}^{T}\vartheta_d(a_i)(\lambda_a+\lambda_b)N_{se}(t,a_i)$$
$$- (\mu(a_i)+\tau_m(a_i)N_{se}(t,a_i) \quad (3.1.7)$$

$$\frac{dN_{si}(t,a_i)}{dt} = \sum_{i=0}^{L}\tau_m(a_i)N_{se}(t,a_i) - \sum_{i=0}^{L}\sum_{j=0}^{T}\vartheta_d(a_i)(\lambda_a+\lambda_b)N_{si}(t,a_i)$$
$$- (\mu(a_i)+\epsilon_m(a_i)\beta_m(a_i))N_{si}(t,a_i) \quad (3.1.8)$$

$$\frac{dN_{sr}(t,a_i)}{dt} = \sum_{i=0}^{L}\epsilon_m(a_i)\beta_m(a_i)N_{si}(t,a_i) - (\gamma_m(a_i) + \mu(a_i))N_{sr}(t,a_i) \quad (3.1.9)$$

$$\frac{dN_{rr}(t,a_i)}{dt} = \sum_{i=0}^{L}\vartheta_m(a_i)\lambda_M(N_{es}(t,a_i)+N_{is}(t,a_i))I_m - \mu(a_i)N_{rr}(t,a_i)$$
$$+ \sum_{i=0}^{L}\sum_{j=0}^{T}\vartheta_d(a_i)(\lambda_a+\lambda_b)(N_{se}(t,a_i)+N_{si}(t,a_i)) \quad (3.1.10)$$

$$\frac{dS_d(t,e_j)}{dt} = \Lambda_d(e_j)(1+\xi_d\cos(2\pi t+T)) - \sum_{j=0}^{T}\lambda_d S_d(t,e_j)I_d(t,e_j) - (\mu_d(e_j)+\delta_d(e_j))S_d(t,e_j) \quad (3.1.11)$$

$$\frac{dE_d(t,e_j)}{dt} = \sum_{j=0}^{T}\lambda_d S_d(t,e_j)I_d(t,e_j) - (\alpha_d(e_j)+\mu_d(e_j)+\delta_d(e_j))E_d(t,e_j) \quad (3.1.12)$$

$$\frac{dI_d(t,e_j)}{dt} = \sum_{j=0}^{T} \alpha_d(e_j)E_d(t,e_j) - (\mu_d(e_j) + \delta_d(e_j))I_d(t,e_j) \tag{3.1.13}$$

$$\frac{dS_m}{dt} = \varsigma_m(1 + \kappa_m \cos(2\pi t + T)) - \lambda_m S_m N_{si}(t,a_i) - \mu_m S_m \tag{3.1.14}$$

$$\frac{dE_m}{dt} = \lambda_m S_m N_{si}(t,a_i) - (\mu_m + \alpha_m)E_m \tag{3.1.15}$$

$$\frac{dI_m}{dt} = \alpha_m E_m - \mu_m I_m \tag{3.1.16}$$

together with the initial conditions

$$\left.\begin{aligned} &N_{ss}(0,a_i) = N_{0ss}(a_i), N_{es}(0,a_i) = N_{0es}(a_i), N_{is}(0,a_i) = N_{0is}(a_i), \\ &N_{rs}(0,a_i) = N_{0rs}(a_i), N_{se}(0,a_i) = N_{0se}(a_i), N_{si}(0,a_i) = N_{0si}(a_i), \\ &N_{sr}(0,a_i) = N_{0sr}(a_i) S_d(0,e_j) = S_{0d}, E_d(0,e_j) = E_{0d}, I_d(0,e_j) = I_{0d}, \\ &S_m(0) = S_{0m}, E_m(0) = E_{0m}, I_m(0) = I_{0m} \end{aligned}\right\} \tag{3.1.17}$$

The table below (table 3.1) provide definition to parameters used in the model formulation. These parameters are factors contributing to the spread and transmission of malaria-Lassa fever co-infection.

Table 3.1: The description of parameters of the malaria-Lassa fever co-infection model.

Definition	Symbols
Recruitment term of the susceptible humans	$\zeta(a_i)$
Recruitment term of susceptible mosquito	ς_m
Recruitment term of susceptible rodent	$\Lambda_d(e_j)$
Biting rate of the mosquito	b
Interacting rate of rodent	$w_2(e_j)$
Interacting rate of human	$w_1(a_i)$
Transmission rate of malaria in human	$c_m(a_i)$
Transmission rate of malaria in mosquito	σ_m
Transmission rate of Lassa fever in human by infectious human	$d_1(a_i)$
Transmission rate of Lassa fever in human by infectious rodent	$d_2(a_i)$
Transmission rate of Lassa fever in rodent by infectious rodent	$\beta_d(e_j)$
Per capita death rate of humans	$\mu(a_i)$
Per capita death rate of mosquitoes	μ_m
Per capital death rate of rodent	$\mu_d(e_j)$
death rate of rodent due to hunting	$\delta_d(e_j)$
Seasonal variation of mosquito	κ_m
Seasonal variation of rodent	ξ_d
Progression rate of Lassa fever in the exposed human host	$\tau(a_i)$
Progression rate of malaria in the exposed human host	$\tau_m(a_i)$
Progression rate of Lassa fever in exposed rodent	$\alpha_d(e_j)$
Progression rate of malaria in exposed mosquito	α_m
Proportion of effective treatment of infectious human for malaria	$\epsilon_m(a_i)$
Treatment rate of infectious human for malaria	$\beta_m(a_i)$
Proportion of effective treatment of exposed human for Lassa fever	$\gamma_v(a_i)$
Diagnostic for treatment of exposed human for Lassa fever	$\alpha(a_i)$
Proportion of effective treatment of infectious human for Lassa fever	$\sigma(a_i)$
Treatment rate of infectious human for Lassa fever	$\eta_v(a_i)$
Rate of loss of immunity to malaria	$\gamma_m(a_i)$

3.2 STUDY TWO

Determination of equilibrium points in Malaria-Lassa fever coinfection model

3.2.1 Equilibrium points

Disease-free and endemic points of equilibrium are the two major types of points of equilibrium in mathematical epidemiology. The former denotes a non-trivial stable-state solution in which all infected compartments in the system are zero, while the latter denotes a positive stable-state solution in which the disease is prevalent.

Definition 3.1: (Lungu, et al, 2007): An equilibrium point of the system of differential equations (3.1.1) is a steady state $\bar{x}$ satisfying $\mathbf{f}(\bar{x}) = 0$ for all time t. This definition means that points at which the system (3.1.2) is equal to zero are referred to as points of equilibrium or steady-state solutions.

3.3 STUDY THREE

The next generation matrix

3.3.1 Basic reproduction number derivation

The basic reproduction number, usually denoted by R_0, is a crucial concept in epidemiological model analysis. This number represents the average number of secondary infections produced by an infective individual during the course of their illness, assuming that the entire population is susceptible (Diekmann et al 1990). In other words, R_0 reflects average number of secondary cases caused by a typical infected case over an infectious period in a totally susceptible population. To obtain R_0 for epidemiological model involving more than one infected class, a technique due to Diekmann et al (1990) is suitable. This technique known as the next generation matrix, was explicitly studied by Van den Driessche and Watmough (2002) and is summarized below:

Following the idea of Diekmann et.al (1990), FV^{-1} is called the next generation matrix.

$$\mathbf{F} = \left[\frac{\partial \mathcal{F}_i}{\partial x_i}(\bar{x})\right] \quad \text{and} \quad \mathbf{V} = \left[\frac{\partial \mathcal{V}_i}{\partial x_i}(\bar{x})\right]$$

. Therefore, the threshold parameter, R_0, is given by

$$R_0 = \rho(\mathbf{FV^{-1}}) \tag{3.3.1}$$

where ρ is the spectral radius of the product, $\mathbf{FV^{-1}}$ known as the next generation matrix; $\mathbf{F}$ represent the rate of appearance of new infections in infected compartment and $\mathbf{V}$ denote the rate of transfer of individuals in infected compartment.

3.4 STUDY FOUR

Local and Global stability of the theorem

3.4.1 Local stability

Definition 3.2: Stability properties characterize how a system behaves if its state is initiated close to, but not precisely at a given equilibrium point.

An equilibrium point is stable whenever the system state is initiated near that point, the state remains near it, perhaps even tending towards the equilibrium point as time increases.

3.4.2 Global stability

Lyapunov function

Definition 3.3: (Derrick and Grossman, 1976): A function V defined on a region Ω of the state space and containing $\bar{x}$ is a Lyapunov function if it satisfies the following:

(i) V is continuously differentiable,

(ii) V is positive definite, and

(iii) the derivative of V along the solution of the system (3.1.2) is defined by

$$\dot{V} = \frac{\partial V}{\partial x_1}\frac{dx_1}{dt} + \frac{\partial V}{\partial x_2}\frac{dx_2}{dt} + ... + \frac{\partial V}{\partial x_n}\frac{dx_n}{dt} = \frac{\partial V}{\partial x_i}f_i.$$

It should be noted that the construction of these types of functions is an art rather than a rule, since there are no clear formulae for providing them. However, whenever such a function is found, satisfying specific properties, many stability results can be obtained (Ayoola, 2012). The following theorem of epidemiological model are to be considered.

Theorem 3.1: (Derrick and Grossman, 1976): Given the system $\dot{x} = Ax$ where A is the matrix of the linearised nonlinear system (3.1.2.). Then,

(i) the equilibrium point, $\bar{x}$, is stable if all the eigenvalues of A have only imaginary parts.

(ii) the equilibrium point, $\bar{x}$, is asymptotically stable if all the eigenvalues of A have negative real parts.

(iii) the equilibrium point is unstable in all other cases.

Lyapunov stability theorem

Theorem 3.2: (Lungu et al, 2007): If there exist a Lyapunov function $\dot{V}(\bar{x})$ and such that $\dot{V} \leq 0$, then the equilibrium point $\bar{x}$ is stable. If, furthermore, the

function $\dot{V}$ is strictly negative for every point then the stability is asymptotic.

Lasalle's invariance principle

Theorem 3.3: (Lasalle, 1976): Given a Lyapunov function $V(x)$ such that $\dot{V} \leq 0$ on a positive invariant set Ω and if the largest invariant set within $\{x \in \Omega : \dot{V}(x) = 0\}$ is $\{\bar{x}\}$. Then $\bar{x}$ is globally asymptotically stable in Ω.

3.5 STUDY FIVE

Sensitivity analysis

3.5.1 Sensitivity analysis of malaria-Lassa fever co-infection model

In order to determine the parameters or factors most essential in the transmission dynamics and spread of the diseases (malaria-Lassa fever co-infection), we described a sensitivity analysis of the formulated model (3.1.3)-(3.1.16) in the sense of Chitnis et al (2008) and Iddi et al (2012).

Definition 3.4: The normalized forward sensitivity analysis index, of a variable, v to a parameter p denoted by Υ_p^v, is denoted as a ratio of the relative change in the variable to the relative change in the parameter

$$\Upsilon_p^v = \frac{\partial v}{\partial p} \times \frac{p}{v}.$$

3.6 STUDY SIX

Co-existence

3.6.1 Co-existence possibility of malaria-Lassa fever model

We shall use the idea of Nannyonga et al, (2012) to investigate the effect of endemic malaria mortality rate of Lassa fever patients

Theorem 3.4: (Nannyonga et al, 2012) Trypanosomiasis at endemic state will invade into malaria endemic state if

$$\omega_m > \frac{y\mathcal{R}_{0t}^2(\mathcal{R}_{0t}^2-1) - x\mathcal{R}_{0m}^2(1+yz(\mathcal{R}_{0t}^2-1))}{g\mathcal{R}_{0m}^2(\mathcal{R}_{0t}^2-1)(1+yz(\mathcal{R}_{0t}^2-1))} \tag{3.6.1}$$

and vice versa if the role of m and t are interchanged in (3.6.1) by symmetry. Therefore, since infection with malaria increases the susceptibility of a host to other pathogen, then, even when the basic reproduction number for malaria is less than unity, trypanosomiasis will invade and co-exist with malaria.

3.7 STUDY SEVEN

Subharmonic bifurcation

3.7.1 Existence of subharmonic bifurcation theorem

Consider the following differential equations:

$$\left.\begin{aligned} \bar{x}' &= -v\bar{y} + \varepsilon f_1(\bar{x},\bar{y},\bar{z},t,\varepsilon,\delta) \\ \bar{y}' &= v\bar{x}(1+\bar{y}) + \tfrac{v\Delta_3\bar{x}\bar{z}}{\Delta_2+\Delta_3} + v^2\delta\cos 2\pi t\left(1+\bar{y}+\tfrac{\Delta_3\bar{z}}{\Delta_2+\Delta_3}\right) \\ &+ \varepsilon f_2(\bar{x},\bar{y},\bar{z},t,\varepsilon,\delta) \\ \varepsilon\bar{z}' &= -(\Delta_2+\Delta_3)\bar{z} + \varepsilon f_3(\bar{x},\bar{y},\bar{z},t,\varepsilon,\delta) \end{aligned}\right\} \tag{3.7.1}$$

where

$$f_i(x,y,z,t+1,\varepsilon,\delta) = f_i(x,y,z,t,\varepsilon,\delta)$$
$$f_i(0,0,0,t,0,0) = 0 \quad i = 1,2,3.$$

Now, setting $\varepsilon = \delta = 0$ in (3.7.1) (Since ε and δ are treated as small parameters) we obtain the reduced equations:

$$\left.\begin{aligned} \bar{x}' &= -v\bar{y} \\ \bar{y}' &= v\bar{x}(1+\bar{y}) \\ \bar{z} &= 0 \end{aligned}\right\}. \tag{3.7.2}$$

Theorem 3.5: (Ira and Smith, 1983): Let $\bar{x}_n(t), \bar{y}_n(t) = \bar{x}_n(t+\alpha), \bar{y}_n(t+\alpha)$ represent solution of a periodic equation (3.7.2), where $n > \frac{2\pi}{v}$. Suppose that

$$\gamma_2 \equiv v^2\int_0^n \bar{y}(t)\cos 2\pi t dt \neq 0 \tag{3.7.3}$$
$$\gamma_1 = \frac{-2r}{v}$$

(Area interior to Γ_n) and for $\alpha_h\varepsilon[0,n), |\varepsilon| \ll 1, |\delta| \ll 1$, let

$$\mathbf{B}(\alpha_h,\varepsilon,\delta) = -\gamma_1\varepsilon + \gamma_2\delta\cos 2\pi\alpha_h + 0(|\varepsilon|+|\delta|)^2. \tag{3.7.4}$$

If $(\bar{x}_n,\bar{y}_n)$ span the n- periodic equations (3.7.2) about $(\bar{x}_0,\bar{y}_0)$, and $\mathbf{B}(\alpha_h,\varepsilon,\delta) = 0$, subsequently, equation (3.7.1) has an n-periodic solution $(\bar{x},\bar{y},\bar{z})$ as given below

$$\left.\begin{aligned} \bar{x}(t) &= \bar{x}_n(t+\alpha_h+0(|\varepsilon|+(1+|\delta|)) \\ \bar{y}(t) &= \bar{y}_n(t+\alpha_h+0(|\varepsilon|+|\delta|) \\ \bar{z}(t) &= -\tfrac{\varepsilon\Delta_2\bar{y}'(t+\alpha_h)}{v^2(\Delta_2+\Delta_3)} + 0(|\varepsilon|+|\delta|)^2 \end{aligned}\right\}. \tag{3.7.5}$$

3.7.2 Harmonic and periodic motions

Definition 3.5:(Chow and Shaw 1986): A motion, if described in time by a sine or cosine function, is said to be harmonic.

Definition 3.6: (Chow and Shaw 1986): A motion is said to be periodic if after a period **T** or various integer it has the same pattern. For the description of the feature, we can write $u(t) = u(t + kT)$, for $k = \pm 1, \pm 2, \pm 3, ...$

3.7.3 Subharmonic

Definition 3.7: (Chow and Shaw 1986): subharmonic refers to the appearance of the power spectrum corresponding to a signal arising from a period- doubling (or subharmonic) bifurcation.

3.7.4 The Fredholm alternative theorems

A first understanding of the problem of solving an integral equation

$$y = Ky + f$$

can be made by introducing the Fredholm Alternative Theorems in the context of integral equations.

I. Exactly one of the following holds.

(a) First Alternative if f is in $L^2\{0, 1\}$, then

$$y(X) = \int_0^1 K(X, t)y(t)dt + f(X)$$

has one and only one solution.

(b) Second Alternative $y(X) = \int_0^1 K(X, t)y(t)dt$ has a nontrivial solution.

II. (a) if the first alternative holds for the equation

$$y(X) = \int_0^1 K(X, t)y(t)dt + f(X)$$

Then it also holds for the equation

$$z(X) = \int_0^1 K(X,t)z(t)dt + g(X)$$

(b) In either alternative, the equation

$$y(X) = \int_0^1 K(X,t)y(t)dt$$

and it adjoint equation

$$z(X) = \int_0^1 K(X,t)z(t)dt$$

possess similar linearly independent solutions number.

III. Suppose the second alternative holds. Then

$$y(X) = \int_0^1 K(X,t)y(t)dt + f(X)$$

has a solution if and only if

$$\int_0^1 f(t)z(t)dt = 0$$

for each solution z of the adjoint equation

$$z(X) = \int_0^1 K(X,t)z(t)dt$$

Definition 3.7.1. *An adjoint equation is a linear differential equation generally obtained from its primary equation through integration by part.*

3.8 STUDY EIGHT

Control theory

3.8.1 Optimal control problem

Optimal control is the method of determining a dynamic system's control and state trajectories over time to minimize a performance index (Bryson, 1996).

Problem statement: Consider a nonlinear system

$$\dot{x} = f(x,u) \quad x \in R^n, \quad u \in R^m \tag{3.8.1}$$

The trajectory (x^*, u^*) that satisfies the dynamics and minimizes cost is obtain as

$$\max_u \int_0^T P(x,u)dt + K(x(T), u(T))$$

The typical cost function: quadratic cost

$$J = \frac{1}{2}\int_0^T (x^T Q x + u^T R u)dt + x^T(T)P_1 x(T).$$

System:

$$\dot{x} = f(x,u)x = R^n$$

$$x(0) = given \quad u \in \Omega.$$

Cost:

$$J = \int_{0,\psi(x(T))=0}^T P(x,u) + K(x(T))$$

Hamiltonian:

$$H = P + \lambda^T f = P + \sum \lambda_i f_i$$

Theorem 3.6: If (x^*, u^*) is optimal, then there exists $\lambda^*(t)$ and $v*$ such that

$$\left.\begin{array}{rcl} \dot{x}_i & = & \frac{\partial H}{\partial \lambda_i} \quad -\lambda_i \frac{\partial H}{\partial x_i} \quad x(0) \quad given \quad \psi(x(T)) = 0 \\ \lambda(T) & = & \frac{\partial K}{\partial x}(x(T)) + \frac{\partial \psi^T}{\partial x} v \end{array}\right\} \tag{3.8.2}$$

and

$$H(x^*(t), u^*(t), \lambda^*(t) \leq H(x^*(t), u, \lambda^*(t)) \quad \forall \quad u \in \Omega$$

3.8.2 Application of Pontryagin's maximum principle

First, formulate problem in standard form

$$\begin{array}{rcl} \dot{x} & = & f(x,u) \quad x \in R^n \\ x(0) \quad given & & u \in \Omega \subset R^p \\ J & = & \displaystyle\int_{0,\psi(x(T))=0}^T P(x,u)dt + v(x(T)) \end{array}$$

second, compute Hamiltonian

$$H = L + \lambda^T f = L + \sum \lambda_i f_i$$

Third, compute necessary condition

$$\left.\begin{array}{rcl} \dot{x}_i & = & \frac{\partial H}{\partial \lambda_i} \quad - \lambda_i \frac{\partial H}{\partial x_i} \quad x(0) \quad given \quad \psi(x(T)) = 0 \\ \lambda(T) & = & \frac{\partial K}{\partial x}(x(T)) + \frac{\partial \psi^T}{\partial x} v \end{array}\right\} \tag{3.8.3}$$

fourth, find the optimal input

$$u = arg\min \; H(x^*(t), u\lambda^*(t))$$

finally, Solve for the optimal trajectory: Substitute optimal input into necessary conditions and solved boundary value problem. In general, this is hard to do in closed form. However, we can convert this to a computational problem.

3.9 STUDY NINE

Simulation

3.9.1 Numerical simulation

Simulation, according to Shannon (1975), is "the method of designing a model of a real system and conducting experiments with this model for the motive either of understanding the behaviour of the system or of evaluating various techniques (within the limits imposed by a criterion or set of criteria) for the operation of the system. This was achieved using Maple and MATLAB software packages.

This study investigates and compared numerical results from simulations with the following scenarios (i) $u_2 \neq 0, u_3 \neq 0, u_1 = 0$ (ii)$u_1 \neq 0, u_3 \neq 0, u_2 = 0$ (iii) $u_1 \neq 0, u_2 \neq 0, u_3 = 0$ (iv)$u_1 \neq 0, u_2 \neq 0, u_2 \neq 0$. For numerical simulations we have used the following weight factors $m_1 = 50, m_2 = 150, m_3 = 30$, with initial state variables $N_{ss}(0) = 500, N_{es}(0) = 20, N_{is}(0) = 0, N_{rs}(0) = 10, N_{se}(0) = 20, N_{si}(0) = 0, N_{sr}(0) = 10, N_{rr} = 0, S_m(0) = 2000, E_m(0) = 100, I_m(0) = 30, S_d(0) = 2000, E_d(0) = 100, I_d(0) = 30$. The controls (u_1, u_2, u_3) are used to optimize the objective function J, with weight factors $m_1 = 50, m_2 = 150, m_3 = 30$.

CHAPTER FOUR

RESULTS

4.1 STUDY ONE

Analysis of the malaria-Lassa fever co-infection model

4.1.1 Existence of solutions on feasible region

Here, we provide the following results which guarantee that the malaria-Lassa fever co-infection model governed by system (3.1.3)-(3.1.16) is mathematical well-posed in a feasible region Ω defined by

$$\Omega = \Omega_h \times \Omega_d \times \Omega_m \subset \mathcal{R}_+^8 \times \mathcal{R}_+^3 \times \mathcal{R}_+^3$$

where

$\Omega_h = \{N_{ss}(t,a_i), N_{es}(t,a_i), N_{is}(t,a_i), N_{rs}(t,a_i), N_{se}(t,a_i),$
$N_{si}(t,a_i), N_{sr}(t,a_i), N_{rr}(t,a_i) \in \mathcal{R}^8 : N_h(t,a_i) \leq \sum_{i=0}^{L} \frac{\zeta(a_i)}{\mu(a_i)}\},$

$$\Omega_d = \{S_d(t,e_j), E_d(t,e_j), I_d(t,e_j), \in \mathcal{R}_+^3 : N_d(t,e_j) \leq \sum_{j=0}^{T} \frac{\Lambda_d(e_j)(1+\xi_d \cos(2\pi t+T))}{\mu_d(e_j)+\delta_d(e_j)}\}$$

and

$$\Omega_m = \{S_m(t), E_m(t), I_m(t), \in \mathcal{R}_+^3 : N_m(t) \leq \frac{\varsigma_m(1+\kappa_m \cos(2\pi t+T))}{\mu_m}\}$$

Theorem 4.1: The feasible region Ω defined by

$\Omega = \{N_{ss}(t,a_i), N_{es}(t,a_i), N_{is}(t,a_i), N_{rs}(t,a_i), N_{se}(t,a_i), N_{si}(t,a_i), N_{sr}(t,a_i), N_{rr}(t,a_i)$
$, S_d(t,e_j), E_d(t,e_j), I_d(t,e_j), S_m(t) E_m(t), I_m(t) \in \mathcal{R}^{14} : N_h(0,a_i) \leq N_h(t,a_i) \leq$
$\sum_{i=0}^{L} \frac{\zeta(a_i)}{\mu(a_i)}, N_d(0,e_j) \leq N_d(t,e_j) \leq \sum_{j=0}^{T} \frac{\Lambda_d(e_j)(1+\xi_d \cos(2\pi t+T))}{\mu_d(e_j)+\delta_d(e_j)}, N_m(0) \leq N_m(t) \leq$

$\frac{\varsigma_m(1+\kappa_m\cos(2\pi t+T))}{\mu_m}\}$ with initial conditions $N_{ss}(0,a_i)\geq 0, N_{es}(0,a_i)\geq 0, N_{is}(0,a_i)\geq 0, N_{rs}(0,a_i)\geq 0, N_{se}(0,a_i)\geq 0, N_{si}(0,a_i)\geq 0, N_{sr}(0,a_i)\geq 0, N_{rr}(0,a_i)\geq 0, S_d(0,e_j)\geq 0, E_d(0,e_j)\geq 0, I_d(0,e_j)\geq 0, S_m(0)\geq 0, E_m(0)\geq 0, I_m(0)\geq 0$ is positive invariant for system (3.1.3) - (3.1.16).

