MATHEMATICAL MODELS FOR MALARIA CO-INFECTIONS WITH PERSISTENT PAEDIATRIC INFECTIONS IN KENYA

BY

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Abstract

Despite many years of study and advanced biological, medical and mathematical understanding of diseases together with commitment to child survival, malaria and persistent infectious diseases of childhood continue to inflict the developing nations, especially the Sub-Saharan Africa in large proportions. In 1990 the Kenyan under-five mortality rate was reported as 97 deaths per 1000 live births, but in 2006 it had increased to 121 deaths per 1000 live births. Kenya is thus among the countries with least progress towards Millennium Development Goal Four (MDG 4) of 32 deaths per 1000 live births in 2015. In malaria endemic places, malaria co-infections with persistent infections like meningitis, pneumonia and rotavirus are common. Furthermore, these diseases have a high symptom overlap with malaria thus frequently leading to clinical misdiagnosis and its associated problems.

The objective of the study was to develop and analyse, using the stability concepts of differential equations, deterministic mathematical models for the co-infection of malaria with meningitis, pneumonia and rotavirus among Kenyan children under the age of five years. This is because children in this age group have not developed sufficient immunity and are thus more vulnerable to infection.

The symptom overlap between malaria and these persistent infections, in resource scarce settings typical of the developing world, is a cause for concern. This is because in such settings diagnosis is often clinically done. Our analysis indicate that protection against a second infection is desirable in minimizing the effects of co-infection. Without laboratory diagnosis, the presence or absence of a co-infection may not be established

Chapter 1

Introduction

Infectious diseases continue to cause suffering and mortality in human population, especially in the developing world, despite significant advances in medical science. The situation is compounded by the fact that infectious disease agents adapt and evolve, so that new infectious diseases have emerged and some existing diseases have re-emerged [25]. About 29,000 children under the age of five die every day, mainly from preventable causes. More than 70% of child deaths every year are attributable to six causes: diarrhoea, malaria, neonatal infection, pneumonia, preterm delivery, or lack of oxygen at birth. Some of the deaths are caused by diseases such as measles or tetanus while others result indirectly from marginalization, conflict and HIV/AIDS. These deaths occur mainly in the developing world. For instance, an Ethiopian child is 30 times more likely to die by his or her fifth birthday than a child in Western Europe. South-central Asia has the highest number of neonatal deaths, while sub-Saharan Africa has the highest rates of deaths overally in children. Millennium Development Goal Four(MDG 4) is to reduce child mortality by two-thirds, from 93 children of every 1,000 dying before age

five in 1990 to 31 of every 1,000 in 2015 [58]. A good understanding of the transmission dynamics of infectious diseases can lead to better approaches in devising prevention and treatment strategies of these diseases.

Mathematical models of the dynamics of diseases can significantly contribute to the understanding of infectious diseases and guide the choice of intervention measures. Although mathematical modelling dates as far back as the year 1760, deterministic modelling seems to have begun in ernest in the 20th century [25]. To date models continue to be developed and applied to study the dynamics of diseases. For instance mathematical models have been applied in controlling schistosomiasis, a parasitic disease that can damage internal organs and impair cognitive growth and development in children [23].

1.1 Background of the Study

Humans acquire malaria following infective bites from infected Anopheles female mosquitoes during blood feeding. *Plasmodium falciparum* is the parasite species largely responsible for most human malaria infections in Africa. Each year 350-500 million cases of malaria occur worldwide, and over one million people die, most of them young children less than five years of age in sub-Saharan Africa [64]. In 2002 malaria was the fourth cause of death in children in developing countries. In Malawi in 2001, malaria was responsible for 22% of all hospital admissions, 26% of all outpatient visits and 28% of all hospital deaths. In Kenya malaria accounts for 19% of all hospital admissions, 30% of all outpatient visits,

with an estimate of 20% of all deaths in children less than five years of age being attributed to the disease [32].

People living in malaria-endemic areas are frequently exposed to other diseases such as pneumonia, meningitis, rotavirus and sepsis. Some of these diseases not only take advantage of the compromised immunity due to the prolonged malaria exposure, but also have symptom overlap with malaria. Therefore the diagnostic challenge is that a symptom may be due to a single infection or co-infection. For example, in malaria-endemic areas if an acute febrile patient is found to be malaria-positive, malaria is naturally assumed to be the sole cause of the fever. Failure to diagnose other co-infections means a delay in the initiation of their therapy and possibly ensuing sever complications to the patient [24].

Intervention efforts employed in malaria-endemic countries include insecticide-treated nets (ITNs), intermittent preventive treatment in pregnancy (IPTp) and infancy (IPTi) and artemisinin-based combination therapy (ACT) [64]. Research on the effectiveness of these interventions and the potential confounding effects of severe peadiatric co-infections is still lacking. In this study, we develop models for malaria in children that enable us to gain more insights into the epidemiological consequences of the common co-infections and possible remedial measures. This study focuses on children under the age of five years because they are most likely to suffer from the severe effects of malaria with other deadly infections since they have not developed sufficient naturally acquired immunity [57].

1.1.1 Malaria and Meningitis in Children

Meningitis is an inflammation of the membranes (meninges) and cerebrospinal fluid surrounding the brain and spinal cord, usually due to the spread of an infection. The symptoms include headache, fever and a stiff neck. The causative agent may be viral, fungal or bacterial infection. Bacterial meningitis can be fatal, with complications ranging from brain related infection or damage (such as deafness, paralysis, seizure and even mental retardation) to spread of infection through the blood.

In a study carried out in Kenya, 4% of the children admitted in the hospital were found to be infected with both malaria and acute bacterial meningitis. It was noted in the study that both malarial parasites and bacteria played a major role in the pathogenesis in the group of children with high mortality [3].

1.1.2 Malaria and Pneumonia in Children

The term pneumonia refers to any infection of the lung, and may be fatal since it affects a respiratory organ. The cause of the infection may be viral or bacterial. The viruses which cause pneumonia include *influenza* A and B viruses; respiratory syncytial virus (RSV); and *haemophilus parainfluenzae* types 1, 2 and 3. The most common cause of bacterial pneumonia is *Streptococcus pneumoniae*. This form of pneumonia is characterised by an abrupt onset of illness with shaking chills, fever

and production of a rust-colored sputum. Other bacteria causing pneumonia include *Haemophilus influenzae* type b, group A *streptococcus*, and *Mycobacterium tuberculosis* (TB). Approximately 150 million new cases of pneumonia occur annually among children younger than 5 years worldwide, accounting for approximately 10-20 million hospitalizations. Ninety-five percent of all episodes of clinical pneumonia in young children worldwide occur in developing countries [49]. Pneumonia accounts for one fifth of all childhood deaths worldwide, with approximately 2 million children dying each year [6].

Malaria and pneumonia are the leading causes of death among children in malarious countries in sub-Saharan Africa, each contributing $20-26\%$ of the total under-five mortality [26, 30]. A study carried out in Uganda showed that 27 (19%) out of the 139 children enrolled in an urban hospital were co-infected with both malaria and pneumonia [26]. Another study carried out in Uganda also showed that out of 2,944 malaria cases in under-fives at 14 health centres, 37% had pneumonia [30]. The most common causes of deaths in Kenyan children after the neonatal period are pneumonia, diarrhoea, measles, malaria, and malnutrition or a combination of these conditions [40].

1.1.3 Malaria and Rotavirus in Children

Rotavirus is a pathogen of the gastrointestinal tract that causes severe acute gastroenteritis and diarrhoea in infants and young children [62].

Human rotavirus infections are ubiquitous. Some review analyses show that rotavirus accounted for 6% of diarrhoea episodes and 20% of deaths caused by diarrhoea in children less than five years of age in developing countries [43]. Rotaviruses are shed in high concentrations in stools of infected children and are transmitted by the faecal-oral route, both through close person-to-person contact and through fomities such as toys and countertops. Rotaviruses are also transmitted through other modes, such as focally-contaminated food, water and respiratory droplets.

In a study carried out in Ghana, it was observed that 11.8% of the 243 children examined were co-infected with *Plasmodium falciparum* and enteropathogens, where rotavirus was also found to be the common enteropathogen present in more than half of the patients [46].

1.2 Statement of the problem

The infant mortality in Kenya can largely be attributed to preventable childhood diseases. Recent reviews show that these diseases often occur simultaneously, largely because of shared or overlapping risk factors, or because one disorder increases the risk of the other. Furthermore, published models on the dynamics of malaria co-infections with persistent infections like meningitis, pneumonia and rotavirus are rare and yet these co-infections are common. Therefore, research on the effectiveness of disease intervention strategies, especially in the light of malaria co-infections with persistent peadiatric infections is necessary to help realise the MDG

4 of 32 deaths per 1000 live births by 2015.

1.3 Objectives of the study

The broad objective of this research was to develop compartmental models to study the co-dynamics of malaria and persistent paediatric infections such as meningitis, pneumonia and rotavirus among children under the age of five years in Kenya.

The specific objectives of this research were:

(i) To describe, formulate and analyse deterministic models for each of the co-infections considered.

(ii) To determine whether there is a possibility of a backward bifurcation in the models formulated

(iii) To evaluate the increase or decrease in the number of malaria co-infection cases attributed to the persistent infections in children who live in malaria-endemic regions.

(iv) To propose remedial measures needed to minimize the effects of co-infection.

1.4 Scope of the Study

This study was carried out at Maseno University, Kenya, Africa, and the information and data about the diseases considered was obtained from the Ministries of Medical Services and Public Health and relevant bodies such as UNICEF, WHO.

1.5 Outcomes and research impact

(i) This study results in an improved understanding of the dynamics and effects of co-infection with malaria and persistent paediatric diseases.

(ii) The study also gives an insight on possible intervention measures for minimizing the effects of co-infections.

Chapter 2

Literature review

2.1 Mathematical models for malaria

A number of mathematical models have been developed and analysed to explain the dynamics of infectious diseases in humans. Many of these models are described by systems of ordinary differential equations formulated under reasonable assumptions and parameters. Mathematical models for malaria infection in humans have also been developed, with the pioneering work done by Ross [48]. For example, in [35], a malaria model with partial immunity in humans is presented. In this work, a compartmental ordinary differential equations model in which the human population is subdivided into groups of susceptible, incubating, infective and recovered individuals while the mosquito population is subdivided into groups of susceptible, incubating and infective vectors is formulated. An explicit formula for the basic reproduction number is derived. Existence of disease-free and endemic equilibria is shown. Using a numerical example, it is demonstrated that models having the same reproductive number but different numbers of progression stages can exhibit different

transient transmission dynamics.

Similarly in [28] a model for the transmission of malaria is presented. Contrary to [35], the model excludes the incubating stages for both the human and vector populations. The results of the study suggest that, if the disease-induced death rate is large enough, there may be endemic equilibrium when the reproduction number is less than unity and the model exhibits backward bifurcation and saddle-node bifurcation, which implies that a reproduction number less than one is not sufficient to eradicate malaria. An intra-host model for the dynamics of malaria and the immune system is developed and analysed in [56]. It is established that if the basic reproduction number is greater than one, a unique endemic equilibrium that is globally stable exists and that the parasites persist at the endemic steady state. The numerical analysis shows that in the presence of immune response, the endemic equilibrium is unstable.

Human migration and travel also greatly affect the dynamics of infectious diseases. In [55], a host-vector model for malaria with infective immigrants is developed and analysed. The model is shown to exhibit a unique endemic equilibrium state if the fraction of the infective immigrants is positive. When this fraction approaches zero, there is a sharp threshold for which malaria can be reduced. A deterministic model analysing the effect of control strategies on the transmission dynamics of malaria is presented in [13]. The model theoretically assesses the potential impact of personal protection, treatment and possible vaccination strategies. The analysis shows that vaccination and personal protection, as well as treatment meeting certain conditions, can reduce the spread of malaria in a

community.

2.2 Mathematical Models for Meningitis

An age-structured model of meningococcal meningitis is formulated and analysed in [39]. This model considers disease transmission by the normal infectives and carriers. The reproductive number computed is a sum of two reproductive numbers corresponding to infections by infectives and carriers. Stability conditions for equilibria points are derived and it is shown that the disease persists whenever the reproduction number is greater than one.

2.3 Mathematical Models for Rotavirus

The rotavirus transmission model in [63] observes the levels of cross-immunity necessary to suppress similar strains. The authors address the issue of heterogeneity among strains of the same pathogen by looking at three different models. These are the altered susceptibility, the altered infectivity and the partial immunity models based on Susceptible-Infected-Recovered (SIR) and Susceptible-Infected-Susceptible (SIS) framework, to propose different interaction mechanisms, and examine their consequences in terms of equilibrium results. The study [52] examines the role of maternal antibodies in age-structured models with and without vaccination. The study delves further into the dynamics of passive immunity, and consider only one strain of rotavirus. In yet another study, the dy-

namics of rotavirus infections are studied using a simple mathematical model that includes the impact of breast feeding, seasonality and the possibility of control via vaccination [51].

2.4 Malaria co-infection models

A deterministic model of co-infection of HIV and malaria is presented in [42]. This model was analysed both analytically and numerically. The analysis shows that the malaria-only-sub-model and HIV-malaria co-infection model undergo the phenomenon of backward bifurcation, and the HIV-only model has a globally-asymptotically stable disease free-equilibrium whenever the reproduction number is less one. The numerical analysis shows that the two diseases coexist whenever the reproduction number of each of the two diseases exceed unity and the number of new cases of malaria at a steady state seems to be higher than those of HIV at all time. It was also shown that a reduction in sexual activity of individuals with malaria symptoms results in a decrease in the number of new cases of HIV and the mixed HIV-malaria infection while increasing the number of malaria cases [42].

In yet another study [1], a mathematical model to describe the dual infection of HIV and malaria is developed. From this model, it was established that the dual infection of HIV and malaria fuels the spread of both diseases. The model was applied to a setting in Kisumu, Kenya, with an adult population of about 200,000 and it was estimated that since

1980, the interaction was responsible for 8,500 new HIV infection cases and 98,000 excess malaria episodes. The research emphasized the need for more concerted health services for early and effective treatment and prevention of malaria in the HIV-infected persons.

The analysis of the mathematical model exploring malaria and tuberculosis co-dynamics shows that there is a synergistic relation between the diseases [50]. In [34], a mathematical model for malaria and meningitis co-infection among children under five years of age is developed and analysed. The analysis shows that the disease-free equilibrium of the model may not be globally asymptotically stable whenever the basic reproduction number is less than unity. The Centre Manifold theorem is used to show that the model has a unique endemic equilibrium which is locally asymptotically stable when the basic reproduction number is less than unity and unstable otherwise. The authors deduce further that a reduction in malaria infection cases either through protection or prompt effective treatment, which is dependent on the socio-economic status of a community, would reduce the number of new co-infection cases.

Chapter 3

Modelling the dynamics of Malaria-Meningitis Co-infection among children

A study carried out in Kenya showed that 4% of the children admitted in the hospital were infected with both malaria and acute bacterial meningitis. The study noted that co-infection played a major role in the group of children with high mortality [3]. We present an overview of meningitis and thereafter develop a mathematical model to study the dynamics of malaria-meningitis co-infection.

3.1 Overview of Meningitis

Meningitis is an infectious disease characterized by inflammation of the meninges (the tissues that surround the brain or spinal cord), usually due to the spread of an infection into the cerebral spinal fluid (CSF). The

cause of the infection may be bacterial, viral, fungal or parasitic. Some of the risk factors for the disease are a compromised immune system due to illness, such as HIV/AIDS or use of immunosuppressant drugs. The symptoms of meningitis include neck and/or back pain, headache, high fever and a stiff neck. These symptoms can develop over several hours, or they may take 1 to 2 days. Bacterial meningitis may cause acute or chronic brain injury leading to death or disability (such as deafness, paralysis, seizure and even mental retardation) [53]. The seasonal outbreak of meningitis in the African meningitis belt, a band of sub-Saharan Africa, usually results into a high disease mortality and morbidity [29]. An outbreak in 1996-1997 claimed more than 25,000 lives, with about 250,000 cases of illness across ten countries. However, in 2008 there were only 27,000 cases across the entire belt [47].

