MODELLING THE IMPACT OF MISDIAGNOSIS AND TREATMENT ON THE DYNAMICS OF MALARIA CONCURRENT AND CO-INFECTION WITH PNEUMONIA AND TYPHOID

BY

Okaka Colletta Akinyi

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SCHOOL OF MATHEMATICS STATISTICS AND ACTUARIAL SCIENCE

MASENO UNIVERSITY

Abstract

Mathematical models of malaria-pneumonia and malaria- typhoid concurrent and co-infection have been formulated to establish the effects of misdiagnosing pneumonia and typhoid as malaria. We performed stability analysis on the disease-free equilibrium (DFE) and the endemic equilibrium. The existence of locally asymptotic stability (LAS) of the DFE is investigated based on the reproduction number R_0. The DFE is shown to be locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$. The results show that the DFE is not globally asymptotically stable (GAS) even when $R_0 < 1$. Instead, backward bifurcation occurs at $R_0 = 1$. Backward bifurcation implies that having $R_0 < 1$, although necessary, is not sufficient for curtailing endemicity of the disease. The general bifurcation theory and the center manifold theory were applied to determine the existence and stability of the endemic equilibrium near the threshold. A model for accurate diagnosis and prompt treatment of pneumonia is developed to compare the global stability of its disease-free and endemic equilibria with that of the case of misdiagnosis. Sensitivity analysis on both models show that the most sensitive parameter is the rate of misdiagnosis. For the malaria-typhoid model, the rate of becoming a carrier is also very sensitive. A major finding of this study is that misdiagnosis of pneumonia and typhoid leads to high endemicity of both diseases. Moreover, despite overuse of anti-malarials, misdiagnosis makes elimination of malaria not possible. Results of this study will help health care providers understand how misdiagnosis errors are made, reduce misdiagnosis and improve patient care.

Chapter 1

Introduction

Infectious diseases are the most prevalent and important causes of ill health throughout the world. However, they are more prevalent in the developing countries, and their impact is most severe among the poor people who have least physical and financial resources. They also have limited or no access to integrated health care prevention tools and medication [38]. Malaria, pneumonia and typhoid are the leading causes of death among the poor in the developing countries [61].

Although malaria, pneumonia and typhoid are caused by different organisms and transmitted via different mechanisms, malaria symptoms are clinically indistinguishable from those of the other two diseases especially at their initial stages. These diseases are associated with poverty and individuals in the areas endemic to these diseases are at a substantial risk of contracting at least one of them, but can also easily get multiple infection [38].

Malaria, pneumonia and typhoid are best distinguished by correct

diagnosis. However, some diagnosis approaches currently used to diagnose these diseases may not be accurate [16]. The most widely used approach is the clinical diagnosis. It is unreliable because it relies totally on the symptoms of the disease, yet the symptoms of malaria, pneumonia and typhoid are non-specific. Those of pneumonia and typhoid mimic those of malaria [50]. As a result of the diagnostic challenges, it is very common to have patients in a region endemic with malaria like Kenya undergo malaria treatment even if their diagnosis has not been confirmed, or their laboratory test results show negative test to malaria [50]. This leads to mistreatment, over treatment with anti-malaria and delays in seeking care for those with the other fatal diseases [47, 54].

The enormous number of people affected by misdiagnosis of pneumonia and typhoid necessitates the use of mathematical modelling to gain insight into the impact of the dynamics of misdiagnosis of pneumonia and typhoid as malaria. The need to develop in depth mathematical models to study the effect of misdiagnosis is further expressed in the synergistic tendency of the increased number of carriers when typhoid is misdiagnosed.

Using mathematical modelling we have evaluated the impact of misdiagnosis and treatment of symptoms of malaria using anti-malarial drugs [49]. The mathematical models help in building a positive perspective towards the use of diagnostic tests before prescribing and dispensing of anti-malarial drugs. The true cases of malaria will then be correctly treated, hence reducing misuse of anti-malarials and the rapid spreading

of resistance to anti-malarials which is threatening the ability to treat malaria effectively in nearly all the malaria endemic regions of the globe. At the same time people with alternative diagnoses especially pneumonia or typhoid, both of which are potentially fatal, will be better targeted with the appropriate treatment without delays.

We have developed mathematical models through ordinary differential equations and used them to study the impact of misdiagnosis on the dynamics of malaria concurrent and co-infection with pneumonia and typhoid.

1.1 Background of the Study

Despite the existence of other diseases that share similar symptomatology as malaria and are even more fatal, anti- malarials are used within an environment that is characterized by a great degree of lack of concern [5]. This casual manner of use is largely as a result of many years of surprisingly successful use of the most common anti- malaria drugs particularly chloroquine (CQ) [5]. In many situations practices that could best be described as misuse of drugs is routine, and in some cases, institutionalized and promoted [5, 60, 14].