Proof: If the total human population size is given by $N_h(t,a_i) = N_{ss}(t,a_i) + N_{es}(t,a_i) + N_{is}(t,a_i) + N_{rs}(t,a_i) + N_{se}(t,a_i) + N_{si}(t,a_i) + N_{sr}(t,a_i) + N_{rr}(t,a_i)$, the total rodent population size is $N_d(t,e_j) = S_d(t,e_j) + E_d(t,e_j) + I_d(t,e_j)$ and the total size of mosquito population is $N_m(t) = S_m(t) + E_m + I_m$. Then from (3.1.3)-(3.1.16)

$$\frac{dN_h(t,a_i)}{dt} \leq \zeta(a_i) - \sum_{i=0}^{L}\mu(a_i)N_h(t,a_i) \tag{4.1.1}$$

$$\frac{dN_d}{dt} \leq \Lambda_d(e_j)(1+\xi_d\cos(2\pi t+T)) - \sum_{i=0}^{L}(\mu_d(e_j)+\delta_d(e_j))N_d(t,e_j) \tag{4.1.2}$$

$$\frac{dN_m}{dt} \leq \varsigma_m(1+\kappa_m\cos(2\pi t+T)) - \mu_m N_m \tag{4.1.3}$$

solving the differential inequalities (4.1.1), (4.1.2) and (4.1.3) one after the other gives

$$N_h(t,a_i)e^{\mu_h(a_i)t} \leq N_h(0,a_i) + \sum_{i=0}^{L}\frac{\Lambda(a_i)}{\mu_h(a_i)}e^{\mu_h(a_i)t} - \sum_{i=0}^{L}\frac{\Lambda(a_i)}{\mu_h(a_i)}$$

so that

$$N_h(t,a_i) \leq N_h(0,a_i)e^{-\mu_h(a_i)t} + \sum_{i=0}^{L}\frac{\Lambda(a_i)}{\mu_h(a_i)} - \sum_{i=0}^{L}\frac{\Lambda(a_i)}{\mu_h(a_i)}e^{-\mu_h(a_i)t}$$

this implies

$$N_h(t,a_i) \leq \sum_{i=0}^{L}\frac{\Lambda(a_i)}{\mu_h(a_i)}(1-e^{-\mu_h(a_i)t}) + N_h(0,a_i)e^{-\mu_h(a_i)t} \tag{4.1.4}$$

similarly for (4.1.2) we have

$$N_d(t,e_j)e^{(\mu_d(e_j)+\delta_d(e_j))t} \leq \sum_{j=0}^{T} N_d(0,e_j) + \frac{\Lambda_d(e_j)(1+\xi_d\cos(2\pi t+T))}{\mu_d(e_j)+\delta_d(e_j)} e^{(\mu_d(e_j)+\delta_d(e_j))t} - \frac{\Lambda_d(e_j)(1+\xi_d\cos(2\pi t+T))}{\mu_d(e_j)+\delta_d(e_j)}$$

so that

$$N_d(t,e_j) \leq \sum_{j=0}^{T} N_d(0,e_j)e^{-(\mu_d(e_j)+\delta_d(e_j))t} + \frac{\Lambda_d(e_j)(1+\xi_d\cos(2\pi t+T))}{\mu_d(e_j)+\delta_d(e_j)} - \frac{\Lambda_d(e_j)(1+\xi_d\cos(2\pi t+T))}{\mu_d(e_j)+\delta_d(e_j)} e^{-(\mu_d(e_j)+\delta_d(e_j))t}$$

this implies

$$N_d(t,e_j) \leq \sum_{j=0}^{T} \frac{\Lambda_d(e_j)(1+\xi_d\cos(2\pi t+T))}{\mu_d(e_j)+\delta_d(e_j)}(1-e^{-(\mu_d(e_j)+\delta_d(e_j))t}) + N_d(0,e_j)e^{-(\mu_d(e_j)+\delta_d(e_j))t} \tag{4.1.5}$$

Also

$$N_m(t)e^{\mu_m t} \leq N_m(0) + \frac{\varsigma_m(1+\kappa_m\cos(2\pi t+T))}{\mu_m} e^{\mu_m t} - \frac{\varsigma_m(1+\kappa_m\cos(2\pi t+T))}{\mu_m}$$

so that

$$N_m(t) \leq N_m(0)e^{-\mu_m t} + \frac{\Lambda_m}{\mu_m} - \frac{\varsigma_m(1+\kappa_m\cos(2\pi t+T))}{\mu_m} e^{-\mu_m t}$$

this implies

$$N_m(t) \leq \frac{\varsigma_m(1+\kappa_m\cos(2\pi t+T))}{\mu_m}(1-e^{-\mu_m t}) + N_m(0)e^{-\mu_m t} \tag{4.1.6}$$

Taking the limits of (4.1.4), (4.1.5) and (4.1.6) as $t \to \infty$ gives $N_h(t,a_i) \leq \sum_{i=0}^{L} \frac{\zeta(a_i)}{\mu_h(a_i)}$, $N_d(t,e_j) \leq \sum_{j=0}^{T} \frac{\Lambda_d(e_j)(1+\xi_d\cos(2\pi t+T))}{\mu_d(e_j)+\delta_d(e_j)}$
and $N_m(t) \leq \frac{\varsigma_m(1+\kappa_m\cos(2\pi t+T))}{\mu_m}$. Thus the following feasible region Ω

$$= \{N_{ss}(t,a_i), N_{es}(t,a_i), N_{is}(t,a_i), N_{rs}(t,a_i), N_{se}(t,a_i), N_{si}(t,a_i), N_{sr}(t,a_i),$$
$$N_{rr}(t,a_i), S_d(t,e_j), E_d(t,e_j), I_d(t,e_j), S_m, E_m, I_m \in \mathcal{R}^{14} : N_h(t,a_i) \leq \sum_{i=0}^{L} \frac{\zeta(a_i)}{\mu(a_i)},$$
$$N_d(t,e_j) \leq \sum_{j=0}^{T} \frac{\Lambda_d(e_j)(1+\xi_d \cos(2\pi t + T))}{\mu_d(e_j) + \delta_d(e_j)}, N_m(t) \leq \frac{\varsigma_m(1+\kappa_m \cos(2\pi t + T))}{\mu_m}\}$$

4.2 STUDY TWO

Disease-free and endemic equilibrium point

4.2.1 Equilibrium points

Disease-free equilibrium points are steady-state solutions where there is no malaria-Lassa fever co-infection. Thus, the disease-free equilibrium point, ϵ_0 for the malaria-Lassa fever model (3.1.3)-(3.1.16) implies that $N^*_{ss}(a_i) \neq 0, N^*_{es}(a_i) = N^*_{is}(a_i) = N^*_{se}(a_i) = N^*_{si}(a_i) = N^*_{rr}(a_i) = 0, S^*_d(e_j) \neq 0, E^*_d(e_j) = I^*_d(e_j) = 0, S^*_m \neq 0, E^*_m = I^*_m = 0$ and putting these into (3.1.3), (3.1.6), (3.1.9), (3.1.11) and (3.1.14) yields $N^*_{rs}(a_i) = 0, N^*_{sr} = 0, N^*_{ss}(a_i) = \frac{\zeta(a_i)}{\mu(a_i)},$, $S^*_d = \frac{\Lambda_d(1+\xi_d\cos(2\pi t+T))}{\mu_d+\delta_d}$ and $S^*_m = \frac{\varsigma_m(1+\kappa_m\cos(2\pi t+T))}{\mu_m}$ respectively. Consequently, we obtain ϵ_0 as

$$\epsilon_0 = \left(\frac{\zeta(a_i)}{\mu(a_i)}, 0, 0, 0, 0, 0, 0, 0, \frac{\Lambda_d(e_j)(1+\xi_d\cos(2\pi t+T))}{\mu_d(e_j)+\delta_d(e_j)}, 0, 0, \frac{\varsigma_m(1+\kappa_m\cos(2\pi t+T))}{\mu_m}, 0, 0\right) \tag{4.2.1}$$

The points at which the differential equations of the system (3.1.3)-(3.1.16) equal to zero are referred to as equilibrium points or steady state solutions. It is important to note that there is no trivial equilibrium points as long as the recruitment terms $\zeta(a_i)$, $\Lambda_d(e_j)(1+\xi_d\cos(2\pi t+T))$ and $\Lambda_m(1+\xi_m\cos(2\pi t+T))$ are not zero. This implies that the equilibrium points $(N_{ss}(t,a_i), N_{es}(t,a_i), N_{is}(t,a_i), N_{rs}(t,a_i), N_{se}(t,a_i), N_{si}(t,a_i), N_{sr}(t,a_i), N_{rr}(t,a_i), S_d(t,e_j), E_d(t,e_j), I_d(t,e_j), S_m, E_m, I_m) \neq (0,0,0,0,0,0,0,0,0,0,0,0,0,0,0)$.

Subsequently, we shall analyse model (3.1.3)-(3.1.16) by showing the existence of the endemic equilibrium and stability properties of both the disease free and endemic equilibria through the basic reproduction number of the model.

4.3 STUDY THREE

Threshold parameter, $R_{0L}(t,a)$ and $R_{0M}(t,a)$

4.3.1 Basic reproduction number, $R_{0L}(t,a)$ and $R_{0M}(t,a)$

The basic reproduction numbers for Lassa fever and malaria denoted by $R_{0L}(t,a)$ and $R_{0M}(t,a)$ can be obtained through the next-generation matrix approach described by VanDen Driessche and Watmough (2002). Considering only the diseased compartments, the rate of appearance of new infections and the transfer rate are given, respectively, by

$$\mathcal{F}(x) = \begin{pmatrix} \sum_{i=0}^{L}\sum_{j=0}^{T}(\lambda_a + \lambda_b)N_{ss}(t,a_i) \\ 0 \\ \sum_{j=0}^{T}\lambda_d S_d(t,e_j)I_d(t,e_j) \\ 0 \end{pmatrix}$$

and

$$\mathcal{V}(x) = \begin{pmatrix} \sum_{i=0}^{L}(\mu(a_i) + \gamma_1(a_i)\alpha(a_i) + \tau(a_i))N_{es}(t,a_i) \\ \sum_{i=0}^{L}(\mu(a_i) + \eta_1(a_i)\sigma(a_i))N_{is}(t,a_i) - \tau(a_i)N_{es}(t,a_i) \\ \sum_{j=0}^{T}(\alpha_d(e_j) + \mu_d(e_j) + \delta_d(e_j))E_d(t,e_j) \\ \sum_{j=0}^{T}(\mu_d(e_j) + \delta_d(e_j))I_d(t,e_j) - \alpha_d(e_j)E_d(t,e_j) \end{pmatrix}$$

Finding the derivative of $\mathcal{F}$ and $\mathcal{V}$ at the disease-free equilibrium point π_0 gives $\mathbf{F}$ and $\mathbf{V}$ respectively, where

$$\mathbf{F} = \begin{pmatrix} 0 & \sum_{i=0}^{L}\sum_{j=0}^{T} \frac{\sigma_0(e_j)(1+w_1(e_j)\cos(2\pi t+T))\zeta(a_i)}{\mu(a_i)} & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & Q \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

and

$$\mathbf{V} = \begin{pmatrix} \sum_{i=0}^{L}(\mu(a_i)+\gamma_1(a_i)\alpha(a_i)+\tau(a_i)) & 0 & 0 & 0 \\ -\sum_{i=0}^{L}\tau(a_i) & \sum_{i=0}^{L}(\mu(a_i)+\eta_1(a_i)\sigma(a_i)) & 0 & 0 \\ 0 & 0 & g & 0 \\ 0 & 0 & -\sum_{j=0}^{T}\alpha_d(e_j) & W \end{pmatrix}$$

where $g = \sum_{j=0}^{T}(\alpha_d(e_j)+\mu_d(e_j)+\delta_d(e_j))$ and $W = \sum_{j=0}^{T}(\alpha_d(e_j)+\mu_d(e_j))$

$Q = \sum_{j=0}^{T} \frac{\rho_0(e_j)(1+w_2(e_j)\cos(2\pi t+T))\Lambda_d(e_j)(1+\xi_d\cos(2\pi t+T))}{\mu_d(e_j)+\delta_d(e_j)}$ so that

$$\mathbf{FV^{-1}} = \begin{pmatrix} A_{11} & \sum_{i=0}^{L} \frac{\sigma_0(a_i)(1+w_1(a_i)\cos(2\pi t+T))\zeta(a_i)}{\mu(a_i)(\mu(a_i)+\eta_1(a_i)\sigma(a_i))} & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & A_{33} & A_{34} \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

where

$$A_{11} = \sum_{i=0}^{L} \frac{\sigma_0(a_i)(1+w_1(a_i)\cos(2\pi t+T))\zeta(a_i)\tau(a_i)}{\mu(a_i)(\mu(a_i)+\gamma_1(a_i)\alpha(a_i)+\tau(a_i))(\mu(a_i)+\eta_1(a_i)\sigma(a_i))}$$

$$A_{33} = \sum_{j=0}^{T} \frac{\alpha_d(e_j)\beta_0(e_j)(1 + w_2(e_j)\cos(2\pi t + T))\Lambda_d(e_j)(1 + \xi_d \cos(2\pi t + T))}{\mu_d(e_j) + \delta_d(e_j)}$$

$$A_{34} = \sum_{j=0}^{T} \frac{\beta_0(e_j)(1 + w_2(e_j)\cos(2\pi t + T))\Lambda_d(e_j)(1 + \xi_d \cos(2\pi t + T))}{\mu_d(e_j) + \delta_d(e_j)}$$

R_{0L} is the spectral radius of $\mathbf{FV^{-1}}$ given as

$$R_{0L}(a,t) = \sum_{i=0}^{L} \frac{\sigma_0(a_i)(1 + w_1(a_i)\cos(2\pi t + T))\zeta(a_i)\tau(a_i)}{\mathcal{R}_{rf}} \tag{4.3.1}$$

where $\mathcal{R}_{rf} = \mu(a_i)(\eta_v(a_i)\sigma(a_i) + \mu(a_i))(\gamma_v(a_i)\alpha(a_i) + \tau(a_i) + \mu(a_i))$
using similar argument, the basic reproduction number for malaria is given by

$$\mathcal{R}_{0M}(a,t) = \sqrt{\sum_{i=0}^{L} \frac{\tau_m(a_i)\sigma_0(a_i)(1 + b\cos(2\pi t + T))\zeta(a_i)\varsigma_m(1 + \kappa_m \cos(2\pi t + T))\alpha_m\phi_0}{\mu(a_i)(\tau_m(a_i) + \mu(a_i))(\epsilon_m(a_i)\beta_m(a_i) + \mu(a_i))\mu_m(\alpha_m + \mu_m)\mu_m}} \tag{4.3.2}$$

$$\mathcal{R}_{0M}(a,t) = \sqrt{\mathcal{R}_{hm}\mathcal{R}_{mm}} \tag{4.3.3}$$

where $\mathcal{R}_{mm} = \frac{\varsigma_m(1+\kappa_m \cos(2\pi t T))\alpha_m\phi_0}{\mu_m(\alpha_m+\mu_m)\mu_m}$ and $\mathcal{R}_{hm} = \frac{\tau_m(a_i)\sigma_0(a_i)(1+b\cos(2\pi t T))\zeta(a_i)}{\mu(a_i)(\tau_m(a_i)+\mu(a_i))(\epsilon_m(a_i)\beta_m(a_i)+\mu(a_i))}$
Thus, (4.3.1) and (4.1.3) are basic reproduction numbers for Lassa fever and malaria.

4.4 STUDY FOUR

4.4.1 Existence of endemic equilibrium- local stability

Using the basic reproduction number obtained from the model (3.1.3)-(3.1.16), we analyse the stability of the equilibrium point in the following result.

Theorem 4.2: Malaria-Lassa fever co-infection model (3.1.3) - (3.1.16) has no endemic equilibrium when $R_{es1}(a), R_{es2}(a), R_{0M}(a), R_{em1}(a), R_{em2}(a) < 1$ and a unique endemic equilibrium exist when $R_{es1}(a), R_{es2}(a), R_{0M}(a), R_{em1}(a)$, $R_{em2}(a) > 1$.

Proof: Let $E_e^{**} = (N_{ss}^{**}(a_i), N_{es}^{**}(a_i), N_{is}^{**}(a_i), N_{rs}^{**}(a_i), N_{se}^{**}(a_i), N_{si}^{**}(a_i), N_{sr}^{**}(a_i), S_m^{**}, E_m^{**}, I_m^{**}, S_d^{**}(e_j), E_d^{**}(e_j), I_d^{**}(e_j))$ be a non trivial equilibrium of the model (3.1.3)-(3.1.16). The steady state of the malaria-Lassa fever co-infection model (3.1.3)-(3.1.16) are

$$N_{ss}^{**}(a) = \sum_{i=0}^{L} \frac{\zeta(a_i)(R_{em2}^2(a)-1)}{\mu(a_i)R_{0M}^2(a)(R_{em1}^2(a)-1)},$$

$$N_{se}^{**}(a) = \sum_{i=0}^{L} \frac{\zeta(a_i)(\gamma_m(a_i)+\mu(a_i))(\mu(a_i)+\epsilon_m(a_i)\beta_m(a_i))(R_{0M}^2(a)-1)}{\tau_m(a_i)\epsilon_m(a_i)\beta_m(a_i)R_{0M}^2(a)(R_{em1}(a)-1)\gamma_m(a_i)},$$

$$N_{si}^{**}(a) = \sum_{i=0}^{L} \frac{\zeta(a_i)(\gamma_m(a_i)+\mu(a_i))(R_{0M}^2(a)-1)}{\gamma_m(a_i)R_{0M}^2(a)(R_{em1}(a)-1)},$$

$$N_{sr}^{**}(a) = \sum_{i=0}^{L} \frac{\zeta(a_i)(R_{0M}^2(a)-1)}{R_{0M}^2(a)(R_{em1}^2(a)-1)\gamma_m(a_i)},$$

$$S_m^{**} = \sum_{i=0}^{L} \frac{\varsigma(a_i)(1+\kappa\cos(2\pi t+T))\beta_m(a_i)R_{0M}^2(a)(R_{em1}^2(a)-1)\gamma_m(a_i)}{\lambda_m(\gamma_m(a_i)+\mu(a_i))\zeta(a_i)(R_{0M}^2(a)-1)+R_{0M}^2(a)(R_{em1}^2(a)-1)\gamma_m(a_i)M_0},$$

$$E_m^{**} = \sum_{i=0}^{L} \frac{\varsigma_m\epsilon_m(a_i)\beta_m(a_i)\lambda_m(\gamma_m(a_i)+\mu(a_i))\zeta(a_i)(R_{0M}^2(a)-1)}{R_{0M}^2(a)(R_{em1}^2(a)-1)\gamma_m(a_i)(\mu_m+\alpha_m)\epsilon_m(a_i)\beta_m(a_i)M_1},$$

$$I_m^{**} = \sum_{i=0}^{L} \frac{\alpha_m\epsilon_m(a_i)\beta_m(a_i)\varsigma_m\lambda_m(\gamma_m(a_i)+\mu(a_i))\zeta(a_i)(R_{0M}^2(a)-1)}{R_{0M}^2(a)(R_{em1}^2(a)-1)\mu_m(\mu_m+\alpha_m)\epsilon_m(a_i)\beta_m(a_i)M_1},$$

where

$M_0 = \epsilon_m(a_i)\beta_m(a_i)(\mu_m+\xi_m\varsigma_m)$ and $M_2 = \lambda_m(\gamma_m(a_i)+\mu(a_i))\zeta(a_i)(R_{0M}^2(a)-1)+$ $R_{0M}^2(a)(R_{em1}^2(a)-1)\gamma_m(a_i)\epsilon_m(a_i)\beta_m(a_i)\mu_m$,

$$R^2_{em1}(a) = \sum_{i=0}^{L} \frac{(\mu(a_i)\mu_m(\mu_m+\alpha_m) + \alpha_m\lambda_M\varsigma_m(1+\kappa_m\cos(2\pi t+T))\theta_m}{\gamma_m(a_i)\alpha_m\lambda_M\varsigma_m(1+\kappa_m\cos(2\pi t+T))\tau_m(a_i)\epsilon_m(a_i)\beta_m(a_i)},$$

$$R^2_{em2}(a) = \sum_{i=0}^{L} \frac{(\mu(a_i)\mu_m(\mu_m+\alpha_m)R^2_{0M}(a) + \alpha_m\lambda_M\varsigma_m(1+\kappa_m\cos(2\pi t+T)))\theta_m}{\gamma_m(a_i)\alpha_m\lambda_M\varsigma_m(1+\kappa_m\cos(2\pi t+T))\tau_m(a_i)\epsilon_m(a_i)\beta_m(a_i)},$$

$\theta_m = (\mu(a_i)+\tau_m(a_i))(\gamma_m(a_i)+\mu(a_i))(\mu(a_i)+\epsilon_m(a_i)\beta_m(a_i))$. Therefore,

$$I^*_M = N^*_{se}+N^*_{si} = \sum_{i=0}^{L} \frac{(\gamma_m(a_i)+\mu(a_i))(\mu(a_i)+\epsilon_m(a_i)\beta_m(a_i))\zeta(a_i)(R^2_{0M}(a)-1)+\theta_k}{\tau_m(a_i)\epsilon_m(a_i)\beta_m(a_i)R^2_{0M}(a)\gamma_m(a_i)(R^2_{em1}(a)-1)},$$

where

$\theta_k = \zeta(a_i)(\gamma_m(a_i)+\mu(a_i))(R^2_{0M}(a)-1)\tau_m(a_i)\epsilon_m(a_i)\beta_m(a_i)$

Similarly for Lassa fever class, we have the following stationary states:

$$N^{**}_{ss}(a) = \sum_{j=0}^{T}\sum_{i=0}^{L} \frac{\zeta(a_i)\mu(a_i)R_{es1}(a)(\mu(a_i)+\gamma_1(a_i)\alpha(a_i)+\tau(a_i))(\mu(a_i)+\eta_1(a_i)\sigma(a_i))}{\lambda_a[\gamma_1(a_i)\alpha(a_i)(\mu(a_i)+\eta_1(a_i)\sigma(a_i))+\tau(a_i)\eta_1(a_i)\sigma(a_i)]},$$

$$N^{**}_{es}(a) = \sum_{j=0}^{T}\sum_{i=0}^{L} \frac{(\mu(a_i)+\eta_1(a_i)\sigma(a_i))\zeta(a_i)\mu(a_i)R_{es1}(a)}{\gamma_1(a_i)\alpha(a_i)(\mu(a_i)+\eta_1(a_i)\sigma(a_i))+\tau(a_i)\eta_1(a_i)\sigma(a_i)},$$

$$N^{**}_{is}(a) = \sum_{i=0}^{L}\sum_{j=0}^{T} \frac{\tau(a_i)\mu(a_i)\zeta(a_i)R_{es1}(a)}{\gamma_1(a_i)\alpha(a_i)(\mu(a_i)+\eta_1(a_i)\sigma(a_i))+\tau(a_i)\eta_1(a_i)\sigma(a_i)},$$

$$N^{**}_{rs}(a) = \sum_{i=0}^{L}\sum_{j=0}^{T} \zeta(a_i)R_{es1}(a_i),$$

$$S^{**}_{d}(e) = \sum_{j=0}^{T} \frac{\Lambda_d(e_j)(1+\xi_d\cos(2\pi t+T))}{\lambda_d R_{es2}(a)+\mu_d(e_j)+\delta_d(e_j)},$$

$$E^{**}_{d}(e) = \sum_{j=0}^{T} \frac{\lambda_d R_{es2}(a)\Lambda_d(e_j)(1+\xi_d\cos(2\pi t+T))}{(\lambda_d R_{es2}(a)+\mu_d(e_j)+\delta_d(e_j))(\alpha_d(e_j)+\mu_d(e_j)+\delta_d(e_j))},$$

$$I^{**}_{d}(e) = \frac{\alpha_d(e_j)\Lambda_d(e_j)(1+\xi_d\cos(2\pi t+T))\beta_2(e_j)(\alpha_d(e_j)+\mu_d(e_j)+\delta_d(e_j)+A_d R_{es2}(a)}{(\mu_d(e_j)+\delta_d(e_j))(\alpha_d(e_j)+\mu_d(e_j)+\delta_d(e_j))\beta_2(e_j)w_2(e_j)}$$

where

$$R_{es1}(a) = \sum_{i=0}^{L}\sum_{j=0}^{T} \frac{\lambda_a[\gamma_(a_i)\alpha(a_i)(\mu(a_i)+\eta_1(a_i)\sigma(a_i))+\tau(a_i)\eta_1(a_i)\sigma(a_i)]}{(\mu(a_i)+\eta_1(a_i)\sigma(a_i))[(\mu(a_i)+\gamma_1(a_i)\alpha(a_i)+\tau(a_i))+\mu(a_i)\lambda_a\theta_s]}$$

$$R_{es2} = \sum_{i=0}^{L}\sum_{j=0}^{T} \frac{\alpha_d(e_j)\Lambda_d(e_j)(1+\xi_d\cos(2\pi t+T))\beta_2(e_j)(\alpha_d(e_j)+\mu_d(e_j)+\delta_d(e_j)}{(\mu_d(e_j)+\delta_d(e_j))(\alpha_d(e_j)+\mu_d(e_j)+\delta_d(e_j))\beta_2(e_j)w_2(e_j)}$$

$\theta_s = \mu(a_i)+\gamma_1(a_i)\alpha(a_i),\ A_d = \Lambda_d(e_j)(1+\xi_d\cos(2\pi t+T))(\mu_d(e_j)+\delta_d(e_j))$

Similarly,

$$I_L^{**} = N_{es}^{**}(a_i) + N_{is}^{**}(a_i) = \sum_{i=0}^{L}\sum_{j=0}^{T} \frac{(\mu(a_i) + \eta_1(a_i)\sigma(a_i))\mu(a_i)R_{es1}(a) + \tau(a_i)\mu(a_i)R_{es1}(a)}{\gamma(a_i)\alpha(a_i)(\mu(a_i) + \eta_1(a_i)\sigma(a_i) + \tau(a_i)\eta_1(a_i)\sigma(a_i))}.$$

Endemic state exist whenever $R_{es1}(a), R_{es2}(a), R_{0M}(a), R_{em1}(a), R_{em2}(a) > 1$

4.4.2 Global stability analysis

Here, we explore the global asymptotic stability of the disease-free and endemic equilibria for the special case with no loss of immunity acquired by the recovered individuals and no reduction in each mosquito and rodent group. Accordingly, we have the following results.

Theorem 4.3: The disease-free equilibrium point ϵ_0 of the model (3.1.3)- (3.1.16) with control measures is globally asymptotically stable in Ω if $R_{0L}(a) \leq 1$ and $R_{0M}(a) \leq 1$.

Proof: Consider the following lyapunov function

$$\mathcal{P} = \mu(a_i)(\eta_1(a_i)\sigma(a_i)u_2+\mu(a_i))N_{es}(t,a_i)+\frac{\sigma_0(1+w_1(a_i)\cos(2\pi t+T))\zeta(a_i)\tau(a_i)N_{is}(t,a_i)}{\tau(a_i)}$$

$$+\mu(a_i)N_h(t,a_i)(\epsilon_m(a_i)\beta_m(a_i)u_2+\mu(a_i))\mu_m(\alpha_m+\mu_m)N_{se}(t,a_i)$$

$$+\frac{\tau_m(a_i)c_0(a_i)(1+b\cos(2\pi t+T))\zeta(a_i)\alpha_m\varsigma_m(1+\kappa_m\cos(2\pi t+T))\phi_0 N_{si}(t,a_i)}{\tau_m}$$

$$+\frac{\sigma_0(1+w_1(a_i)\cos(2\pi t+T))\zeta(a_i)\tau(a_i)I_d(t,e_j)}{\mu_d(e_j)\mu(a_i)(\eta_1(a_i)\sigma(a_i)u_2+\mu(a_i))(\gamma_1(a_i)\alpha(a_i)u_2+\tau(a_i)+\mu(a_i))}$$

$$+\frac{\tau_m(a_i)c_0(a_i)(1+b\cos(2\pi t+T))\zeta(a_i)\alpha_m\varsigma_m(1+\kappa_m\cos(2\pi t+T))\phi_0 I_m(t)}{\mu(a_i)N_h(t,a_i)(\tau_m(a_i)+\mu(a_i))(\epsilon_m(a_i)\beta_m(a_i)u_2+\mu(a_i))\mu_m(\alpha_m+\mu_m)}$$

$$+\frac{\sigma_0(1+w_1(a_i)\cos(2\pi t+T))\zeta(a_i)\tau(a_i)E_d(t,e_j)}{(\alpha_d(e_j)+\mu_d(e_j)+\delta_d(e_j))(\eta_1(a_i)\sigma(a_i)u_2+\mu(a_i))(\gamma_1(a_i)\alpha(a_i)u_2+\tau(a_i)+\mu(a_i))}$$

$$+\frac{\tau_m(a_i)c_0(a_i)(1+b\cos(2\pi t+T))\zeta(a_i)\alpha_m\varsigma_m(1+\kappa_m\cos(2\pi t+T))\phi_0 E_m(t)}{\mu(a_i)N_h(t,a_i)(\tau_m(a_i)+\mu(a_i))(\epsilon_m(a_i)\beta_m(a_i)u_2+\mu(a_i))\mu_m(\alpha_m+\mu_m)} \tag{4.4.1}$$