Early diagnosis, though challenging, and medication of cases of acute bacterial meningitis leads to a reduction in death and neurologic sequelae. The challenge in the clinical diagnosis is greater in malaria endemic areas. For example, at a tertiary centre in Malawi, meningitis was included in the admission differential diagnosis in only 42% of the subsequently proven bacterial meningitis cases, most having been initially thought to be malaria [41]. Similarly, a study carried out at a Kenyan district hospital found out that clinicians correctly included a diagnosis of meningitis at the initial clinical assessment in only 30% of admissions for whom a final diagnosis of meningitis was confirmed [18].

3.2 Model Description and Formulation

To study the dynamics of malaria-meningitis co-infection we formulate a model in which the total human population at any time t, denoted N_H is subdivided into subpopulations of susceptible humans (S_H), those exposed to malaria parasites only (E_1), individuals infected with malaria (I_1), those infected with meningitis (I_2), individuals exposed to malaria and infected with meningitis (E_{12}) and individuals infected with both malaria and meningitis (I_c). The total vector population at any time t, denoted N_v is subdivided into subpopulation of susceptible (S_v), exposed (E_v) and infectious (I_v). This means that

$$N_H = S_H + E_1 + I_1 + I_2 + E_{12} + I_c \tag{3.2.1}$$

and

$$N_v = S_v + E_v + I_v \tag{3.2.2}$$

The rates of infection of susceptible humans with malaria and meningitis are λ_{ma} and λ_{me} respectively, while that of susceptible vectors with malaria is λ_v. Let ψ and γ be malaria and meningitis induced mortality in humans respectively, and suppose that μ_H and μ_v are per capita natural death rates of the human and mosquito populations respectively. The constant per capita recruitment rate into the susceptible human and vector populations are Λ_H and Λ_v respectively. The rates at which exposed human and vector populations develop malaria clinical symptoms are σ_H and σ_v respectively, while the rate at which humans progress from the E_{12} class to the I_c class is $\epsilon\sigma_H$, where ϵ is a modification parameter representing the assumption that meningitis infected individuals exposed

to malaria develop malaria symptoms at a faster rate than those who are not infected with meningitis. Define ϕ_1 as the rate at which individuals infected with malaria recover, ϕ_2 as the recovery rate from meningitis and ϕ_3 as the recovery rate from both infections. The recovered individuals do not acquire temporary immunity to either or both diseases and thus become susceptible again.

We assume that infection with meningitis when one is exposed to malaria takes place at an advanced stage of this exposure. The parameter θ accounts for the increased susceptibility to infection with meningitis for individuals infected with malaria, while the parameter ρ accounts for the decreased susceptibility to infection with malaria for individuals infected with meningitis because of decreased contact due to ill health. The individuals displaying symptoms of both malaria and meningitis suffer malaria-induced mortality at the rate $\vartheta\psi$, where the parameter ϑ accounts for the assumed increase in malaria-related mortality due to the dual infection with meningitis and also suffer meningitis-induced mortality at the rate $\eta\gamma$, where the parameter η accounts for the assumed increase in meningitis-related mortality due to the dual infection with malaria. Let α denote the number of bites per human per mosquito (biting rate of mosquitoes), β_m as the transmission probability of malaria in humans per bite, β_v as the transmission probability of malaria in vectors from any infected human, β as the effective contact rate for infection with meningitis.

This yields

$$\lambda_{ma} = \frac{\alpha\beta_m I_v}{N_H} \tag{3.2.3}$$

$$\lambda_v = \frac{\alpha\beta_v(I_1 + \delta I_c)}{N_H} \tag{3.2.4}$$

$$\lambda_{me} = \frac{\beta(I_2 + E_{12} + \kappa I_c)}{N_H}, \tag{3.2.5}$$

where δ and κ model the relative infectiousness of the co-infected individual as compared to their counterparts.

From the above definitions and variables we have the following model

$$\begin{aligned}
\frac{dS_H}{dt} &= \Lambda_H - \lambda_{ma}S_H - \lambda_{me}S_H + \phi_1 I_1 + \phi_2 I_2 + \phi_3 I_c - \mu_H S_H, \\
\frac{dE_1}{dt} &= \lambda_{ma}S_H - \lambda_{me}E_1 - \sigma_H E_1 - \mu_H E_1, \\
\frac{dI_1}{dt} &= \sigma_H E_1 - \theta\lambda_{me}I_1 - \psi I_1 - \phi_1 I_1 - \mu_H I_1, \\
\frac{dI_2}{dt} &= \lambda_{me}S_H - \rho\lambda_{ma}I_2 - \phi_2 I_2 - \gamma I_2 - \mu_H I_2, \\
\frac{dE_{12}}{dt} &= \rho\lambda_{ma}I_2 + \lambda_{me}E_1 - (\epsilon\sigma_H + \gamma + \mu_H)E_{12}, \\
\frac{dI_c}{dt} &= \epsilon\sigma_H E_{12} + \theta\lambda_{me}I_1 - (\phi_3 + \vartheta\psi + \eta\gamma + \mu_H)I_c, \\
\frac{dS_v}{dt} &= \Lambda_v - \lambda_v S_v - \mu_v S_v, \\
\frac{dE_v}{dt} &= \lambda_v S_v - \sigma_v E_v - \mu_v E_v, \\
\frac{dI_v}{dt} &= \sigma_v E_v - \mu_v I_v.
\end{aligned} \tag{3.2.6}$$

3.3 Positivity of Solutions

Model (3.2.6) describes the human and mosquito populations and therefore we show that the associated state variables are non-negative for all time $t \geq 0$ and that the solutions of the model (3.2.6) with positive initial data remain positive for all time $t \geq 0$. We assume the associated parameters as non-negative for all time $t \geq 0$.

Lemma 3.1. *Let the initial data be* $\{(S_H(0), S_v(0) > 0), (E_1(0), I_1(0), I_2(0), E_{12}(0), I_c(0), E_v(0), I_v(0)) \geq 0\} \in \tilde{\Psi}$. *Then the solution set* $\{S_H, E_1, I_1, I_2, E_{12}, I_c, S_v, E_v, I_v\}(t)$ *is positive for all* $t > 0$.

Proof. Considering the first equation in (3.2.6) i.e

$$\frac{dS_H}{dt} = \Lambda_H - \lambda_{ma} S_H - \lambda_{me} S_H + \phi_1 I_1 + \phi_2 I_2 + \phi_3 I_c - \mu_H S_H,$$

This equation may be transformed into an equality by dropping the positive terms on the right hand side. Thus

$$\begin{aligned} \frac{dS_H}{dt} &\geq -(\lambda_{ma} + \lambda_{me} + \mu_H) S_H \\ \int \frac{1}{S_H} dS_H &\geq -\int (\lambda_{ma} + \lambda_{me} + \mu_H) dt \\ S_H(t) &\geq S_H(0) e^{-(\int (\lambda_{ma} + \lambda_{me}) dt + \mu_H t)} \geq 0 \end{aligned}$$

Similarly from the second equation in (3.2.6) i.e

$$\frac{dE_1}{dt} = \lambda_{ma} S_H - \lambda_{me} E_1 - \sigma_H E_1 - \mu_H E_1,$$

we have

$$\begin{aligned} \frac{dE_1}{dt} &\geq -(\lambda_{me} + \sigma_H + \mu_H)E_1 \\ \int \frac{1}{E_1} dE_1 &\geq -\int (\lambda_{me} + \sigma_H + \mu_H)dt \\ E_1(t) &\geq E_1(0)e^{-(\int(\lambda_{me}+\sigma_H+\mu_H)t} \geq 0 \end{aligned}$$

We can proceed in a similar manner and show that all the state variables are positive for all time t. □

3.4 Boundedness of solutions

We show that all feasible solutions are uniformly-bounded in a proper subset $\Psi = \Psi_H \times \Psi_v$.

Lemma 3.2. *Solutions of the model (3.2.6) are contained in the region* $\Psi = \Psi_H \times \Psi_v$.

Proof. To show that all feasible solutions are uniformly-bounded in a proper subset Ψ, we split the model (3.2.6) into the human component (N_H) and the mosquito component (N_v), given by equations (3.2.1) and (3.2.2) respectively.

Let

$$(S_H, E_1, I_1, I_2, E_{12}, I_c) \in \mathbb{R}^6_+$$

be any solution with non-negative initial conditions. From a theorem on differential inequality in [4] it follows that

$$\limsup_{t\to\infty} S_H(t) \leq \frac{\Lambda_H}{\mu_H}.$$

Taking the time derivative of N_H along a solution path of the model (3.2.6) gives

$$\frac{dN_H}{dt} = \Lambda_H - \mu_H N_H - \psi I_1 - \gamma I_2 - (\vartheta\psi + \eta\gamma) I_c$$

Then,

$$\frac{dN_H}{dt} \leq \Lambda_H - \mu_H N_H$$

From the theorem in [4] on differential inequality it follows that

$$0 \leq N_H \leq \frac{\Lambda_H}{\mu_H} + N_H(0) e^{-\mu_H t}$$

where $N_H(0)$ represents the value of (3.2.1) evaluated at the initial values of the respective variables. Thus as $t \to \infty$, we have

$$0 \leq N_H \leq \frac{\Lambda_H}{\mu_H} \tag{3.4.1}$$

This shows that N_H is bounded and all the feasible solutions of the human-only component of model (3.2.6) starting in the region Ψ_H approach, enter or stay in the region, where

$$\Psi_H = \{(S_H, E_1, I_1, I_2, E_{12}, I_c) : N_H \leq \frac{\Lambda_H}{\mu_H}\}$$

Similarly,let

$$(S_v, E_v, I_v) \in \mathbb{R}^3_+$$

be any solution with non-negative initial conditions. Then

$$\limsup_{t\to\infty} S_v(t) \leq \frac{\Lambda_v}{\mu_v}.$$

Taking the time derivative of N_v along a solution path of the model (3.2.6) gives

$$\frac{dN_v}{dt} = \Lambda_v - \mu_v N_v$$

The mosquito-only component (3.2.2) has a varying population size. Therefore,

$$\frac{dN_v}{dt} < \Lambda_v - \mu_v N_v$$

From the theorem in [4] on differential inequality it follows that

$$0 \leq N_v \leq \frac{\Lambda_v}{\mu_v} + N_v(0)e^{-\mu_v t}$$

where $N_v(0)$ represents the value of (3.2.2) evaluated at the initial values of the respective variables. Thus as $t \to \infty$, we have

$$0 \leq N_v \leq \frac{\Lambda_v}{\mu_v} \tag{3.4.2}$$

This shows that N_v is bounded and all the feasible solutions of the mosquito-only component of model (3.2.6) starting in the region Ψ_v approach, enter or stay in the region, where

$$\Psi_v = \{(S_v, E_v, I_v) : N_v \leq \frac{\Lambda_v}{\mu_v}\}$$

Thus it follows from (3.4.1) and (3.4.2) that N_H and N_v are bounded and all the possible solutions of the model starting in Ψ will approach, enter

or stay in the region $\Psi = \Psi_H \times \Psi_v \; \forall t \geq 0$. □

Thus Ψ is positively invariant under the flow induced by (3.2.6). Existence, uniqueness and continuation results also hold for the model (3.2.6) in Ψ. Hence model (3.2.6) is well-posed mathematically and epidemiologically and it is sufficient to consider its solutions in Ψ.

3.5 Equilibrium States of the model

The equilibrium points of the model (3.2.6) are obtained by setting the left hand side of the model to zero and solving simultaneously, giving rise to two possible equilibrium points namely: the disease-free and the endemic equilibrium points. We assume there is no trivial equilibrium point since there is constant recruitment into human and vector populations.

3.5.1 Disease-free equilibrium point of the model

In the absence of infection by either or both diseases, the model (3.2.6), has a steady-state solution called the disease-free equilibrium (DFE) denoted by E^0. We define the "*diseased*" classes as the human or mosquito populations that are either exposed or infectious. Define the positive orthant in $\mathbb{R}^9$ by $\mathbb{R}^9_+$ and the boundary of $\mathbb{R}^9_+$ by $\partial\mathbb{R}^9_+$.

Lemma 3.3. *For all equilibrium points on* $\Psi \cap \partial\mathbb{R}^9_+$, $E_1 = I_1 = I_2 = E_{12} = I_c = E_v = I_v = 0$

The positive DFE for human and mosquito populations for the model (3.2.6) are

$$N_H = \frac{\Lambda_H}{\mu_H} \text{ and } N_v = \frac{\Lambda_v}{\mu_v}. \tag{3.5.1}$$

Lemma 3.4. *The model (3.2.6) has exactly one DFE,*
$E^0 = (\frac{\Lambda_H}{\mu_H}, 0, 0, 0, 0, 0, \frac{\Lambda_v}{\mu_v}, 0, 0)$

Proof. The proof of the lemma requires that we show that DFE is the only equilibrium point of (3.2.6) on $\Psi \cap \partial\mathbb{R}^9_+$. Substituting E^0 into (3.2.6) shows all derivatives equal to zero, hence DFE is an equilibrium point. From Lemma 3.3, the only equilibrium point for N_H is $\frac{\Lambda_H}{\mu_H}$ and the only equilibrium point for N_v is $\frac{\Lambda_v}{\mu_v}$. Thus the only equilibrium point for $\Psi \cap \partial\mathbb{R}^9_+$ is the DFE. □

3.6 The Basic Reproduction number R_0

The global dynamics of the model (3.2.6) is highly dependent on an important epidemiological parameter called the basic reproduction number R_0. It is defined as the average number of secondary infections an infectious individual would cause over his infectious period in an entirely susceptible population. We specifically define the basic reproduction number, R_{mm} as the number of secondary malaria (or meningitis) infections due to a single malaria (or a single meningitis-infective) individual. When $R_{mm} < 1$, it means an infectious individual is causing, on average, less than one new infection and thus the disease does not invade the population. On the other hand, when $R_{mm} > 1$, then an infectious individual is causing, on average, more than one new infection and thus the disease invades and

persist in the population. We determine R_{mm} using the next generation operator approach in [15, 59]. To employ this method, we rewrite (3.2.6) beginning with the infected classes $E_1, I_1, I_2, E_{12}, I_c, E_v, I_v$ followed by the uninfected classes S_H, S_v. This yields

$$\begin{aligned}
\frac{dE_1}{dt} &= \frac{\alpha\beta_m I_v}{N_H}S_H - \frac{\beta(I_2+E_{12}+\kappa I_c)}{N_H}E_1 - \sigma_H E_1 - \mu_H E_1,\\
\frac{dI_1}{dt} &= \sigma_H E_1 - \theta\frac{\beta(I_2+E_{12}+\kappa I_c)}{N_H}I_1 - \psi I_1 - \phi_1 I_1 - \mu_H I_1,\\
\frac{dI_2}{dt} &= \frac{\beta(I_2+E_{12}+\kappa I_c)}{N_H}S_H - \rho\frac{\alpha\beta_m I_v}{N_H}I_2 - \phi_2 I_2 - \gamma I_2 - \mu_H I_2,\\
\frac{dE_{12}}{dt} &= \rho\frac{\alpha\beta_m I_v}{N_H}I_2 + \frac{\beta(I_2+E_{12}+\kappa I_c)}{N_H}E_1 - (\epsilon\sigma_H + \gamma + \mu_H)E_{12},\\
\frac{dI_c}{dt} &= \epsilon\sigma_H E_{12} + \theta\frac{\beta(I_2+E_{12}+\kappa I_c)}{N_H}I_1 - (\phi_3 + \vartheta\psi + \eta\gamma + \mu_H)I_c,\\
\frac{dE_v}{dt} &= \frac{\alpha\beta_v(I_1+\delta I_c)}{N_H}S_v - \sigma_v E_v - \mu_v E_v,\\
\frac{dI_v}{dt} &= \sigma_v E_v - \mu_v I_v.\\
\frac{dS_H}{dt} &= \Lambda_H - \frac{\alpha\beta_m I_v}{N_H}S_H - \frac{\beta(I_2+E_{12}+\kappa I_c)}{N_H}S_H\\
&\quad +\phi_1 I_1 + \phi_2 I_2 + \phi_3 I_c - \mu_H S_H,\\
\frac{dS_v}{dt} &= \Lambda_v - \frac{\alpha\beta_v(I_1+\delta I_c)}{N_H}S_v - \mu_v S_v,
\end{aligned} \tag{3.6.1}$$