Over the years of treatment of malaria, there have been few interventions to ensure proper tests of malaria are done before malarial drugs are used [50]. Both CQ and sulfadoxine pyrimethamine (SP) were inexpensive, making it more cost effective to treat malaria presumptively rather

than to attempt to get the microscopic confirmation, especially when the diagnostic equipment is unavailable within the easily accessible health centres [5]. In particular the readily use of anti- malarial drugs in Kenya is quite different from that of other drugs, due to the high prevalence and intensity of malaria cases. In areas of intense transmission, anti- malarial drugs are readily given to treat fevers and headaches, even in the absence of malaria [39]. The practice of assuming that symptoms similar to those of malaria, are as a result of malaria infection is very common and is a major health concern [51]. Research findings show that many illnesses including malaria are treated without laboratory tests [24]. This practice has resulted in patterns such as overuse, underuse, irregular use or misuse of anti- malarial medicines and deaths due to the other common infections, which could have been prevented [29, 51].

In the health facilities, there is a lot of reliance on clinical diagnosis rather than diagnostic tests. The use of familiar symptoms like headache and fever to diagnose malaria leads to misdiagnosis of other diseases with similar symptoms for example pneumonia and typhoid. These non-malarial diseases have high mortalities in Kenya, and their mortality rates increase with delays caused by wrong diagnosis, and their endemicity also rises. Studies have shown that a physician's clinical diagnosis is 50% correct in high malarial season and 10% in the low season [43]. A substantial number, sometimes the majority of those treated for malaria are not actually infected with malaria parasites, or they may be co-infected with pneumonia or typhoid. Apart from threatening the lives of the people who

are not infected with malaria, over diagnosis of malaria leads to overuse of anti-malarials. This potentially increases the risk of spread of drug resistant malaria.

Treatment of individuals with malaria like symptoms with anti-malarials regardless of their malaria infection status is also a common practice in home management of fevers and other common malarial symptoms [51]. The patterns of use of anti- malarial include self prescription, sharing of drugs with friends and relatives and premature discontinuation of treatment course [24]. Patients perception of disease symptoms as minor, or their thinking that they are sufficiently familiar with the disease and how to treat it, makes them believe they do not need to visit a health facility and therefore avoid the inconvenience and cost of doing that. Help is usually sought from commercial pharmacists, retail shops or licensed [14] and unlicensed drug sellers [57]. Such informal treatment increases the risk of incorrect dosage, incorrect treatment and reactions of different medicines which have a negative impact on the body. Most patients reporting at the health facilities would have initially gone through home-based treatment or local drug shops. Thus seeking health care from practitioners may be due to severe or recurrent episodes of the symptoms [24].

Misdiagnosis threatens the lives of people infected with other diseases. The clinical manifestations of malaria which are associated with fever, headache, shivering, dehydration and body aches are manifested by many other diseases and unless a test for parasites is done well, the patient may be misdiagnosed. Many of these diseases if not treated in time, are fa-

tal, and death occur in $10\% - 30\%$ of untreated cases of pneumonia and typhoid infections. There has been high risk of a patient dying due to severe pneumonia and typhoid disease because of the focus on malaria [20]. There is also a waste of malaria expensive drugs on patients not infected with malaria parasites. The high levels of morbidity and mortality thus underscores the importance of mathematical modelling to gain insight into the dynamics of misdiagnosis, and to determine the effective control strategies.

1.2 Malaria, Pneumonia and Typhoid

1.2.1 Malaria

Malaria is a parasitic infection which is common in the tropics. Four species of the parasite namely plasmodium falciparum, plasmodium vivax, plasmodium ovale and plasmodium malariae infect humans. Plasmodium falciparum causes the most serious illness and is the most widespread in the tropics. Malaria disease affects $300 - 500$ million people yearly in the sub-Saharan Africa and it is estimated that about $1.5 - 3$ million people, mostly non-immune die of malaria every year [63]. In Kenya malaria accounts for 19% of hospital admissions, 30% of all outpatient visits, and an estimated 20% of all deaths in children less than 5 years of age [13]. In recent years the disease has been subjected to massive control efforts [63] with varying degrees of success. However, the disease has resurged in many parts of Kenya especially Nyanza region, Rift valley and central

Kenya.

Problems of both treatment and control of malaria are more complex and intractable today than ever before. The increasing problems of drug resistance of the parasite and insecticide resistance of vectors makes the disease continue to be a heavy burden on tropical communities and the governments. The parasites are transmitted indirectly from human to human by the bite of the infectious female mosquitoes of the genus anopheles. Following the mosquito bite there is an incubation period of 7-14 days. The patient then develops headache, fever, malaise, fever with rigors, sweating mylagia (muscle pains), shivering and vomiting. Some patients have diarrhea and cough due to secondary bacterial infection. In severe untreated cases there is dehydration anemia, jaundice and coma.