In what follows, the time derivative of $\mathcal{P}$ given by (4.4.1) along the solutions of the model (3.1.3)-(3.1.16) with control measures yields

$$\dot{\mathcal{P}} = \mu(a_i)(\eta_1(a_i)\sigma(a_i)u_2 + \mu(a_i)) \left(\sum_{i=0}^{L} \sum_{j=0}^{T} (\lambda_a + \lambda_b) N_{ss}(t, a_i)(1 - u_1) \right)$$

$$- \mu(a_i)(\eta_1(a_i)\sigma(a_i)u_2 + \mu(a_i)) \left(\sum_{j=0}^{T} \vartheta_m(a_i)\lambda_M N_{es}(t, a_i) I_m(1 - u_1) \right)$$

$$- \mu(a_i)(\eta_1(a_i)\sigma(a_i)u_2 + \mu(a_i))(\mu(a_i) + \gamma_1(a_i)\alpha(a_i)u_2 + \tau(a_i))N_{es}(t, a_i)$$

$$+ \frac{\sigma_0(1 + w_1(a_i)\cos(2\pi t + T))\zeta(a_i)\tau(a_i)}{\tau(a_i)} \left(\sum_{i=0}^{L} \tau(a_i) - \sum_{i=0}^{L} \vartheta_m(a_i)\lambda_M N_{is}(t, a_i) I_m(1 - u_1) \right)$$

$$- \frac{\sigma_0(1 + w_1(a_i)\cos(2\pi t + T))\zeta(a_i)\tau(a_i)}{\tau(a_i)} (\mu(a_i) + \eta_1(a_i)\sigma(a_i)u_2 N_{is}(t, a_i))$$

$$+ \mu(a_i)N_h(t, a_i)(\epsilon_m(a_i)\beta_m(a_i)u_2 + \mu(a_i))(\alpha_m + \mu_m)(\lambda_M N_{is}(t, a_i) I_m(1 - u_1))$$

$$- \mu(a_i)N_h(t, a_i)(\epsilon_m(a_i)\beta_m(a_i)u_2 + \mu(a_i))(\alpha_m + \mu_m) \left(\sum_{i=0}^{L} \sum_{j=0}^{T} \vartheta_d(e_j)(\lambda_a + \lambda_b) N_{se}(t, a_i)(1 - u_1) \right)$$

$$\mu(a_i)N_h(t, a_i)(\epsilon_m(a_i)\beta_m(a_i)u_2 + \mu(a_i))(\alpha_m + \mu_m)(\mu(a_i) + \tau_m(a_i)N_{se}(t, a_i))$$

$$+ \frac{\tau_m(a_i)c_0(a_i)c_0(a_i)(1 + b\cos(2\pi t + T))\zeta(a_i)\varsigma_m\alpha_m\phi_0}{\tau_m(a_i)}$$

$$\times \left(\sum_{i=0}^{L} \tau_m(a_i) N_{se}(t, a_i) - \sum_{i=0}^{L} \sum_{j=0}^{T} \vartheta_d(e_j)(\lambda_a + \lambda_b) N_{si}(t, a_i)(1 - u_1) \right)$$

$$- \frac{\tau_m(a_i)c_0(a_i)(1 + b\cos(2\pi t + T))\zeta(a_i)\varsigma_m\alpha_m\phi_0}{\tau_m(a_i)} (\mu(a_i) + \epsilon_m(a_i)\beta_m(a_i)u_2) N_{si}(t, a_i)$$

$$+ \frac{\sigma_0(a_i)(1 + w_1(a_i)\cos(2\pi t + T))\zeta(a_i)\tau(a_i)}{\mu_d(e_j)\mu(a_i)(\eta_1(a_i)\sigma(a_i)u_2 + \mu(a_i))(\mu(a_i) + \gamma_1(a_i)\alpha(a_i)u_2 + \tau(a_i))}$$

$$\times \left(\sum_{j=0}^{T} \alpha_d(e_j) E_d(t, e_j) - (\mu(e_j) + \delta_d(e_j)) I_d(t, e_j) \right)$$

$$+ \frac{c_0(a_i)c_0(a_i)(1 + b\cos(2\pi t + T))\tau_m(a_i)\zeta(a_i)\varsigma_m(1 + \kappa_m\cos(2\pi t + T))\alpha_m\phi_0}{\mu(a_i)N_h(t, a_i)(\tau_m(a_i) + \mu(a_i))(\epsilon_m(a_i)\beta_m(a_i)u_2 + \mu(a_i))\mu_m^2(\alpha_m + \mu_m)} (\alpha_m E_m + \mu_m I_m)$$

$$+\frac{\sigma_0(a_i)(1+w_1(a_i)\cos(2\pi t+T))\zeta(a_i)\tau(a_i)}{(\alpha_d(e_j)+\mu_d(e_j)+\delta_d(e_j))(\eta_1(a_i)\sigma(a_i)u_2+\mu(a_i))(\gamma_1(a_i)\alpha(a_i)u_2+\tau(a_i)\mu(a_i))}$$
$$\times\left(\sum_{j=0}^{T}(\lambda_d(t)S_d(t,e_j)I_d(t,e_j)-(\alpha_d(e_j)+\mu_d(e_j)+\delta_d(e_j))E_d(t,e_j)\right)$$
$$+\frac{\tau_m(a_i)c_0(a_i)(1+b\cos(2\pi t+T))\zeta(a_i)\varsigma_m(1+\kappa_m\cos(2\pi t+T))\alpha_m\phi_0\lambda_{hm}}{\mu(a_i)N_h(t,a_i)(\tau_m(a_i)+\mu(a_i))(\epsilon_m(a_i)\beta_m(a_i)u_2+\mu(a_i))\mu_m(\alpha_m+\mu_m)}$$

where

$$\lambda_{hm}=\lambda_m S_m N_{si}(t,a_i)(1-u_1)-(\mu_m+\alpha_m)E_m$$

Ignoring certain term and simplifying further we have

$$\begin{aligned}\dot{\mathcal{P}}<&-\mu(a_i)(\eta_1(a_i)\sigma(a_i)u_2+\mu(a_i))(\mu(a_i)+\gamma_1(a_i)\alpha(a_i)u_2+\tau(a_i))N_{es}(t,a_i)\\&+\sigma_0(1+w_1(a_i)\cos(2\pi t+T))\zeta(a_i)\tau(a_i)N_{es}(t,a_i)\\&-\frac{\sigma_0(1+w_1(a_i)\cos(2\pi t+T))\zeta(a_i)\tau(a_i)(\eta_1(a_i)\sigma(a_i)u_2)N_{is}(t,a_i)}{\tau(a_i)}\\&-\mu(a_i)N_h(t,a_i)(\epsilon_m(a_i)\beta_m(a_i)u_2+\mu(a_i))\mu_m(\alpha_m+\mu_m)(\mu(a_i)+\tau_m(a_i))N_{se}(t,a_i)\\&+\tau_m(a_i)c_0(a_i)(1+b\cos(2\pi t+T))\epsilon_m(a_i)\beta_m(a_i)u_2\zeta(a_i)\alpha_m\phi_0N_{se}(t,a_i)\\&-\frac{\tau_m(a_i)c_0(a_i)(1+b\cos(2\pi t+T))\varsigma_m(1+\kappa_m(2\pi t+T))\zeta(a_i)\alpha_m\phi_0(\mu(a_i)+\epsilon_m(a_i)\beta_m(a_i)u_2)N_{si}(t,a}{\tau_m(a_i)}\\&-\frac{\tau_m(a_i)c_0(a_i)(1+b\cos(2\pi t+T))\varsigma_m(1+\kappa_m(2\pi t+T))\zeta(a_i)\alpha_m\phi_0I_m(t)}{\mu(a_i)N_h(t,a_i)(\mu(a_i)+\tau_m(a_i))(\epsilon_m(a_i)\beta_m(a_i)u_2+\mu(a_i))\mu_m(\alpha_m+\mu_m)}\end{aligned}\quad(4.4.2)$$

(4.1.46) becomes

$$\begin{aligned}\dot{\mathcal{P}}<&\sigma_0w_1(a_i)\zeta(a_i)\tau(a_i)(\mathcal{R}_{0L}(a)-1)N_{es}(t,a_i)\\&-\frac{\mu(a_i)(\gamma_1(a_i)\alpha(a_i)u_2+\tau(a_i)+\mu(a_i))(\eta_1(a_i)\sigma(a_i)u_2+\mu(a_i))^2\mathcal{R}_{0L}(a)N_{is}(t,a_i)}{\tau(a_i)}\\&+\mu(a_i)N_h(t,a_i)(\tau_m(a_i)+\mu(a_i))(\epsilon_m(a_i)\beta_m(a_i)u_2+\mu(a_i))\mu_m(\alpha_m+\mu_m)(\mathcal{R}_{0M}^2(a)-1)N_{se}(t,a_i)\\&-\frac{(\epsilon_m(a_i)\beta_m(a_i)u_2+\mu(a_i))^2\mu(a_i)N_h(t,a_i)(\tau_m(a_i)+\mu(a_i))\mu_m(\alpha_m+\mu_m)\mathcal{R}_{0M}^2(a)}{\tau_m(a_i)}-\mathcal{R}_{0M}^2(a)I_m(t)\end{aligned}\quad(4.4.3)$$

$\dot{\mathcal{P}}<0$ if $\mathcal{R}_{0L}(a)\leq 1$ and $\mathcal{R}_{0M}(a)\leq 1$.

It is important to note that all the trajectories starting in the feasible region where

the solution have biological meaning approach the positively invariant subset of the set where $\dot{\mathcal{P}} = 0$. This maximum invariant set in
$\{(N_{ss}(t,a_i), N_{es}(t,a_i), N_{is}(t,a_i), N_{rs}(t,a_i), N_{se}(t,a_i), N_{si}(t,a_i), N_{sr}(t,a_i),$
$N_{rr}(t,a_i), S_d, E_d, I_d, S_m, E_m, I_m) \in \Omega : \dot{\mathcal{P}} = 0\}$ is the singleton ϵ_0. In this set $N_h(t,a_i) \to \frac{\Lambda(a_i)}{\mu(a_i)}, N_d(t,e_j) \to \frac{\Lambda_d(e_j)(1+\xi_d\cos(2\pi t+T))}{\mu_d(e_j)+\delta(e_j)}$ and $N_m(t) \to \frac{\varsigma_m(1+\xi_d\cos(2\pi t+T))}{\mu_m}$ as $t \to +\infty$. This shows that all solutions approach the disease-free stationary state. Thus, when $\mathcal{R}_{0M}(a), \mathcal{R}_{0L}(a) \leq 1$ both diseases will be eliminated from the system. If $\mathcal{R}_{0M}(a), \mathcal{R}_{0L}(a) > 1$, then $\dot{\mathcal{P}}$ may be > 0 for $N_{es} = N_{is} = N_{se} = N_{si} = I_d = I_m$ close to the disease-free state except for $N_{es} = N_{is} = N_{se} = N_{si} = I_d = I_m = 0$. Thus the disease-free state is globally asymptotically stable when $\mathcal{R}^2_{0M}(a), \mathcal{R}_{0L}(a) \leq 1$

The global stability analysis of the endemic equilibrium is next explored. To achieve this, we use the nonlinear Lyapunov function of Goh-Volterra type which has been found to be very successful. See, for instance, Niger and Gumel (2008) for the application of this Lyapunov function.

Theorem 4.4: The unique endemic equilibrium, E_e, of the model (3.1.3)-(3.1.16) is globally asymptotically stable if $\mathcal{R}_{0M}(a) > 1$, $\mathcal{R}_{0L}(a) > 1$ and $0 \leq u_1 \leq 1$.
Proof: Let $\mathcal{R}_{0L}(a), \mathcal{R}_{0M}(a) > 1$ and $0 \leq u_1 \leq 1$ so that a unique endemic equilibrium exists and consider the following nonlinear Lyapunov function defined by

$$\mathcal{N} = N_{ss}(t,a_i) - N_{ss}^{**}(a_i) - N_{ss}^{**}(a_i)\ln\left(\frac{N_{ss}(t,a_i)}{N_{ss}^{**}(a_i)}\right) + N_{es}(t,a_i) - N_{es}^{**}(a_i)$$
$$- N_{es}^{**}(a_i)\ln\left(\frac{N_{es}(t,a_i)}{N_{es}^{**}(a_i)}\right) + N_{se}(t,a_i) - N_{se}^{**}(a_i) - N_{se}^{**}(a_i)\ln\left(\frac{N_{se}(t,a_i)}{N_{se}^{**}(a_i)}\right)$$
$$+ \frac{\mu(a_i)+\gamma_1(a_i)\alpha(a_i)u_2+\tau(a_i)}{\tau(a_i)}\left[N_{is}(t,a_i) - N_{is}^{**}(a_i) - N_{is}^{**}(a_i)\ln\left(\frac{N_{is}(t,a_i)}{N_{is}^{**}(a_i)}\right)\right]$$
$$+ \frac{\mu(a_i)+\tau_m(a_i)}{\tau_m(a_i)}\left[N_{si}(t,a_i) - N_{si}^{**}(a_i) - N_{si}^{**}(a_i)\ln\left(\frac{N_{is}(t,a_i)}{N_{si}^{**}(a_i)}\right)\right]$$
$$+S_d(t,e_j) - S_d^{**}(e_j) - S_d^{**}(e_j)\ln\left(\frac{S_d(t,e_j)}{S_d^{**}(e_j)}\right) + E_d(t,e_j) - E_d^{**}(e_j) - E_d^{**}(e_j)\ln\left(\frac{E_d(t,e_j)}{E_d^{**}(e_j)}\right)$$
$$+ \frac{\mu_d(e_j)+\alpha_d(e_j)+\delta_d(e_j)}{\alpha(e_j)}\left[I_d(t,e_j) - I_d^{**}(e_j) - I_d^{**}(e_j)\ln\left(\frac{I_d(t,e_j)}{I_d^{**}(e_j)}\right)\right]$$
$$+S_m - S_m^{**} - S_m^{**}\ln\left(\frac{S_m}{S_m^{**}}\right) + E_m - E_m^{**} - E_m^{**}\ln\left(\frac{E_m}{E_m^{**}}\right) + \frac{\alpha_m+\mu_m}{\alpha_m}\left[I_m - I_m^{**} - I_m^{**}\ln\left(\frac{I_m}{I_m^{**}}\right)\right] \tag{4.4.4}$$

with Lyapunov time- derivative obtained as

$$\dot{\mathcal{N}} = \dot{N}_{ss}(t,a_i) - \left(\frac{N_{ss}^{**}(a_i)}{N_{ss}(t,a_i)}\right)\dot{N}_{ss}(t,a_i) + \dot{N}_{es}(t,a_i) - \left(\frac{N_{es}^{**}(a_i)}{N_{es}(t,a_i)}\right)\dot{N}_{es}(t,a_i)$$
$$+ \dot{N}_{se}(t,a_i) - \left(\frac{N_{se}^{**}(a_i)}{N_{se}(t,a_i)}\right)\dot{N}_{se}(t,a_i)$$
$$+ \frac{\mu(a_i)+\gamma_1(a_i)\alpha(a_i)u_2+\tau(a_i)}{\tau(a_i)}\left[\dot{N}_{is}(t,a_i) - \left(\frac{N_{is}^{**}(a_i)}{N_{is}(t,a_i)}\right)\dot{N}_{is}(t,a_i)\right]$$
$$+ \frac{\mu(a_i)+\tau_m(a_i)}{\tau_m(a_i)}\left[\dot{N}_{si}(t,a_i) - \left(\frac{N_{si}^{**}(a_i)}{N_{si}(t,a_i)}\right)\dot{N}_{si}(t,a_i)\right]$$
$$+ \dot{S}_d(t,e_j) - \left(\frac{S_d^{**}(e_j)}{S_d(t,e_j)}\right)\dot{S}_d(t,e_j) + \dot{E}_d(t,e_j) - \left(\frac{E_d^{**}(e_j)}{E_d(t,e_j)}\right)\dot{E}_d(t,e_j)$$
$$+ \frac{\mu_d(e_j)+\alpha_d(e_j)+\delta_d(e_j)}{\alpha(e_j)}\left[\dot{I}_d(t,e_j) - \left(\frac{I_d^{**}(e_j)}{I_d(t,e_j)}\right)\dot{I}_d(t,e_j)\right]$$
$$+ \dot{S}_m - \left(\frac{S_m^{**}}{S_m}\right)\dot{S}_m + \dot{E}_m - \left(\frac{E_m^{**}}{E_m}\right)\dot{E}_m + \frac{\alpha_m+\mu_m}{\alpha_m}\left[\dot{I}_m - \left(\frac{I_m^{**}}{I_m}\right)\dot{I}_m\right] \tag{4.4.5}$$

Using appropriate equations of the model (3.1.3)-(3.1.16)with control measures in

(4.4.5), further gives

$$\dot{\mathcal{N}} = \sum_{i=0}^{L} \zeta(a_i) \left(1 + \frac{N_{ss}^{**}(a_i)}{N_{ss}(t,a_i)}\right) - \sum_{i=0}^{L} \mu(a_i) N_{ss}(t,a_i) \left(1 + \frac{N_{ss}^{**}(a_i)}{N_{ss}(t,a_i)}\right)$$
$$+ \sum_{i=0}^{L} \sum_{j=0}^{T} (\lambda_a + \lambda_b) N_{ss}^{**}(a_i)(1-u_1(t)) + \sum_{i=0}^{L} \lambda_M N_{ss}^{**}(a_i) I_m (1-u_1(t))$$
$$- \sum_{i=0}^{L} \sum_{j=0}^{T} \frac{(\lambda_a + \lambda_b) N_{ss}(t,a_i) N_{es}^{**}(a_i)(1-u_1(t))}{N_{es}(t,a_i)} + (\mu(a_i) + \gamma_1(a_i)\alpha(a_i)u_2(t) + \tau(a_i)) N_{es}^{**}(a_i))$$
$$- \sum_{i=0}^{L} \frac{\lambda_M N_{ss}(t,a_i) N_{se}^{**}(a_i) I_m (1-u_1(t))}{N_{se}(t,a_i)} + (\mu(a_i) + \tau_m(a_i)) N_{se}^{**}(a_i)$$
$$- \sum_{i=0}^{L} \frac{(\mu(a_i) + \gamma_1(a_i)\alpha(a_i)u_2(t) + \tau(a_i))\vartheta_m(a_i)\lambda_M N_{is}(t,a_i) I_m (1-u_1(t))}{\tau(a_i)}$$

$$
\begin{aligned}
&- \frac{(\mu(a_i)+\gamma_1(a_i)\alpha(a_i)u_2(t)+\tau(a_i))(\mu(a_i)+\eta_1(a_i)\sigma(a_i)u_2(t))N_{is}(t,a_i)}{\tau(a_i)} \\
&- \sum_{i=0}^{L} \frac{(\mu(a_i)+\gamma_1(a_i)\alpha(a_i)u_2(t)+\tau(a_i))N_{is}^{**}(a_i)N_{es}(t,a_i)}{N_{is}(t,a_i)} \\
&+ \sum_{i=0}^{L} \frac{\vartheta_m(a_i)\lambda_M N_{is}^{**}(a_i)I_m(t)(1-u_1(t))(\mu(a_i)+\gamma_1(a_i)\alpha(a_i)u_2(t)+\tau(a_i))}{\tau(a_i)} \\
&+ \frac{(\mu(a_i)+\gamma_1(a_i)\alpha(a_i)u_2(t)+\tau(a_i))N_{is}^{**}(a_i)(\mu(a_i)+\eta_1(a_i)\sigma(a_i)u_2(t))}{\tau(a_i)} \\
&- \sum_{i=0}^{L}\sum_{j=0}^{T} \frac{\vartheta_d(a_i)(\lambda_a+\lambda_b)N_{si}(t,a_i)(\mu(a_i)+\tau_m(a_i))(1-u_1(t))}{\tau_m(a_i)} \\
&- \frac{(\mu(a_i)+\epsilon_m(a_i)\beta_m(a_i)u_2(t))(\mu(a_i)+\tau_m(a_i))N_{si}(t,a_i)}{\tau_m(a_i)} \\
&- \sum_{i=0}^{L} \frac{(\mu(a_i)+\tau_m(a_i))N_{si}^{**}(a_i)N_{se}(t,a_i)}{N_{si}(t,a_i)} \\
&- \sum_{i=0}^{L}\sum_{j=0}^{T} \frac{\vartheta(a_i)(\lambda_a+\lambda_b)N_{si}^{**}(a_i)(1-u_1(t))(\mu(a_i)+\tau_m(a_i))}{\tau_m(a_i)} \\
&+ \frac{(\mu(a_i)+\epsilon_m(a_i)\beta_m(a_i)u_2(t))N_{si}^{**}(a_i)(\mu(a_i)+\tau_m(a_i))}{\tau_m(a_i)} \\
&+\sum_{j=0}^{T}\Lambda_d(e_j)(1+\xi_d\cos(2\pi t+T))\left(1+\frac{S_d^{**}(a_i)}{S_d(t,e_j)}\right)-\sum_{j=0}^{T}(\mu_d(e_j)+\delta(e_j))S_d(t,e_j)\left(1+\frac{S_d^{**}(a_i)}{S_d(t,e_j)}\right) \\
&+\sum_{j=0}^{T}\lambda_d(t)S_d^{**}(e_j)I_d(t,e_j)(1-u_3(t))-\sum_{j=0}^{T}\frac{\lambda_d(t)S_d(t,e_j)I_d(t,e_j)E_d^{**}(e_j)(1-u_3(t))}{E_d(t,e_j)} \\
&+(\alpha_d(e_j)+\mu_d(e_j)+\delta_d(e_j))E_d^{**}(e_j))-\frac{(\alpha_d(e_j)+\mu_d(e_j)+\delta_d(e_j))(\mu_d(e_j)+\delta_d(e_j))I_d(t,e_j)}{\alpha_d(e_j)} \\
&-\frac{(\alpha_d(e_j)+\mu_d(e_j)+\delta_d(e_j))I_d^{**}(e_j)E_d(t,e_j)}{I_d(t,e_j)}+\frac{(\alpha_d(e_j)+\mu_d(e_j)+\delta_d(e_j))I_d^{**}(e_j)(\mu_d(e_j)+\delta_d(e_j))}{\alpha_d(e_j)} \\
&\varsigma_m(1+\xi_m\cos(2\pi t+T))\left(1+\frac{S_m^{**}}{S_m}\right)-\mu_m S_m\left(1+\frac{S_m^{**}}{S_m}\right)-\frac{(\alpha_m+\mu_m)I_m^{**}E_m}{I_m} \\
&+\frac{\mu_m(\alpha_m+\mu_m)I_m}{\alpha_m}+\frac{(\alpha_m+\mu_m)I_m^{**}}{\alpha_m}+\lambda_m S_m^{**}N_{si}(t,a_i)(1-u_1(t)) \\
&-\frac{\lambda_m S_m N_{si}(t,a_i)(1-u_1(t))E_m^{**}}{E_m}+(\mu_m+\alpha_m)E_m^{**}
\end{aligned}
\tag{4.4.6}
$$

At the endemic equilibrium, it is seen from (3.1.3)-(3.1.16) that

$$\begin{aligned}
\mu(a_i)+\gamma(a_i)\alpha(a_i)+\tau(a_i) &= \frac{(\lambda_a^{**}+\lambda_b^{**})N_{ss}^{**}(a_i)-\vartheta(a_i)\lambda_M N_{es}^{**}(a_i)I_m^{**}}{N_{es}^{**}(a_i)}\\
\mu(a_i)+\eta_1(a_i)\sigma(a_i) &= \frac{\tau(a_i)N_{es}^{**}(a_i)-\vartheta_m(a_i)\lambda_M N_{is}^{**}(a_i)I_m^{**}}{N_{is}^{**}(a_i)}\\
\mu(a_i)+\tau_m(a_i) &= \frac{\lambda_M^{*}N_{ss}^{**}(a_i)I_m^{**}-\vartheta_d(a_i)(\lambda_a^{**}+\lambda_b^{**})N_{se}^{**}(a_i)}{N_{se}^{**}(a_i)}\\
\mu(a_i)+\epsilon_m(a_i)\beta_m(a_i) &= -\frac{\vartheta_d(a_i)(\lambda_a^{**}+\lambda_b^{**})N_{si}^{**}(a_i)+\tau_m(a_i)N_{se}^{**}(a_i)}{N_{si}^{**}(a_i)}\\
\alpha_d(e_j)+\mu_d(e_j)+\delta_d(e_j) &= \frac{\lambda_d^{**}S_d^{**}(e_j)I_d^{**}(e_j)}{E_d^{**}(e_j)}\\
\mu_d(e_j)+\delta_d(e_j) &= \frac{\alpha_d(e_j)E_d^{**}(e_j)}{I_d^{**}(e_j)}\\
\mu_m+\alpha_m &= \frac{\lambda_m^{**}S_m^{**}N_{si}^{**}(a_i)}{E_m^{**}}\\
\Lambda_d(a_i)(1+\xi_d\cos(2\pi t+T)) &= \lambda_d^{**}S_d^{**}(e_j)I_d^{**}(e_j)+(\mu_d(e_j)+\delta_d(e_j))S_d^{**}(e_j)\\
\zeta(a_i) &= (\lambda_a^{**}+\lambda_b^{**})N_{ss}^{**}(a_i)+\lambda_M^{**}N_{ss}^{**}(a_i)I_m^{**}+\mu(a_i)N_{ss}^{**}(a_i)\\
\varsigma_m(1+\kappa_m\cos(2\pi t+T)) &= \lambda_m^{**}S_m^{**}N_{si}^{**}(a_i)+\mu_m S_m^{**}
\end{aligned}$$

$$\mu_m=\frac{\alpha_m E_m^{**}}{I_m^{**}} \tag{4.4.7}$$

Using (4.4.7) in (4.4.6)and then add and subtract the following systematically

$\sum_{i=0}^{L}\sum_{j=0}^{T}(\lambda_a^{**}+\lambda_b^{**})N_{ss}^{**}(a_i)(1-u_1)$, $\lambda_M^{**}N_{ss}^{**}(a_i)I_m^{**}(1-u_1)$

$\sum_{i=0}^{L}\sum_{j=0}^{T}\frac{(\lambda_a^{**}+\lambda_b^{**})N_{ss}^{**}(a_i)(1-u_1)I_h(t,a_i)f^2(N_h^{**})}{I_h^{**}(a_i)f(N_h)}$,

$\frac{\lambda_M^{**}N_{ss}^{**}I_h(t,a_i)f^2(N_h^{**})(1-u_1)}{I_h^{**}(a_i)f(N_h)}$, $\lambda_d^{**}S_d^{**}(e_j)I_d^{**}(e_j)(1-u_3)$, $\frac{\lambda_d^{**}S_d^{**}(e_j)I_d(t,a_i)(1-u_3)f^2(N_d^{**}}{I_d^{**}(e_j)f(N_d)}$

$\lambda_m^{**} S_m^{**} N_{si}^{**}(a_i)(1-u_1)$, $\frac{\lambda_m^{**} S_m^{**} N_{si}(t,a_i)(1-u_1) f^2(N_m^{**})}{N_{si}^{**}(a_i) f(N_m)}$

one gets

$$\dot{\mathcal{N}} = \sum_{i=0}^{L} \mu(a_i) N_{ss}^{**}(a_i) \left(2 - \frac{N_{ss}^{**}(a_i)}{N_{ss}(t,a_i)} - \frac{N_{ss}(t,a_i)}{N_{ss}^{**}(a_i)}\right)$$

$$+ \sum_{i=0}^{L}\sum_{j=0}^{T} (\lambda_a + \lambda_b) N_{ss}^{**}(a_i)(1-u_1) f(N_h^{**})$$

$$\times \left[4 - \frac{N_{ss}^{**}(a_i)}{N_{ss}(t,a_i)} - \frac{N_{es}^{**}(a_i) N_{ss}(t,a_i)}{N_{ss}^{**}(a_i) N_{es}(t,a_i)} - \frac{N_{is}^{**}(a_i) N_{es}(t,a_i)}{N_{is}(t,a_i)} - \frac{I_h(t,a_i) f(N_h^{**})}{I_h^{**}(a_i) f(N_h)}\right]$$

$$- \sum_{i=0}^{L}\sum_{j=0}^{T} N_{ss}^{**}(a_i)(1-u_1) f(N_h^{**})$$

$$\times \left[2 - \frac{I_h(t,a_i) f(N_h^{**}}{I_h^{**}(a_i) f(N_h)} - \frac{f(N_h)}{f(N_h^{**})}\right] - \sum_{i=0}^{L} c_0(1+b\cos(2\pi t+T))(a_i) N_{ss}^{**}(a_i) I_m^{**}(1-u_1) f(N_h^{**})$$

$$\times \left[2 - \frac{I_h(t,a_i) f(N_h^{**}}{I_h^{**}(a_i) f(N_h)} - \frac{f(N_h)}{f(N_h^{**})}\right] - \sum_{i=0}^{L} c_0(1+b\cos(2\pi t+T)) N_{ss}^{**}(a_i) I_m^{**}(1-u_1) f(N_h^{**})$$

$$\times \left[4 - \frac{N_{ss}^{**}(a_i)}{N_{ss}(t,a_i)} - \frac{N_{se}^{**}(a_i) I_m N_{ss}(t,a_i)}{N_{ss}^{**}(a_i) N_{se}(t,a_i) I_m^{**}} - \frac{N_{si}^{**}(a_i) N_{se}(t,a_i) I_m}{N_{si}(t,a_i) I_m^{**}} - \frac{I_h(t,a_i) f(N_h^{**})}{I_h^{**}(a_i) f(N_h)}\right]$$

$$- \sum_{i=0}^{L} \vartheta_m(a_1) c_0(a_i)(1+b\cos(2\pi t+T)) N_{es}^{**}(a_i) I_m^{**}(1-u_1) f(N_h^{**}) \left[1 - \frac{N_{is}^{**}(a_i) N_{es}(t,a_i)}{N_{is}(t,a_i)}\right]$$

$$- \sum_{i=0}^{L}\sum_{j=0}^{T} \vartheta_d(a_i)(\lambda_a^{**} + \lambda_b^{**}) N_{se}^{**}(a_i)(1-u_1) f(N_h^{**}) \left[1 - \frac{N_{si}^{**}(a_i) N_{se}(t,a_i)}{N_{si}(t,a_i)}\right]$$

$$+ \sum_{j=0}^{T} (\mu_d(e_j) + \delta_d(e_j)) S_d^{**}(e_j) \left(2 - \frac{S_d^{**}(e_j)}{S_d(t,a_i)} - \frac{S_d(t,a_i)}{S_d^{**}(e_j)}\right)$$

$$+ \sum_{j=0}^{T} \lambda_d S_d^{**}(e_j) I_d^{**}(e_j)(1-u_3) f(N_d^{**})$$

$$\times \left[4 - \frac{S_d^{**}(e_j)}{S_d(t,e_j)} - \frac{I_d^{**}(e_j) E_d(t,e_j)}{E_d^{**}(e_j) I_d(t,e_j)} - \frac{S_d(t,e_j) I_d(t,e_j) E_d^{**}(e_j)}{S_d^{**}(e_j) I_d^{**}(e_j) E_d(t,e_j)} - \frac{I_d(t,e_j) f(N_d^{**})}{I_d^{**}(e_j) f(N_d)}\right]$$

$$- \sum_{j=0}^{T} \lambda_d(t) S_d^{**}(e_j) I_d^{**}(e_j)(1-u_3) f(N_d^{**}) \left[2 - \frac{I_d(t,e_j) f(N_d^{**})}{f(N_d)(I_d^{**}(e_j))^2} - \frac{f(N_d) I_d(t,e_j)}{I_d^{**}(e_j) f(N_d^{**})}\right]$$

$$+\mu_m S_m^{**}\left(2-\frac{S_m^{**}}{S_m}-\frac{S_m}{S_m^{**}}\right)+\lambda_m S_m^{**}N_{si}^{**}(a_i)(1-u_1)f(N_m^{**})$$
$$\times\left[4-\frac{S_m^{**}}{S_m}-\frac{I_m^{**}E_m}{E_m^{**}I_m}-\frac{S_m N_{si}(t,a_i)E_m^{**}}{S_m^{**}N_{si}^{**}(a_i)E_m}-\frac{I_m f(N_m^{**})}{I_m^{**}f(N_m)}\right]$$
$$-\lambda_m S_m^{**}N_{si}^{**}(a_i)(1-u_1)f(N_m^{**})\left[2-\frac{N_{si}(t,a_i)f(N_m^{**})}{N_{si}^{**}(a_i)f(N_m)}-\frac{N_{si}(t,a_i)f(N_m^{**}}{(N_{si}^{**}(a_i))^2f(N_m)}\right]$$