Define $\mathcal{F}_i$ as the rate of appearance of new infections in the class or compartment i and $\mathcal{V}_i = \mathcal{V}_i^- - \mathcal{V}_i^+$, where $\mathcal{V}_i^-$ is the rate of transfer of individuals out of compartment i, and $\mathcal{V}_i^+$ is the rate of transfer of individuals into compartment i by all other means. Therefore

$$\mathcal{F}_i = \begin{pmatrix} \frac{\alpha\beta_m I_v}{N_H} S_H \\ 0 \\ \frac{\beta(I_2+E_{12}+\kappa I_c)}{N_H} S_H \\ \rho\frac{\alpha\beta_m I_v}{N_H} I_2 + \frac{\beta(I_2+E_{12}+\kappa I_c)}{N_H} E_1 \\ \theta\frac{\beta(I_2+E_{12}+\kappa I_c)}{N_H} I_1 \\ \frac{\alpha\beta_v(I_1+\delta I_c)}{N_H} S_v \\ 0 \end{pmatrix}$$

and

$$\mathcal{V}_i = \begin{pmatrix} (\frac{\beta(I_2+E_{12}+\kappa I_c)}{N_H} + \sigma_H + \mu_H)E_1 \\ (\theta\frac{\beta(I_2+E_{12}+\kappa I_c)}{N_H} + \psi + \phi_1 + \mu_H)I_1 - \sigma_H E_1 \\ (\rho\frac{\alpha\beta_m I_v}{N_H} + \phi_2 + \gamma + \mu_H)I_2 \\ (\epsilon\sigma_H + \gamma + \mu_H)E_{12} \\ (\phi_3 + \vartheta\psi + \eta\gamma + \mu_H)I_c - \epsilon\sigma_H E_{12} \\ (\sigma_v + \mu_v)E_v \\ \mu_v I_v - \sigma_v E_v \end{pmatrix}$$

The Jacobian of $\mathcal{F}_i$ at the disease-free equilibrium is denoted F, and is given by

$$F = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & \alpha\beta_m \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \beta & \beta & \beta\kappa & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \frac{\alpha\beta_v\Lambda_v\mu_H}{\Lambda_H\mu_v} & 0 & 0 & \frac{\alpha\beta_v\delta\Lambda_v\mu_H}{\Lambda_H\mu_v} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

Similarly, the Jacobian of $\mathcal{V}_i$ at the disease-free equilibrium is denoted V, and is given by

$$V=\begin{pmatrix} h_1 & 0 & 0 & 0 & 0 & 0 & 0 \\ -\sigma_H & h_2 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & h_3 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & h_4 & 0 & 0 & 0 \\ 0 & 0 & 0 & -\epsilon\sigma_H & h_5 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & h_6 & 0 \\ 0 & 0 & 0 & 0 & 0 & -\sigma_v & \mu_v \end{pmatrix}$$

where $h_1 = \sigma_H+\mu_H$, $h_2 = \psi+\phi_1+\mu_H$, $h_3 = \phi_2+\gamma+\mu_H$, $h_4 = \epsilon\sigma_H+\gamma+\mu_H$ $h_5 = \phi_3 + \vartheta\psi + \eta\gamma + \mu_H$ and $h_6 = \sigma_v + \mu_v$.

The basic reproduction number R_{mm} is by definition [15] the spectral radius of the matrix FV^{-1}. The eigenvalues of the matrix FV^{-1} are

$0, 0, 0, 0, \frac{\beta}{\phi_2+\gamma+\mu_H}$ and $\pm\sqrt{\frac{\alpha^2\beta_m\beta_v\sigma_H\sigma_v\mu_H\Lambda_v}{\Lambda_H\mu_v^2(\sigma_H+\mu_H)(\sigma_v+\mu_v)(\phi_1+\psi+\mu_H)}}$.
Therefore R_{mm} is given by

$$R_{mm} = \max\{\sqrt{\frac{\alpha^2\beta_m\beta_v\sigma_H\sigma_v\mu_H\Lambda_v}{\Lambda_H\mu_v^2(\sigma_H+\mu_H)(\sigma_v+\mu_v)(\phi_1+\psi+\mu_H)}}, \frac{\beta}{\phi_2+\gamma+\mu_H}\}. \tag{3.6.2}$$

Denoting $R_{ma} = \sqrt{\frac{\alpha^2\beta_m\beta_v\sigma_H\sigma_v\mu_H\Lambda_v}{\Lambda_H\mu_v^2(\sigma_H+\mu_H)(\sigma_v+\mu_v)(\phi_1+\psi+\mu_H)}}$
and $R_{me} = \frac{\beta}{\phi_2+\gamma+\mu_H}$,
we have $R_{mm} = \max\{R_{ma}, R_{me}\}$.

R_{ma} is a measure of the average number of secondary malaria infections in human or mosquito population caused by a single infective human or mosquito introduced into an entirely susceptible population. R_{ma} can be expressed as

$$R_{ma} = \sqrt{R_{mH} \times R_{mV}}$$

where

$$R_{mH} = \frac{\alpha\beta_v\sigma_H\mu_H\Lambda_v}{\Lambda_H\mu_v(\sigma_H + \mu_H)(\phi_1 + \psi + \mu_H)} \tag{3.6.3}$$

and

$$R_{mV} = \frac{\beta_m\alpha\sigma_v}{\mu_v(\sigma_v + \mu_v)} \tag{3.6.4}$$

The equation (3.6.3) represents the total number of malaria infections in mosquitoes caused by a single infected human. It is directly proportional to the biting rate α, the probability of survival till infectious stage for humans $\frac{\sigma_H}{\sigma_H+\mu_H}$ and the mean time spent in the infective class $\frac{1}{\phi_1+\psi+\mu_H}$. On the other hand (3.6.4) represents the total number of secondary malaria infections in humans caused by one infected mosquito. This number is highly dependent on the mosquito biting rate α and the probability of mosquito survival till the infectious stage $\frac{\sigma_v}{\sigma_v+\mu_v}$.

Remark 3.5. From (3.6.4), it is evident that strategies for the reduction of malaria infections in humans should target reduction of the mosquito biting rate α through protection such as the use of insecticide treated nets. Methods that aim at vector elimination or reduction such as draining stagnant water breeding grounds and spraying would reduce the probability of mosquito survival till the infectious stage and thus reduce malaria infections in humans.

Similarly, R_{me} is a measure of the average number of secondary meningitis infections in humans caused by a single infective human introduced into an entirely susceptible population. The following lemma follows from Theorem 2 of [59].

Corollary 3.6. *The disease-free equilibrium E^0 of the model (3.2.6) is locally asymptotically stable whenever $R_{mm} < 1$ and unstable when $R_{mm} > 1$.*

3.7 Global stability of the disease-free equilibrium

The global asymptotic stability (GAS) of the disease-free state of the model is investigated using the theorem by Castillo-Chavez *et.al* [10]. We rewrite the model as

$$\begin{aligned} \frac{dX}{dt} &= H(X, Z), \\ \frac{dZ}{dt} &= G(X, Z), G(X, 0) = 0 \end{aligned} \tag{3.7.1}$$

where $X = (S_H, S_v)$ and $Z = (E_1, I_1, I_2, E_{12}, I_c, E_v, I_v)$, with the components of $X \in \mathbb{R}^2$ denoting the uninfected population and the components of $Z \in \mathbb{R}^7$ denoting the infected population.

The disease-free equilibrium is now denoted as

$$E^0 = (X^*, 0), X^* = (\frac{\Lambda_H}{\mu_H}, \frac{\Lambda_v}{\mu_v}). \tag{3.7.2}$$

The conditions in (3.7.3) must be met to guarantee a local asymptotic stability:

$$\begin{aligned} \frac{dX}{dt} &= H(X,0), X^* \text{ is globally asymptotically stable (GAS)} \\ G(X,Z) &= PZ - \widehat{G}(X,Z), \widehat{G}(X,Z) \geq 0 \text{ for } (X,Z) \in \Omega \end{aligned} \tag{3.7.3}$$

where $P = D_z G(X^*, 0)$ is an M-matrix (the off-diagonal elements of P are non-negative) and Ω is the region where the model makes biological sense. If the system (3.7.1) satisfies the conditions of (3.7.3) then the theorem below holds.

Thecrem 3.7. *The fixed point $E^0 = (X^*, 0)$ is a globally asymptotically stable equilibrium of system (3.7.1) provided that $R_{mm} < 1$ and the assumptions in (3.7.3) are satisfied.*

Proof. From the model system (3.2.6) and (3.7.1), we have

$$H(X,0) = \begin{pmatrix} \Lambda_H - \mu_H S_H \\ \Lambda_v - \mu_v S_v \end{pmatrix}$$

$$G(X,Z) = PZ - \widehat{G}(X,Z)$$

where

$$P = \begin{pmatrix} -h_6 & 0 & 0 & 0 & 0 & 0 & \alpha\beta_m \\ \sigma_H & -h_7 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & h_8 & \beta & \beta\kappa & 0 & 0 \\ 0 & 0 & 0 & -h_9 & 0 & 0 & 0 \\ 0 & 0 & 0 & \epsilon\sigma_H & -h_{10} & 0 & 0 \\ 0 & \alpha\beta_v & 0 & 0 & \alpha\beta_v\delta & -h_{11} & 0 \\ 0 & 0 & 0 & 0 & 0 & \sigma_v & -\mu_v \end{pmatrix}$$

and

$$\widehat{G}(X,Z) = \begin{pmatrix} \widehat{G}_1(X,Z) \\ \widehat{G}_2(X,Z) \\ \widehat{G}_3(X,Z) \\ \widehat{G}_4(X,Z) \\ \widehat{G}_5(X,Z) \\ \widehat{G}_6(X,Z) \\ \widehat{G}_7(X,Z) \end{pmatrix} = \begin{pmatrix} \alpha\beta_m I_v(1-\frac{S_H}{N_H}) + \lambda_{me}E_1 \\ \theta\lambda_{me}I_1 \\ \rho\lambda_{ma}I_2 + \beta(I_2 + E_{12} + \kappa I_c)(1-\frac{S_H}{N_H}) \\ -(\lambda_{me}E_1 + \rho\lambda_{ma}I_2) \\ -\theta\lambda_{me}I_1 \\ \alpha\beta_v(I_1 + \delta I_c)(1-\frac{S_v}{N_H}) \\ 0 \end{pmatrix}$$

where $h_6 = \sigma_H + \mu_H$, $h_7 = \psi + \phi_1 + \mu_H$, $h_8 = \beta - (\phi_2 + \gamma + \mu_H)$, $h_9 = \epsilon\sigma_H + \gamma + \mu_H$, $h_{10} = \phi_3 + \vartheta\psi + \eta\gamma + \mu_H$ and $h_{11} = \sigma_v + \mu_v$.
$\widehat{G}_4(X,Z) < 0$, $\widehat{G}_5(X,Z) < 0$ and so the conditions in (3.7.3) are not met so E^0 may not be globally asymptotically stable when $R_{mm} < 1$. □

This implies that there is the possibility of future disease outbreaks when the conditions favouring the outbreaks are prevailing. During such outbreaks individuals tend to take protective measures against infection.

We thus investigate the dynamics of (3.2.6) by considering, in turns, two scenarios of maximum protection.

Case I: Maximum protection against malaria

Suppose individuals are fully protected against infective mosquito bites during a malaria outbreak, i.e $\alpha = 0$, then there would be no new malaria infections. In this case, the basic reproduction number of the model (3.2.6) would be given by $R_{mm} = R_{me}$ and the matrix $\widehat{G}(X, Z)$ would become

$$\widehat{G}(X,Z) = \begin{pmatrix} \widehat{G}_1(X,Z) \\ \widehat{G}_2(X,Z) \\ \widehat{G}_3(X,Z) \\ \widehat{G}_4(X,Z) \\ \widehat{G}_5(X,Z) \\ \widehat{G}_6(X,Z) \\ \widehat{G}_7(X,Z) \end{pmatrix} = \begin{pmatrix} \lambda_{me} E_1 \\ \theta \lambda_{me} I_1 \\ \beta(I_2 + E_{12} + \kappa I_c)(1 - \frac{S_H}{N_H}) \\ -\lambda_{me} E_1 \\ -\theta \lambda_{me} I_1 \\ 0 \\ 0 \end{pmatrix}.$$

Once again we note that $\widehat{G}_4(X, Z) < 0$, $\widehat{G}_5(X, Z) < 0$ and so the disease-free equilibrium is not globally stable. However, due to the fast dynamics of meningitis, with an incubation period ranging between hours and two days compared to about 14 days for malaria [53], we may overlook the term $\lambda_{me} E_1$. This is because malaria exposed individuals may not substantially influence the dynamics of the co-infection. Global stability can then be achieved if individuals already infected with malaria are protected

against infection with meningitis. For children, this protection could be realised in the form of childhood immunizations against meningitis.

Case II: Maximum protection against meningitis

If on the other hand individuals take fully protective measures against meningitis during an outbreak so that there are no new meningitis infections, then $\beta = 0$. Consequently only $\widehat{G}_4(X, Z) = -\rho\lambda_{ma} I_2 < 0$. To achieve global stability for the disease-free equilibrium of the co-infection we would need to protect meningitis infected individuals against malaria infection.

We thus observe that protection against only one infection may not yield much during an outbreak of one disease where the other is endemic. It would be helpful, especially for diseases with symptom overlap, to conduct laboratory tests to confirm or rule out co-infection with a view to initiating correct and timely prophylaxis.

3.8 Backward bifurcation and Local stability of the Endemic equilibrium

A bifurcation point is a point in parameter space where the number of equilibrium points, or their stability properties, or both, change. As noted earlier, an infectious disease does not invade a population of susceptibles when the basic reproduction number is less than unity. However, when the basic reproduction number is greater than unity, then the invasion

occurs. The occurrence of backward bifurcation then implies that the endemic equilibrium does exist even if the basic reproduction number is less than unity. The epidemiological implication of backward bifurcation is that reducing the basic reproduction number to less than unity is not sufficient to control an epidemic.

When the basic reproduction number is unity each infectious individual causes one new infection. From [17], therefore, whether a disease invades with the basic reproduction number equal to unity will be determined by whether the basic reproduction number increases or decreases as the disease increases along the centre manifold. When backward bifurcation occurs, the diseases-free equilibrium may not be globally asymptotically stable even if the basic reproduction number is less than unity and thus a stable endemic state co-exists with the diseases-free equilibrium. We employ the theorem by [8, 9] to investigate the possible occurrence of backward bifurcation.

For purpose of convenience, we reproduce the theorem below.

Theorem 3.8. *Castillo-Chavez and Song [9]*

Consider the following general system of ordinary differential equations with a parameter ϕ

$$\frac{dx}{dt} = f(x, \phi), \quad f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}^n \text{ and } f \in \mathbb{C}^2(\mathbb{R}^n \times \mathbb{R})$$

where 0 *is an equilibrium point of the system (i.e.*$f(0, \phi) \equiv 0$ *for all* ϕ*) and*

1. $A = D_x f(0,0) = (\frac{\partial f_i}{\partial x_j}(0,0))$ *is the linearization matrix of the system around the equilibrium point* 0 *with* ϕ *evaluated at* 0*;*

2. *Zero is a simple eigenvalue of A and all other eigenvalues of A have negative real parts;*

3. *Matrix A has a right eigenvector w and a left eigenvector v corresponding to the zero eigenvalue.*

Let f_k be the kth component of f and

$$a = \sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0),$$
$$b = \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \beta_m^*}(0,0)$$

then the local dynamics of the system around the equilibrium point 0 is totally determined by the signs of a and b. Particularly,

(i) $a > 0$, $b > 0$, when $\beta_m^* < 0$ with $|\beta_m^*| \ll 1$, $(0,0)$ is locally asymptotically stable and there exists a positive unstable equilibrium; when $0 < \beta_m^* \ll 1$, $(0,0)$ is unstable and there exists a negative and locally asymptotically stable equilibrium.

(ii) $a < 0$, $b < 0$, when $\beta_m^* < 0$ with $|\beta_m^*| \ll 1$, $(0,0)$ is unstable; when $0 < \beta_m^* \ll 1$, $(0,0)$ is asymptotically stable and there exists a positive unstable equilibrium.

(iii) $a > 0$, $b < 0$, when $\beta_m^* < 0$ with $|\beta_m^*| \ll 1$, $(0,0)$ is unstable, and there exists a negative and locally asymptotically stable equilibrium; when $0 < \beta_m^* \ll 1$, $(0,0)$ is stable and there exists a positive unstable equilibrium.

(iv) $a < 0$, $b > 0$, *when* β_m^* *changes from negative to positive,* $(0,0)$ *changes its stability from stable to unstable. Correspondingly a negative equilibrium becomes positive and locally asymptotically stable.*

Particularly, if $a > 0$ *and* $b > 0$, *then a backward bifurcation occurs at* $\beta_m^* = 0$.

To apply this theorem we make the following change of variables. Let $S_H = x_1, E_1 = x_2, I_1 = x_3, I_2 = x_4, E_{12} = x_5, I_{12} = x_6, S_v = x_7, E_v = x_8, I_v = x_9$ so that $N_H = x_1+x_2+x_3+x_4+x_5+x_6$ and $N_v = x_7+x_8+x_9$. The model (3.2.6) can be rewritten in the form $\frac{dX}{dt} = F(x)$ where $X = (x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8, x_9)$ and $F = (f_1, f_2, f_3, f_4, f_5, f_6, f_7, f_8, f_9)$ as

$$\begin{aligned}
\frac{dx_1}{dt} &= f_1 = \Lambda_H - \lambda_{ma}^c x_1 - \lambda_{me}^c x_1 + \phi_1 x_3 + \phi_2 x_4 + \phi_3 x_6 - \mu_H x_1,\\
\frac{dx_2}{dt} &= f_2 = \lambda_{ma}^c x_1 - \lambda_{me}^c x_2 - (\sigma_H + \mu_H) x_2,\\
\frac{dx_3}{dt} &= f_3 = \sigma_H x_2 - \theta\lambda_{me}^c x_3 - (\psi + \phi_1 + \mu_H) x_3,\\
\frac{dx_4}{dt} &= f_4 = \lambda_{me}^c x_1 - \rho\lambda_{ma}^c x_4 - (\phi_2 + \gamma + \mu_H) x_4,\\
\frac{dx_5}{dt} &= f_5 = \rho\lambda_{ma}^c x_4 + \lambda_{me}^c x_2 - (\epsilon\sigma_H + \gamma + \mu_H) x_5,\\
\frac{dx_6}{dt} &= f_6 = \epsilon\sigma_H x_5 + \theta\lambda_{me}^c x_3 - (\phi_3 + \vartheta\psi + \eta\gamma + \mu_H) x_6,\\
\frac{dx_7}{dt} &= f_7 = \Lambda_v - (\lambda_v^c + \mu_v) x_7,\\
\frac{dx_8}{dt} &= f_8 = \lambda_v^c x_7 - (\sigma_v + \mu_v) x_8,\\
\frac{dx_9}{dt} &= f_9 = \sigma_v x_8 - \mu_v x_9.
\end{aligned} \tag{3.8.1}$$

where $\lambda_{ma}^c = \frac{\alpha\beta_m x_9}{N_H^c}$, $\lambda_v^c = \frac{\alpha\beta_v(x_3+\delta x_6)}{N_H^c}$ and $\lambda_{me}^c = \frac{\beta(x_4+x_5+\kappa x_6)}{N_H^c}$.
The jacobian of (3.8.1) at the DFE E^o is given by

$$J(E^o)=\begin{pmatrix} -\mu_H & 0 & \phi_1 & -\beta+\phi_2 & -\beta & -\beta\kappa+\phi_3 & 0 & 0 & -\alpha\beta_m \\ 0 & -K_1 & 0 & 0 & 0 & 0 & 0 & 0 & \alpha a \\ 0 & \sigma_H & -K_2 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & K_3 & \beta & \beta\kappa & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -K_4 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \epsilon\sigma_H & -K_5 & 0 & 0 & 0 \\ 0 & 0 & -\alpha\beta_v p & 0 & 0 & -\alpha\delta\beta_v p & -\mu_v & 0 & 0 \\ 0 & 0 & 0 & \alpha\beta_v p & 0 & 0 & \alpha\delta\beta_v p & 0 & -K_6 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \sigma_v & -\mu_v \end{pmatrix}$$

where $K_1 = \sigma_H + \mu_H$, $K_2 = \psi + \phi_1 + \mu_H$, $K_3 = \beta - (\phi_2 + \gamma + \mu_H)$, $K_4 = \epsilon\sigma_H + \gamma + \mu_H$, $K_5 = \phi_3 + \vartheta\psi + \eta\gamma + \mu_H$, $K_6 = \sigma_v + \mu_v$ and $p = \frac{\mu_H \Lambda_v}{\Lambda_H \mu_v}$.

To analyze the dynamics of (3.8.1), we compute the eigenvectors of its jacobian at the DFE.

This jacobian has a right eigenvector denoted by

$W = (w_1, w_2, w_3, w_4, w_5, w_6, w_7, w_8, w_9)^T$ and is given by

$$\begin{aligned}
w_1 &= \frac{\phi_1 w_3 - \alpha\beta_m w_9}{\mu_H} \\
w_2 &= \frac{\alpha\beta_m w_9}{K_1} \\
w_3 &= \frac{\alpha\beta_m \sigma_H w_9}{K_1 K_2} \\
w_4 &= 0 \\
w_5 &= 0 \\
w_6 &= 0 \\
w_7 &= \frac{-\alpha\beta_v p w_3}{\mu_v} \\
w_8 &= \frac{\mu_v w_9}{\sigma_v} \\
w_9 &= w_9
\end{aligned}$$

The left eigenvector is defined by $V = (v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9)^T$

and is given by

$$\begin{aligned}
v_1 &= 0 \\
v_2 &= \frac{\sigma_H v_3}{K_1} \\
v_3 &= v_3 \\
v_4 &= \frac{-\alpha^2 \beta_m \beta_v p \sigma_H v_3}{K_1 K_3 K_6} \\
v_5 &= \frac{\beta v_4 + \epsilon \sigma_H v_6}{K_4} \\
v_6 &= \frac{\beta \kappa v_4 - \alpha \delta \beta_v p v_7}{K_5} \\
v_7 &= \frac{\alpha^2 \delta \beta_m \beta_v p \sigma_H v_3}{\mu_v K_1 K_6} \\
v_8 &= \frac{\alpha \beta_m \sigma_H v_3}{K_1 K_6} \\
v_9 &= 0
\end{aligned}$$

Consider the case when $R_{mm} = 1$ (assuming that $R_{me} < R_{ma}$) and choose $\beta_m = \beta_m^*$ as a bifurcation parameter. Solving for β_m from $R_{mm} = R_{ma} = 1$ gives

$$\beta_m = \beta_m^* = \frac{\Lambda_H \mu_v^2 (\sigma_H + \mu_H)(\sigma_v + \mu_v)(\psi + \phi_1 + \mu_H)}{\alpha^2 \beta_v \sigma_H \sigma_v \mu_H \Lambda_v} \tag{3.8.2}$$

We next evaluate the associated non-vanishing second order partial derivatives of f so as to obtain a and b. At the DFE, these are given by

$$\begin{aligned}
a &= \sum_{k,i,j=2}^{8} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0) \\
b &= \sum_{k,i=2}^{8} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \beta_m^*}(0,0)
\end{aligned}$$

since $v_1 = v_9 = 0$.

The functions that yield non-vanishing second order partial derivatives are

$$\begin{aligned} f_2 &= \frac{\alpha\beta_m x_9}{N_H^c}x_1 - \frac{\beta(x_4 + x_5 + \kappa x_6)}{N_H^c}x_2 - (\sigma_H + \mu_H)x_2 \\ &= \frac{\alpha\beta_m\mu_H x_9}{\Lambda_H}(N_H^c - x_2 - x_3 - x_4 - x_5 - x_6) - \frac{\beta\mu_H(x_4 + x_5 + \kappa x_6)}{\Lambda_H}x_2 - \\ &\quad (\sigma_H + \mu_H)x_2 \\ f_7 &= \Lambda_v - \frac{\alpha\beta_v(x_3 + \delta x_6)}{N_H^c}x_7 - \mu_v x_7 \\ &= \Lambda_v - \frac{\alpha\beta_v\mu_H(x_3 + \delta x_6)x_7}{\Lambda_H} - \mu_v x_7 \end{aligned}$$

These derivatives are

$$\frac{\partial^2 f_2}{\partial x_2 \partial x_9} = \frac{\partial^2 f_2}{\partial x_9 \partial x_2},\ \frac{\partial^2 f_2}{\partial x_3 \partial x_9} = \frac{\partial^2 f_2}{\partial x_9 \partial x_3},\ \text{and}\ \frac{\partial^2 f_7}{\partial x_3 \partial x_7} = \frac{\partial^2 f_7}{\partial x_7 \partial x_3}$$

where

$$\frac{\partial^2 f_2}{\partial x_2 \partial x_9} = -\frac{\alpha\beta_m\mu_H}{\Lambda_H},\ \frac{\partial^2 f_2}{\partial x_3 \partial x_9} = -\frac{\alpha\beta_m\mu_H}{\Lambda_H},\ \text{and}\ \frac{\partial^2 f_7}{\partial x_3 \partial x_7} = -\frac{\alpha\beta_v\mu_H}{\Lambda_H}$$

$$a = \frac{-2\mu_H}{\Lambda_H}(v_2 w_2 w_9 \alpha\beta_m + v_2 w_3 w_9 \alpha\beta_m + v_7 w_3 w_7 \alpha\beta_v) \tag{3.8.3}$$

For b, the derivatives are $\frac{\partial f_2}{\partial \beta_m^*} = \alpha x_9$, $\frac{\partial^2 f_2}{\partial \beta_m^* \partial x_9} = \alpha$. Thus

$$b = v_2 w_9 \alpha > 0. \tag{3.8.4}$$

Thus, provided (3.8.3) and (3.8.4) hold, we have established the following theorem

Theorem 3.9. *The unique endemic equilibrium of the model (3.2.6) is locally asymptotically stable when $R_{mm} < 1$ and unstable when $R_{mm} > 1$. Furthermore, by* ***Theorem 3.8****, item (i), the model would undergo*

backward bifurcation when $a > 0$. *This would be the case if* $|v_7 w_3 w_7 \alpha \beta_v| > (v_2 w_2 w_9 \alpha \beta_m + v_2 w_3 w_9 \alpha \beta_m)$.

$$|v_7 w_3 w_7 \alpha \beta_v| = \frac{\alpha^4 \beta_m^3 \beta_v \sigma_H^3 \delta p^2 w_9^2 v_3}{\mu_v^2 K_1^3 K_2^2 K_6} \tag{3.8.5}$$

From (3.8.5) it is evident that the occurrence of backward bifurcation is favoured by a high mosquito biting rate, high probabilities of transmission of malaria in both human and vectors and a high probability of survival till the infectious stage. The latter is proportional to the rate of progression from the exposed class to the infectious class. An individual with a low level of immunity would progress to the infectious class faster. Therefore efforts to control malaria infections among children must address issues affecting immunity such as breastfeeding and nutrition among other things.

3.9 Numerical simulations

To illustrate some of the theoretical results arrived at, simulations of the model (3.2.6) are done using Matlab. Since the study targeted children under the age of five years in Kenya, some of the parameters values used in the simulation are specific to this age while others are allowed to vary within realistic limits. Table 1 below summarizes the parameter values used in the simulations.

Parameter	symbol	Value	Source
Recruitment rate of humans	Λ_H	$9.6274 \times 10^{-5}\,\text{day}^{-1}$	[11]
Recruitment rate of mosquitoes	Λ_v	$0.071\,\text{day}^{-1}$	[21]
Natural death rate of children	μ_H	$2.537 \times 10^{-5}\,\text{day}^{-1}$	[11]
Natural death rate of mosquitoes	μ_v	$0.1429\,\text{day}^{-1}$	[12]
Malaria-induced death rate	ψ	$4.49312 \times 10^{-4}\,\text{day}^{-1}$	[19]
Meningitis-induced death rate	γ	$6.8445 \times 10^{-4}\,\text{day}^{-1}$	[20]
Transmission probability for malaria in humans	β_m	$0.8333\,\text{day}^{-1}$	[12]
Transmission probability for malaria in mosquitoes	β_v	$Variable\,\text{day}^{-1}$	Variable
Contact rate for meningitis infection	β	$Variable\,\text{day}^{-1}$	Variable
Biting rate of mosquitoes	α	$(0.125, 1)\,\text{day}^{-1}$	[22]
Modification parameters	δ, κ	$1.0005, 1.05$	Assumed
Modification parameters	ϵ, ρ, θ	$1.0025, 1.0025, 0.80$	Assumed
Modification parameters	η, ϑ	$1.0005, 1.00025$	Assumed
Recovery rate from malaria	ϕ_1	0.00556	[16]
Recovery rate from meningitis	ϕ_2	0.00065	Estimate
Recovery rate from co-infection	ϕ_3	0.00075	Estimate
Rate at which humans exposed to malaria develop symptoms	σ_H	0.08333	[12]
Rate at which vectors exposed to malaria develop symptoms	σ_v	0.1	[12]

Table1: Parameter Values

3.10 Discussion

In the absence of good nutrition, sanitation and affordable health care, preventable infectious diseases such as malaria and meningitis continue to thrive. These diseases are not only a threat to child survival but also the associated economic burden is a major hindrance to poverty reduction. The applicability or importance of an epidemiological model lies in its ability to provide biologically meaningful interpretations and the possible disease control measures. Possible disease control strategies would be to reduce or guard against incidences of co-infection by keeping the prevalence of each disease at low levels or complete eradication of either disease. This could be achieved through prompt recognition of symptoms, correct diagnosis, effective treatment (and quarantine where possible) and prevention as we illustrate here.

From $R_{me} = \frac{\beta}{\phi_2+\gamma+\mu_H}$, we could rightly claim that R_{me} is directly proportional to the mean time spent in the infective class given by $\frac{1}{\phi_2+\gamma+\mu_H}$. Clearly in the presence of prompt and effective treatment of meningitis infectives $\phi_2 \to \infty$ as $\gamma \to 0$. The implication of this is that $R_{me} \to 0$ and thus no new meningitis infections, since$\frac{1}{\phi_2+\gamma+\mu_H} \to 0$. Unfortunately, the treatment costs for meningitis infection are relatively higher as observed in the study conducted in Kenya by [2]. Besides, recent major advances in vaccine developments may not benefit the poor due to high costs and poor

3.9.1 The relationship between the reproduction number and disease progression

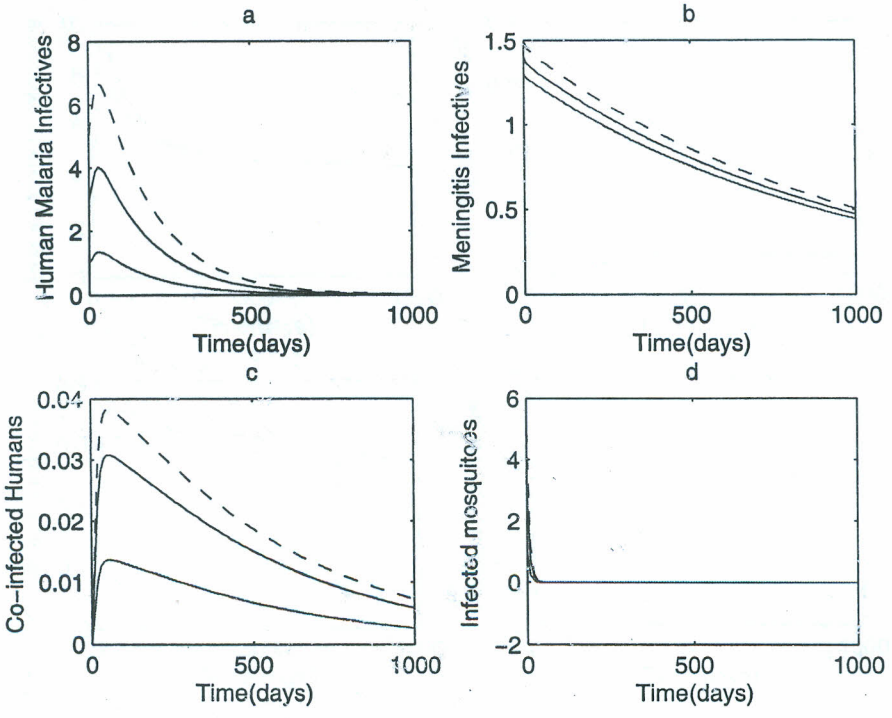

Figure 3.9.1: Simulation of model (3.2.6), with $\alpha = 0.125, \beta_v = 0.125$ and $\beta = 0.0003$, giving $R_{ma} = 0.318905, R_{me} = 0.22062, R_{mm} = 0.318905$, with varying initial conditions.