Further simplification gives

$$\dot{\mathcal{N}}=-A_1-A_2-\sum_{i=0}^{L}\sum_{j=0}^{T}(\lambda_a+\lambda_b)N_{ss}^{**}(a_i)(1-u_1)f(N_h^{**})$$
$$\times\left[2-\frac{I_h(t,a_i)f(N_h^{**})}{I_h^{**}(a_i)f(N_h)}-\frac{f(N_h)}{f(N_h^{**}}\right]-\sum_{i=0}^{L}\lambda_m N_{ss}^{**}(a_i)I_m^{**}(1-u_1)f(N_h^{**})$$
$$\times\left[2-\frac{I_h(t,a_i)f(N_h^{**})}{I_h^{**}(a_i)f(N_h)}-\frac{f(N_h)}{f(N_h^{**}}\right]-A_3-\sum_{i=0}^{L}\vartheta_m(a_i)\lambda_m N_{es}^{**}(a_i)I_m^{**}(1-u_1)f(N_h^{**})$$
$$\times\left[1-\frac{N_{is}^{**}(a_i)N_{es}(t,a_i)}{N_{is}(t,a_i)N_{es}^{**}(a_i)}\right]-\sum_{i=0}^{L}\sum_{j=0}^{T}\vartheta(a_i)(\lambda_a+\lambda_b)$$
$$\times N_{se}^{**}(a_i)(1-u_1)f(N_h^{**})\left[1-\frac{N_{si}^{**}(a_i)N_{se}(t,a_i)}{N_{si}(t,a_i)N_{se}^{**}(a_i)}\right]-A_4-A_5$$
$$-\sum_{j=0}^{T}\lambda_d S_d^{**}(e_j)I_d^{**}(e_j)(1-u_1)f(N_d^{**})\left[2-\frac{I_d(t,e_j)f(N_d^{**})}{f(N_d)(I_d^{**}(e_j))^2}-\frac{f(N_d)I_d(t,e_j)}{I_d^{**}(e_j)f(N_d^{**})}\right]-A_6-A_7$$
$$-\lambda_m S_m^{**}N_{si}^{**}(a_i)(1-u_1)f(N_m^{**})\left[2-\frac{N_{si}(t,a_i)f(N_m)}{N_{si}^{**}(a_i)f(N_m)}-\frac{N_{si}(t,a_i)f(N_m^{**}}{(N_{si}^{**}(a_i))^2f(N_m)}\right] \tag{4.4.8}$$

where

$$A_1=\sum_{i=0}^{L}\mu(a_i)N_{ss}^{**}(a_i)\left(2-\frac{N_{ss}^{**}(a_i)}{N_{ss}(t,a_i)}-\frac{N_{ss}(t,a_i)}{N_{ss}^{**}(a_i)}\right)$$

$$A_2=\sum_{i=0}^{L}\sum_{j=0}^{T}(\lambda_a+\lambda_b)N_{ss}^{**}(a_i)(1-u_1)f(N_h^{**})$$
$$\times\left[4-\frac{N_{ss}^{**}(a_i)}{N_{ss}(t,a_i)}-\frac{N_{es}^{**}(a_i)N_{ss}(t,a_i)}{N_{ss}^{**}(a_i)N_{es}(t,a_i)}-\frac{N_{is}^{**}(a_i)N_{es}(t,a_i)}{N_{is}(t,a_i)}-\frac{I_h(t,a_i)f(N_h^{**})}{I_h^{**}(a_i)f(N_h)}\right]$$

$$A_3 = \sum_{i=0}^{L} \lambda_m(t) N_{ss}^{**}(a_i) I_m^{**}(1-u_1) f(N_h^{**})$$
$$\times \left[4 - \frac{N_{ss}^{**}(a_i)}{N_{ss}(t,a_i)} - \frac{N_{se}^{**}(a_i) I_m N_{ss}(t,a_i)}{N_{ss}^{**}(a_i) N_{se}(t,a_i) I_m^{**}} - \frac{N_{si}^{**}(a_i) N_{se}(t,a_i) I_m}{N_{si}(t,a_i) I_m^{**}} - \frac{I_h(t,a_i) f(N_h^{**})}{I_h^{**}(a_i) f(N_h)} \right]$$

$$A_4 = \sum_{j=0}^{T} (\mu_d(e_j) + \delta_d(e_j)) S_d^{**}(e_j) \left(2 - \frac{S_d^{**}(e_j)}{S_d(t,a_i)} - \frac{S_d(t,a_i)}{S_d^{**}(e_j)} \right)$$

$$A_5 = \sum_{j=0}^{T} \lambda_d S_d^{**}(e_j) I_d^{**}(e_j)(1-u_3) f(N_d^{**})$$
$$\times \left[4 - \frac{S_d^{**}(e_j)}{S_d(t,e_j)} - \frac{I_d^{**}(e_j) E_d(t,e_j)}{E_d^{**}(e_j) I_d(t,e_j)} - \frac{S_d(t,e_j) I_d(t,e_j) E_d^{**}(e_j)}{S_d^{**}(e_j) I_d^{**}(e_j) E_d(t,e_j)} - \frac{I_d(t,e_j) f(N_d^{**})}{I_d^{**}(e_j) f(N_d)} \right]$$

$$A_6 = \mu_m S_m^{**} \left(2 - \frac{S_m^{**}}{S_m} - \frac{S_m}{S_m^{**}} \right)$$

$$A_7 = \lambda_m S_m^{**} N_{si}^{**}(a_i)(1-u_1) f(N_m^{**})$$
$$\times \left[4 - \frac{S_m^{**}}{S_m} - \frac{I_m^{**} E_m}{E_m^{**} I_m} - \frac{S_m N_{si}(t,a_i) E_m^{**}}{S_m^{**} N_{si}^{**}(a_i) E_m} - \frac{I_m f(N_m^{**})}{I_m^{**} f(N_m)} \right]$$

We need to show that $A_1 \geq 0$, $A_2 \geq 0$, $A_3 \geq 0$, $A_4 \geq 0$, $A_5 \geq 0$, $A_6 \geq 0$ and $A_7 \geq 0$. To do this, using the fact that the arithmetic mean is greater than or equal to the geometric mean (AM - GM inequality), we have

$(N_{ss}^{**}(a_i))^2 + (N_{ss}(t,a_i))^2 - 2N_{ss}^{**}(a_i) N_{ss}(t,a_i) \geq 0$

so that,

$\left(\frac{N_{ss}^{**}(a_i)}{N_{ss}(t,a_i)} + \frac{N_{ss}(t,a_i)}{N_{ss}^{**}(a_i)} - 2 \right) \geq 0$. Hence, $\mathcal{L}_1 \geq 0$.

Further, let $x = \frac{N_{ss}^{**}(a_i)}{N_{ss}(t,a_i)}$, $y = \frac{N_{es}^{**}(a_i) f(N_h)}{N_{es}(t,a_i) f(N_h^{**})}$, $z = \frac{N_{is}^{**}(a_i) f(N_h^{**})}{N_{is}(t,a_i) f(N_h^{**})}$.

Then,

$\left[\frac{N_{ss}^{**}(a_i)}{N_{ss}(t,a_i)} + \frac{N_{es}^{**}(a_i) N_{ss}(t,a_i)}{N_{ss}^{**}(a_i) N_{es}(t,a_i)} + \frac{N_{is}^{**}(a_i) N_{es}(t,a_i)}{N_{is}(t,a_i)} + \frac{I_h(t,a_i) f(N_h^{**})}{I_h^{**}(a_i) f(N_h)} - 4 \right]$ can be written as

$$f(x,y,z) = x + \frac{y}{x} + \frac{z}{y} + \frac{1}{z} - 4 \tag{4.4.9}$$

It is suffice to show that $f(x,y,z) \geq 0$. Since $f_x = f_y = f_z = 0$ gives rise to

$x = y = z$ and that $f_{xx} > 0$, $f_{yy} > 0$, $f_{zz} > 0$, one see that the minimum of $f(x, y, z)$ is attainable at $x = y = z$. In what follows, (4.4.8) is reduced to $(x-1)^2 \geq 0$ or $(y-1)^2 \geq 0$ or $(z-1)^2 \geq 0$ with equality if and only if $x = 1$ or $y = 1$ or $z = 1$ respectively. Hence, $A_2 \geq 0$. The proof of $A_3 \geq 0, A_5 \geq 0$ and $A_7 \geq 0$ is similar to $A_2 \geq 0$ while that of $A_4 \geq 0$ and $A_6 \geq 0$ is similar to $A_1 \geq 0$, it follows from (4.1.52) that $\dot{\mathcal{N}} \leq 0$ with $\dot{\mathcal{N}} = 0$ if and only if $N_{ss}(t, a_i) = N_{ss}^{**}(a_i), N_{es}(t, a_i) = N_{es}^{**}(a_i), N_{is}(t, a_i) = N_{is}^{**}(a_i), N_{se}(t, a_i) = N_{se}^{**}(a_i), N_{si}(t, a_i) = N_{si}^{**}(a_i) S_d(t, e_j) = S_d^{**}(e_j), E_d(t, e_j) = E_d^{**}(e_j), I_d(t, e_j) = I_d^{**}(e_j), S_m = S_m^{**}, E_m = E_m^{**}, I_m = I_m^{**}$, $0 \leq u_1 \leq 1$, $0 \leq u_3 \leq 1$. Therefore by LaSalle's principle, the largest compact invariant subset of the set where $\dot{\mathcal{N}} = 0$ is the endemic equilibrium point E_e. Thus, every solution in $\mathcal{R}$ approaches E_e for $R_{0L}(a), R_{0M}(a) > 1$, $0 \leq u_1 \leq 1$, $0 \leq u_3 \leq 1$ and E_e is globally asymptotically stable. This complete the proof.

4.5 STUDY FIVE

Sensitivity

4.5.1 Sensitivity analysis

The sensitivity indices of the basic reproduction number $R_{0M}(a, t)$ and $R_{0L}(a, t)$ to the parameters of the model (3.1.3)-(3.1.16) are computed as follows:

$$\Upsilon_b^{R_{0M}} = \frac{\partial R_{0M}}{\partial b} \times \frac{b}{R_{0M}} = \frac{b(1 + \cos(2\pi t + T))\zeta(a_i)}{2(1 + \cos(2\pi t + T)\zeta(a_i))}$$

$$\Upsilon_{\varsigma_m}^{R_{0M}} = \frac{\partial R_{0M}}{\partial \varsigma_m} \times \frac{\varsigma_m}{R_{0M}} = \frac{1}{2}$$

$$\Upsilon_{\kappa_m}^{R_{0M}} = \frac{\partial R_{0M}}{\partial \kappa_m} \times \frac{\kappa_m}{R_{0M}} = \frac{\kappa_m(1 + \cos(2\pi t + T))}{2(1 + \cos(2\pi t + T))}$$

$$\Upsilon^{R_{0M}}_{\phi_0} = \frac{\partial R_{0M}}{\partial \phi_0} \times \frac{\phi_0}{R_{0M}} = 1$$

$$\Upsilon^{R_{0M}}_{\sigma_0} = \frac{\partial R_{0M}}{\partial \sigma_0} \times \frac{\sigma_0}{R_{0M}} = \frac{1}{2}$$

$$\Upsilon^{R_{0M}}_{\zeta(a_i)} = \frac{\partial R_{0M}}{\partial \zeta(a_i)} \times \frac{\zeta(a_i)}{R_{0M}} = \frac{1}{2}$$

$$\Upsilon^{R_{0M}}_{\mu_m} = \frac{\partial R_{0M}}{\partial \mu_m} \times \frac{\mu_m}{R_{0M}} = -\frac{(2\alpha_m + 3\mu_m)}{2(\alpha_m + \mu_m)}$$

$$\Upsilon^{R_{0M}}_{\epsilon_m(a_i)} = \frac{\partial R_{0M}}{\partial \epsilon_m(a_i)} \times \frac{\epsilon_m(a_i)}{R_{0M}} = -\frac{\beta_m(a_i)\epsilon_m(a_i)}{2(\epsilon_m(a_i)\beta_m(a_i) + \mu(a_i))}$$

$$\Upsilon^{R_{0M}}_{\beta_m(a_i)} = \frac{\partial R_{0M}}{\partial \beta_m(a_i)} \times \frac{\beta_m(a_i)}{R_{0M}} = -\frac{\beta_m(a_i)\epsilon_m(a_i)}{2(\epsilon_m(a_i)\beta_m(a_i) + \mu(a_i))}$$

$$\Upsilon^{R_{0M}}_{\alpha_m} = \frac{\partial R_{0M}}{\partial \alpha_m} \times \frac{\alpha_m}{R_{0M}} = -\frac{\mu_m^3}{2(\alpha_m + \mu(a_i))}$$

$$\Upsilon^{R_{0M}}_{\alpha_m} = \frac{\partial R_{0M}}{\partial \alpha_m} \times \frac{\alpha_m}{R_{0M}} = \frac{\mu_m^3}{2(\alpha_m + \mu(a_i))}$$

$$\Upsilon^{R_{0M}}_{\tau_m(a_i)} = \frac{\partial R_{0M}}{\partial \tau_m(a_i)} \times \frac{\tau_m(a_i)}{R_{0M}} = \frac{\mu(a_i)\tau_m(a_i)}{2(\tau_m(a_i) + \mu(a_i))}$$

$$\Upsilon^{R_{0M}}_{\mu(a_i)} = \frac{\partial R_{0M}}{\partial \mu(a_i)} \times \frac{\mu(a_i)}{R_{0M}} = \frac{-\mu(a_i)(\tau_m(a_i) + \mu(a_i)) - (\tau_m(a_i) + 2\mu(a_i))(\epsilon_m(a_i)\beta_m(a_i) + \mu(a_i))}{\mu(a_i)(\tau_m(a_i) + \mu(a_i))(\epsilon_m(a_i)\beta_m(a_i) + \mu(a_i))}$$

$$\Upsilon^{R_{0L}}_{\sigma_o} = \frac{\partial R_{0L}}{\partial \sigma_0} \times \frac{\sigma_0}{R_{0L}} = 1$$

$$\Upsilon^{R_{0L}}_{w_i(a_i))} = \frac{\partial R_{0L}}{\partial w_1(a_i)} \times \frac{w_1(a_i)}{R_{0L}} = \frac{w_1(a_i)(1+\cos(2\pi t+T)\zeta(a_i)\tau(e_j)}{1+\cos(2\pi t+T)\zeta(a_i)\tau(e_j)}$$

$$\Upsilon^{R_{0L}}_{\zeta(a_i))} = \frac{\partial R_{0L}}{\partial \zeta(a_i)} \times \frac{\zeta(a_i)}{R_{0L}} = 1$$

$$\Upsilon^{R_{0L}}_{\tau(a_i))} = \frac{\partial R_{0L}}{\partial \tau(a_i)} \times \frac{\tau(a_i)}{R_{0L}} = \frac{\gamma_v(a_i)+\mu(a_i)}{\gamma_v(a_i)\alpha(a_i)+\tau(a_i)+\mu(a_i)}$$

$$\Upsilon^{R_{0L}}_{\mu(a_i))} = \frac{\partial R_{0L}}{\partial \mu(a_i)} \times \frac{\mu(a_i)}{R_{0L}} = \frac{-(\eta_v(a_i)\sigma(a_i)+\mu(a_i))-\Gamma_v}{(\eta_v(a_i)\sigma(a_i)+\mu(a_i))(\gamma_v(a_i)\alpha(a_i)+\tau(a_i)+\mu(a_i))}$$

$$\Upsilon^{R_{0L}}_{\eta_v(a_i))} = \frac{\partial R_{0L}}{\partial \eta_v(a_i)} \times \frac{\eta_v(a_i)}{R_{0L}} = \frac{-\sigma(a_i)\eta_v(a_i)}{(\eta_v(a_i)\sigma(a_i)+\mu(a_i))}$$

$$\Upsilon^{R_{0L}}_{\sigma(a_i))} = \frac{\partial R_{0L}}{\partial \sigma(a_i)} \times \frac{\sigma(a_i)}{R_{0L}} = \frac{-\sigma(a_i)\eta_v(a_i)}{(\eta_v(a_i)\sigma(a_i)+\mu(a_i))}$$

$$\Upsilon^{R_{0L}}_{\gamma_v(a_i))} = \frac{\partial R_{0L}}{\partial \gamma_v(a_i)} \times \frac{\gamma_v(a_i)}{R_{0L}} = \frac{-\gamma_v(a_i)\alpha(a_i)}{(\gamma_v(a_i)\alpha(a_i)+\tau(a_i)+\mu(a_i))}$$

$$\Upsilon^{R_{0L}}_{\alpha(a_i))} = \frac{\partial R_{0L}}{\partial \alpha(a_i)} \times \frac{\alpha(a_i)}{R_{0L}} = \frac{-\gamma_v(a_i)\alpha(a_i)}{(\gamma_v(a_i)\alpha(a_i)+\tau(a_i)+\mu(a_i))}$$

where $\Gamma_v = (\eta_v(a_i)\sigma(a_i)+2\mu(a_i))(\gamma_v(a_i)\alpha(a_i)+\tau(a_i)+\mu(a_i))$.
In a similar manner, we can obtain the sensitivity indices of the basic reproduction number, $R_{0M}(a,t)$ and $R_{0L}(a,t)$ to the other parameters of the model. The detailed sensitivity indices of $R_{0M}(a,t)$ and $R_{0L}(a,t)$, using the parameter values provided in Table 4.2 are shown in Table 4.1 and the implications of the signs of the sensitivity indices of the basic reproduction number,$R_{0M}(a,t)$ and $R_{0L}(a,t)$ with respect to its associated parameters are discussed in chapter 5.

The Table below (Table 4.1) gives information on how changes in the model parameters affect the basic reproduction numbers, $R_{0L}(a,t)$ and $R_{0M}(a,t)$. The positive sensitivity index parameters in Table 4.1 contributed most significantly to the transmission of the diseases.

Table 4.1: Sensitivity indices of$R_{0M}(a,t)$ and $R_{0L}(a,t)$ to model parameter.

Parameter	Sensitivity sign	Index value
$\zeta(a_i)$	+	$\frac{1}{2}$
b	+	0.000038
κ_m	+	0.26
$\phi_0(a_i)$	+	$\frac{1}{2}$
μ_m	+	1.28
α_m	+	0.0012
$\tau_m(a_i)$	+	0.000027
$w_1(a_i)$	+	0.56
$\sigma_0(a_i)$	+	$\frac{1}{2}$
$\tau(a_i)$	+	0.0053
ς_m	+	$\frac{1}{2}$
$\mu(a_i)$	-	-2.17
ϵ_m	-	-0.5
$\beta_m(a_i)$	-	-0.5
$\eta_v(a_i)$	-	-10.86
$\sigma(a_i)$	-	-1086
$\alpha(a_i)$	-	-0.054
$\gamma_v(a_i)$	-	-0.054

4.6 STUDY SIX

Invasion and co-existence

4.6.1 Possibility of co-existence in Malaria-Lassa fever co-infection model

Since malaria is already endemic in many part of the world, we assumed that to have a co-infection of both diseases, infectious rodent or human with Lassa fever have to interact with individuals that are already infected with malaria. This would simply implies that the recruitment into the susceptible pool of Lassa fever is already infected with malaria; that is $\zeta(a_i) = I_M^*$. With this new definition, after setting the malaria subpopulation to zero and solve the resulting Lassa fever system the following stationary state is obtained

$$\begin{aligned}
\bar{N}_{ss}^{**}(a_i) &= \sum_{i=0}^{L}\sum_{j=0}^{T} g_1(R_{es1}(a)-1)V_a(\mathcal{R}_{om}(a)-1) \\
&\times \left[\frac{(\mu(a_i)+\epsilon_m(a_i)\beta_m(a_i))+\tau_m(a_i)\epsilon_m(a_i)\beta_m(a_i)}{\tau_m(a_i)\epsilon_m(a_i)\beta_m(a_i)\mathcal{R}_{0M}(a)\gamma_m(a_i)(\mathcal{R}_{em1}(a)-1)}\right] \\
\bar{N}_{es}^{**}(a_i) &= \sum_{i=0}^{L}\sum_{j=0}^{T} g_2(R_{es1}(a)-1) \\
&\times \left[\frac{(\gamma_m(a_i)+\mu(a_i))^2(\mu(a_i)+\epsilon_m(a_i)\beta_m(a_i))\zeta(a_i)(\mathcal{R}_{0M}(a)-1)V_b}{\tau_m(a_i)\epsilon_m(a_i)\beta_m(a_i)\mathcal{R}_{0M}(a)\gamma_m(a_i)(\mathcal{R}_{em1}(a)-1)}\right] \\
\bar{N}_{is}^{**}(a_i) &= \sum_{i=0}^{L}\sum_{j=0}^{T} g_3(R_{es1}(a)-1) \\
&\times \left[\frac{(\gamma_m(a_i)+\mu(a_i))(\mu(a_i)+\epsilon_m(a_i)\beta_m(a_i))\zeta(a_i)(\mathcal{R}_{0M}(a)-1)V_b}{\tau_m(a_i)\epsilon_m(a_i)\beta_m(a_i)\mathcal{R}_{0M}(a)\gamma_m(a_i)(\mathcal{R}_{em1}(a)-1)}\right] \\
\bar{N}_{rs}^{**}(a_i) &= \sum_{i=0}^{L}\sum_{j=0}^{T} (R_{es1}(a)-1)V_a(\mathcal{R}_{om}(a)-1) \\
&\times \left[\frac{(\mu(a_i)+\epsilon_m(a_i)\beta_m(a_i))+\tau_m(a_i)\epsilon_m(a_i)\beta_m(a_i)}{\tau_m(a_i)\epsilon_m(a_i)\beta_m(a_i)\mathcal{R}_{0M}(a)\gamma_m(a_i)(\mathcal{R}_{em1}(a)-1)}\right]
\end{aligned}$$

where

$V_a = \zeta(a_i)(\gamma_m + \mu(a_i)),\ V_b = \tau_m(a_i)\epsilon_m(a_i)\beta_m(a_i),$

$$g_1 = \sum_{i=0}^{L}\sum_{j=0}^{T} \frac{(\mu(a_i)+\gamma_1\alpha_1(a_i)+\tau(a_i))(\mu(a_i)+\eta_1(a_i)\sigma(a_i))\mu(a_i)(R_{es1}(a)-1)}{\lambda_a\theta_1[\gamma_1(a_i)\alpha(a_i)(\mu(a_i)+\eta_1(a_i)\sigma(a_i))+\tau(a_i)\eta_1(a_i)\sigma(a_i)]}$$

$$g_2 = \sum_{i=0}^{L}\sum_{j=0}^{T} \frac{(\mu(a_i)+\eta_1(a_i)\sigma(a_i))\mu(a_i)(R_{es}(a)-1)}{\gamma_1(a_i)\alpha(a_i)(\mu(a_i)+\eta_1(a_i)\sigma(a_i))+\tau(a_i)\eta_1(a_i)\sigma(a_i)}$$

$$g_3 = \sum_{i=0}^{L}\sum_{j=0}^{T} \frac{\tau(a_i)\mu(a_i)}{\gamma_1(a_i)\alpha(a_i)(\mu(a_i)+\eta_1(a_i)\sigma(a_i))+\tau(a_i)\eta_1(a_i)\sigma(a_i)}$$

From these equations, we let $I^*_{TM} = \bar{N}^{**}_{es}(a_i) + \bar{N}^{**}_{is}(a_i)$

$$I^*_{TM} = \sum_{i=0}^{L}\sum_{j=0}^{T}(g_2+g_3)V_a(\mathcal{R}_{0M}(a)-1)\left[\frac{(\mu(a_i)+\epsilon_m(a_i)\beta_m(a_i))+\tau_m(a_i)\epsilon_m(a_i)\beta_m(a_i)}{\tau_m(a_i)\epsilon_m(a_i)\beta_m(a_i)\mathcal{R}_{0M}(a)\gamma_m(a_i)(\mathcal{R}_{em1}(a)-1)}\right]$$

$$I^*_{TM} = \sum_{i=0}^{L}\sum_{j=0}^{T}\frac{\bar{T}(R_{es1}(a)-1)(\mathcal{R}^2_{om}(a)-1)}{\mathcal{R}^{\in}{}_{0M}(a)(\mathcal{R}_{em1}(a)-1)} > 0$$

$$\frac{\bar{T}(R_{es}(a)-1)(\mathcal{R}^2_{0M}(a)-1)}{\mathcal{R}^{\in}{}_{0M}(a)(\mathcal{R}_{em1}(a)-1)} > 0$$

where,

$$\bar{T} = \sum_{i=0}^{L}\sum_{j=0}^{T}(g_2+g_3)V_a\left[\frac{(\mu(a_i)+\epsilon_m(a_i)\beta_m(a_i))+\tau_m(a_i)\epsilon_m(a_i)\beta_m(a_i)}{\tau_m(a_i)\epsilon_m(a_i)\beta_m(a_i)\gamma_m(a_i)}\right]$$

and this implies that the endemic equilibrium is feasible if both $\mathcal{R}^2_{0M}(a),\ R_{es1}(a) > 1$. From this expression it can be noted that for the co-infection of Lassa fever and malaria to prevail, both $\mathcal{R}^2_{0M}(a),\ R_{es1}(a) > 1$. From definition, the force of infection is defined as the transmission probability times the prevalence of the disease in the population. Thus, for humans to successfully transmit to the Lassa virus,

$$\begin{aligned}\lambda_d &= \frac{\beta_d(e_j)w_2(e_j)I^*_{TM}}{N_d(t,e_j)}\\ \lambda_d &= \sum_{i=0}^{L}\sum_{j=0}^{T}\frac{\bar{T}\beta_d(e_j)w_2(e_j)R_{es}(a)(\mathcal{R}^2_{0M}(a)-1)}{N_d(t,e_j)\mathcal{R}^2_{0M}(a)(\mathcal{R}^2_{em1}-1)}\end{aligned}$$

Transmission is reduced as $\beta_d(e_j) \to 0$. The increase in $\beta_d(e_j)$ will in turn increase the basic reproduction number. However, Transmission is reduced if rodent and human interaction is reduced i.e as $w_2(e_j) \to 0$. Hence, we can conclude that if

both malaria and Lassa fever exist in the population, Protection against rodent and human interaction, mosquito biting rate will reduce the reproduction number. Therefore the infections will be eradicated completely in the population.

Whether or not Lassa fever, at endemic state will invade into malaria endemic state can only be judged by looking at the growth rate of the aggregate contributions of Lassa fever into the population.