Whenever the respective reproduction numbers are less than unity, the infections reduce in time (Fig.3.9.1). However when the reproduction numbers are greater than unity the infections become endemic (Fig.3.9.2).

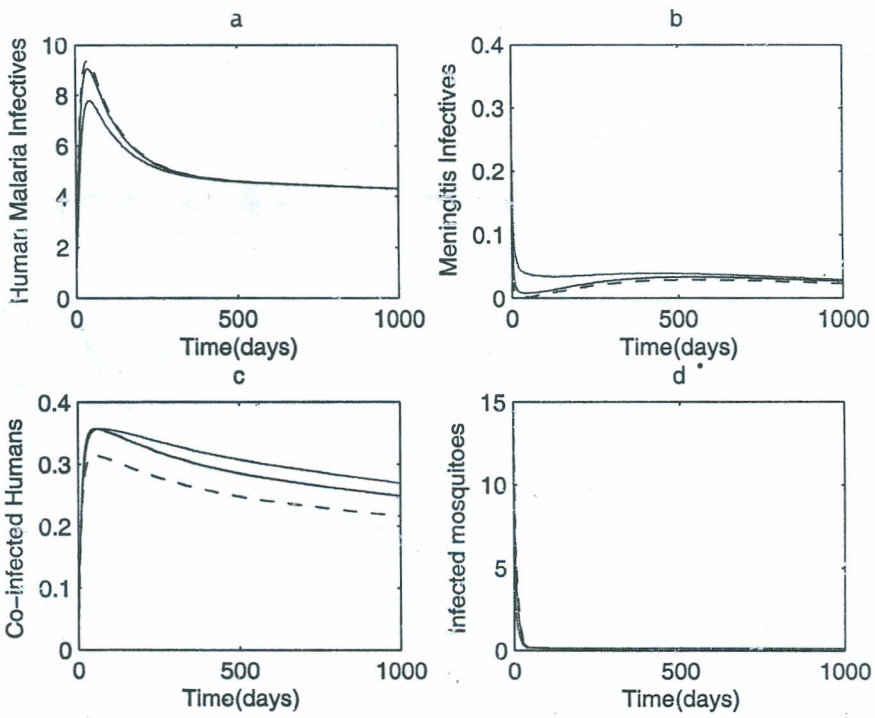

Figure 3.9.2: Simulation of model (3.2.6), with $\alpha = 0.6, \beta_v = 0.6$ and $\beta = 0.0015$, giving $R_{ma} = 3.35369, R_{me} = 1.1031, R_{mm} = 3.35369$, with varying initial conditions.

3.9.2 The effect of meningitis infection on malaria

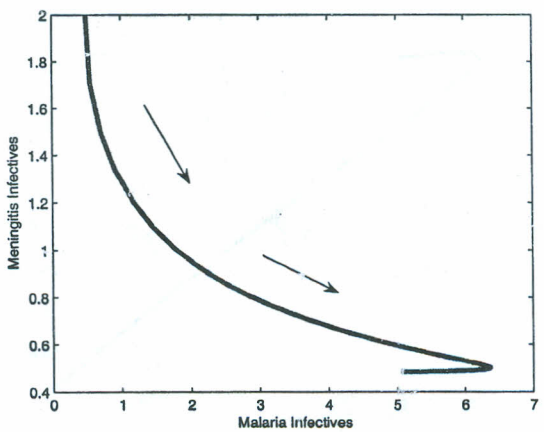

Figure 3.9.3: The effect of meningitis infection on malaria

This graph shows that whenever the number of meningitis infection cases reduce, the individuals' mobility increase and can thus be infected with malaria. Consequently the malaria infection cases go up.

3.9.3 The effect of malaria on co-infection

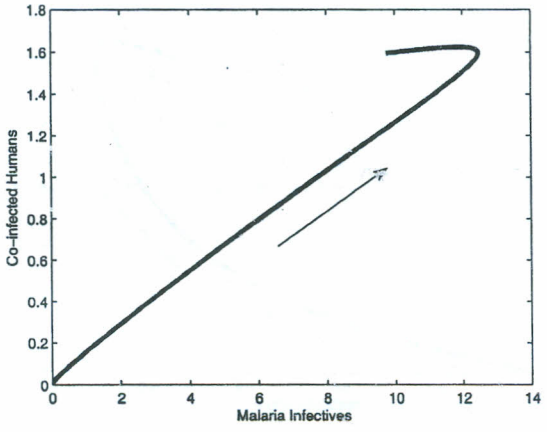

Figure 3.9.4: The effect of malaria on co-infection

When infection with malaria is not sever, the infected individual is mobile and may come into contact with one infected with meningitis and thus increase the number of co-infection cases as shown in Fig. 3.9.4.

3.9.4 The effect of meningitis on co-infection

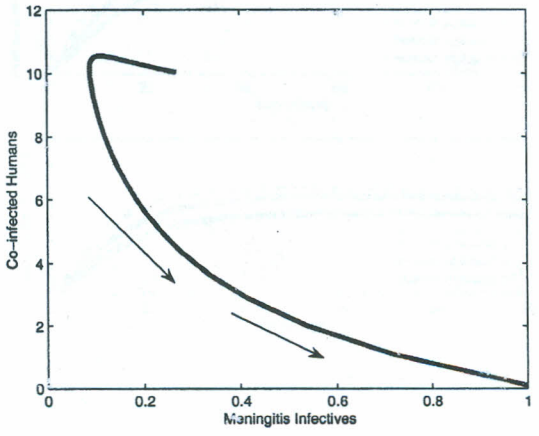

Figure 3.9.5: The effect of meningitis on co-infection

Infection with meningitis usually reduces the mobility of those infected, for instance due to hospitalization. These individuals' likelihood of infection with malaria is thus reduced and consequently the number of co-infection cases reduce.

3.9.5 The effect of varying mosquito biting rate, α

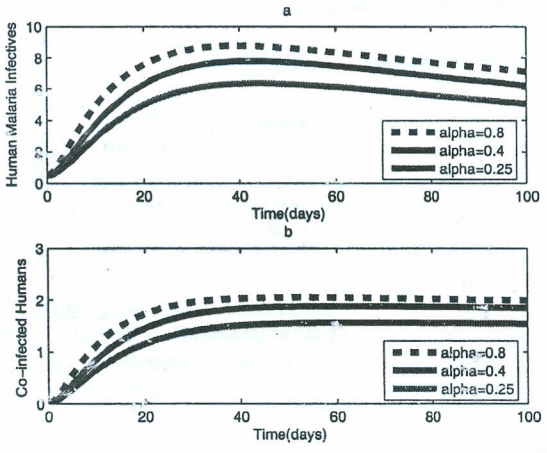

Figure 3.9.6: The effect of varying the mosquito biting rate, α

We investigate the effect of varying the mosquito biting rate on the classes I_1, and I_c. From Fig.3.9.6(a, b), It is evident that a higher biting rate results into increased malaria infections. Furthermore co-infection cases also rise supporting the fact that malaria infection causes immunosuppression. Thus a reduction of the biting rate through such means as use of insecticide treated nets and indoor residual spraying would reduce infections in humans.

3.9.6 The effect of varying the contact rate, β

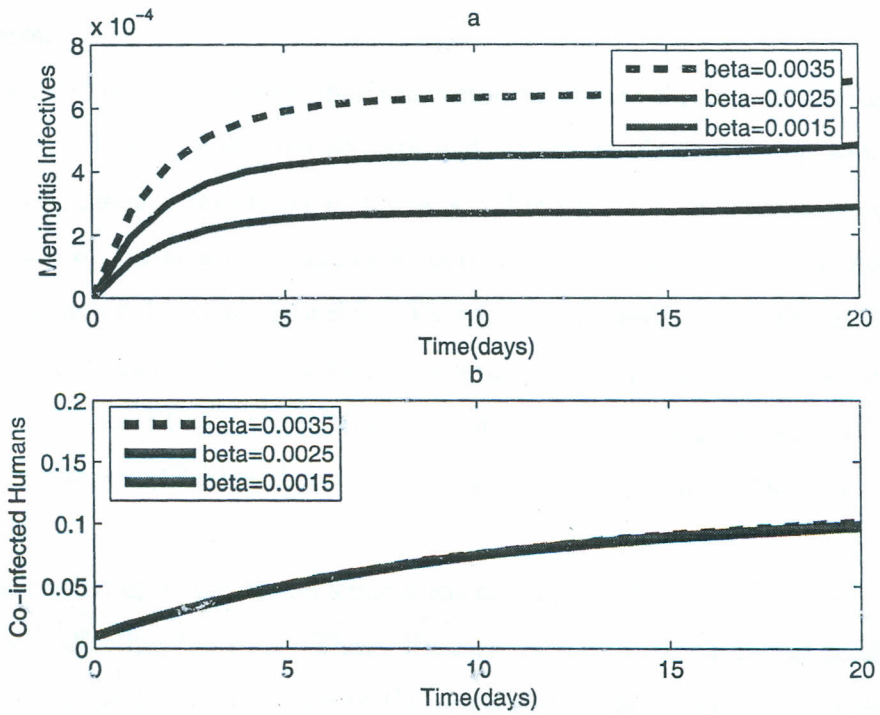

Figure 3.9.7: The effect of varying the contact rate, β

Fig.3.9.7 (a) shows that the higher the contact rate the higher the number of meningitis cases. However, Fig.3.9.7 (b) shows that there is no appreciable increase in the number of co-infection cases due to a higher contact rate. This is probably due to the fact that meningitis attack is usually sever leading to hospitalization. This reduces the chances of malaria infection.

infrastructure for their delivery. This translates to increased susceptibility to meningitis infection. Since bacterial meningitis is highly infectious, the situation is compounded by the fact that in low socio-economic settings people reside in crowded places such as slums thus increasing the contact rates.

As noted earlier, a reduction of the vector biting rate through such means as use of insecticide treated nets and indoor residual spraying would reduce malaria infections in humans. However, a combination of optimal control strategies including both preventive and treatment measures would be most desirable. Therefore it is needful to scale up the cost-effective interventions used in malaria-endemic areas such insecticide-treated nets (ITNs), intermittent preventive treatment in pregnancy (IPTp) and infancy (IPTi) and artemisinin-based combination therapy (ACT) [64].

People living in malaria-endemic areas are exposed to other diseases typically affecting the poor. These diseases not only take advantage of the compromised immunity due to the prolonged malaria exposure, coupled with limited and untimely chemotherapy but also present with malaria-like symptoms. This means that for an acute febrile patient that is infected with malaria, laboratory diagnosis for infections such as meningitis, pneumonia and diarrhea should be done so as to rule out or confirm co-infection. Failure to diagnose other co-infections means a delay in the initiation of their therapy and possibly ensuing sever complications to the patient [24]. As noted above malaria is endemic in low socio-economic settings. We also observe that in such settings the health facilities are usually few and inadequate in terms of equipment and personnel. This

could possibly lead to non performance of comprehensive laboratory tests. Consequently, most patients with fever resort to buying cheap and ineffective over-the-counter drugs, thus fueling the spread of disease.

Chapter 4

Modelling the dynamics of Malaria-Pneumonia co-infection among children

A study carried out in Uganda showed that 27 (19%) out of the 139 children enrolled in an urban hospital were co-infected with both malaria and pneumonia [26]. Another study carried out in Uganda also showed that out of 2,944 malaria cases in under-fives at 14 health centres, 37% had pneumonia [30]. The most common causes of deaths in Kenyan children after the neonatal period are pneumonia, diarrhoea, measles, malaria, and malnutrition or a combination of these conditions [40]. In this chapter, beginning with an overview of pneumonia, we explore the co-dynamics of malaria and pneumonia by formulating and analysing a co-infection model.

4.1 Overview of Pneumonia

Pneumonia is an air-bone respiratory disease caused by infection inside the lungs. It may be contracted by breathing in droplets containing disease causing organisms, released into air when an infected person coughs or sneezes. Pneumonia may also be contracted when bacteria or viruses that are normally present in the mouth, throat, or nose inadvertently enter the lung. The most common cause of bacterial pneumonia is *S. pneumoniae*. The symptoms of pneumonia include: cough, difficult breathing, fever, muscle aches, loss of appetite and lethargy. The risk factors for pneumonia include smoking and second-hand smoke, alcohol and drug abuse, crowded living conditions and certain medical conditions. These include conditions that interfere with the gag reflex, weaken the immune system and organ transplant. Children have a higher risk of developing pneumonia if they have weakened immune systems.

Statistics show that of all children outpatients suffering from respiratory complications, 25 percent of the cases are confirmed to be pneumonia. The Kenyan case is no different the percentage being 18. Pneumonia mortality in children is very high especially in the developing world, with an estimate of 5,500 deaths per day [58, 64].

4.2 Model Description and Formulation

The total human population size N_H at any time is subdivided into the classes: susceptible S_H, infectious with malaria I_M, infectious with pneu-

monia I_P and symptomatically infectious with malaria and pneumonia I_{MP} . The human population is not assumed to be constant since birth, migration, emigration and death occur. However we assume that the probability of survival till the infectious state for individuals exposed to malaria as well as those exposed to pneumonia is unity and therefore exclude the class of individuals exposed to these diseases. The constant per capita recruitment rate into the susceptible human population is Λ_H. The vector population N_V is subdivided into the susceptible S_V and infectious I_V classes. The per capita recruitment rate into the susceptible vector population is Λ_V and is assumed to be density dependent. Let μ_H and μ_V be per capita natural death rates of the human and mosquito populations respectively.

Due to malaria related immunodeficiency we include the modification parameter ϑ to account for the increased susceptibility to infection with pneumonia. The human population suffer disease induced mortality at the rate σ. The expected decrease in contact due to ill health as a result of pneumonia disease is accounted for by the parameter $0 < \varepsilon < 1$. Movement back to the susceptible class upon recovery from the class I_{MP} is at the rate ϕ. Let the rate of recovery from I_P to S_H be τ, while that from I_M to S_H be π.

The rates of infection of susceptible humans with malaria and pneumonia are λ_M and λ_P respectively while that of susceptible vectors is λ_V. Define α as the number of bites per human per mosquito, β_m as the transmission probability of malaria in humans, β_v as the probability that

a mosquito becomes infected with malaria from any infected human, β_p as the probability that one individual is being infected with pneumonia by one infectious individual and c is the per capita contact rate. This yields the following forces of infection

$$\lambda_M = \frac{\alpha\beta_m I_V}{N_H} \tag{4.2.1}$$

$$\lambda_v = \frac{\alpha\beta_v(I_M + \delta I_{MP})}{N_H} \tag{4.2.2}$$

$$\lambda_P = \frac{\beta_p c(I_P + \kappa I_{MP})}{N_H} \tag{4.2.3}$$

where δ and κ are modification parameters accounting for the relative infectiousness of the co-infected individual as compared to their counterparts. From the above definitions and variables we have the following model with nonnegative initial conditions

$$\begin{aligned}
\frac{dS_H}{dt} &= \Lambda_H - \lambda_M S_H - \lambda_P S_H - \mu_H S_H + \pi I_M + \tau I_P + \phi I_{MP} \\
\frac{dI_M}{dt} &= \lambda_M S_H - \vartheta\lambda_P I_M - \sigma_M I_M - \pi I_M - \mu_H I_M \\
\frac{dI_P}{dt} &= \lambda_P S_H - \varepsilon\lambda_M I_P - \sigma_P I_P - \tau I_P - \mu_H I_P \\
\frac{dI_{MP}}{dt} &= \varepsilon\lambda_M I_P + \vartheta\lambda_P I_M - (\sigma_M + \sigma_P + \sigma_{MP} + \phi + \mu_H) I_{MP} \\
\frac{dS_V}{dt} &= \Lambda_V N_V - \lambda_V S_V - \mu_V S_V \\
\frac{dI_V}{dt} &= \lambda_V S_V - \mu_V I_V
\end{aligned} \tag{4.2.4}$$

Since $N_H = S_H + I_M + I_P + I_{MP}$ and $N_V = S_V + I_V$, we have

$$\begin{aligned} \frac{dN_H}{dt} &= \Lambda_H - \mu_H N_H - \sigma_M I_M - \sigma_P I_P - (\sigma_M + \sigma_P + \sigma_{MP}) I_{MP} \\ \frac{dN_V}{dt} &= (\Lambda_V - \mu_V) N_V \end{aligned} \tag{4.2.5}$$

From (4.2.5) we note that in the absence of infection $\frac{dN_H}{dt} = \Lambda_H - \mu_H N_H$, so that N_H would approach the carrying capacity $\frac{\Lambda_H}{\mu_H}$. The vector population, on the other hand, would grow exponentially for $\Lambda_V > \mu_V$, be constant for $\Lambda_V = \mu_V$ and decline for $\Lambda_V < \mu_V$.

Model (4.2.4) describes the human and mosquito populations and therefore it can be shown that the associated state variables are non-negative for all time $t \geq 0$ and that the solutions of the model (4.2.4) with positive initial data remains positive for all time $t \geq 0$ and are uniformly-bounded. We assume the associated parameters as non-negative for all time $t \geq 0$. Thus (4.2.4) is mathematically well posed and its dynamics can be considered in a proper subset Ω.

4.3 Equilibria Points of the Model

The steady states of the model (4.2.4) are investigated, conveniently, by first reducing the number of the variables. This is achieved by normalizing each class of the human and vector populations. Define $s_h = \frac{S_H}{N_H}$, $i_m = \frac{I_M}{N_H}$, $i_p = \frac{I_P}{N_H}$, $i_{mp} = \frac{I_{MP}}{N_H}$, $s_v = \frac{S_V}{N_V}$ and $i_v = \frac{I_V}{N_V}$ as the proportions of the classes $S_H, I_M, I_P, I_{MP}, S_V$ and I_V respectively. Let $\rho = \frac{N_V}{N_H}$, which is

regarded as a constant since a mosquito takes a constant number of blood meals per unit time independent of the population density of the human host[60]. Then we have the normalised system given by the equations below:

$$\begin{aligned}
\frac{ds_h}{dt} &= \frac{\Lambda_H}{N_H} - [\frac{\Lambda_H}{N_H} - \sigma_M i_m - \sigma_P i_p - (\sigma_M + \sigma_P + \sigma_{MP})i_{mp} \\
&\quad +\alpha\beta_m\rho i_v + \beta_p c(i_p + \kappa i_{mp})]s_h + \pi i_m + \tau i_p + \phi i_{mp} \\
\frac{di_m}{dt} &= \alpha\beta_m\rho i_v s_h - [\frac{\Lambda_H}{N_H} + \vartheta\beta_p c(i_p + \kappa i_{mp}) + (\sigma_M + \pi) - \sigma_P i_p \\
&\quad -\sigma_M i_m - (\sigma_M + \sigma_P + \sigma_{MP})i_{mp}]i_m \\
\frac{di_p}{dt} &= \beta_p c(i_p + \kappa i_{mp})s_h - \varepsilon\alpha\beta_m\rho i_v i_p - [\frac{\Lambda_H}{N_H} + (\sigma_P + \tau) \\
&\quad -\sigma_M i_m - \sigma_P i_p - (\sigma_M + \sigma_P + \sigma_{MP})i_{mp}]i_p \\
\frac{di_{mp}}{dt} &= \varepsilon\alpha\beta_m\rho i_v i_p + \vartheta\beta_p c(i_p + \kappa i_{mp})i_m - [\frac{\Lambda_H}{N_H} + (\sigma_M + \sigma_P + \sigma_{MP} + \phi) \\
&\quad -\sigma_M i_m - \sigma_P i_p - (\sigma_M + \sigma_P + \sigma_{MP})i_{mp}]i_{mp} \\
\frac{ds_v}{dt} &= \Lambda_V(1 - s_v) - \alpha\beta_v(i_m + \delta i_{mp})s_v \qquad (4.3.1) \\
\frac{di_v}{dt} &= \alpha\beta_v(i_m + \delta i_{mp})s_v - \Lambda_V i_v
\end{aligned}$$

and

$$\frac{dN_H}{dt} = \{\frac{\Lambda_H}{N_H} - \mu_H - \sigma_M i_m - \sigma_P i_p - (\sigma_M + \sigma_P + \sigma_{MP})i_{mp}\}N_H \qquad (4.3.2)$$

We may reduce (4.3.1) to a four dimensional system by eliminating s_h and s_v, since $s_h = 1 - i_m - i_p - i_{mp}$ and $s_v = 1 - i_v$. This yields

$$\begin{aligned}
\frac{di_m}{dt} &= \alpha\beta_m\rho i_v s_h - [\frac{\Lambda_H}{N_H} + \vartheta\beta_p c(i_p + \kappa i_{mp}) + (\sigma_M + \pi) - \sigma_P i_p \\
&\quad -\sigma_M i_m - (\sigma_M + \sigma_P + \sigma_{MP})i_{mp}]i_m \\
\frac{di_p}{dt} &= \beta_p c(i_p + \kappa i_{mp})s_h - \varepsilon\alpha\beta_m\rho i_v i_p - [\frac{\Lambda_H}{N_H} + (\sigma_P + \tau) \\
&\quad -\sigma_M i_m - \sigma_P i_p - (\sigma_M + \sigma_P + \sigma_{MP})i_{mp}]i_p \\
\frac{di_{mp}}{dt} &= \varepsilon\alpha\beta_m\rho i_v i_p + \vartheta\beta_p c(i_p + \kappa i_{mp})i_m - [\frac{\Lambda_H}{N_H} + (\sigma_M + \sigma_P + \sigma_{MP} + \phi) \\
&\quad -\sigma_M i_m - \sigma_P i_p - (\sigma_M + \sigma_P + \sigma_{MP})i_{mp}]i_{mp} \\
\frac{di_v}{dt} &= \alpha\beta_v(i_m + \tilde{\sigma} i_{mp})s_v - \Lambda_V i_v \qquad (4.3.3)
\end{aligned}$$

with the feasible region $\Omega = \{(i_m, i_p, i_{mp}, i_v) \in \mathbf{R}^4_+ : i_m \geq 0, i_p \geq 0, i_{mp} \geq 0, i_m + i_p + i_{mp} \leq 1, 0 \leq i_v \leq 1\}$

The equilibrium points of (4.3.2) and (4.3.3) are obtained by equating the derivatives to zero and solving for the variables. Thus solving (4.3.2) at an equilibrium point yields

$$\frac{\Lambda_H}{N_H} = \mu_H + \sigma_M i_m + \sigma_P i_p + (\sigma_M + \sigma_P + \sigma_{MP})i_{mp} \qquad (4.3.4)$$

Upon substituting (4.3.4) into (4.3.3) after setting the derivatives to zero,

we obtain

$$\begin{aligned}
0 &= \alpha\beta_m\rho i_v(1-i_m-i_p-i_{mp})-[\vartheta\beta_p c(i_p+\kappa i_{mp})+\sigma_M+\pi+\mu_H]i_m \\
0 &= \beta_p c(i_p+\kappa i_{mp})(1-i_m-i_p-i_{mp})-\varepsilon\alpha\beta_m\rho i_v i_p-[\sigma_P+\tau+\mu_H]i_p \\
0 &= \varepsilon\alpha\beta_m\rho i_v i_p+\vartheta\beta_p c(i_p+\kappa i_{mp})i_m-[\sigma_M+\sigma_P+\sigma_{MP}+\phi+\mu_H]i_{mp} \\
0 &= \alpha\beta_v(i_m+\delta i_{mp})(1-i_v)-\Lambda_V i_v \qquad (4.3.5)
\end{aligned}$$

Solving the last equation of (4.3.5), we have

$$i_v^* = \frac{\alpha\beta_v(i_m^*+\delta i_{mp}^*)}{\alpha\beta_v(i_m^*+\delta i_{mp}^*)+\Lambda_V} \qquad (4.3.6)$$

Suppose $i_p = i_{mp} = 0$, so that only malaria is present in the population. Then, substituting (4.3.6) into the first equation in (4.3.5) yields

$$0 = -\{\alpha^2\beta_m\beta_v\rho+\alpha\beta_v(\sigma_M+\pi+\mu_H)\}(i_m^*)^2+\{\alpha^2\beta_m\beta_v\rho-\Lambda_V(\sigma_M+\pi+\mu_H)\}i_m^* \qquad (4.3.7)$$

Solving for i_m^* from (4.3.7) gives either $i_m^* = 0$, which corresponds to a disease-free equilibrium or

$$i_m^* = \frac{\alpha^2\beta_m\beta_v\rho-\Lambda_V(\sigma_M+\pi+\mu_H)}{\alpha^2\beta_m\beta_v\rho+\alpha\beta_v(\sigma_M+\pi+\mu_H)} \qquad (4.3.8)$$

From (4.2.5), it is evident that at a stationary point $\Lambda_V = \mu_V$, which upon substitution in (4.3.8) yields

$$i_m^* = \frac{(R_m^2-1)\mu_v}{R_m^2+\alpha\beta_v} \qquad (4.3.9)$$

where

$$R_m = \sqrt{\frac{\alpha^2 \beta_m \beta_v \mu_H \Lambda_v}{\Lambda_H \mu_v^2 (\sigma_M + \pi + \mu_H)}}$$

is the basic reproduction number for malaria.
We state this result in the following lemma

Lemma 4.1. *An endemic equilibrium $i_m^* > 0$, for malaria-only case exists provided $R_m > 1$*

Suppose $i_m = i_{mp} = 0$, so that only pneumonia is present in the population, then the second equation in (4.3.5) becomes

$$\{\beta_p c i_p^* - \beta_p c + (\sigma_P + \tau + \mu_H)\} i_p^* = 0$$

from which either $i_p^* = 0$, which corresponds to the disease free equilibrium or

$$i_p^* = 1 - \frac{1}{R_p} \tag{4.3.10}$$

where

$$R_p = \frac{c\beta_p}{\tau + \sigma_P + \mu_H}$$

is the basic reproduction number for pneumonia. We state this result in the following lemma

Lemma 4.2. *An endemic equilibrium $i_p^* > 0$, for pneumonia-only case exists provided $R_p > 1$*

Solving for i^*_{mp} from the third equation in (4.3.5) yields

$$i^*_{mp} = \frac{\varepsilon\alpha\beta_m\rho i^*_v i^*_p + \vartheta\beta_p c i^*_p i^*_m}{(\sigma_M + \sigma_P + \sigma_{MP} + \phi + \mu_H) - \vartheta\kappa\beta_p c i^*_m} \tag{4.3.11}$$

Since the state variables are taken as greater or equal to zero for $t \geq 0$, from (4.3.10) $i^*_{mp} = 0$ if and only if $i^*_v = i^*_m = i^*_p = 0$, which would be a disease-free equilibrium. However, $i^*_{mp} > 0$ if $i^*_v > 0, i^*_m > 0, i^*_p > 0$, which would be an endemic equilibrium. Thus

Lemma 4.3. *An endemic equilibrium $i^*_{mp} > 0$ exists provided $R_{mp} > 1$*

where R_{mp} is the number of secondary malaria (or pneumonia) infections due to a single malaria (or a single pneumonia-infective) individual. The basic reproduction number R_{mp} is given by

$$R_{mp} = \max\{R_m, R_p\}. \tag{4.3.12}$$

4.4 Local Stability of the disease-free equilibrium

Theorem 4.4. *The disease-free equilibrium of (4.3.3) is locally stable provided $R_m < 1$ and $R_p < 1$. This implies $R_{mp} < 1$ since $R_{mp} = max\{R_m, R_p\}$.*

Proof. The local stability of the disease-free equilibrium of (4.3.3) can be

studied from its Jacobian at the disease-free equilibrium. The Jacobian of (4.3.3) at the disease-free equilibrium, denoted $J(\mathcal{E}^0)$, is given by

$$J(\mathcal{E}^0) = \begin{pmatrix} -K_1 & 0 & 0 & \alpha\beta_m\rho s_h \\ 0 & K_2 & \kappa\beta_p c s_h & 0 \\ 0 & 0 & -K_3 & 0 \\ \alpha\beta_v s_v & 0 & \delta\alpha\beta_v s_v & -\mu_v \end{pmatrix} \tag{4.4.1}$$

where $K_1 = (\frac{\Lambda_H}{N_H} + \sigma_M + \pi)$, $K_2 = \beta_p c s_h - (\sigma_P + \tau + \frac{\Lambda_H}{N_H})$ and $K_3 = (\sigma_M + \sigma_P + \sigma_{MP} + \phi + \frac{\Lambda_H}{N_H})$ This Jacobian has a distinct negative eigenvalue given by $-(\sigma_M + \sigma_P + \sigma_{MP} + \phi + \frac{\Lambda_H}{N_H})$. To obtain the other eigenvalues we reduce (4.4.1) to the 3×3 block matrix A defined by

$$A = \begin{pmatrix} -K_1 & 0 & \alpha\beta_m\rho s_h \\ 0 & K_2 & 0 \\ \alpha\beta_v s_v & 0 & -\mu_v \end{pmatrix} \tag{4.4.2}$$

The matrix A has an eigenvalue given by $K_2 = \beta_p c s_h - (\sigma_P + \tau + \frac{\Lambda_H}{N_H})$. From the condition of boundedness of solutions i.e. $0 \leq N_H \leq \frac{\Lambda_H}{\mu_H}$, K_2 may be expressed as $R_p s_h - 1$. This eigenvalue is negative if and only if $R_p < 1$. The local stability is studied by examining the trace and determinant of of the 2×2 block matrix B defined by

$$B = \begin{pmatrix} -(\sigma_M + \pi + \mu_H) & \alpha\beta_m\rho s_h \\ \alpha\beta_v s_v & -\mu_v \end{pmatrix} \tag{4.4.3}$$

Clearly the trace of B is negative and its determinant is given by $detB = 1 - R_m^2 s_h s_v$. This determinant is positive if and only if $R_m < 1$. This ends the proof. □

4.5 Global Stability of the disease-free equilibrium

If we consider malaria as having a higher steady state i.e $R_{mp} = R_m$, then

Theorem 4.5. *The disease-free equilibrium of (4.3.3) is globally stable provided* $R_m \leq 1$.

Proof. We may study the global stability of (4.3.3) by using the following LaSalle-Lyapunov function. Consider the function defined by

$$L(i_m, i_v) = \alpha\beta_v i_m + (\sigma_M + \pi + \mu_H) i_v. \tag{4.5.1}$$

The time derivative of (4.5.1) along the solutions of (4.3.3) is given by

$$\begin{aligned}
L' &= \alpha\beta_v \frac{di_m}{dt} + (\sigma_M + \pi + \mu_H)\frac{di_v}{dt} \\
&= \alpha\beta_v\{\alpha\beta_m\rho i_v s_h - [\frac{\Lambda_H}{N_H} + \vartheta\beta_p c(i_p + \kappa i_{mp}) + (\sigma_M + \pi) - \sigma_P i_p \\
&\quad -\sigma_M i_m - (\sigma_M + \sigma_P + \tau_{MP})i_{mp}]i_m\} \\
&\quad +(\sigma_M + \pi + \mu_H)[\alpha\beta_v(i_m + \delta i_{mp})s_v - \Lambda_V i_v] \\
&\leq \alpha^2\beta_v\beta_m\rho i_v s_h - (\sigma_M + \pi + \mu_H)\mu_v i_v \\
&\leq \frac{\alpha^2\beta_v\beta_m\mu_H\Lambda_v}{\mu_v\Lambda_H} i_v s_h - (\sigma_M + \pi + \mu_H)\mu_v i_v \\
&\leq (\sigma_M + \pi + \mu_H)\mu_v\{\frac{\alpha^2\beta_v\beta_m\mu_H\Lambda_v}{\mu_v^2\Lambda_H(\sigma_M + \pi + \mu_H)} s_h - 1\}i_v \\
&\leq (\sigma_M + \pi + \mu_H)\mu_v\{R_m^2 s_h - 1\}i_v \qquad (4.5.2)
\end{aligned}$$

Thus $R_m \leq 1$ ensures that $L' \leq 0\ \forall\ i_m, i_v \geq 0$. Furthermore $L' = 0$ whenever $R_m = 1$ and/or $i_v = 0$. LaSalle's invariance principle then implies that the disease-free equilibrium is globally stable in the interior of Ω. This completes the proof of the theorem. □

If we consider pneumonia as having a higher steady state i.e $R_{mp} = R_p$, then

Theorem 4.6. *The disease-free equilibrium of (4.3.3) is globally stable provided* $R_p \leq 1$.