Let the aggregate contribution of Lassa fever infected be I_0. Then

$$\frac{dI_0}{dt} = \frac{dN_{es}(t,a_i)}{dt} + \frac{dN_{is}(t,a_i)}{dt} + \frac{dI_d}{dt}$$

$$\begin{aligned}\frac{dI_0}{dt} = \sum_{i=0}^{L}\sum_{j=0}^{T}(\lambda_a + \lambda_b(t))N_{ss}(t,a_i) - \sum_{i=0}^{L}\vartheta_m(a_i)\lambda_M(t)N_{es}(t,a_i)I_m \\ - (\mu(a_i) + \gamma_v(a_i)\alpha(a_i) + \tau(a_i))N_{es}(t,a_i) \\ + \sum_{i=0}^{L}\tau(a_i)N_{es}(t,a_i) - \sum_{i=0}^{L}\vartheta_m(a_i)\lambda_M(t)N_{is}(t,a_i)I_m - (\mu(a_i) \\ + \eta_v(a_i)\sigma(a_i))N_{is}(t,a_i) + \sum_{j=0}^{T}\alpha_d(e_j)E_d(t,e_j) - (\mu_d(e_j) + \delta_d(e_j))I_d(t,e_j)\end{aligned}$$

At endemic state

$$\begin{aligned}\frac{dI_0}{dt} = \sum_{i=0}^{L}\sum_{j=0}^{T}(\lambda_a+\lambda_b)N_{ss}^{**}(a_i) - \sum_{i=0}^{L}\vartheta_m(a_i)\lambda_M N_{es}^{**}(a_i)I_m^{**} - (\mu(a_i)+\gamma_1(a_i)\alpha(a_i)+\tau(a_i))N_{es}^{**}(a_i) \\ + \sum_{i=0}^{L}\tau(a_i)N_{es}^{**}(a_i) - \sum_{i=0}^{L}\vartheta_m(a_i)\lambda_M N_{is}^{**}(a_i)I_m^{**} - (\mu(a_i) + \eta_1(a_i)\sigma(a_i))N_{is}^{**}(a_i) \\ + \sum_{i=0}^{L}\alpha_d(e_j)E_d^{**}(e_j) - (\mu_d(e_j) + \delta_d(e_j))I_d^{**}(e_j)\end{aligned}$$

$$\frac{dI_0}{dt} = \sum_{i=0}^{L}\sum_{j=0}^{T} \frac{(\lambda_a(+\lambda_b)\zeta(a_i)(\mathcal{R}^2_{em2}(a)-1)}{\mu(a_i)\mathcal{R}^2_{0M}(a)(\mathcal{R}^2_{em2}(a)-1)} - (\mu(a_i)+\gamma_1(a_i)\alpha(a_i)+\tau(a_i))N^{**}_{es}(a_i)$$
$$- \sum_{i=0}^{L} \frac{\vartheta_m(a_i)\lambda_M(\mu(a_i)+\eta_1(a_i)\sigma(a_i)\zeta(a_i)\mu(a_i)R_{es}(a)I^{**}_m}{\gamma_1\alpha(a_i)(\mu(a_i)+\eta_1(a_i)\sigma(a_i))+\tau(a_i)\eta_1(a_i)\sigma(a_i)} + \sum_{i=0}^{L}\tau(a_i)N^{**}_{es}$$
$$+ \sum_{i=0}^{L}\sum_{j=0}^{T} \frac{\vartheta_m(a_i)\lambda_M(t)\tau(a_i)\mu(a_i)\zeta(a_i)R_{es1}(a)}{\gamma_1\alpha(a_i)(\mu(a_i)+\eta_1(a_i)\sigma(a_i))+\tau(a_i)\eta_1(a_i)\sigma(a_i)} + \sum_{j=0}^{T}\alpha_d(e_j)E^{**}(e_j)$$
$$- (\mu(a_i)+\eta_1(a_i)\sigma(a_i))N^{**}_{is}(a_i) - (\mu_d(e_j)+\delta_d(e_j))I^{**}_d(e_j).$$

Substituting for $\lambda_M,\ \lambda_a, \lambda_b,\ I^{**}_m$, simplifying and then ignoring some terms we gets

$$\frac{dI_0}{dt} > \sum_{i=0}^{L}\sum_{j=0}^{T} \frac{x_a\zeta(a_i)(\mathcal{R}^2_{em2}(a)-1)}{\mu(a_i)\mathcal{R}^2_{0M}(a)(\mathcal{R}_{em1}(a)-1)} - \vartheta_m(a_i)(x_a+x_b)$$

this implies that

$$\vartheta_m(a_i) > \sum_{i=0}^{L}\sum_{j=0}^{T} \frac{x_a\zeta(a_i)(\mathcal{R}^2_{em2}(a)-1)}{\mu(a_i)\mathcal{R}^2_{0M}(a)(\mathcal{R}_{em1}(a)-1)(x_a+x_b)} \tag{4.6.1}$$

where

$$x_a = \sum_{i=0}^{L}\sum_{j=0}^{T} \frac{\rho_0(a_i)(1+w_2(e_j)\cos(2\pi t+T))R_{es2}(a)[\gamma_1\alpha(a_i)(\mu(a_i)+\eta_1(a_i)\sigma(a_i))]+y_a}{\gamma_1\alpha(a_i)(\mu(a_i)+\eta_1(a_i)\sigma(a_i))+\tau(a_i)\eta_1(a_i)\sigma(a_i)}$$
$$x_b = \sum_{i=0}^{L}\sum_{j=0}^{T} \frac{\vartheta_m(a_i)c_0(a_i)(1+b\cos(2\pi t+T))(\mu(a_i)+\eta_1(a_i)\sigma(a_i)\mu(a_i)R_{es1}(a)\alpha_m y_b}{\gamma_1(a_i)\alpha(a_i)(\mu(a_i)+\eta_1(a_i)\sigma(a_i))\mathcal{R}^2_{0M}(a)(\mathcal{R}^2_{0M}(a)-1)y_c}$$
$$x_c = \sum_{i=0}^{L}\sum_{j=0}^{T} \frac{\vartheta_m(a_i)c_0(a_i)(1+b\cos(2\pi t+T))\tau(a_i)\mu(a_i)\zeta(a_i)R_{es1}(a)\alpha_m y_b}{\gamma_i(a_i)\alpha(a_i)(\mu(a_i)+\eta_1(a_i)\sigma(a_i))+y_d}$$

and

$$
\begin{aligned}
y_a &= \sigma_0(a_i)(1 + w_1(a_i)\cos(2\pi t + T))\tau(a_i)\mu(a_i)\zeta(a_i)R_{es1}(a) \\
y_b &= \epsilon_m(a_i)\beta_m(a_i)\varsigma_m(1 + \kappa_m\cos(2\pi t + T))\phi_0(\gamma_m(a_i) + \mu(a_i)\zeta(a_i))(\mathcal{R}_{0M}^2(a) - 1) \\
y_c &= \mu_m(\mu_m + \alpha_m)\epsilon_m(a_i)\beta_m(a_i)M_2 \\
y_d &= \tau(a_i)\eta_1(a_i)\sigma(a_i)\mathcal{R}_{0M}^2(a)(\mathcal{R}_{0M}^2(a) - 1)\mu_m(\mu_m + \alpha_m)\epsilon_m(a_i)\beta_m(a_i)M_2
\end{aligned}
$$

Then malaria will invade the Lassa fever endemic state if (4.6.1) holds and vice versa if the role of m and d are interchanged in (4.6.1) by symmetry. After invasion, whether both pathogen co-exist will depend on the values of the respective reproduction number $\mathcal{R}_{em2}(a),\ \mathcal{R}_{em1}(a_), \mathcal{R}_{0M}, R_{es1}(a)$

4.7 STUDY SEVEN

Subharmonic bifurcation

4.7.1 Analysis of existence of subharmonic bifurcation

Here, we assume that recruitment rate and contact rate are periodic of period one year and then take a year as our unit of time. The human recruitment and mortality rates, $\zeta(a_i)$, $\mu(a_i)$ and vectors recruitment and mortality rates $\varsigma_m(1+\xi_m\cos(2\pi t+T))$, $\Lambda_d(1+\xi_d\cos(2\pi t+T))$, μ_m and $\mu_d(e_j)+\delta_d(e_j)$ will be such that $\frac{1}{\zeta(a_i)}$, $\frac{1}{\mu(a_i)}$, $\frac{1}{\varsigma_m(1+\kappa_m\cos(2\pi t+T))}$, $\frac{1}{\Lambda_d(1+\xi_d\cos(2\pi t+T))}$, $\frac{1}{\mu_m}$ and $\frac{1}{\mu_d(e_j)+\delta(e_j)}$ are 50 years. We exploit the fact that $\mu_(a_i)$, $\zeta(a_i)$, μ_m, $\varsigma_m(1+\kappa_m\cos(2\pi t+T))$, $\Lambda_d(1+\xi_d\cos(2\pi t+T))$, $\frac{1}{\mu(a_i)+\eta_v(a_i)\sigma(a_i)}$ and $\frac{1}{\mu(a_i)+\epsilon_m(a_i)\beta_m(a_i)}$ are $0(10^{-2})$ by introducing a small parameters ϵ as follows:

$$\left.\begin{aligned}
c_0(a_i)I_m^{**} &= \tfrac{I_m^{**}(\mu_m+c_0(a_i)(1+b\cos(2\pi t+T)))\zeta(a_i)}{\mu_m\mu_h(a_i)(\mathcal{R}_{0M}^2(a,t)-1)}=\epsilon,\\
\mu(a_i)(\mathcal{R}_{0M}^2(a,t)-1) &= \tfrac{c_0(a_i)I_m^{**}}{\mathcal{R}_{0M}^2(a,t)-1}=\epsilon,\\
\mu(a_i)(\mathcal{R}_{0L}^2(e,t)-1) &= \tfrac{\rho_0(a_i)I_d^{**}}{\mathcal{R}_{0L}^2(e,t)-1}=\epsilon,\\
\mu(a_i)+\eta_v(a_i)\sigma(a_i) &= \tfrac{\Delta_2}{\epsilon},\\
\mu(a_i)+\epsilon_m(a_i)\beta_m(a_i) &= \tfrac{\Delta_3}{\epsilon},\\
0<\epsilon\ll 1.
\end{aligned}\right\} \quad (4.7.1)$$

Now, we make a change of variables (x,y,z) by setting

$$N_{ss}(t,a_i)=N_{ss}^{**}(a_i)(1+x), N_{is}(t,a_i)=N_{is}^{**}(a_i)(1+y), N_{si}(t,a_i)=N_{si}^{**}(a_i)(1+z). \quad (4.7.2)$$

Putting (4.7.1)and (4.7.2) into the model equations (3.1.3), (3.1.5) and (3.1.8)yields the following system of equations which has the property that when $w_2(e_j) = w_1(a_i) = 0$ and $b = 0$, the endemic equilibrium becomes $(x, y, z) = 0$

$$\left.\begin{aligned}
\dot{x} &= -\epsilon[((\eta + 2\Phi) + (b + w_1(a_i) + w_2(e_j))\cos(2\pi t + T))x \\
&+ (1 + (b + w_1(a_i) + w_2(e_j))\cos(2\pi t + T))z \\
&+ (b + w_1(a_i) + w_2(e_j))\cos(2\pi t + T) + (1 + (b + w_1(a_i) + w_2(e_j))\cos(2\pi t + T)xz] \\
\dot{y} &= \tfrac{\Delta_2}{\epsilon}[(b + w_1(a_i) + w_2(e_j))\cos(2\pi t + T) + z(1 + (b + w_1(a_i) + w_2(e_j))\cos(2\pi t + T)) \\
&+ x(1 + (b + w_1(a_i) + w_2(e_j))\cos(2\pi t + T)) + b\cos(2\pi t + T)) - y] \\
\dot{z} &= \tfrac{\Delta_3}{\epsilon}[y - z]
\end{aligned}\right\} \tag{4.7.3}$$

where

$$\eta \equiv \frac{\mathcal{R}_{0M}(a,t)}{\mathcal{R}_{0M}(a,t) - 1} > 1$$

$$\Phi \equiv \frac{\mathcal{R}_{0L}(a,t)}{\mathcal{R}_{0L}(a,t) - 1} > 1.$$

Now, we obtain the eigenvalues of the linearized system about the endemic steady state when $b = w_1(a_i) = w_2(e_j) = 0$.

Lemma 4.1: The eigenvalues corresponding to the linearized system

$$\begin{pmatrix} \dot{x} \\ \dot{y} \\ \dot{z} \end{pmatrix} = \begin{pmatrix} -\epsilon(\eta + 2\Phi) & 0 & -\epsilon \\ \frac{D_2}{\epsilon} & -\frac{\Delta_2}{\epsilon} & \frac{\Delta_2}{\epsilon} \\ 0 & \frac{\Delta_3}{\epsilon} & -\frac{\Delta_3}{\epsilon} \end{pmatrix} \begin{pmatrix} x \\ y \\ z \end{pmatrix}$$

are given by $\lambda_+, \lambda_-, \lambda_3$ below:$\lambda_\pm(\epsilon) = \epsilon r \pm i\nu + 0(\epsilon^2)$, where

$$\left.\begin{aligned}
\nu &= \sqrt{\tfrac{\Delta_2\Delta_3}{\Delta_2+\Delta_3}} \\
r &= \tfrac{\Delta_2\Delta_3 - (\Delta_2+\Delta_3)^2(\eta+2\Phi)}{2(\Delta_2+\Delta_3)^2} < 0 \\
\lambda_3(\epsilon) &= -\tfrac{(\Delta_2+\Delta_3)}{\epsilon} + 0(\epsilon)
\end{aligned}\right\} \tag{4.7.4}$$

Proof:The eigenvalue of the matrix is given as

$$\begin{vmatrix} -\epsilon(\eta+2\Phi)-\lambda & 0 & -\epsilon \\ \frac{\Delta_2}{\epsilon} & -\frac{\Delta_2}{\epsilon}-\lambda & \frac{\Delta_2}{\epsilon} \\ 0 & \frac{D_3}{\epsilon} & -\frac{\Delta_3}{\epsilon}-\lambda \end{vmatrix} = 0$$

$$\implies (-\epsilon(\eta+2\Phi)-\lambda)\left[\left(\frac{\Delta_2}{\epsilon}+\lambda\right)\left(\frac{\Delta_3}{\epsilon}+\lambda\right)-\frac{\Delta_2\Delta_3}{\epsilon^2}\right]-\epsilon\left(\frac{\Delta_2\Delta_3}{\epsilon^2}\right)=0$$

$$\implies (-\epsilon(\eta+2\Phi)-\lambda)\left[\frac{\Delta_2\Delta_3}{\epsilon^2}+\frac{\lambda\Delta_2}{\epsilon}+\frac{\lambda\Delta_3}{\epsilon}+\lambda^2-\frac{\Delta_2\Delta_3}{\epsilon^2}\right]-\epsilon\left(\frac{\Delta_2\Delta_3}{\epsilon^2}\right)=0$$

$$\implies (-\epsilon(\eta+2\Phi)-\lambda)\left[\frac{\lambda\Delta_2}{\epsilon}+\frac{\lambda\Delta_3}{\epsilon}+\lambda^2\right]-\left(\frac{\Delta_2\Delta_3}{\epsilon}\right)=0$$

$$\implies (\epsilon(\eta+2\Phi)+\lambda)\left[\frac{\lambda\Delta_2}{\epsilon}+\frac{\lambda\Delta_3}{\epsilon}+\lambda^2\right]+\left(\frac{\Delta_2\Delta_3}{\epsilon}\right)=0$$

so that

$$\lambda^3+\lambda^2\left[\epsilon(\eta+2\Phi)+\frac{\Delta_2}{\epsilon}+\frac{\Delta_3}{\epsilon}\right]+\lambda[\Delta_2(\eta+2\Phi)+d_3(\eta+2\Phi)]+\left(\frac{\Delta_2\Delta_3}{\epsilon}\right)=0$$

Thus, the eigenvalues are given by
$\lambda_+, \lambda_-, \lambda_3$ below:$\lambda_\pm(\epsilon) = \epsilon r \pm i\nu + 0(\epsilon^2)$, where

$$\left.\begin{array}{lcl} \nu & = & \sqrt{\frac{\Delta_2\Delta_3}{\Delta_2+\Delta_3}} \\ r & = & \frac{\Delta_2\Delta_3-(\Delta_2+\Delta_3)^2(\eta+2\Phi)}{2(\Delta_2+\Delta_3)^2} < 0 \\ \lambda_3(\epsilon) & = & -\frac{(\Delta_2+D_3)}{\epsilon}+0(\epsilon) \end{array}\right\}$$

Therefore, the endemic steady state is locally asymptotically stable but the attraction is weak. Furthermore, we make a change of variables in equation (4.7.3) when

$b = w_1(a_i) = w_2(e_j) = 0$. Now, let

$$\left.\begin{array}{rcl} \bar{b} & = & \frac{b}{\epsilon} \\ \bar{w}_1(a_i) & = & \frac{w_1(a_i)}{\epsilon} \\ \bar{w}_2(e_j) & = & \frac{w_2(e_j)}{\epsilon} \\ \bar{x} & = & \nu\left[\frac{x}{\epsilon} - \frac{\epsilon\Delta_3(z-y)}{(\Delta_2+\Delta_3)^2}\right] \\ \bar{y} & = & \frac{\Delta_3 y+\Delta_2 z}{\Delta_2+\Delta_3} \\ \bar{z} & = & z-y \end{array}\right\}, \tag{4.7.5}$$

Equation (4.7.3) indicates that $z - y$ should be small, say ϵ. So, (4.7.5) gives

$$\left.\begin{array}{rcl} x & = & \frac{\epsilon\bar{x}}{\nu} + 0(\epsilon^3) \\ y & = & \bar{y} + 0(\epsilon) \\ z & = & \bar{y} - 0(\epsilon) \end{array}\right\}. \tag{4.7.6}$$

Equation(4.7.6) therefore means that the proportion of infectious to exposed persons is $\frac{\epsilon_m(a_i)\beta_m(a_i)+\eta_v(a_i)\sigma(a_i)}{\tau(a_i)+\tau_m(a_i)}$ to order ϵ.

Substituting (4.7.5) in (4.7.3) and remove the bar over b, $w_1(a_i)$ and $w_2(e_j)$ we obtain

$$\left.\begin{array}{rcl} \bar{x}' & = & -\nu\bar{y} + \epsilon f_1(\bar{x},\bar{y},\bar{z},t+T\pi,\epsilon,b,w_1(a_i),w_2(e_j)) \\ \bar{y}' & = & \nu\bar{x}(1+\bar{y}) + \frac{v\epsilon\Delta_3\bar{x}\bar{z}}{\Delta_2+\Delta_3} + v^2(b+w_1(a_i)+w_2(e_j))\cos(2\pi t+T)\left(1+\bar{y}+\frac{\Delta_3\bar{z}}{\Delta_2+\Delta_3}\right) \\ & + & \epsilon f_2(\bar{x},\bar{y},\bar{z},t+T,\pi,\epsilon,b,w_1(a_i),w_2(e_j)) \\ \epsilon\bar{z}' & = & -(\Delta_2+\Delta_3)\bar{z} + \epsilon f_3(\bar{x},\bar{y},\bar{z},t+T,\epsilon,\pi,b,w_1(a_i),w_2(e_j)) \end{array}\right\} \tag{4.7.7}$$

where

$$\left.\begin{aligned}
f_1(\bar{x},\bar{y},\bar{z},t+T,\pi,b,w_1(a_i),w_2(e_j),\epsilon) &= -\bar{x}\left(\eta+2\Phi-\tfrac{\Delta_2\Delta_3}{(\Delta_2+\Delta_3)^2}\right)\\
&- \bar{x}\left(\bar{y}-\tfrac{\Delta_3\bar{z}}{\Delta_2+\Delta_3)}\right)\left(1-\tfrac{\Delta_2\Delta_3}{(\Delta_2+\Delta_3)^2}\right)\\
&+ 0(|\varepsilon|+|b|+|w_1(a_i)|+|w_2(e_j)|)\\
f_2(\bar{x},\bar{y},\bar{z},t+T,\pi,b,w_1(a_i),w_2(e_j),\epsilon) &= \tfrac{v^2\Delta_3\bar{z}}{(\Delta_2+\Delta_3)^2}\left(1+\bar{y}-\tfrac{\Delta_3\bar{z}}{\Delta_2+\Delta_3)}\right)\\
&+ 0(|\epsilon|+|b|+|w_1(a_i)|+|w_2(e_j)|)\\
f_3(\bar{x},\bar{y},\bar{z},t+T,\pi,b,w_1(a_i),w_2(e_j),\epsilon) &= -\Delta_2 v^{-1}\bar{x}\left(1+\bar{y}-\tfrac{\Delta_3\bar{z}}{\Delta_2+\Delta_3)}\right)\\
&+ 0(|\epsilon|+|b|+|w_1(a_i)|+|w_2(e_j)|)
\end{aligned}\right\}.$$

We will treat ϵ, b, $w_1(a_i)$ and $w_2(e_j)$ as small parameters in (4.7.7). Setting $\epsilon = b = w_1(a_i) = w_2(e_j) = 0$ in (4.7.7) we obtain the reduced equations given by

$$\left.\begin{aligned}
\bar{x}'(t) &= -\nu\bar{y}(t)\\
\bar{y}'(t) &= \nu\bar{x}(t)(1+\bar{y}(t))\\
\bar{z} &= 0
\end{aligned}\right\}. \tag{4.7.8}$$

Now, we show that the system (4.7.8) is conservative with first integral as follow:

$$\bar{x}''(t) = \nu\bar{y}'(t)$$

and

$$\bar{y}(t) = \frac{\bar{x}'}{-\nu}(t)$$

$$\bar{x}''(t) + \nu^2\bar{x}(t) - \nu\bar{x}(t)\bar{x}'(t) = 0.$$

Integrate with respect to t we have

$$\frac{-\nu\bar{x}^2(t)}{2} + \nu^2\ln(1+\bar{y}(t)) - \nu\bar{y}(t) = o$$

$$\frac{d}{dt}\left[\frac{-\nu\bar{x}^2(t)}{2}+\nu^2\ln(1+\bar{y}(t))-\nu\bar{y}(t)\right]=0$$

$$\frac{d}{dt}\left[\nu\bar{x}^2(t)-2\nu^2\ln(1+\bar{y}(t))+2\nu\bar{y}(t)\right]=0$$

$$V=\nu x^2(t)+2\nu y(t)-2\nu^2\ln(1+y(t)).$$

Setting $\nu=1$ we have

$$V=x^2+2y-2\ln|1+y|.$$

A system is conservative if there a function $V(x,y)$ such that $\frac{dV}{dt}=0$ along the solution curves of x and y.

$$\frac{dV}{dt}=\frac{dV}{dx}.\frac{dx}{dt}+\frac{dV}{dy}.\frac{dy}{dt}$$

$$\frac{dV}{dt}=2x(-\nu y)+\left[2-\frac{2}{1+y}\right](\nu x(1+y))$$

$$\frac{dV}{dt}=-2x\nu y+2\nu x(1+y)-2\nu x=0.$$

Now, we write $u=\ln(1+y)$ and use (4.7.8) to write a second order differential equation for u we obtain

$$y=e^u-1$$

$$u'=\frac{\nu x(1+y)}{1+y}$$

$$u'=\nu x$$

$$u''+\nu^2(e^u-1)=0.$$

For every integer $n, \frac{2\pi}{\nu}<n<\infty$, there exist a periodic solution of (4.7.8), $(\bar{x}_n(t),\bar{y}_n(t))$ of at least period n. Thus, we have the following results:

Theorem 4.5: Let $(\bar{x}_n(t),\bar{y}_n(t))=\bar{x}_n(t+\tau_h(a_i)),\bar{y}_n(t+\tau_h(a_i))$ represent a periodic solution of equation (4.7.8), where $n>\frac{2\pi}{\nu}$. Let

$$\beta_{h1}(a_i)=\frac{-2r}{\nu}\ (Area\ interior\ to\ \Gamma_n)$$

and for $\tau_h(a_i)\epsilon[0,n), |\epsilon| \ll 1, |\epsilon, b, w_1(a_i), w_2(e_j)| \ll 1$, let

$$\mathbf{B}(\tau_h(a_i), \epsilon, b, w_1(a_i), w_2(e_j)) = -\beta_{h1}(a_i)\epsilon + \beta_{h1}(a_i)(b + w_1(a_i) + w_2(e_j)) \cos 2\pi\tau_h(a_i) + 0(|\epsilon| + |(b, w_1(a_i), w_2(e_j)|)^2. \quad (4.7.9)$$

If $(\bar{x}'_n, \bar{y}'_n)$ spans the n- periodic equations (4.7.8) about $(\bar{x}_n, \bar{y}_n)$, and $\mathbf{B}(\tau_h(a_i), \epsilon, b, w_1(a_i), w_2(e_j)) = 0$, then equation (4.7.7) has an n-periodic solution $(\bar{x}, \bar{y}, \bar{z})$ as

$$\left.\begin{aligned} \bar{x}(t) &= \bar{x}_n(t + \tau_h(a_i) + 0(|\epsilon| + (1 + |b| + |w_1(a_i)| + |w_2(e_j))|) \\ \bar{y}(t) &= \bar{y}_n(t + \tau_h(a_i) + 0(|\epsilon| + |b| + |w_1(a_i)| + |w_2(e_j)|) \\ \bar{z}(t) &= -\tfrac{\epsilon\Delta_2\bar{y}'(t+\tau_h(a_i))}{v^2(\Delta_2+\Delta_3)} + 0(|\varepsilon| + ||b| + |w_1(a_i)| + |w_2(e_j)|)^2 \end{aligned}\right\}. \quad (4.7.10)$$

Proof: Let (4.7.7) be written as $\tau_1 = \frac{t}{\epsilon}$. Also, let

$$\left.\begin{aligned} \bar{x}'(t) &= \epsilon[-\nu\bar{y} + \varepsilon f_1(\bar{x}, \bar{y}, \bar{z}, \theta, \epsilon, b, w_1(a_i), w_2(e_j)] \\ \bar{y}'(t) &= \epsilon[\nu\bar{x}(1 + \bar{y}) + \tfrac{\nu\Delta_3\bar{x}\bar{z}}{\Delta_2\Delta_3} + \nu^2(b + w_1(a_i) + w_2(e_j)) \cos 2\pi\theta(1 + \bar{y} + \tfrac{\Delta_3\bar{z}}{\Delta_2+\Delta_3}) \\ &+ \epsilon f_3] \\ \bar{z}'(t) &= -(\Delta_2 + \Delta_3)\bar{z} + \epsilon f_3 \\ b' &= 0 \\ w'_1 &= 0 \\ w'_2 &= 0 \\ \theta' &= \epsilon \end{aligned}\right\}. \quad (4.7.11)$$

Note that "$\prime$" $= \frac{d}{d\tau_1}$ and f_i are given to lowest order by

$$f_1(\bar{x},\bar{y},\bar{z},\theta,\epsilon,b,w_1(a_i),w_2(e_j)) = -\bar{x}(\eta+2\Phi-\frac{\Delta_2\Delta_3}{(\Delta_2+\Delta_3)^2}-\bar{x}(\bar{y}+\frac{\Delta_3\bar{z}}{\Delta_2+\Delta_3})(1-\frac{\Delta_2\Delta_3}{(\Delta_2+\Delta_3)^2}) + 0(|\epsilon|+|b|+|w_1(a_i)|+|w_2(e_j)|)$$

$$f_2(\bar{x},\bar{y},\bar{z},\theta,\epsilon,b,w_1(a_i),w_2(e_j)) = \frac{v^2\Delta_3\bar{z}}{(\Delta_2+\Delta_3)^2}(1+\bar{y}+\frac{\Delta_3\bar{z}}{\Delta_2+\Delta_3})+0(|\epsilon|+|b|+|w_1(a_i)|+|w_2(e_j)|)$$

$$f_3(\bar{x},\bar{y},\bar{z},\theta,\epsilon,b,w_1(a_i),w_2(e_j)) = \Delta_2 v^{-1}\bar{x}(1+\bar{y}+\frac{\Delta_3\bar{z}}{\Delta_2+\Delta_3})+0(|\epsilon|+|b|+|w_1(a_i)|+|w_2(e_j)|) \tag{4.7.12}$$

We can see (4.7.11) as X^ϵ on $R^6\times S^1$ since the right hand side is periodic in θ. X^0 given by $\xi:\bar{z}=0$ have a manifold of equilibria.

Given the set $K_c = \{(\bar{x},\bar{y},0,b,w_1(a_i),w_2(e_j),\theta)\in R^6\times S^1 : |\bar{x}|\le c, |\bar{y}|\le c, |b|\le c, |w_1(a_i)|\le c, |w_2(e_j)|\le c\}$ on ξ, The smooth function which is the center manifold is given by

$$\bar{z} = \epsilon h(\bar{x},\bar{y},\theta,\epsilon,b,w_1(a_i),w_2(e_j)),\ (\bar{x},\bar{y},\theta,\epsilon,b,w_1(a_i),w_2(e_j))\in K_c x(-\epsilon_0,\epsilon_0) \tag{4.7.13}$$

for small $\epsilon_0>0$.