Proof. Consider the Lyapunov candidate

$$L(i_p) = (\tau + \sigma_P + \mu_H)i_p. \qquad (4.5.3)$$

The time derivative of (4.5.4) along the solutions of (4.3.3) is given by

$$\begin{aligned} L' &= (\tau+\sigma_P+\mu_H)\frac{di_p}{dt} \\ &= (\tau+\sigma_P+\mu_H)\{\beta_p c(i_p+\kappa i_{mp})s_h - \varepsilon\alpha\beta_m\rho i_v i_p - [\frac{\Lambda_H}{N_H}+(\sigma_P+\tau) \\ &\quad -\sigma_M i_m - \sigma_P i_p - (\sigma_M+\sigma_P+\sigma_{MP})i_{mp}]i_p\} \\ &\leq (\tau+\sigma_P+\mu_H)[\beta_p c s_h - (\tau+\sigma_P+\mu_H)]i_p \\ &\leq (\tau+\sigma_P+\mu_H)[R_p s_h - 1]i_p \end{aligned} \tag{4.5.4}$$

Thus $R_p \leq 1$ ensures that $L' \leq 0 \; \forall \; i_p \geq 0$. Furthermore $L' = 0$ whenever $R_p = 1$ and/or $i_p = 0$. LaSalle's invariance principle then implies that the disease-free equilibrium is globally stable in the interior of Ω. This completes the proof of the theorem. □

4.6 Effect of Treatment on the dynamics of the co-infection

Intervention efforts employed in malaria-endemic countries include insecticide-treated nets (ITNs), intermittent preventive treatment in pregnancy (IPTp) and infancy (IPTi) and artemisinin-based combination therapy (ACT) [64]. However, the treatment of malaria in poor resource settings, especially in the developing world, still remains a challenge. This is because of the high cost, poor disease surveillance, lack of effective diagnostic equipment, the quality of antimalarial drugs and parasite-drug resistance, poor supply and distribution chain among other reasons. There are global efforts aimed at reducing malaria mortality and burden. For example, the

United States government's six-year comprehensive effort, with an investment of 63 billion US dollars, to reduce the burden of disease and promote healthy communities and families around the world called the Global Health Initiative (GHI), announced in 2009.

To investigate the potential impact of treatment on disease progression, we carry out sensitivity analysis of the reproduction numbers.
Since children under the age of five years have not developed sufficient immunity, we consider the malaria recovery rate π as a function of treatment. Differentiating R_m partially with respect to π yields

$$\frac{\pi}{R_m}\frac{\partial R_m}{\partial \pi} = -\frac{\pi}{2(\sigma_M + \pi + \mu_H)} \tag{4.6.1}$$

The negative sign in (4.6.1) indicates that there is an expected decline in the rate of new malaria infections when malaria treatment is scaled up.
Similarly, if the pneumonia recovery rate τ is considered as a function of treatment, then

$$\frac{\tau}{R_p}\frac{\partial R_p}{\partial \tau} = -\frac{\tau}{(\sigma_P + \tau + \mu_H)} \tag{4.6.2}$$

which also suggests an expected decline in the rate of new pneumonia infections when pneumonia treatment is scaled up. In addition, an effective pneumonia vaccine would ensure that during contact of a vaccinated susceptible with an infective $\beta_p \to 0$ and hence $R_p \to 0$.

4.7 Numerical Simulations

4.7.1 The effect of pneumonia on malaria

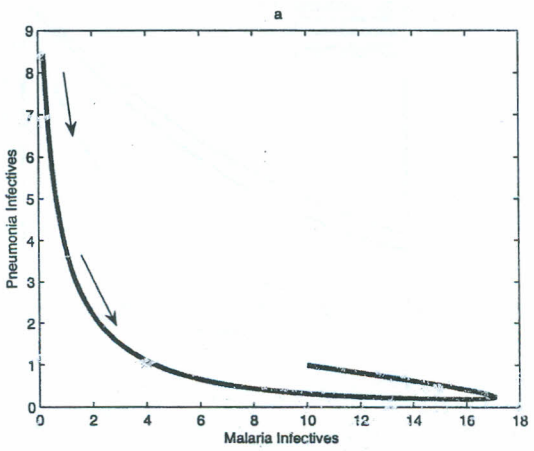

Figure 4.7.1: The effect of malaria on pneumonia

We observe from this graph that a decrease in pneumonia cases would lead to an increase in malaria cases probably due to increased mobility.

4.7.2 The effect of varying the co-infection recovery rate, ϕ

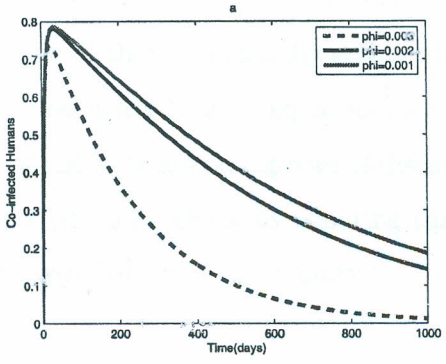

Figure 4.7.2: The effect of varying the co-infection recovery rate, ϕ This graph shows that a higher co-infection recovery rate would lead to a reduction in co-infection cases. This makes the case for comprehensive laboratory diagnosis to rule out or confirm co-infection so that the right treatment is initiated on time.

4.8 Discussion

We formulated a co-infection model for malaria and pneumonia and established the existence of its disease-free and endemic states. The local and global stability of the normalised model were then analysed. It was shown that if either disease is at a higher prevalence then the disease-free equilibrium is locally stable provided the co-infection reproduction number is less than unity. Suitable Lyapunov functions were constructed to investigate the global stability of the disease-free equilibrium. We established that it is globally stable whenever the co-infection reproduction number is less than or equal to unity. Biologically speaking, this suggests that the invasion and spread of disease in a population of susceptibles can be kept under check by ensuring that the basic reproduction number of either infection is under unity.

The potential impact of treatment on the dynamics of the co-infection was investigated by carrying out sensitivity analysis of the reproduction numbers. Considering recovery rate as a function of treatment, the analysis shows an expected decline in the rate of new infections when treatment is scaled up. From the numerical simulation, i.e. Fig 4.7.2, we also observe that if the co-infection recovery rate is high then the number of co-infection cases reduce significantly. Therefore in regions where malaria is endemic, it would be advisable to conduct laboratory tests to rule out or confirm co-infection. This would ensure that infections such as pneumonia, which have a symptom overlap with malaria are timely identified and treated.

Chapter 5

Modelling the dynamics of Malaria-Rotavirus co-infection among children

Mathematical models for the co-infection of *P. falciparum* and rotavirus in children are rare, yet review shows a number of reported cases where the two coexist. In a study carried out in Ghana , it was observed that 11.8% of the 243 children examined were co-infected with *P. falciparum* and enteropathogens, where rotavirus was also found to be common enteropathogens present in more than half of the patients [46].

5.1 Overview of Rotavirus

Rotavirus is a pathogen of the gastrointestinal tract that causes severe acute gastroenteritis and diarrhea in infants and young children less than five years of age worldwide [62]. Severe rotavirus infections occur most

commonly in infants and children between 6 and 24 months of age. Its symptoms include vomiting, watery diarrhoea, and low-grade fever. There are seven species of rotavirus, referred to as A, B, C, D, E, F and G. Humans are primarily infected by species A, B and C, most commonly by species A. The diagnosis of a rotavirus infection is commonly made clinically, although a rapid antigen stool test is available. Rotavirus is primarily transmitted by the faecal-oral route, via contact with contaminated hands, surfaces and objects [7] and possibly by the respiratory route [14]. The incubation period is about two days [27]. Reinfection does occur, however, with each infection, immunity develops, subsequent infections are less severe [36]. Indeed, it has been observed in the study [61] that children who experienced two natural rotavirus infection had complete protection against moderate-to-severe diarrhea compared to children without a previous infection. It has also been established that both symptomatic and asymptomatic infections confer similar degree of protection [61].

It is estimated that about 95% of children worldwide will have experienced a rotavirus infection by age five [44] with an annual mortality in excess of 600,000 among children [45]. Rotavirus-related hospitalizations can account for as many as 2.5% of all hospitalizations of children. Some review analyses show that rotavirus accounted for 6% of diarrhea episodes and 20% of deaths caused by diarrhea in children less than five years of age in developing countries [43]. In Kenya, rotavirus causes more than 7,500 deaths each year. The results of a study on rotavirus infections among HIV-infected children in Nairobi, Kenya, indicate that rotavirus is

an important viral etiological agent causing diarrhea in HIV-seropositive children [33].

5.2 Model Description

Although it is possible to have some level of immunity to rotavirus due to breastfeeding [5], in this model we shall assume that all the malaria-negative and rotavirus-negative children are susceptible. We subdivide the total human population N_H into the classes: susceptible S_H, infectious with malaria I_M, latently infected with rotavirus L_R, symptomatically infected with rotavirus I_R, infectious with malaria and latently infected with rotavirus I_{ML_R} and symptomatically infected with both malaria and rotavirus I_{MR}. The latent stage of the rotavirus disease has been considered because of the fact that exposed individuals can transmit the disease before and after they develop symptoms [44]. The total mosquito population N_V is subdivided into the susceptible S_V and infectious I_V classes.

This means that

$$N_H = S_H + I_M + L_R + I_R + I_{ML_R} + I_{MR} \tag{5.2.1}$$

and

$$N_V = S_V + I_V \tag{5.2.2}$$

The rates of infection of susceptible humans with malaria and rotavirus are λ_M and λ_R respectively while that of susceptible vectors is λ_v . The constant per capita recruitment rate into the susceptible human

and vector populations are Λ_H and Λ_v respectively. The rate at which humans progress from the L_R class to the I_R class is ψ and let $\vartheta = \vartheta_M + \vartheta_R$ be the disease induced mortality in humans. Further, natural death occur in all human and vector sub-populations at the rates $\mu_H$and μ_v. Malarial infection has a depressant effect on the immune system. Acute malarial parasitemia has a profound immunosuppressant effect, probably through the activation of suppressor T cells. In an malaria endemic area, young children may suffer from severe infections (bacterial or protozoal diseases) as either super-infections or co-infections due to this immunosuppression. We thus define the parameter θ to account for the increased susceptibility to infection with rotavirus for individuals infected with malaria. The expected decrease in contact due to ill health as a result of rotavirus disease is accounted for by the parameter $0 < \rho < 1$. The individuals displaying symptoms of both malaria and rotavirus suffer malaria-induced mortality at the rate $\delta\vartheta_M$, where the parameter δ accounts for the assumed increase in malaria-related mortality due to the dual infection with rotavirus and also suffer rotavirus-induced mortality at the rate $\kappa\vartheta_R$, where the parameter κ accounts for the assumed increase in rotavirus-related mortality due to the dual infection with malaria. The rates of recovery back into the susceptible class from malaria, symptomatic rotavirus and symptomatic dual infections are given by γ_1, γ_2 and γ_3 respectively.

The force of infection associated with malaria infection in humans is

$$\lambda_M = \frac{\beta_m b_m I_V}{N_H} \tag{5.2.3}$$

where β_m is the transmission probability of malaria in humans and b_m is

the per capita biting rate of mosquitoes.

The force of infection associated with malaria infection in vectors is

$$\lambda_v = \beta_v b_m \frac{(I_M + I_{ML_R} + \alpha I_{MR})}{N_H} \tag{5.2.4}$$

where β_v is the transmission probability of malaria in vectors, b_m is the per capita biting rate of mosquitoes and α is a modification parameter accounting for the assumed increased likelihood of infection of vectors from humans with dual malaria-rotavirus infection as compared to acquiring infection from humans with malaria only.

The force of infection associated with rotavirus infection is

$$\lambda_R = \beta_R \frac{L_R + I_{ML_R} + \phi(I_R + I_{MR})}{N_H} \tag{5.2.5}$$

where β_R is the effective contact rate for rotavirus infection and the modification parameter ϕ accounts for the the fact that individuals displaying rotavirus symptoms are more infectious than individuals latently infected with rotavirus. From the above definitions and variables we have the

following model

$$\begin{aligned}
\frac{dS_H}{dt} &= \Lambda_H - \lambda_M S_H - \lambda_R S_H - \mu_H S_H + \gamma_1 I_M + \gamma_2 I_R + \gamma_3 I_{MR} \\
\frac{dI_M}{dt} &= \lambda_M S_H - \theta\lambda_R I_M - \gamma_1 I_M - \vartheta_M I_M - \mu_H I_M \\
\frac{dL_R}{dt} &= \lambda_R S_H - \lambda_M L_R - \psi L_R - \mu_H L_R \\
\frac{dI_R}{dt} &= \psi L_R - \rho\lambda_M I_R - \vartheta_R I_R - \gamma_2 I_R - \mu_H I_R \qquad (5.2.6) \\
\frac{dI_{ML_R}}{dt} &= \lambda_M L_R + \theta\lambda_R I_M - \epsilon\psi I_{ML_R} - (\vartheta_M + \mu_H) I_{ML_R} \\
\frac{dI_{MR}}{dt} &= \rho\lambda_M I_R + \epsilon\psi I_{ML_R} - (\delta\vartheta_M + \kappa\vartheta_R + \gamma_3 + \mu_H) I_{MR} \\
\frac{dS_V}{dt} &= \Lambda_v - \lambda_v S_V - \mu_v S_V \\
\frac{dI_V}{dt} &= \lambda_v S_V - \mu_v I_V
\end{aligned}$$

Model (5.2.6) describes the human population and therefore it can be shown that the associated state variables are non-negative for all time $t \geq 0$ and that the solutions of the model (5.2.6) with positive initial data remain positive for all time $t \geq 0$ and are uniformly-bounded. We assume the associated parameters as non-negative for all time $t \geq 0$. Thus (5.2.6) is mathematically well posed and its dynamics can be considered in the region $\Psi = \Psi_H \times \Psi_v$, where

$$\Psi_H = \{(S_H, I_M, L_R, I_R, I_{ML_R}, I_{MR}) : N_H \leq \frac{\Lambda_H}{\mu_H}\} \qquad (5.2.7)$$

and

$$\Psi_v = \{(S_V, I_V) : N_V \leq \frac{\Lambda_v}{\mu_v}\} \qquad (5.2.8)$$

5.3 Disease-free equilibrium point

We denote the disease-free equilibrium (DFE) point by E^0 and define the "*diseased*" classes as the human or mosquito populations that are either exposed or infectious. Define the positive orthant in $\mathbb{R}^8$ by $\mathbb{R}^8_+$ and the boundary of $\mathbb{R}^8_+$ by $\partial\mathbb{R}^8_+$.

Lemma 5.1. *For all equilibrium points on* $\Psi \cap \partial\mathbb{R}^8_+$, $I_M = L_R = I_R = I_{ML_R} = I_{MR} = I_V = 0$

The positive DFE for human and mosquito populations for the model (5.2.6) are

$$N_H = \frac{\Lambda_H}{\mu_H} \text{ and } N_V = \frac{\Lambda_v}{\mu_v}. \tag{5.3.1}$$

Lemma 5.2. *The model (5.2.6) has exactly one DFE,* $E^0 = (\frac{\Lambda_H}{\mu_H}, 0, 0, 0, 0, 0, \frac{\Lambda_v}{\mu_v}, 0)$

Proof. The proof of the proposition requires that we show that DFE is the only equilibrium point of (5.2.6) on $\Psi \cap \partial\mathbb{R}^8_+$. Substituting E^0 into (5.2.6) shows all derivatives equal to zero, hence DFE is an equilibrium point. From Lemma 5.1, the only equilibrium point for N_H is $\frac{\Lambda_H}{\mu_H}$ and the only equilibrium point for N_V is $\frac{\Lambda_v}{\mu_v}$. Thus the only equilibrium point for $\Psi \cap \partial\mathbb{R}^8_+$ is DFE. □

5.3.1 Local stability of the disease-free equilibrium

We investigate the disease-free equilibrium for the model using the basic reproduction number. We define the basic reproduction number here,

R_{mr} as the number of secondary malaria (or rotavirus) infections due to a single malaria (or a single rotavirus-infective) individual. We determine R_{mr} using the next generation operator approach [59]. The associated next generation matrices are

$$F=\begin{pmatrix} 0 & 0 & 0 & 0 & 0 & \beta_m b_m \\ 0 & \beta_r & \phi\beta_r & \beta_r & \phi\beta_r & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ \beta_v b_m n & 0 & 0 & \beta_v b_m n & \alpha\beta_v b_m n & 0 \end{pmatrix}$$

and

$$V=\begin{pmatrix} h_1 & 0 & 0 & 0 & 0 & 0 \\ 0 & h_2 & 0 & 0 & 0 & 0 \\ 0 & -\psi & h_3 & 0 & 0 & 0 \\ 0 & 0 & 0 & h_4 & 0 & 0 \\ 0 & 0 & 0 & -\epsilon\psi & h_5 & 0 \\ 0 & 0 & 0 & 0 & 0 & \mu_v \end{pmatrix}$$

where $h_1 = \gamma_1 + \vartheta_M + \mu_H$, $h_2 = \psi + \mu_H$, $h_3 = \gamma_2 + \vartheta_R + \mu_H$, $h_4 = \epsilon\psi + \vartheta_M + \mu_H$, $h_5 = \gamma_3 + \delta\vartheta_M + \kappa\vartheta_R + \mu_H$ and $n = \frac{\mu_H \Lambda_v}{\Lambda_H \mu_v}$.