The flow (4.7.11) constricted to the center manifold gives

$$\left.\begin{array}{rcl} \bar{x}'(t) & = & \epsilon[-\nu\bar{y} + \epsilon\bar{f}_1] \\ \bar{y}'(t) & = & \epsilon[\nu\bar{x}(1+\bar{y}) + v^2(b + w_1(a_i) + w_2(e_j))\cos 2\pi\theta(1+\bar{y}) + \epsilon\bar{f}_2] \\ b'(a_i) & = & 0 \\ w_1'(a_i) & = & 0 \\ w_2'(e_j) & = & 0 \\ \theta' & = & \epsilon \end{array}\right\}. \tag{4.7.14}$$

where $\bar{f}_1(\bar{x}, \bar{y}, \theta, \epsilon, b, w_1(a_i), w_2(e_j)) = f_1(\bar{x}, \bar{y}, \epsilon h, \theta, \varepsilon, b, w_1(a_i), w_2(e_j))$

$$\bar{f}_2(\bar{x}, \bar{y}, \theta, \epsilon, b, w_1(a_i), w_2(e_j)) = \frac{\nu\Delta_3\bar{x}h}{\Delta_1 + \Delta_3} + \frac{v^2\Delta_3 b w_1(a_i)w_2(e_j)}{\Delta_2 + \Delta_3}\cos 2\pi\theta h + f_2(\bar{x}, \bar{y}, \epsilon h, \theta, \epsilon, b, w_1(a_i), w_2(e_j))$$

This shows that the local invariance of the center manifold is

$$h(\bar{x}, \bar{y}, \theta, b, w_1(a_i), w_2(e_j), \theta, 0) = \frac{1}{\Delta_2 + \Delta_3} f_3(\bar{x}, \bar{y}, 0, \theta, 0, b, w_1(a_i), w_2(e_j)). \tag{4.7.15}$$

Thus we have

$$\left.\begin{array}{rcl} \bar{x}'(t) & = & \nu\bar{y} + \epsilon\bar{x}(2r - \xi_1\bar{y}) \\ \bar{y}'(t) & = & \nu\bar{x}(1+\bar{y}) + \nu^2(b + w_1(a_i) + w_2(e_j))\cos(2\pi t + T)(1+\bar{y}) - \epsilon\xi_2\bar{x}^2(1+\bar{y}). \end{array}\right\}. \tag{4.7.16}$$

which is our fast time t. In obtaining (4.7.16) we have made use of (4.7.15), ignore

the higher order in $(\epsilon, bw_1(aI_w(ej)$ and then introduce the notation:

$$\xi_2 = \frac{\Delta_2 \Delta_3}{(\Delta_2 + \Delta_3)^2}$$

$r < 0$ as in (4.7.4) $\xi_1 = 1 - \xi_2$. Equation (4.7.16) is a perturbation of the conservation system (4.7.8)

Now, we use equation (4.7.16) to prove the existence of subharmonic solutions of period n near $\Gamma_n = \{(\bar{x}_n(t), \bar{y}_n(t)) : 0 < t < n$. Suppose equation (4.7.16) have an asymptotically stable subharmonic of order $n, (\bar{x}(t), \bar{y}(t))$, near Γ_n then $(x(t), y(t), z(t))$ is asymptotically stable in (4.7.7) where

$$z(t) = \varepsilon h(x(t), y(t), b, w_1(a_i), w_2(e_j), t, \varepsilon) \tag{4.7.17}$$

Suppose that $(u_1(t), u_2(t))$ is an n-periodic solution (4.7.16) near $\Gamma_n \; \forall \; t$. Then

$$\begin{vmatrix} u_1(t - \tau_h(a_i)) \\ u_2(t - \tau_h(a_i)) \end{vmatrix} = \begin{vmatrix} \bar{x}_n(t) \\ \bar{y}_n(t) \end{vmatrix} + \begin{vmatrix} v_1(t) \\ v_2(t) \end{vmatrix}$$

for small $\tau_h(a_i), 0 < \alpha_h(a_i) < n$. The phase $\tau_h(a_i)$ is introduced to account for the arbitrary degradation of the phase $(\bar{x}_n(t), \bar{y}_n(t))$. The perturbation v satisfies $v_1(0) = 0$ and the equation

$$v' = A(t)v + \epsilon \begin{pmatrix} \bar{x}_n(t)(2r - \xi_1 \bar{y}_n(t)) \\ \xi_n \bar{x}_n^2(t)(1 + \bar{y}_n(t)) \end{pmatrix} + (b + w_1(a_i) + w_2(e_j)) \begin{pmatrix} 0 \\ \nu^2 \cos(2\pi t - \tau_h(a_i))(1 + \bar{y}_n(t)) \end{pmatrix} \tag{4.7.18}$$

where

$$A(t) = \nu \begin{pmatrix} 0 & -1 \\ 1 + \bar{y}_n(t) & \bar{x}_n(t) \end{pmatrix}$$

. Thus, equation

$$W' = -A(t)^t W \tag{4.7.19}$$

has one n-periodic solution up to a constant multiple.

$$\int_0^n \left(\epsilon \begin{pmatrix} \bar{x}_n(t)(2r - \xi_1 \bar{y}_n(t)) \\ \xi_n \bar{x}_n^2(t)(1 + \bar{y}_n(t)) \end{pmatrix} + (b + w_1(a_i) + w_2(e_j)) \begin{pmatrix} 0 \\ \nu^2 \cos(2\pi t - \tau_h(a_i))(1 + \bar{y}_n(t)) \end{pmatrix} \right)$$

$$\times \begin{pmatrix} \bar{x}_n(t) \\ \frac{\bar{y}_n}{(1+y_n)} \end{pmatrix} dt = 0 \tag{4.7.20}$$

is the necessary and sufficient condition for the solvability of (4.7.18). In order to see that (4.7.20) coincides with the first two terms in (4.7.9) note that y_n is even in t and

$$\int_0^n \bar{x}_n^2 \bar{y}_n dt = \frac{1}{v} \int_0^n \bar{x}_n^2 \bar{x}_n' dt = 0$$

so that

$$\begin{aligned} \int_0^n ((2r - \xi_1 \bar{y}_n)\bar{x}_n^2 + \xi_2 \bar{x}^2 \bar{y}_n) dt &= 2r \int_0^n \bar{x}_n^2 (1 + \bar{y}_n) dt \\ &= \frac{-2r}{\nu} \int_0^n \bar{x}_n \bar{y}_n dt \\ &= \frac{-2r}{\nu} \int_{\Gamma_n} x dy \\ &= \frac{-2r}{\nu} \int_{int} \int_{\Gamma_n} dx dy \\ &= \frac{-2r}{\nu} \ (Area\ interior\ to\ \Gamma_n) \end{aligned}$$

This complete the proof.

4.8 STUDY EIGHT

Optimal control theory

4.8.1 Optimal control of malaria-Lassa fever co-infection model

We introduce into the model (3.1.3)-(3.1.16), time dependent preventive $u_1(t)$, treatment $u_2(t)$ and use of insecticide or pesticide $u_3(t)$ effort as controls to curtail the spread of malaria-Lassa fever co-infection. The function $0 \leq u_1(t) \leq 1$ represent the control on the use of mosquitoes treated bed net for personal protection and use of rodent-proof container, use of infection control measure such as complete equipment sterilization, improving home hygiene and strict barrier nursing such as masks, gloves, gowns and goggles to prevent human to human contact. The function $0 \leq u_2(t) \leq 1$ is the control on treatment of malaria and Lassa fever. The insecticide used for treating mosquito bed net is lethal to the mosquitoes and other insects and also repels the mosquitoes, thus reducing the number that attempt to feed on people in the sleeping areas with the nets. However, the mosquitoes can still feed on humans outside the preventive areas, and so we have included the spraying of insecticide. Furthermore, Use of pesticide in and around homes can help reduce rodent population. Thus, each mosquitoes and rodents group are reduced by insecticide or pesticide $u_3(t)$, where, $0 \leq u_3(t) \leq 1$, is the control function representing spray of insecticide or pesticide aimed at reducing the mosquito and rodent sub-population. Hence, transition dynamics is given by

$$\frac{dN_{ss}(t,a_i)}{dt} = \zeta(a_i) - \sum_{i=0}^{L}\sum_{j=0}^{T}(\lambda_a+\lambda_b)N_{ss}(t,a_i)(1-u_1) - \sum_{i=0}^{L}\lambda_M N_{ss}(t,a_i)I_m(1-u_1)$$
$$- \mu(a_i)N_{ss}(t,a_i) + \gamma_m(a_i)N_{sr}(t,a_i) \quad (4.8.1)$$

$$\frac{dN_{es}(t,a_i)}{dt} = \sum_{i=0}^{L}\sum_{j=0}^{T}(\lambda_a+\lambda_b)N_{ss}(t,a_i)(1-u_1) - \sum_{i=0}^{L}\vartheta_m(a_i)\lambda_M N_{es}(t,a_i)I_m(1-u_1)$$
$$- (\mu(a_i) + \gamma_1(a_i)\alpha(a_i)u_2 + \tau(a_i))N_{es}(t,a_i) \quad (4.8.2)$$

$$\frac{dN_{is}(t,a_i)}{dt} = \sum_{i=0}^{L}\tau(a_i)N_{es}(t,a_i) - \sum_{i=0}^{L}\vartheta_m(a_i)\lambda_M N_{is}(t,a_i)I_m(1-u_1)$$
$$- (\mu(a_i) + \eta_1(a_i)\sigma(a_i)u_2)N_{is}(t,a_i) \quad (4.8.3)$$

$$\frac{dN_{rs}(t,a_i)}{dt} = \sum_{i=0}^{L}(\gamma_1(a_i)\alpha(a_i)u_2N_{es}(t,a_i) + \eta_1(a_i)\sigma(a_i)u_2N_{is}(t,a_i)) - \mu(a_i)N_{rs}(t,a_i)$$
$$(4.8.4)$$

$$\frac{dN_{se}(t,a_i)}{dt} = \sum_{i=0}^{L}\lambda_M N_{ss}(t,a_i)I_m(1-u_1) - \sum_{i=0}^{L}\sum_{j=0}^{T}\vartheta_d(a_i)(\lambda_a+\lambda_b)N_{se}(t,a_i)(1-u_1)$$
$$- (\mu(a_i) + \tau_m(a_i))N_{se}(t,a_i) \quad (4.8.5)$$

$$\frac{dN_{si}(t,a_i)}{dt} = \sum_{i=0}^{L}\tau_m(a_i)N_{se}(t,a_i) - \sum_{i=0}^{L}\sum_{j=0}^{T}\vartheta_d(a_i)(\lambda_a+\lambda_b)N_{si}(t,a_i)(1-u_1)$$
$$- (\mu(a_i) + \epsilon_m(a_i)\beta_m(a_i)u_2)N_{si}(t,a_i) \quad (4.8.6)$$

$$\frac{dN_{sr}(t,a_i)}{dt} = \sum_{i=0}^{L} \epsilon_m(a_i)\beta_m(a_i)u_2 N_{si}(t,a_i) - (\gamma_m(a_i) + \mu(a_i))N_{sr}(t,a_i) \quad (4.8.7)$$

$$\frac{dN_{rr}(t,a_i)}{dt} = \sum_{i=0}^{L} \vartheta_m(a_i)\lambda_M(N_{es}(t,a_i) + N_{is}(t,a_i))(1-u_1)I_m - \mu(a_i)N_{rr}(t,a_i) + \sum_{i=0}^{L}\sum_{j=0}^{T} \vartheta_d(a_i)(\lambda_a + \lambda_b)(N_{se}(t,a_i) + N_{si}(t,a_i))(1-u_1) \quad (4.8.8)$$

$$\frac{dS_d(t,e_j)}{dt} = \Lambda_d(e_j)(1 + \xi_d \cos(2\pi t + T)) - \sum_{j=0}^{T} \lambda_d S_d(t,e_j)I_d(t,e_j) - (\mu_d(e_j) + \delta_d(e_j) + (1-u_3))S_d(t,e_j) \quad (4.8.9)$$

$$\frac{dE_d(t,e_j)}{dt} = \sum_{j=0}^{T} \lambda_d S_d(t,e_j)I_d(t,e_j) - (\alpha_d(e_j) + \mu_d(e_j) + \delta_d(e_j) + (1-u_3))E_d(t,e_j) \quad (4.8.10)$$

$$\frac{dI_d(t,e_j)}{dt} = \sum_{j=0}^{T} \alpha_d(e_j)E_d(t,e_j) - (\mu_d(e_j) + \delta_d(e_j) + (1-u_3))I_d(t,e_j) \quad (4.8.11)$$

$$\frac{dS_m}{dt} = \varsigma_m \Lambda_d(e_j(1 + \kappa_m \cos(2\pi t + T)) - \lambda_m S_m N_{si}(t,a_i)(1-u_1) - (\mu_m + (1-u_3))S_m \quad (4.8.12)$$

$$\frac{dE_m}{dt} = \lambda_m S_m N_{si}(t, a_i)(1 - u_1) - (\mu_m + \alpha_m + (1 - u_3))E_m \tag{4.8.13}$$

$$\frac{dI_m}{dt} = \alpha_m E_m - (\mu_m + (1 - u_3))I_m \tag{4.8.14}$$

4.8.2 Analysis of optimal control

We define our objective (cost) functional as

$$J(u_1, u_2, u_3) = \int_0^{t_f} (m_1 N_{es}(t, a_i) + m_2 N_{is}(t, a_i) + m_2 N_{si}(t, a_i) + m_3 N_m(t) + m_3 N_d(t, e_j) + r_1 u_1^2 + r_2 u_2^2 + r_3 u_3^2) dt \tag{4.8.15}$$

$m_1, m_2, m_3 > 0$ represents the balancing cost factors for prevention, treatment and use of insecticide or pesticide efforts respectively. It is assumed that the cost of prevention, treatment and use of insecticide or pesticide are quadratic in the objective functional (4.8.15). The cost of treatment could come from cost of drug and other cost associated with other health conditions such as surveillance and follow up drug management. similarly, the cost to reduce number of mosquito and rodent populations are associated with cost of public education and insecticide or pesticide.

We seek an optimal control u_1^*, u_2^*, u_3^* such that

$$J((u_1^*, u_2^*, u_3^*) = min\big\{J(u_1, u_2, u_3) : (u_1, u_2, u_3) \in \mathcal{U}\big\} \tag{4.8.16}$$

subject to the optimal control model above where

$$\mathcal{U} = \big\{(u_1, u_2, u_3) : u_r(t) \text{ is piecewise continuous on } [0, t_f], 0 \leq u_r \leq 1,\ r = 1, 2, 3\big\} \tag{4.8.17}$$

The basic framework of this optimal control problem is to prove the existence of the optimal control and characterize the optimal control through the optimality system and prove the uniqueness of the optimality system.

4.8.3 Existence of an optimal control

First we obtain boundedness of the state system given an optimal control set $\mathcal{U}$. We then establish the existence of an optimal control.

Theorem 4.6 Given $(u_1(t), u_2(t), u_3(t)) \in \mathcal{U}$, the state equations (4.8.1)-(3.8.14) has a bounded solution.

Proof: It is a consequence of theorem 4.1.

With the boundedness of the state system established, we now prove the existence of the optimal control using a result in (Fleming, et al 1975).

Theorem 4.7 Given an objective functional (4.8.15) subject to system (4.8.1)-(4.8.14) with initial conditions and the admissible control set (4.8.17) then there exists an optimal control pair $(u_1^*, u_2^*, u_3^*) \in \mathcal{U}$ such that

$$J(u_1^*, u_2^*, u_3^*) = \min_u \ J(u_1(t), u_2(t), u_3(t))$$

if the following conditions are satisfied

(i) The set of controls and corresponding state variables is nonempty;

(ii) The control set $\mathcal{U}$ is convex and closed;

(iii) The right hand side of the state system is bounded by a linear function in the state and control;

(iv) The integrand of the functional is convex on $\mathcal{U}$ and is bounded below by $c_1(|u_1|^2 + |u_2|^2 + |u_3|^2)^{\frac{\delta}{2}} - c_2 - c_3$ where $c_1, c_2, c_3 > 0$ and $\delta > 1$.

Proof: The result in (Theorem 4.1) for the system (4.8.1)-(4.8.14) with bounded coefficient is used to give condition i. The control set is closed and convex by definition. By Theorem 4.1, the right hand side of system (4.8.1)-(4.8.14) satisfies condition iii. It is clear that $m_1 N_{es}(t, a_i) + m_2 N_{is}(t, a_i) + m_2 N_{si}(t, a_i) + m_3 N_m(t) + m_3 N_d(t, e_j) + r_1 u_1^2 + r_2 u_2^2 + r_3 u_3^2$ is convex on $\mathcal{U}$. Further, since the variable states are bounded, there exists $c_1, c_2, c_3 > 0$ and $\delta > 1$ satisfying

$$m_1 N_{es}(t, a_i) + m_2 N_{is}(t, a_i) + m_2 N_{si}(t, a_i) + m_3 N_m(t) + m_3 N_d(t, e_j) + r_1 u_1^2 + r_2 u_2^2 + r_3 u_3^2 \geq c_1(|u_1|^2 + |u_2|^2 + |u_3|^2)^{\frac{\delta}{2}} - c_2 - c_3$$

Therefore an optimal exists.

4.8.4 The optimal system

With the establishment of the existence of an optimal control, we use Pontryagin's maximum principle (Pontryagin 1986) to derive the necessary conditions for this optimal control. With costate variables $\Gamma = (\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6, \lambda_7, \lambda_8, \lambda_9, \lambda_{10}, \lambda_{11}, \lambda_{12}, \lambda_{13}, \lambda_{14},$ we define our Lagrangian as follows.

$$
\begin{aligned}
\mathcal{A} = {} & m_1 N_{es}(t, a_i) + m_2 N_{is}(t, a_i) + m_3 N_{se}(t, a_i) + m_2 N_{si}(t, a_i) \\
& + m_3 N_m(t) + m_3 N_d(t, e_j) + r_1 u_1^2 + r_2 u_2^2 + r_3 u_3^2 \\
& + \lambda_1 \left[\zeta(a_i) - \sum_{i=0}^{L} \sum_{j=0}^{T} (\lambda_a + \lambda_b) N_{ss}(t, a_i)(1 - u_1) - \sum_{i=0}^{L} \lambda_M N_{ss}(t, a_i) I_m (1 - u_1) + g_a \right] \\
& + \lambda_2 \left[\sum_{i=0}^{L} \sum_{j=0}^{T} (\lambda_a + \lambda_b) N_{ss}(t, a_i)(1 - u_1) - \sum_{i=0}^{L} \vartheta_m(a_i) \lambda_M N_{es}(t, a_i) I_m (1 - u_1) + g_b \right] \\
& + \lambda_3 \left[\sum_{i=0}^{L} \tau(a_i) N_{es}(t, a_i) - \sum_{i=0}^{L} \vartheta_m(a_i) \lambda_M N_{is}(t, a_i) I_m (1 - u_1) - (\mu(a_i) + \eta_1(a_i) \sigma(a_i) u_2) N_{is}(t, a_i) \right] \\
& + \lambda_4 \left[\sum_{i=0}^{L} (\gamma_1(a_i) \alpha(a_i) u_2 N_{es}(t, a_i) + \eta_1(a_i) \sigma(a_i) u_2 N_{is}(t, a_i)) - \mu(a_i) N_{rs}(t, a_i) \right]
\end{aligned}
$$

$$+\lambda_5\left[\sum_{i=0}^{L}\lambda_M(t)N_{ss}(t,a_i)I_m(1-u_1)-\sum_{i=0}^{L}\sum_{j=0}^{T}\vartheta_d(a_i)(\lambda_a+\lambda_b)N_{se}(t,a_i)(1-u_1)+g_c\right]$$

$$+\lambda_6\left[\sum_{i=0}^{L}\tau_m(a_i)N_{se}(t,a_i)-\sum_{i=0}^{L}\sum_{j=0}^{T}\vartheta_d(a_i)(\lambda_a+\lambda_b)N_{si}(t,a_i)(1-u_1)+g_d\right]$$

$$+\lambda_7\left[\sum_{i=0}^{L}\epsilon_m(a_i)\beta_m(a_i)u_2N_{si}(t,a_i)-(\gamma_m(a_i)+\mu(a_i))N_{sr}(t,a_i)\right]$$

$$+\lambda_8\left[\sum_{i=0}^{L}\vartheta_m(a_i)\lambda_M(N_{es}(t,a_i)+N_{is}(t,a_i))(1-u_1)I_m-\mu(a_i)N_{rr}(t,a_i)+g_e\right]$$

$$+\lambda_9\left[\Lambda_d(e_j)(1+\xi_d\cos(2\pi t+T))-\sum_{j=0}^{T}\lambda_d(t)S_d(t,e_j)I_d(t,e_j)-g_f\right]$$

$$+\lambda_{10}\left[\sum_{j=0}^{T}\lambda_dS_d(t,e_j)I_d(t,e_j)-(\alpha_d(e_j)+\mu_d(e_j)+\delta_d(e_j)+(1-u_3))E_d(t,e_j)\right]$$

$$+\lambda_{11}\left[\sum_{j=0}^{T}\alpha_d(e_j)E_d(t,e_j)-(\mu_d(e_j)+\delta_d(e_j)+(1-u_3))I_d(t,e_j)\right]$$

$$+\lambda_{12}\left[\varsigma_m(1+\kappa_m\cos(2\pi t+T))-\lambda_mS_mN_{si}(t,a_i)(1-u_1)-(\mu_m+(1-u_3))S_m\right]$$

$$+\lambda_{13}\left[\lambda_mS_mN_{si}(t,a_i)(1-u_1)-(\mu_m+\alpha_m+(1-u_3))E_m\right]$$

$$+\lambda_{14}\left[\alpha_mE_m-(\mu_m+(1-u_3))I_m\right]$$

where

$g_a=-\mu(a_i)N_{ss}(t,a_i)+\gamma_m(a_i)N_{sr}(t,a_i),\ g_b=-(\mu(a_i)+\gamma_1(a_i)\alpha(a_i)u_2+\tau(a_i))N_{es}(t,a_i),$
$g_c=(\mu(a_i)+\tau_m(a_i))N_{se}(t,a_i),\quad g_d=-(\mu(a_i)+\epsilon_m(a_i)\beta_m(a_i)u_2)N_{si}(t,a_i),\quad g_e=$
$\sum_{i=0}^{L}\sum_{j=0}^{T}\vartheta_d(a_i)(\lambda_a(t)+\lambda_b(t))(N_{se}(t,a_i)+N_{si}(t,a_i))(1-u_1),\ g_f=(\mu_d(e_j)+\delta_d(e_j)+$
$(1-u_3))S_d(t,e_j)$

Theorem 4.8: Given an optimal control $u_1^*,\ u_2^*,\ u_3^*$ and solution of the corresponding optimal control model, there exist adjoint (or costate) variables Γ Satisfying

$$\frac{d\lambda_1}{dt}=\sum_{i=0}^{L}\sum_{j=0}^{T}(\lambda_a(t)+\lambda_b(t))(1-u_1)(\lambda_1-\lambda_2)+\sum_{i=0}^{L}\lambda_M(t)I_m(1-u_1)(\lambda_1-\lambda_2)+\mu(a_i)\lambda_1 \tag{4.8.18}$$

$$\frac{d\lambda_2}{dt} = -m_1+\sum_{i=0}^{L} \vartheta(a_i)\lambda_M(t)I_m(1-u_1)(\lambda_2-\lambda_8)-\sum_{i=0}^{L} \tau(a_i)\lambda_3-\gamma_1(a_i)\alpha(a_i)u_2\lambda_4+(\mu(a_i) + \gamma_1(a_i)\alpha(a_i)u_2 + \tau(a_i))\lambda_2 \quad (4.8.19)$$

$$\frac{d\lambda_3}{dt} = \lambda_b N_{ss}(t,a_i)(1-u_1)\lambda_1+\sum_{i=0}^{L} \vartheta(a_i)\lambda_M I_m(1-u_1)(\lambda_3-\lambda_8)+(\mu(a_i)+\eta_1(a_i)\sigma(a_i)u_2)\lambda_3 - \eta_1(a_i)\sigma(a_i)u_2\lambda_4 - m_2 \quad (4.8.20)$$

$$\frac{d\lambda_4}{dt} = \mu(a_i)\lambda_4 \quad (4.8.21)$$

$$\frac{d\lambda_5}{dt} = -m_2+\sum_{i=0}^{L}\sum_{j=0}^{T} \vartheta_d(a_i)(\lambda_a+\lambda_b)(1-u_1)(\lambda_6-\lambda_8)+(\mu(a_i)+\tau_m(a_i))\lambda_5-\sum_{i=0}^{L} \tau_m(a_i)\lambda_6 \quad (4.8.22)$$

$$\frac{d\lambda_6}{dt} = -m_2+\sum_{i=0}^{L}\sum_{j=0}^{T} \vartheta_d(a_i)(\lambda_a+\lambda_b)(1-u_1)(\lambda_6+\lambda_8)+\sum_{i=0}^{L} \epsilon_m(a_i)\beta_m(a_i)u_2(\lambda_6-\lambda_7) + \lambda_m(t)s_m(1-u_3)(\lambda_{12}-\lambda_{13}) \quad (4.8.23)$$

$$\frac{d\lambda_7}{dt} = \gamma_m(a_i)(\lambda_1-\lambda_7)+\mu(a_i)\lambda_7 \quad (4.8.24)$$

$$\frac{d\lambda_8}{dt} = \mu(a_i)\lambda_8 \tag{4.8.25}$$

$$\frac{d\lambda_9}{dt} = \sum_{j=0}^{T} \lambda_d(t) I_d(t, e_j)(\lambda_9 - \lambda_{10}) + (\mu_d(e_j) + \delta_d(e_j) + (1 - u_3))\lambda_9 - m_3 \tag{4.8.26}$$

$$\frac{d\lambda_{10}}{dt} = \alpha_d(e_j)(\lambda_{10} - \lambda_{11}) + (\delta_d(e_j) + (1 - u_3))\lambda_{10} - m_3 \tag{4.8.27}$$

$$\begin{aligned}\frac{d\lambda 11}{dt} &= \sum_{i=0}^{L}\sum_{j=0}^{T} \rho_0(a_i) w_2(e_j) N_{ss}(t, a_i)(1 - u_1)(\lambda_1 - \lambda_2) - m_3 \\ &+ \sum_{i=0}^{L}\sum_{j=0}^{T} \vartheta_d(a_i)\rho_0(a_i)(1 + w_2(e_j)\cos(2\pi t + T)) N_{se}(t, a_i)(1 - u_1)(\lambda_5 - \lambda_8) \\ &+ \sum_{i=0}^{L}\sum_{j=0}^{T} \vartheta_d(a_i \rho_0(a_i)(1 + w_2(e_j)\cos(2\pi t + T))) N_{si}(t, a_i)(1 - u_1)(\lambda_6 - \lambda_8) \\ &+ \sum_{j=0}^{T} \lambda_d(t) S_d(t, e_j)(\lambda_9 - \lambda_{10}) + (\mu_d(e_j) + \delta_d(e_j) + (1 - u_3))\lambda_{11}\end{aligned} \tag{4.8.28}$$

$$\frac{d\lambda_{12}}{dt} = \lambda_m(t) N_{si}(t, a_i)(1 - u_1)(\lambda_{12} - \lambda_{13}) + (\mu_m + (1 - u_3))\lambda_{12} - m_3 \tag{4.8.29}$$

$$\frac{d\lambda_{13}}{dt} = \alpha_m(\lambda_{13} - \lambda_{14}) + (\mu_m + (1 - u_3))\lambda_{13} - m_3 \tag{4.8.30}$$

$$\frac{d\lambda_{14}}{dt} = -m_3+\sum_{i=0}^{L}\lambda_M N_{ss}(t,a_i)(1-u_1)(\lambda_1-\lambda_5)+\sum_{i=0}^{L}\vartheta_m(a_i)\lambda_M N_{es}(t,a_i)(1-u_1)(\lambda_2-\lambda_8)$$
$$+\sum_{i=0}^{L}\vartheta_m(a_i)\lambda_M N_{is}(t,a_i)(1-u_1)(\lambda_3-\lambda_8)+(\mu_m+(1-u_3))\lambda_{14} \quad (4.8.31)$$

with the terminal condition

$$\lambda_1(t_f)=0,\ \lambda_2(t_f)=0,\ \lambda_3(t_f)=0,\ \lambda_4(t_f)=0...,\ \lambda_{14}(t_f)=0. \quad (4.8.32)$$

Furthermore, $u_1^*,\ u_2^*,\ u_3^*$ are represented by

$$u_1^* = max\left(0, min\left(1, \frac{1}{2r_1}\sum_{i=0}^{L}\sum_{j=0}^{T}[\lambda_M N_{ss}(t,a_i)I_m(\lambda_5-\lambda_1)+P_a]\right)\right)$$

$$u_2^* = max\left(0, min\left(1, \frac{1}{2r_2}\sum_{i=0}^{L}[\epsilon_m(a_i)\beta_m(a_i)N_{si}(t,a_i)(\lambda_6-\lambda_7)+P_b]\right)\right)$$

$$u_3^* = max\left(0, min\left(1, \frac{1}{2r_3}\sum_{i=0}^{L}[-S_m\lambda_{12}-E_m\lambda 13-I_m\lambda_{14}+P_c]\right)\right) \quad (4.8.33)$$

where,

$P_a = \vartheta_m(a_i)\Lambda_M N_{is}(t,a_i)I_m(\lambda_8-\lambda_3)+\vartheta(a_i)\lambda_M N_{es}(t,a_i)I_m(\lambda_8-\lambda_2)+\lambda_m S_m N_{si}(t,a_i)(\lambda_{13}-\lambda_{12})+(\lambda_a+\lambda_b)N_{ss}(t,a_i)(\lambda_2-\lambda_1)+\vartheta_d(a_i)(\lambda_a+\lambda_b)N_{si}(t,a_i)(\lambda_8-\lambda_6)+\vartheta(a_i)(\lambda_a+\lambda_b)N_{se}(t,a_i)(\lambda_8-\lambda_5)$

$P_b = \gamma_1(a_i)\alpha(a_i)N_{es}(t,a_i)(\lambda_2-\lambda_4)+\eta_1(a_i)\sigma(a_i)N_{is}(t,a_i)(\lambda_3-\lambda_4)$

$P_c = -S_d(e_j)\lambda_9 - E_d(e_j)\lambda_{10} - I_d(e_j)\lambda_{11}$

Proof:

The differential equations governing the adjoint variables are obtained by differen-

tiation of the Hamiltonian function, evaluated at the optimal control. Then the adjoint system can be written as

$$\frac{d\lambda_1}{dt} = \sum_{i=0}^{L}\sum_{j=0}^{T}(\lambda_a(t)+\lambda_b(t))(1-u_1)(\lambda_1-\lambda_2)+\sum_{i=0}^{L}\lambda_M(t)I_m(1-u_1)(\lambda_1-\lambda_2)+\mu(a_i)\lambda_1$$

$$\frac{d\lambda_2}{dt} = -m_1+\sum_{i=0}^{L}\vartheta(a_i)\lambda_M(t)I_m(1-u_1)(\lambda_2-\lambda_8)-\sum_{i=0}^{L}\tau(a_i)\lambda_3-\gamma_1(a_i)\alpha(a_i)u_2\lambda_4+(\mu(a_i) + \gamma_1(a_i)\alpha(a_i)u_2+\tau(a_i))\lambda_2$$

$$\frac{d\lambda_3}{dt} = \lambda_b N_{ss}(t,a_i)(1-u_1)\lambda_1+\sum_{i=0}^{L}\vartheta(a_i)\lambda_M I_m(1-u_1)(\lambda_3-\lambda_8)+(\mu(a_i)+\eta_1(a_i)\sigma(a_i)u_2)\lambda_3 - \eta_1(a_i)\sigma(a_i)u_2\lambda_4 - m_2$$

$$\frac{d\lambda_4}{dt} = \mu(a_i)\lambda_4$$

$$\frac{d\lambda_5}{dt} = -m_2+\sum_{i=0}^{L}\sum_{j=0}^{T}\vartheta_d(a_i)(\lambda_a+\lambda_b)(1-u_1)(\lambda_6-\lambda_8)+(\mu(a_i)+\tau_m(a_i))\lambda_5-\sum_{i=0}^{L}\tau_m(a_i)\lambda_6$$

$$\frac{d\lambda_6}{dt} = -m_2+\sum_{i=0}^{L}\sum_{j=0}^{T}\vartheta_d(a_i)(\lambda_a+\lambda_b)(1-u_1)(\lambda_6+\lambda_8)+\sum_{i=0}^{L}\epsilon_m(a_i)\beta_m(a_i)u_2(\lambda_6-\lambda_7) + \lambda_m(t)s_m(1-u_3)(\lambda_{12}-\lambda_{13})$$

$$\frac{d\lambda_7}{dt} = \gamma_m(a_i)(\lambda_1 - \lambda_7) + \mu(a_i)\lambda_7$$

$$\frac{d\lambda_8}{dt} = \mu(a_i)\lambda_8$$

$$\frac{d\lambda_9}{dt} = \sum_{j=0}^{T} \lambda_d(t) I_d(t, e_j)(\lambda_9 - \lambda_{10}) + (\mu_d(e_j) + \delta_d(e_j) + (1 - u_3))\lambda_9 - m_3$$

$$\frac{d\lambda_{10}}{dt} = \alpha_d(e_j)(\lambda_{10} - \lambda_{11}) + (\delta_d(e_j) + (1 - u_3))\lambda_{10} - m_3$$

$$\begin{aligned}\frac{d\lambda 11}{dt} &= \sum_{i=0}^{L}\sum_{j=0}^{T} \rho_0(a_i) w_2(e_j) N_{ss}(t, a_i)(1 - u_1)(\lambda_1 - \lambda_2) - m_3 \\ &+ \sum_{i=0}^{L}\sum_{j=0}^{T} \vartheta_d(a_i)\rho_0(a_i)(1 + w_2(e_j)\cos(2\pi t + T)) N_{se}(t, a_i)(1 - u_1)(\lambda_5 - \lambda_8) \\ &+ \sum_{i=0}^{L}\sum_{j=0}^{T} \vartheta_d(a_i\rho_0(a_i)(1 + w_2(e_j)\cos(2\pi t + T))) N_{si}(t, a_i)(1 - u_1)(\lambda_6 - \lambda_8) \\ &+ \sum_{j=0}^{T} \lambda_d(t) S_d(t, e_j)(\lambda_9 - \lambda_{10}) + (\mu_d(e_j) + \delta_d(e_j) + (1 - u_3))\lambda_{11}\end{aligned}$$

$$\frac{d\lambda_{12}}{dt} = \lambda_m(t) N_{si}(t, a_i)(1 - u_1)(\lambda_{12} - \lambda_{13}) + (\mu_m + (1 - u_3))\lambda_{12} - m_3$$

$$\frac{d\lambda_{13}}{dt} = \alpha_m(\lambda_{13} - \lambda_{14}) + (\mu_m + (1 - u_3))\lambda_{13} - m_3$$

$$\frac{d\lambda_{14}}{dt} = -m_3 + \sum_{i=0}^{L} \lambda_M N_{ss}(t, a_i)(1-u_1)(\lambda_1-\lambda_5) + \sum_{i=0}^{L} \vartheta_m(a_i)\lambda_M N_{es}(t, a_i)(1-u_1)(\lambda_2-\lambda_8) + \sum_{i=0}^{L} \vartheta_m(a_i)\lambda_M N_{is}(t, a_i)(1 - u_1)(\lambda_3 - \lambda_8) + (\mu_m + (1 - u_3))\lambda_{14}$$

with terminal or transversality conditions

$$\lambda_1(t_f) = 0,\ \lambda_2(t_f) = 0,\ \lambda_3(t_f) = 0,\ \lambda_4(t_f) = 0...,\ \lambda_{14}(t_f) = 0.$$

On the interior of the control set, where $0 < u_i < 1$, for $i = 1, 2, 3$, we obtain

$$u_1^* = \frac{1}{2r_1} \sum_{i=0}^{L} \sum_{j=0}^{T} [\lambda_M N_{ss}(t, a_i) I_m(\lambda_5 - \lambda_1) + P_a]$$

$$u_2^* = \frac{1}{2r_2} \sum_{i=0}^{L} [\epsilon_m(a_i)\beta_m(a_i) N_{si}(t, a_i)(\lambda_6 - \lambda_7) + P_b]$$

$$u_3^* = \frac{1}{2r_3} \sum_{i=0}^{L} [-S_m\lambda_{12} - E_m\lambda 13 - I_m\lambda_{14} + P_c] \tag{4.8.34}$$

and

$$u_1^* = max\left(0, min\left(1, \tfrac{1}{2r_1} \sum_{i=0}^{L} \sum_{j=0}^{T} [\lambda_M N_{ss}(t, a_i) I_m(\lambda_5 - \lambda_1) + P_a]\right)\right)$$

$$u_2^* = max\left(0, min\left(1, \frac{1}{2r_2}\sum_{i=0}^{L}[\epsilon_m(a_i)\beta_m(a_i)N_{si}(t,a_i)(\lambda_6 - \lambda_7) + P_b]\right)\right)$$

$$u_3^* = max\left(0, min\left(1, \frac{1}{2r_3}\sum_{i=0}^{L}[-S_m\lambda_{12} - E_m\lambda 13 - I_m\lambda_{14} + P_c]\right)\right)$$

The optimality system consists of the optimal control model with the initial conditions, $N_{ss}(0,a_i), N_{es}(0,a_i), N_{is}(0,a_i), N_{rs}(0,a_i), N_{se}(0,a_i), N_{si}(0,a_i), N_{sr}(0,a_i), N_{rr}(0,a_i), S_d$ the costate system (4.8.18)-(4.8.31) with the terminal condition (4.8.32) and the optimality condition (4.8.33). Any optimal control u_1^*, u_2^*, u_3^* must satisfy this optimality system.

4.8.5 Uniqueness of optimality system

Using the bound for the state equations, the adjoint system has bounded coefficients and is linear in each adjoint variable. Hence the solution of the adjoint system are bounded for the final time sufficiently small. Due to this a priori boundedness of the state and adjoint functions and the Lipschitz structure of the optimality system, we obtain uniqueness of the optimal control for small T. The uniqueness of the optimal control pair follows from the uniqueness of the optimality system. The restriction of time interval is very common in optimal control problems. See (Kirschner et al, 1997., Joshi, 2002).

4.9 STUDY NINE

Simulation

4.9.1 Numerical simulations

In order to understand the overall picture of the diseases behaviour, this section provides numerical simulations of the formulated model using Maple and Matlab software packages. The results of the simulations are discussed with the aid of figures as well as the implications of the theoretical results.

The numerical simulations of the system (3.1.3)-(3.1.17) is provided in appendices (I) and (II). It is worth mentioning that some of the values of the parameters as presented in Table 4.2 is the average estimated values that are compatible with malaria and Lassa fever parameter values reported by the World Health Organization and Centre for Disease Control and Prevention.

Table 4.2: The parameters and values of the malaria-Lassa fever co-infection model.

Symbols	Value	Source
$\zeta(a_i)$	0.000215	Estimated
ς_m	0.07	Niger and Gumel (2008)
$\Lambda_d(e_j)$	0.0056	Tomori et al (1998)
b	0.12, 0.67, 3.0	Assumed to vary
$\phi_0(a_i)$	0.09	Blayneh et al (2009)
$\rho_0(e_j)$	0.14, 0.6	Assumed to vary
$\sigma_0(a_i)$	0.15, 0.7	Assumed to vary
$c_m(a_i)$	0.1	Blayneh et al (2009)
σ_m	0.09	Blayneh et al (2009)
$w_1(a_i)$	0.56	Assumed
$d_1(a_i)$	0.00816	Tomori et al (1998)
$d_2(a_i)$	0.06	Tomori et al (1998)
$\beta_d(e_j)$	0.075	Assumed
$\mu(a_i)$	0.0000548	Estimated
μ_m	0.0667	Lashari et al (2012)
$w_2(e_j)$	0.8	Assumed
$\mu_d(e_j)$	0.06	Okuonghae et al (2006)
$\delta_d(e_j)$	0.3	Assumed
$\tau(a_i)$	0.085	Ogabi et al (2012)
κ_m	0-1	Assumed to vary
$\xi_d(e_j)$	0-1	Assumed to vary
$\tau_m(a_i)$	0.0588	Blayneh eta al (2009)
$\alpha_d(e_j)$	0.85	Assumed
α_m	0.0556	Blayneh eta al (2009)
$\epsilon_m(a_i)$	0.05, 0.067, 0.1	Assumed to vary
$\beta_m(a_i)$	0.05, 0.067, 0.1	Assumed to vary
$\gamma_v(a_i)$	0.09	Onuorah et al (2016)
$\alpha(a_i)$	0.05	Okuonghae et al (2006)
$\sigma(a_i)$	0.09	Okuonghae et al (2006)
$\eta_v(a_i)$	0.45	Onuorah et al (2016)
ϑ_i	0.15, 0.1	Assumed to vary
$\gamma_m(a_i)$	0.0013699	Okosun and Makinde (2011)

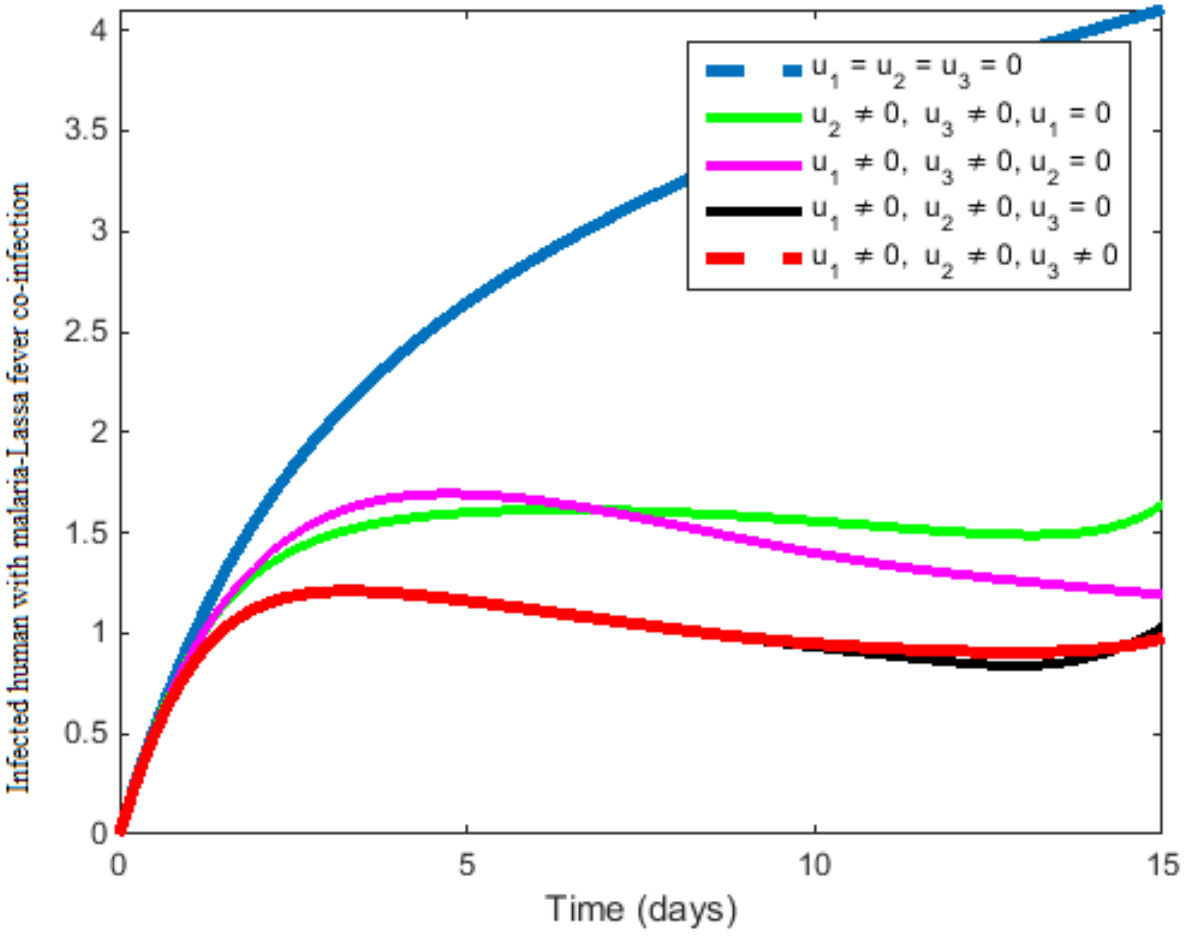

Figure 4.1: Effect of optimal control $u_1,\ u_2,\ u_3$ on infected human in malaria-Lassa fever co-infection model

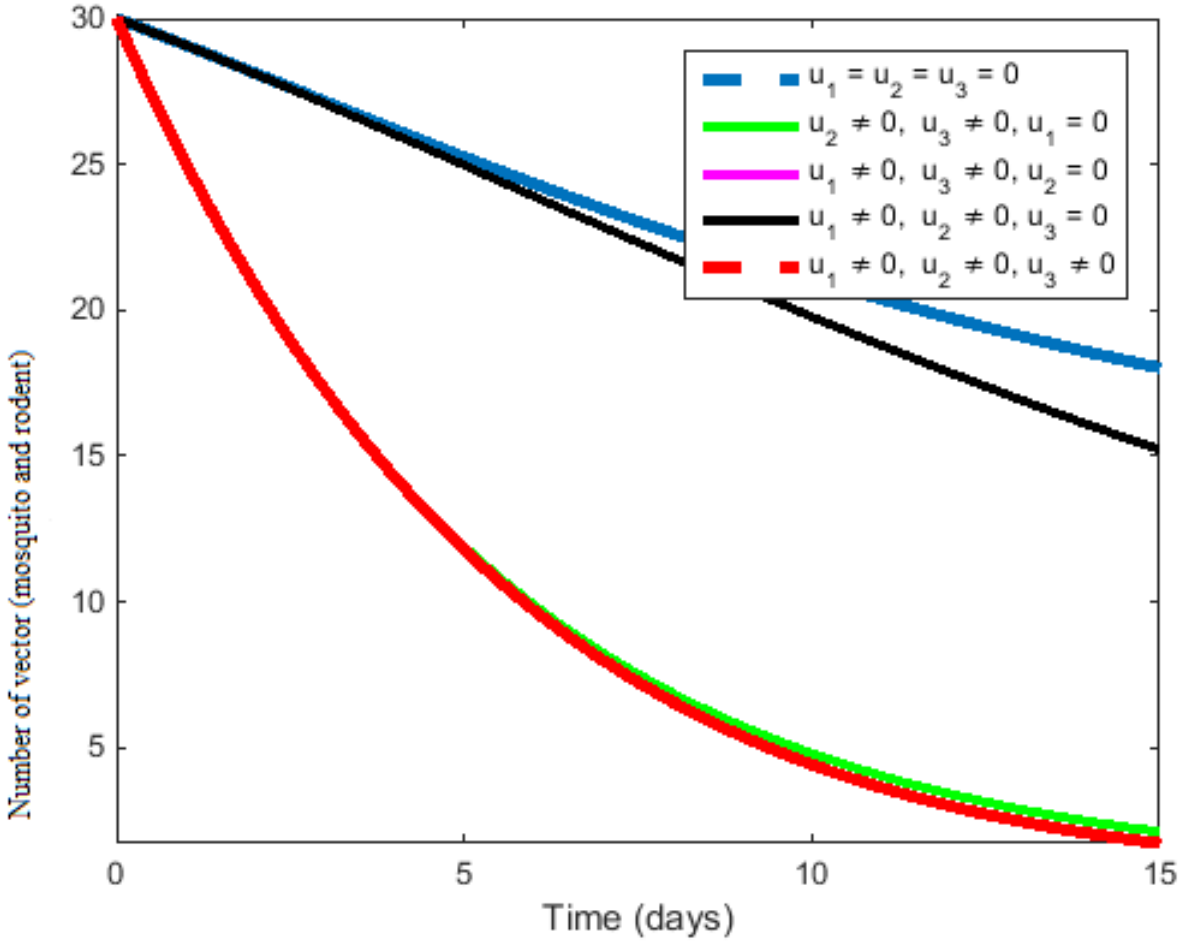

Figure 4.2: Effect of optimal control $u_1,\ u_2,\ u_3$ on mosquitoes and rodents in malaria-Lass fever co-infection model

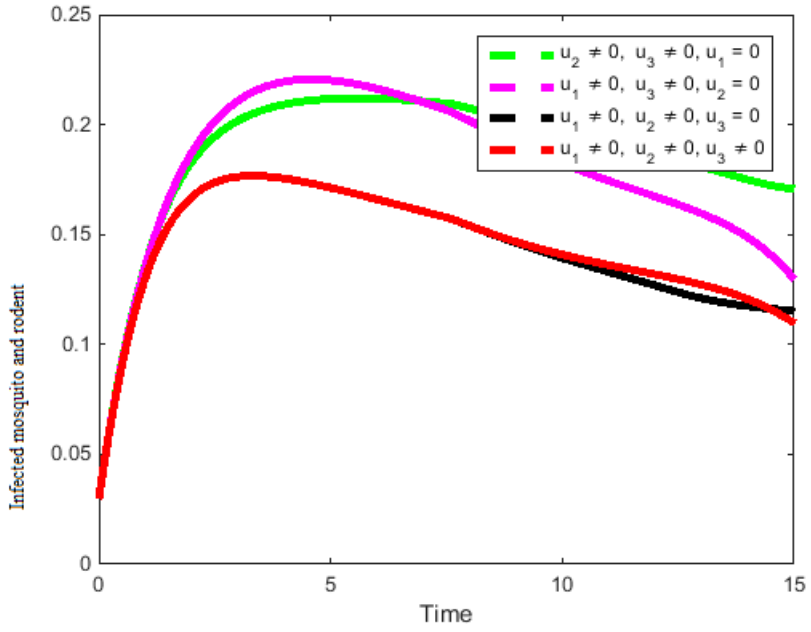

Figure 4.3: Effect of optimal u_1, u_2, u_3 on infected mosquitoes and rodents in malaria-Lassa fever co-infection model

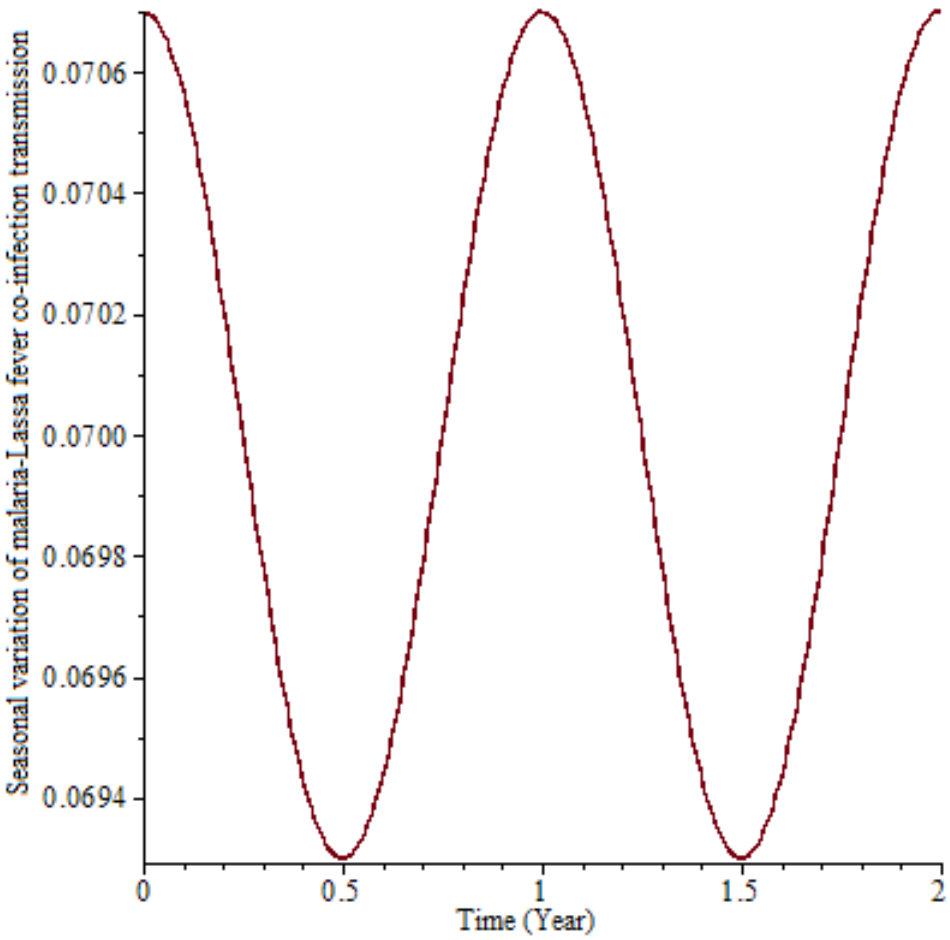

Figure 4.4: Seasonal variation of malaria-Lassa fever co-infection transmission in human population

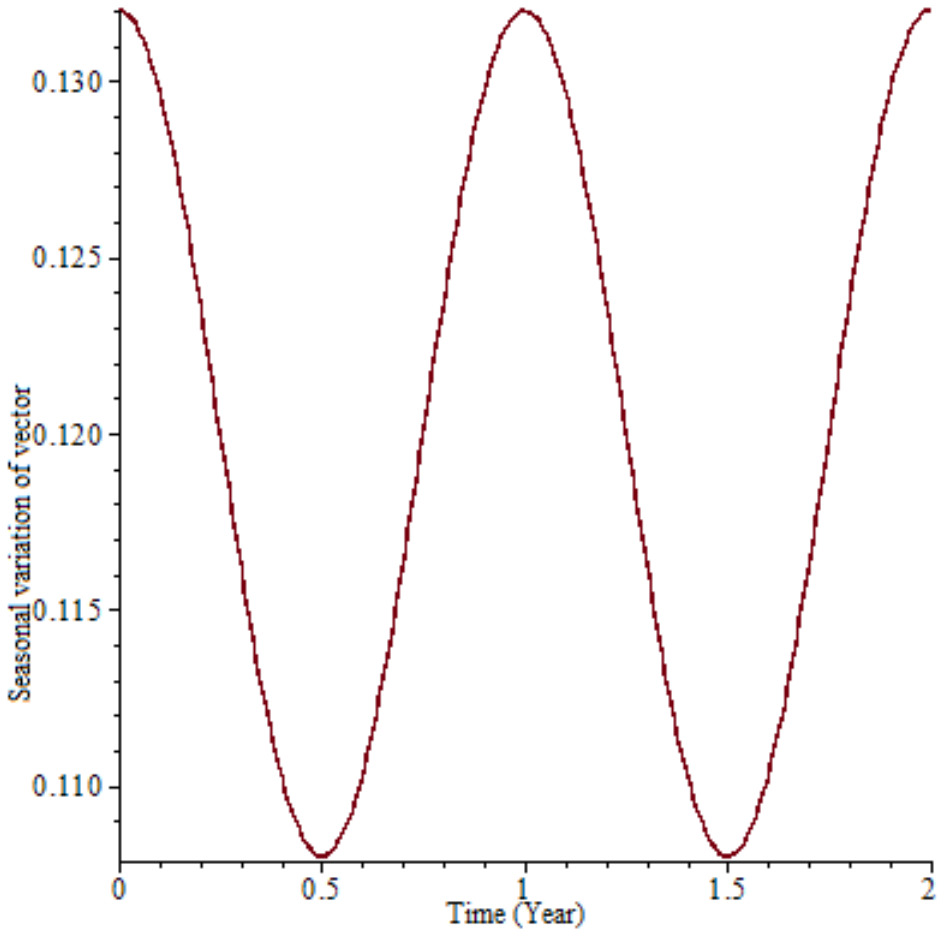

Figure 4.5: Effect of seasonal variation of vector (mosquito and rodent)

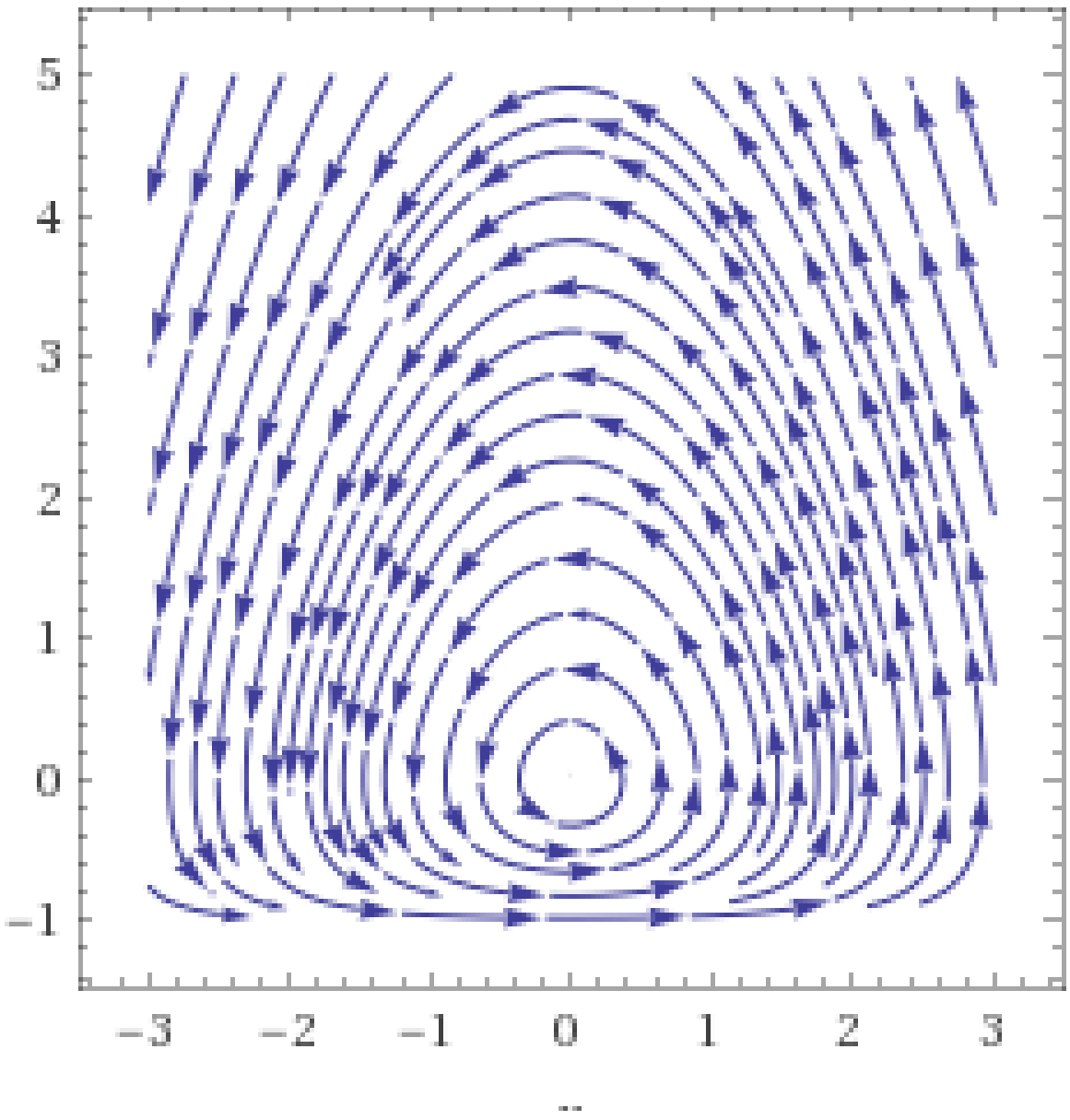

Figure 4.6: A graph showing the behaviour of equation (4.1.18)

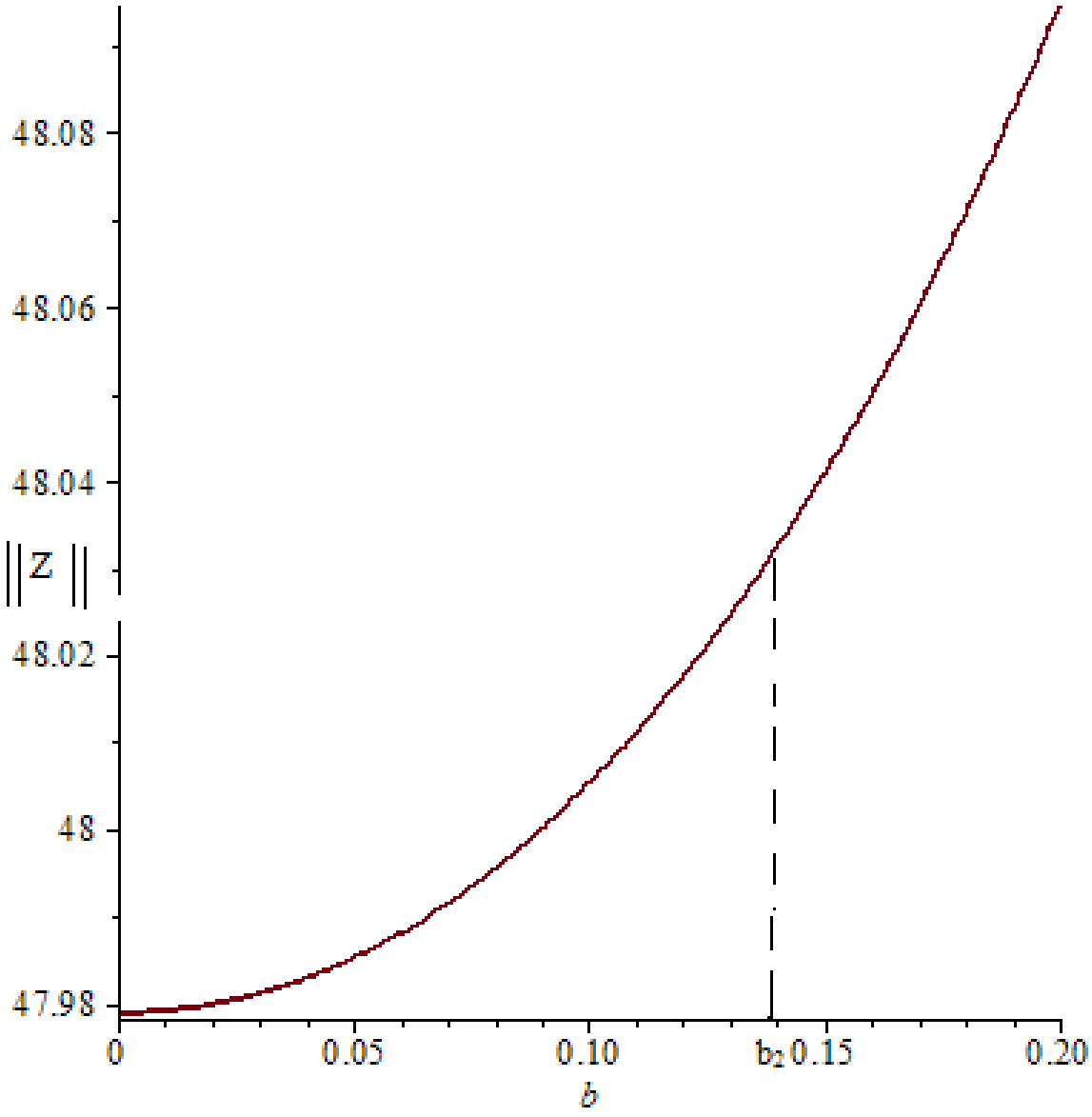

Figure 4.7: A graph of period 1 orbit as a function of b. When $b < b_2$ the period 1 orbit is stable while for $b > b_2$ the orbits are unstable.