The basic reproduction number R_{mr} is the spectral radius of the matrix FV^{-1}. The non-zero eigenvalues of the matrix FV^{-1} are $R_r = \frac{\beta_R}{\psi+\mu_H} + \frac{\phi\beta_r\psi}{(\gamma_2+\vartheta_R+\mu_H)(\psi+\mu_H)}$ and $R_m = \sqrt{\frac{b_m^2 \beta_m \beta_v \mu_H \Lambda_v}{\Lambda_H \mu_v^2 (\gamma_1+\vartheta_M+\mu_H)}}$. Therefore R_{mr} is given by

$$R_{mr} = \max\{R_r, R_m\}. \tag{5.3.2}$$

R_m is a measure of the average number of secondary malaria infections in human or mosquito population caused by a single infective human or

mosquito introduced into an entirely susceptible population. The expression R_m is biologically meaningful. It comprises of the term $\frac{\beta_v b_m}{\mu_v}$ which represents the number of secondary malaria infections in human caused by a single infected mosquito, while the term $\frac{\beta_m b_m \mu_H \Lambda_v}{\Lambda_H \mu_v (\gamma_1 + \vartheta_M + \mu_H)}$ represents the number of secondary malaria infections in mosquitoes caused by a single infected human. Similarly, in R_r, the term $\frac{\beta_R}{\psi + \mu_H}$ is a measure of the average number of secondary rotavirus infections in humans caused by a single latently infected human, while the term $\frac{\phi \beta_r \psi}{(\gamma_2 + \vartheta_R + \mu_H)(\psi + \mu_H)}$ is a measure of the average number of secondary rotavirus infections in humans caused by a single symptomatically infected human introduced into an entirely susceptible population. The following lemma follows from Theorem 2 of [59].

Lemma 5.3. *The the disease-free equilibrium E^0 of the model (5.2.6) is locally asymptotically stable whenever $R_{mr} < 1$ and unstable when $R_{mr} > 1$.*

5.3.2 Global stability of the disease-free equilibrium

We investigate the global asymptotic stability (GAS) of the disease-free equilibrium of the model using the theorem by Castillo-Chavez *et.al* [10]. We rewrite the model as

$$\begin{aligned} \frac{dX}{dt} &= H(X, Z), \\ \frac{dZ}{dt} &= G(X, Z), G(X, 0) = 0 \end{aligned} \tag{5.3.3}$$

where $X = (S_H, S_v)$ and $Z = (I_M, L_R, I_R, I_{ML_R}, I_{MR}, I_v)$, with the components of $X \in \mathbb{R}^2$ denoting the uninfected population and the components of $Z \in \mathbb{R}^6$ denoting the infected population.
The disease-free equilibrium is now denoted as

$$E^0 = (X^*, 0), X^* = (\frac{\Lambda_H}{\mu_H}, \frac{\Lambda_v}{\mu_v}). \tag{5.3.4}$$

The conditions in (5.3.5) must be met to guarantee a local asymptotic stability:

$$\begin{aligned} \frac{dX}{dt} &= H(X,0), X^* \text{ is globally asymptotically stable (GAS)} \\ G(X,Z) &= PZ - \widehat{G}(X,Z), \widehat{G}(X,Z) \geq 0 \text{ for } (X,Z) \in \Omega \end{aligned} \tag{5.3.5}$$

where $P = D_z G(X^*, 0)$ is an M-matrix (the off-diagonal elements of P are non-negative) and Ω is the region where the model makes biological sense. If the system (5.3.3) satisfies the conditions of (5.3.5) then the theorem below holds.

Theorem 5.4. *The fixed point $E^0 = (X^*, 0)$ is a globally asymptotically stable equilibrium of system (5.3.3) provided that $R_{mr} < 1$ and the assumptions in (5.3.5) are satisfied.*

Proof. From the model system (5.2.6) and (5.3.3), we have

$$H(X,0) = \begin{pmatrix} \Lambda_H - \mu_H S_H \\ \Lambda_v - \mu_v S_v \end{pmatrix}$$

$$G(X,Z) = PZ - \widehat{G}(X,Z)$$

where

$$P = \begin{pmatrix} -h_1 & 0 & 0 & 0 & 0 & \beta_m b_m \\ 0 & \beta_R - h_2 & \phi\beta_R & \beta_R & \phi\beta_R & 0 \\ 0 & \psi & -h_3 & 0 & 0 & 0 \\ 0 & 0 & 0 & -h_4 & 0 & 0 \\ 0 & 0 & 0 & \epsilon\psi & -h_5 & 0 \\ \beta_v b_m & 0 & 0 & \beta_v b_m & \alpha\beta_v b_m & -\mu_v \end{pmatrix}$$

and

$$\widehat{G}(X,Z) = \begin{pmatrix} \widehat{G}_1(X,Z) \\ \widehat{G}_2(X,Z) \\ \widehat{G}_3(X,Z) \\ \widehat{G}_4(X,Z) \\ \widehat{G}_5(X,Z) \\ \widehat{G}_6(X,Z) \end{pmatrix} = \begin{pmatrix} \beta_m b_m I_v(1 - \frac{S_H}{N_H}) + \theta\lambda_R I_M \\ \beta_R\{L_R + I_{ML_R} + \phi(I_R + I_{MR})\}(1 - \frac{S_H}{N_H}) \\ \rho\lambda_M I_R \\ -(\lambda_M L_R + \theta\lambda_R I_M) \\ -\rho\lambda_M I_R \\ \beta_v b_m\{(I_M + I_{ML_R} + \alpha I_{MR})\}(1 - \frac{S_V}{N_H}) \end{pmatrix}$$

$\widehat{G}_4(X,Z) < 0$, $\widehat{G}_5(X,Z) < 0$ and so the conditions in (5.3.5) are not met so E^0 may not be globally asymptotically stable when $R_{mr} < 1$. □

However, if maximum protection is provided against co-infection during an outbreak of rotavirus infection in a malaria-endemic region, then global stability of the disease-free equilibrium may be achieved. This is because with such protection $\widehat{G}_4(X,Z) = \widehat{G}_5(X,Z) = 0$. In other words, the fight against malaria and persistent infections such as rotavirus may be won if co-infection cases are kept at a bare minimum.

5.4 Endemic equilibrium of the Model

The endemic equilibrium of the model is studied using the Centre Manifold Theorem [8, 9]. To apply this theorem we make the following change of variables. Let $S_H = x_1, I_M = x_2, L_R = x_3, I_R = x_4, I_{ML_R} = x_5, I_{MR} = x_6, S_v = x_7, I_v = x_8$ so that $N_H = x_1 + x_2 + x_3 + x_4 + x_5 + x_6$ and $N_v = x_7 + x_8$. The model (5.2.6) can be rewritten in the form $\frac{dX}{dt} = F(x)$ where $X = (x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8)$ and $F = (f_1, f_2, f_3, f_4, f_5, f_6, f_7, f_8)$ as

$$\begin{aligned}
\frac{dx_1}{dt} &= f_1 = \Lambda_H - \lambda_M x_1 - \lambda_R x_1 - \mu_H x_1 + \gamma_1 x_2 + \gamma_2 x_4 + \gamma_3 x_6 \\
\frac{dx_2}{dt} &= f_2 = \lambda_M x_1 - \theta\lambda_R x_2 - \gamma_1 x_2 - \vartheta_M x_2 - \mu_H x_2 \\
\frac{dx_3}{dt} &= f_3 = \lambda_R x_1 - \lambda_M x_3 - \psi x_3 - \mu_H x_3 \\
\frac{dx_4}{dt} &= f_4 = \psi x_4 - \rho\lambda_M x_4 - \vartheta_R x_4 - \gamma_2 x_4 - \mu_H x_4 \qquad (5.4.1) \\
\frac{dx_5}{dt} &= f_5 = \lambda_M x_3 + \theta\lambda_R x_2 - \epsilon\psi x_5 - (\vartheta_M + \mu_H) x_5 \\
\frac{dx_6}{dt} &= f_6 = \rho\lambda_M x_4 + \epsilon\psi x_5 - (\delta\vartheta_M + \kappa\vartheta_R + \gamma_3 + \mu_H) x_6 \\
\frac{dx_7}{dt} &= f_7 = \Lambda_v - \lambda_v x_7 - \mu_v x_7 \\
\frac{dx_8}{dt} &= f_8 = \lambda_v x_7 - \mu_v x_8
\end{aligned}$$

where $\lambda_M^c = \frac{\beta_m b_m x_8}{N_H^c}$, $\lambda_v^c = \beta_v b_m \frac{(x_2 + x_5 + \alpha x_6)}{N_H^c}$ and $\lambda_R^c = \beta_R \frac{x_3 + x_5 + \phi(x_4 + x_6)}{N_H^c}$.
The jacobian, $J(E^o)$ of (5.4.1) at the DFE E^o is given by

$$\begin{pmatrix} -\mu_H & -\gamma_1 & -\beta_R & \gamma_2-\phi\beta_R & -\beta_R & \gamma_3-\phi\beta_R & 0 & -\beta_m b_m \\ 0 & -K_1 & 0 & 0 & 0 & 0 & 0 & \beta_m b_m \\ 0 & 0 & K_2 & \phi\beta_R & \beta_R & \phi\beta_R & 0 & 0 \\ 0 & 0 & 0 & K_3 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -K_4 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \epsilon\psi & -K_5 & 0 & 0 \\ 0 & -\beta_v b_m p & 0 & 0 & -\beta_v b_m p & -\alpha\beta_v b_m p & -\mu_v & 0 \\ 0 & \beta_v b_m p & 0 & 0 & \beta_v b_m p & \alpha\beta_v b_m p & 0 & -\mu_v \end{pmatrix}$$

where $K_1 = \gamma_1+\vartheta_M+\mu_H$, $K_2 = \beta_R-(\psi+\mu_H)$, $K_3 = \psi-(\vartheta_R+\gamma_2+\mu_H)$ $K_4 = \epsilon\psi+\vartheta_M+\mu_H$, $K_5 = \delta\vartheta_M+\kappa\vartheta_R+\gamma_3+\mu_H$, and $p = \frac{\mu_H\Lambda_v}{\Lambda_H\mu_v}$.

To analyze the dynamics of (5.4.1), we compute the eigenvectors of the jacobian of (5.4.1) at the DFE. It can be shown that this jacobian has a right eigenvector given by

$W = (w_1, w_2, w_3, w_4, w_5, w_6, w_7, w_8)^T$, where

$w_3 = w_4 = 0, w_5 = 0, w_6 = 0$ and $w_1 = -\frac{(\gamma_1+K_1)w_2}{\mu_H}$, $w_7 = \frac{-\beta_v b_m p w_2}{\mu_v}$, $w_8 = \frac{K_1 w_2}{\beta_m b_m}$, $w_2 = w_2 > 0$

and a left eigenvector given by $V = (v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8)^T$ where

$v_1 = v_3 = v_4 = v_7 = 0$ and $v_5 = \frac{\epsilon\psi v_6}{K_4}$, $v_2 = v_2 > 0$, $v_6 = \frac{\alpha\beta_v b_m p v_8}{K_5}$, $v_8 = \frac{\beta_v b_m v_2}{\mu_v}$.

Consider the case when $R_{mr} = 1$ (assuming that $R_r < R_m$) and choose the transmission probability of malaria in humans $\beta_m = \beta_m^*$ as a bifurcation parameter. Solving for β_m from $R_{mr} = R_m = 1$ gives

$$\beta_m = \beta_m^* = \frac{\Lambda_H \mu_v^2 (\vartheta_M + \gamma_1 + \mu_H)}{b_m^2 \beta_v \mu_H \Lambda_v} \tag{5.4.2}$$

It can be shown after some manipulation involving the evaluation of the associated non-vanishing partial derivatives of f that

$$\begin{aligned} s^* &= \frac{2\mu_H}{\Lambda_H}(v_2 w_1 w_8 \beta_m b_m + v_8 w_2 w_7 \beta_v b_m) \text{ and} \\ r^* &= v_2 w_8 b_m > 0. \end{aligned} \tag{5.4.3}$$

Note that $s^* < 0$ since $w_1 < 0$ and $w_7 < 0$. Thus we have established the following theorem

Theorem 5.5. *Whenever (5.4.3) holds, the model may undergo a forward bifurcation.*

This implies that disease transmission in a population of susceptibles may be contained by a reproduction number less than unity.

5.5 Discussion

We formulated a co-infection model for malaria and rotavirus. The disease-free equilibrium is shown to be locally stable provided the co-infection

reproduction number is less than unity. This equilibrium is not globally stable due to co-infection. However, we observe that maximum protection against co-infection during an outbreak of rotavirus infection in a malaria-endemic region may help achieve this stability. In other words, the fight against malaria and persistent infections such as rotavirus may be won if co-infection cases are kept at a bare minimum. Analysis of the endemic equilibrium, using the Centre manifold theorem, indicates that the model may undergo a forward bifurcation. This suggests that at the endemic state, disease spread may be kept under check if the reproduction number can be brought below unity.

Chapter 6

Conclusion and Recommendations

6.1 Conclusion

In this work, we developed and analysed three co-infection models to study the dynamics of the interaction of meningitis, pneumonia and rotavirus with malaria.

Specifically, in chapter three, we formulated a malaria-meningitis model and analysed the local stability of the disease-free equilibrium in terms of the basic reproduction number of the model. We assumed the malaria basic reproduction number to be greater than the meningitis reproduction number, and consequently used it as the reproduction number for the co-infection model. The analysis shows that the disease-free equilibrium is locally asymptotically stable whenever the reproduction number is less than unity and unstable otherwise. The global asymptotic stability (GAS) of the disease-free state of the model was investigated using the theorem by Castillo-Chavez *et.al.* We showed that it may not be globally

stable indicating the possibility of future disease outbreaks when conditions favouring the same are prevailing. The public health implication is that disease surveillance is an important integral component of the fight against infections. We also established that maximum protection against a second infection may help achieve global stability of the disease-free equilibrium.

We also derived conditions under which the endemic equilibrium of the model would be locally stable. When an endemic equilibrium point is stable, then we would expect manageable levels of disease, with minimal deaths and interventions, at peak times of the re-occurrences. We have also shown the possibility of backward bifurcation occurring for this model. The occurrence of backward bifurcation implies the co-existence of a stable endemic equilibrium with the disease-free equilibrium.

In chapter four we developed a malaria-pneumonia co-infection model. For purposes of convenience, the steady states of the model were analysed after normalizing the variables in the model. We established the existence of the endemic equilibrium when either only malaria or pneumonia is present in the population. The endemic equilibrium for the co-infection model is shown to exist so long as both diseases are present in the population. To investigate the potential impact of treatment on disease dynamics, we carried out sensitivity analysis of the reproduction numbers. The analysis shows that there is an expected decline in new infections when treatment is scaled up.

In chapter five we developed and analysed a malaria-rotavirus co-infection model. The disease-free equilibrium is shown to be locally but not globally stable. Once again protection against a second infection is shown to

result in the attainment of the global stability of the disease-free equilibrium. The analysis of the endemic equilibrium suggests the possibility of occurrence of forward bifurcation. This suggests that at the endemic state, disease spread may be kept under check if the reproduction number can be brought below unity.

6.2 Recommendations

(i) Since people living in malaria-endemic areas are exposed to other diseases which have a symptom overlap with malaria, we recommend comprehensive laboratory diagnosis so as to rule out or confirm co-infection.

(ii) We also recommend that local and global efforts be stepped up to improve access to affordable curative and preventive measures such as medication, vaccines and insecticide-treated nets.

(iii) Due to the possibility of backward bifurcation, we recommend that disease surveillance should be done regularly.

(iv) We also recommend that this research be extended to explore the dynamics of co-infection of HIV/AIDS with these persistent childhood infections.

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