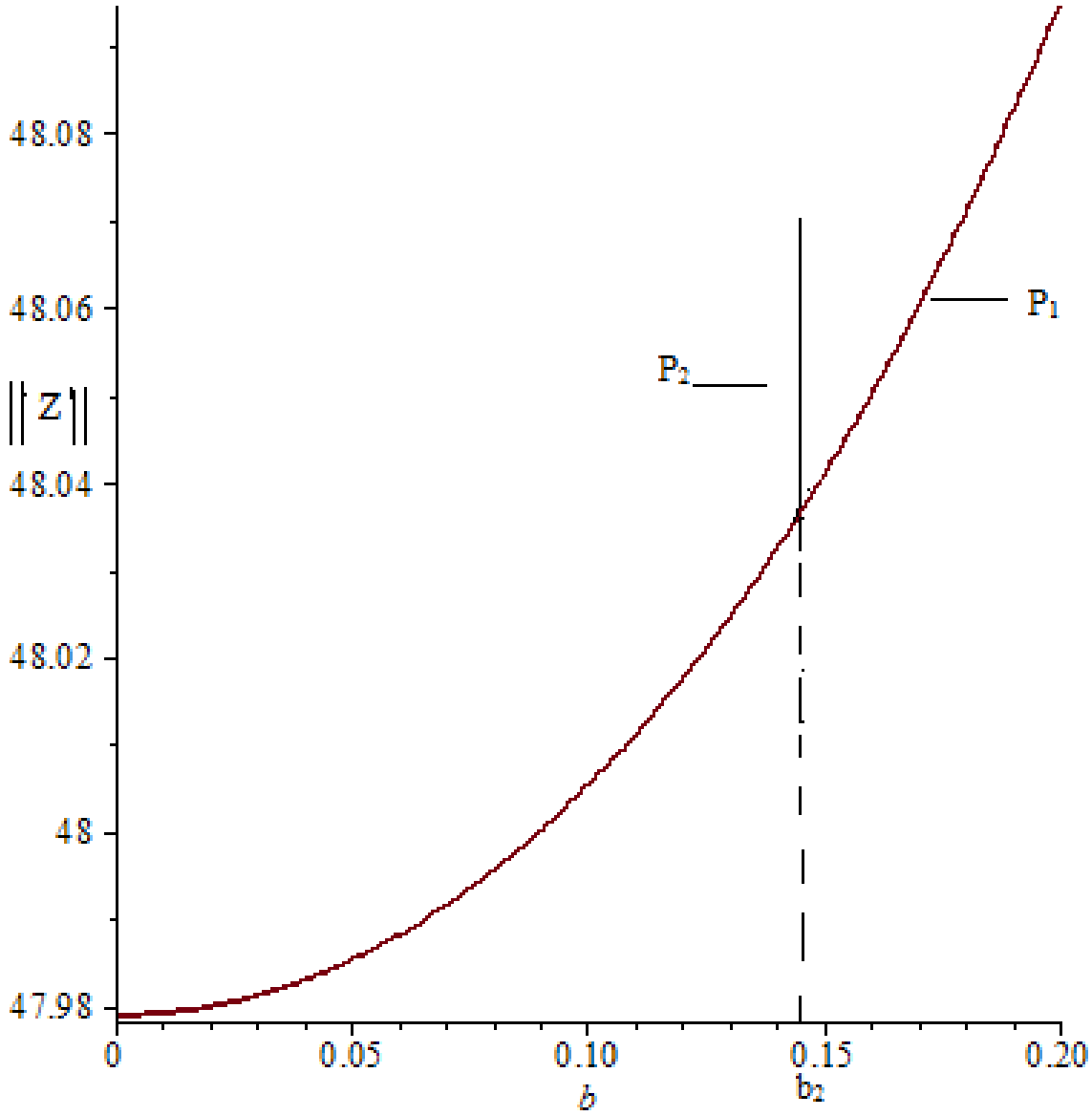

Figure 4.8: A graph showing the bifurcating period 2 (P_2) solution from the period 1 (P_1) solution.

CHAPTER FIVE

DISCUSSION

5.1 The malaria-lassa fever co-infection

Malaria caused by *Plasmodium* parasite is a major vector-borne disease globally. The parasite is transmitted by female Anopheles mosquito into vertebrate host. However, Lassa fever virus is transmitted by rodents through their faeces, urine and saliva. Lassa virus is mostly endemic in West African countries (Tomori et al, 1998; WHO, 2012; Ogabi, et al., 2012). Both malaria and Lassa fever virus are common in developing countries where there is poor sanitation and hygiene, poor infrastructural development, wide area of rural community settlements and presence of vegetation around settlement areas.

Modelling of single infection such as malaria (Tumwiine et al., 2007; Magombedze et al., 2011) and Lassa fever virus (Okuonghae et al, 2006; Ogabi, et al., 2012) have been previously reported. However, there is paucity of information on the co-infection of both diseases, especially incorporating mathematical conditions such as seasonal functionality. Precisely, malaria co-infection with other viral and bacteria diseases have been reported, such as HIV-malaria co-infection mathematical model and malaria-cholera co-infection mathematical model (Okosun and Makinde, 2014). Meanwhile, laboratory experiments have justified co-infection of diseases and how it affects the host immune system. Ademola and Odeniran, 2016 showed the co-infection of malaria and trypanosomiasis in mice model and how it affects the survivability of mice. The findings of this study contribute to a better understanding of the patterns and forces that drive the co-infection of malaria and Lassa fever in endemic areas. This study provides information that malaria infection could be associated with an increased risk of Lassa fever and Lassa fever infection may be associated with an increased risk for malaria. However, malaria-Lassa fever co-infection will not bring the human population (the diseases affect only a segment of the world population) to extinction even when both diseases co-exist.

5.2 Equilibrium point

The nature of the system near the equilibrium point for non-seasonal infections, for example malaria, HIV, Lassa fever etc have been investigated through the basic reproduction number (Okuonghae et al., 2006; Nannyonga et al., 2012; Okosun and Makinde, 2014). However, the nature of the system near the equilibrium point for seasonal malaria-Lassa fever have not been examined through the basic reproduction number, $R_0(a,t)$. The equilibrium point of our model with respect to seasonal incidence function give information that certain seasonal period (e.g. wet season), the vector population increases e.g. female anopheles mosquito and rodents with an implication on the basic reproduction number. There is persistence of infection and the basic reproduction number was observed to grow exponentially during these seasonal period. Hence, seasonal functionality and changes have direct consequences on the model.

5.3 Basic reproduction number, $R_{0M}(a,t)$ and $R_{0L}(a,t)$

The number of secondary infections caused by the introduction of a single infectious individual into an entirely susceptible population is usually defined as the basic reproductive number R_0 for a non-seasonal infection(Diekmann 1990). The basic reproduction number R_0 have been used to examined stability for non seasonal malaria and Lassa fever diseases (Nannyonga et al., 2012; Okuonghae et al., 2006). However, the basic reproduction number, $R_0(a,t)$, for seasonal infection have not been used to examined stability on malaria-Lassa fever co-infection epidemic using mathematical model. Because the number of secondary infections depends on the time of year that the infectious individual is introduced, the interpretation of the basic reproductive number, R_0 (for non-seasonal infection) is not possible for seasonal infections. The basic reproduction number $R_0(a,t)$ computed in this study helps in determining whether or not an infectious disease (seasonal infection such as malaria and Lassa fever) will spread through a population since the number of secondary infections depend on the time of year that the infectious individual is introduced. If $R_0(a,t) < 1$, each infectious individual produces less than one new infected individual so that the disease dies out of the population. Whilst $R_0(a,t) > 1$ means that each infectious individual produces more than one new infected individual so that the disease persists in the population.

5.4 Local and global stability analysis of equilibra

Since infection with multiple parasites, viruses or both are common among populations in developing countries and there may be interactions between parasites, viruses or both, as earlier suggested (Okokhere et al., 2010; Ademola and Odeniran, 2016). This study give insight that *Plasmodium* infected human who were also co-infected with Lassa virus (or vice versa) favoured quick development which shortened pre-patent period of *Plasmodium* and increased parasitaemia than human with *Plasmodium* infection only especially when the vectors (mosquito and rodent) are abundant. This aggravated responses could be the effect of pathogen on host immune system (Okokhere et al., 2010). Major observations from this study are highlighted as follows:

(i) It was observed that if $R_{es1}(a), R_{es2}(a), R_{0M}(a), R_{em1}(a), R_{em2}(a) > 1$, individuals in the population will continue to have malaria and Lassa fever. However, whenever $R_{es1}(a), R_{es2}(a), R_{0M}(a), R_{em1}(a), R_{em2}(a) < 1$ infectious individuals into a completely susceptible population will not lead to an outbreak of the disease Thus, the disease control depends on the initial number of the infected individuals in the population. This result agreed with the results in Okosun and Makinde 2014.

(ii)It was also observed that the globally asymptotically s table disease-free equilibrium point ϵ_0 suggests that co-infection of malaria and Lassa fever can be brought under control irrespective of the initial sizes of the infectious individuals in the population whenever $\mathcal{R}_{0M}(a), \mathcal{R}_{0L}(e) < 1$. Furthermore, the globally asymptotically stable endemic equilibrium ϵ_0, implies that malaria and Lassa fever will establish itself in the population whenever $\mathcal{R}_{0M}(a), \mathcal{R}_{0L}(e) > 1$ and $0 \leq u_1 \leq 1$. This result agreed with the results in Olaniyi et al 2018.

5.5 Sensitivity analysis

Sensitivity analysis to identify the parameter most significantly to the transmission of the disease on mono-infection e.g malaria have been studied by many authors (Chitnis et al, 2008; Okosun and Makinde, 2011; Olaniyi et al, 2018). In particular, Olaniyi and Obabiyi (2013) developed a mathematical model that incorporate vigilant compartment and antibody. Sensitivity analysis of their model were performed, they conclude that the mosquito biting rate contributed most significantly to the

transmission of the disease. To our knowledge sensitivity analysis of malaria-Lassa fever co-infection that incorporate seasonal variation of vectors (mosquito and rodent) have not been studied. This study provide the following information about our model.

The sign of the sensitivity indices of the basic reproduction numbers $R_{0M}(a,t)$ and $R_{0L}(e,t)$ obtained, in Table 4.1 give information on how changes in the model parameters affect the basic reproduction numbers. The parameters with positive indices give information that an increase (or decrease) in the value of each of these parameters will lead to the corresponding increase (or decrease) in $R_{0M}(a,t)$ and $R_{0L}(e,t)$. For example $\Upsilon_{\sigma_0}^{R_{0M}} = 1$ implies that increasing (or decreasing) the rodent contact rate by 10% also increases (or decreases) the basic reproduction number, $R_{0M}(a,t)$, by 10%.

On the other hand, the parameters with negative indices provide information that an increase (or decrease) in the value of each of these parameters will lead to the corresponding decrease (or increase) in $R_{0M}(a,t)$ and $R_{0L}(e,t)$. For example if more than half of the year is rainy season say, $\kappa_m = 0.7$, then we have $\Upsilon_{\kappa_m}^{R_{0M}} = -2.0$. This further suggest that increasing (or decreasing) κ_m by 20% decreases (or increases) $R_{0M}(a,t)$ by 20%. Hence, with sensitivity analysis, one can get insight on the appropriate intervention strategies to prevent and control the transmission of the diseases in the population, especially when there is sufficient rainfall that help the development and survival of the vectors. This result agreed with the results in Chitnis et al 2008 and Olaniyi et al 2018

5.6 Subharmonic bifurcation

Multi-pathogen/multi-host models have recently been formulated to track the dynamics of pathogen interaction over diagnostic factors in treatment landscapes. This model is based on the fact that human diagnosis precedes treatment and is critical to disease progression. The role of diagnostic factor before treatment of two diseases (malaria and Cholera) was studied and found that the basic reproduction number decreased as diagnosis increased (Okosun and Makinde, 2014). However, this study provide information that, for seasonal infection, reducing the basic reproduction number below unity is not enough to eliminate co-infection of

Plasmodium infected human co-infected with Lassa virus or Lassa virus infected human co-infected with *Plasmodium* . Major observations from this study are listed as follows:

It was observed that in addition to a subharmonic period 2 orbit, there exist subharmonic solutions that bifurcate from large amplitude solutions appearing in the reduced equation (4.7.8) when $\varepsilon = w_1 = w_2 = b = 0$. It was observed that lower order subharmonic are more likely to be encountered i.e. the domain of existence for lower order subharmonics may be larger than for higher order subharmonics. This simply means that malaria-Lassa co-infection can be brought under control when vectors abundant time are targeted. Finally, it is important to report the behaviour of the periodic solutions of equation (4.7.7) as a function of seasonal variation of vector, b via numerical simulations. The feature behaviour of figure 4.6 is that the outset is a center nearby periodic orbit with period varying between $\frac{2\pi}{\nu}$ near the outset to $+\infty$ close to the invariant line $y = -1$. Specifically, for all integer n, $\frac{2\pi}{\nu} < n < \infty$, there exist a periodic solution of (4.7.8), $\bar{x}(t)$, $\bar{y}(t)$, of least period n. Figure 4.7 shows that the norm of the solution of equation (4.7.7) represented by $||Z||$ has a monotonic increasing function of b. It was further observed through numerical simulation that at a value of $b_2 = 0.14$ one of the values of the invariant line is -1, signalling the presence of a period doubling (subharmonic bifurcation) orbit bifurcating off the period 1 branch. This simply implies that the endemic equilibrium is asymptotically stable at a value of $b_2 = 0.14$, and the disease will not persist in the population. Moreover, we noticed that if one proceeds to follow the period 1 solutions for $b > b_2$, (ie when $b > 0.14$) the period 1 solutions become unstable (For detailed information see Ira and smith 1983). Thus, the disease will continue to spread or invade the system. Figure 5.8 depicts the stable branch of period 2 solutions (P_2) bifurcating from period 1 (P_1) branch of $b = b_2$. This simply implies that when the value of $b = b_2 = 0.15$, the endemic equilibrium is asymptomatically stable and the disease will not invade the population. However, if $b_2 > 0.15$ the endemic equilibrium is unstable and the disease elimination may not be possible.

5.7 Optimal Control problem and numerical simulations

Optimal control problems have recently piqued the interest of scientists all over the world, for example Olaniyi et al. (2018) looked at how the method of similar solutions could be used to solve time optimal control problems with state constraints. Similarly, many approaches have also been used to investigate optimal control problems in control systems. In particular, Okosun and Makinde (2011) developed a continuous model for malaria vector control (single infection) with the goal of determining how genetically modified mosquitoes should be introduced in the environment using optimal control problem strategies. To our knowledge no work has been done to examine the impact of optimal control on malaria-Lassa fever co-infection. Our results suggest that strict intervention effort (use multiple control measure at a time) is required for quick suppression of the diseases. Efforts should also be made in both government and private hospital by providing modern equipment for diagnosis before treatment to know if the patient has more than one infection. It is known that Lassa fever transmission is driven by the interaction between human and rodent. Thus, the need for human to be protected should be encouraged as a way of keeping the rodent at bay. Being protected requires total adherence of using rodent proof container, rodent control measures and maintenance of sanitary environments. Elimination of vector populations (mosquito and rodent) has a great impact on disease transmission, and this could reduce the threshold parameter below unity (Koella and Anita, 2003). However, this study reveal vector control only is not enough to eliminate co-infection of malaria and Lassa fever. Therefore, suggesting multiple control such as prevention (use of mosquito treated bed net), treatment and use of insecticide (vector control) at a time for both diseases to be completely eliminated. Main observations from this work are highlighted below:

(i) The impact of using multiple control measures at a time is that malaria-Lassa fever co-infection will not invade the population if $u_1 = u_2 = u_3 \neq 0$. However, the disease will continue to persist in the population whenever $u_1 = u_2 = u_3 = 0$ or when only one of u_1, u_2 and u_3 is used as control measure (Okosun and Makinde 2011)

(ii) It was observed via numerical simulations that using multiple control strategies at a time lead to a decrease in the number of infected humans with malaria-Lassa

fever as against increase in the uncontrolled case as shown in figure 4.1. Similarly, in figure 4.2 and 4.3, it is observed that the control strategies lead to decrease in the number of mosquito and rodent as against increase in the uncontrolled cases. It was further Observed that transmission of malaria-Lassa fever co-infection varies seasonally depending on the lengthen or availability of rainfall that helps the development and survival of mosquito and rodent (see figures 4,4 and 4.5) (Okosun and Makinde 2011).

CHAPTER SIX

CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

Compartmental mathematical model describing the transmission of malaria-Lassa fever co-infection in three interacting populations was presented: Human, mosquito and rodent. The formulated model governed by systems of ordinary differential equations were qualitatively and quantitatively analysed to gain more insights into the transmission and spread of the malaria-Lassa co-infection diseases.

The model that incorporates seasonal variation of vectors and diagnostic factor for treatment to investigate the effect of endemic malaria mortality rate of Lassa fever patients was formulated by dividing the human population into eight compartments $N_{ss}, N_{es}, N_{is}, N_{rs}, N_{se}, N_{si}, N_{sr}, N_{rr}$ while the mosquito population was divided into S_m, E_m, I_m and rodent population was divided into S_d, E_d, I_d.

The feasible region where the model is mathematical well-posed was presented. The disease-free and endemic equilibra were determined and their stability properties were investigated via a explicit formula for threshold parameter known as basic reproduction number. This threshold parameter was derived using the next generation matrix method. For a threshold parameter greater than unity, a locally asymptotically stable endemic equilibrium of the model was established. Stable subharmonic solutions of period n for many values of n are proved to coexist simultaneously using perturbation method. Moreover, to extend the stability analysis of the model beyond small region near the equilibra, we explored the global dynamical behaviours of the system around the equilibra. It was proved with the aid of Lyapunov function that the disease-free equilibrium is globally asymptotically stable at threshold parameter less than unity and that the endemic equilibrium is globally asymptotically stable at threshold parameter greater than unity. In addition, Using Pontryagin Maximum Principle, necessary conditions for the opti-

mal control was derived, and existence and uniqueness of optimality system were established. Invasion and co-existence of the malaria-Lassa fever co-infection was established. The parameters most responsible for the disease transmission in the populations were determined with respect to $R_{0M}(a,t)$ and $R_{0L}(e,t)$ by sensitivity analysis. The results of sensitivity analysis showed that vectors biting and contact rate among eleven positive sensitivity index parameters, contributed most significantly to the transmission of the diseases. Among the seven negative sensitivity index parameters, the human death rate was found to be most sensitive to $R_{0M}(a,t)$ and $R_{0L}(e,t)$.

Lastly, to complement the theoretical results of the analysis, numerical simulation of the model were performed to investigate the significant of control strategies (prevention, treatment, use of insecticide and pesticide). Using optimal control theory, It was find that the population of mosquito, rodent and infected human with multiple control at a time decreases than using one control at a time. Furthermore, numerical simulations of the model were established to investigate the effects of some key parameters on the dynamical behaviour of the system. It was showed by graphical illustration that increase in the value of κ_m and $\xi_d(e_j)$ increases the magnitude of the infected humans with malaria-Lassa fever co-infection in the population while decrease in the value of κ_m and $\xi_d(e_j)$ decreases the magnitude of the infected humans with malaria-Lassa fever co-infection in the population.

6.2 Recommendations

Based on the qualitative and quantitative results of the analysis, the following recommendations are enumerated with a view to achieving a malaria-free, Lassa fever-free and malaria-Lassa fever co-infection-free.

(1) Efforts at reducing basic reproduction number of malaria-Lassa fever co-infection (especially when there is sufficient rainfall that helps the development and survival of mosquito and rodent) should be intensified since the model parameters, $\zeta, b, \mu_m, \alpha_m$ (Positive sensitivity signs in table 4.1) that would help in influencing this reduction have been shown

(2) It is known that Lassa fever transmission is driven by the interaction between human and rodent. Thus, the need for human to be protected should be encouraged as a way of keeping the rodent at bay. Being protected requires total adherence of

using rodent proof container, rodent control measures and maintenance of sanitary environments.
(3) Efforts should also be made in both government and private hospital by providing modern equipment for diagnosis before treatment to know if the patient has more than one infection.

6.3 Contributions to knowledge

This work focuses on existence of subharmonic bifurcation results and stability analysis of malaria-Lassa fever co-infection epidemic model with optimal control application. Many researchers have worked on mathematical models describing the feature involved in the transmission of mono-infection of malaria and Lassa fever (Chitnis et al 2006, Gumel et al 2008, Okosun and Makinde 2014, James et al 2015, Onuorah et al 2016). However, models on co-infection of malaria and Lassa fever that incorporate diagnostic factor for treatment and seasonal variation of vectors (Mosquito and rodent) with optimal control application needed for full understanding and management of the co-infection in human with *Plasmodium falciparum* and Lassa virus have not been widely explored in the literature and this is a major motivation for this work. Moreover, to the best of our knowledge, it is the first time to use subharmonic bifurcation to study the transmission dynamic of malaria-Lass fever co-infection. This current study gives insights that strict intervention (using multiple control measures at a time) effort is required for quick suppression of the diseases. Moreover, the use of subharmonic bifurcation technique enable us to know that random effect in the environment could perturb the state of the transmission dynamics from the domain of attraction from one subharmonic (Period-doubling) to another, thus producing aperiodic levels of incidence.

6.4 Further research

This study is not without limitations since a model cannot encompass every features of the problem. Thus, it is suggested that mathematical models are needed to describe the ecology of genetically modified mosquitoes and rodents and of variations in the susceptibility of the vector and the potential impact on malaria and Lassa fever.

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Appendices

Appendix I

Norm of the solution of equation (4.1.13) were used to plot subharmonic period 1 and period 2 orbits.

$$max(abs(RootOf(_Z^3*cos(2*Pi*t))/epsilon)+epsilon^3*conjugate(epsilon*(eta+b*cos(2*Pi*t)))*cos(2*Pi*t)*b+epsilon^3*conjugate(epsilon*(1+b*cos(2*Pi*t)))*cos(2*Pi*t)*b)*_Z^2-(-Delta3*conjugate(Delta3/epsilon)*Delta2*epsilon*conjugate(epsilon*(1+b*cos(2*Pi*t)))*conjugate(Delta2*(1+delta*cos(2*Pi*t))/epsilon)*cos(2*Pi*t)*delta-2*Delta3*conjugate(Delta3/epsilon)*Delta2*epsilon*conjugate(epsilon*(eta+b*cos(2*Pi*t)))*conjugate(Delta2*(1+delta*cos(2*Pi*t))/epsilon)*eta-2*Delta3*conjugate(Delta3/epsilon)*Delta2*epsilon*conjugate(epsilon*(eta+b*cos(2*Pi*t)))*conjugate(Delta2/epsilon)*eta+2*Delta3*conjugate(Delta3/epsilon)*Delta2*epsilon*conjugate(epsilon*(1+b*cos(2*Pi*t)))*conjugate(Delta2*(1+delta*cos(2*Pi*t))/epsilon)*eta+Delta3*conjugate(Delta3/epsilon)*Delta2*epsilon*conjugate(epsilon*(eta+b*cos(2*Pi*t)))*conjugate(Delta2*(1+delta*cos(2*Pi*t))/epsilon)+Delta3*conjugate(Delta3/epsilon)*Delta2*epsilon*conjugate(Delta2/epsilon)*conjugate(epsilon*(eta+b*cos(2*Pi*t)))-Delta3*conjugate(Delta3/epsilon)*Delta2*epsilon*conjugate(epsilon*(1+b*cos(2*Pi*t)))*conjugate(Delta2*(1+delta*cos(2*Pi*t))/epsilon),Delta3*conjugate(Delta3/epsilon)*Delta2*epsilon*conjugate(epsilon*(1+b*cos(2*Pi*t)))*conjugate(Delta2*(1+delta*cos(2*Pi*t))/epsilon)*cos(2*Pi*t)*delta-2*Delta3*conjugate(Delta3/epsilon)*Delta2*epsilon*conjugate(epsilon*(eta+b*cos(2*Pi*t)))*conjugate(Delta2*(1+delta*cos(2*Pi*t))/epsilon)*eta-2*Delta3*conjugate(Delta3/epsilon)*Delta2*epsilon*conjugate(epsilon*(eta+b*cos(2*Pi*t)))*conjugate(Delta2/epsilon)*eta+2*Delta3*conjugate(Delta3/epsilon)*Delta2*epsilon*conjugate(epsilon*$$

$(1+b*cos(2*Pi*t)))*conjugate(Delta2*(1+delta*cos(2*Pi*t))/epsilon)*$
$eta+Delta3*conjugate(Delta3/epsilon)*Delta2*epsilon*conjugate(epsilon*$
$(eta+b*cos(2*Pi*t)))*conjugate(Delta2*(1+delta*cos(2*Pi*t))/epsilon)+$
$Delta3*conjugate(Delta3/epsilon)*Delta2*epsilon*conjugate(Delta2/epsilon)*$
$conjugate(epsilon*(eta+b*cos(2*Pi*t)))-Delta3*conjugate(Delta3/epsilon)*$
$Delta2*epsilon*conjugate(epsilon*(1+b*cos(2*Pi*t)))*conjugate(Delta2*$
$(1+delta*cos(2*Pi*t))/epsilon), index=3)))$

Appendix II

Some Maple code used to plot control strategies of the system (3.1.3)-(3.1.17).

CONTROL VARIABLE

$MYODE := [diff(A(t),t) = a-beta(t)*A(t)*Z(t)+v*R(t)-d*A(t), diff(B(t),t) =$
$beta(t)*A(t)*Z(t)-(e+d)*B(t), diff(C(t),t) = e*B(t)-(f+g+d)*$
$C(t), diff(R(t),t) = f*C(t)-(v+d)*R(t), diff(X(t),t) = rho(t)-alpha(t)*X(t)*$
$C(t)-q*X(t), diff(Y(t),t) = alpha(t)*X(t)*C(t)-(r+q)*Y(t), diff(Z(t),t) =$
$r*Y(t)-(u+q)*Z(t), A(0) = 100, B(0) = 10, C(0) = 5, R(0) = 0, X(0) =$
$1000, Y(0) = 30, Z(0) = 10], numeric; solution := dsolve(MYODE, numeric); with(plots);$

Figure 6.1: Mosquito: The malaria-transmitting agent(vector)