1.2.2 Pneumonia

Pneumonia has been recognized for many centuries since the fourth century BC when peri-pneumonia was described by Hippocrates [59, 1]. Pneumonia is caused by various bacterial species, mycoplasmas, chlamydiae, rickettsiae, parasites and fungi [17]. It is an infection which primarily affects the lungs but can spread to other parts of the body through the blood system. It is a major killer of children and the aged, and HIV infected patients in the developing world. Studies done in the developing world have shown that it accounts for $25\% - 50\%$ of admission in the hospital [16]. It causes 4 - 5 million deaths of children yearly.

In Kenya pneumonia is the most common cause of hospital attendance for both adults and children [33]. Prompt recognition and treatment with an effective drug is crucial as the case-fatality rate is high. It is estimated that $20\% - 30\%$ of the pneumonia patients die each year [33] and death can occur after three days of illness. It is spread from person to person by inhalation of droplets from an infected person and has a short incubation period of $3 - 7$ days. The symptoms are sudden and fatal if not attended to immediately, and death can occur after three days of illness. Ninety five percent of episodes of pneumonia occur in developing countries [54]. The symptoms of the disease include cough with or without rigors, headache, fever, shivering, malaise and chest pains that are worse on breathing.

Malaria and pneumonia are the leading causes of mortality especially among children in the malaria endemic areas in Kenya. Malaria and pneumonia often present similarly and the two diseases are easily confused. More often than not a patient presenting fever, headache and muscle pains is given anti-malarials without ascertaining the exact cause of those symptoms. Those infected with both pneumonia and malaria often have symptom overlap which would otherwise necessitate dual treatment with both anti-malarials and antibiotics if proper tests were done [27, 29]. However most interventions usually target single disease, malaria, thus risking increased incidences of pneumonia [29]. There are always delays in establishing the correct diagnosis as a result of the clinical status, thus accounting for the high morbidity and mortality due to pneumonia. Untreated pneumonia can lead to widespread infection with meningitis,

kidney abscess and bacterial infection of the heart. Many models on co-infection of malaria and pneumonia have been developed but none has ever been developed on misdiagnosis of pneumonia as malaria in malaria-pneumonia concurrent and co-infection. Yet due to the similarity of the symptoms of malaria and pneumonia, misdiagnosis of pneumonia is rampant, hence pneumonia is a major killer in this combination.

1.2.3 Typhoid

Typhoid fever is among the endemic diseases in the tropics and is associated with poverty and under development, with an estimated 12 to 33 million cases occurring annually [22]. The etiological agent of typhoid is salmonella typhi. Human beings are the only reservoir and host for typhoid fever and is transmitted by faecal contaminated water and food in endemic areas [47]. The bacteria can survive for weeks in water or dried sewage. Most cases occur in places with rapid population growth, increased urbanization and rural areas where there is limited safe water supply, poor sanitation and infrastructure, and limited health systems, as is evident in some parts of Kenya.

The first typical manifestations of typhoid which are fever, headache, abdominal pain, splenomegaly and leukopenia are similar to those of malaria [10]. In untreated cases, the rate of mortality is estimated to be between 12% and 30% and several complications such as hemorrhage, intestinal perforation, heart failure, pneumonia, meningitis may occur. When appropriate typhoid fever treatment is started early, the mortality

rate is under one percent and few complications occur [59]. Incubation period is $3-60$ days. Typhoid can kill in $4-7$ days, and most of the time several months are necessary for a patient to recover and be able to work effectively again.

Some people get infected but show no symptoms and thus go unrecognized. These patients become asymptomatic long term carriers showing no symptoms but capable of infecting others (Typhoid Mary) [17]. These chronic carriers may be the source of new outbreaks of typhoid for many years. Among the untreated symptomatic individuals, $2\% - 5\%$ become chronic carriers [66]. In this study we have developed a model for the dynamics of misdiagnosis of typhoid as malaria to help gain insight of high transmissions and mortality rates that arise due to the delays caused by wrong diagnosis and inappropriate treatment of Typhoid.

Despite the availability of the above information, the epidemiological trends for the prevalence and incidence of each disease considered in the misdiagnosis remains unclear. No attention has ever been paid or any emphasis laid on the parameter(s) that makes it impossible to reduce transmission of these diseases to low levels or, to completely eliminate them. There is a lot mentioned about controlling or complete elimination, but "how do we sustain particularly the disease-free equilibrium?". No measurement of the level of disease transmission in relation to $R < 1$ is provided to show whether the disease is decreasing or increasing in incidence. The diagnostic technique commonly used is mostly the simple malaria test. Generally no attention is given to any other infection that

could have similar symptoms to those of malaria.

1.3 Statement of the problem

For many years now, much has been done towards treatment, control and complete elimination of malaria. Many control programmes have been set up to promote effective treatment of malaria, and anti-malarials have been made readily available and accessible for treating malaria cases. Yet there is still very high morbidity and mortality rates due to fever cases. This means cases of pneumonia and typhoid which also cause fever are being treated as malaria. Despite the availability of effective and affordable antibiotics,the epidemiological trend of these diseases is not consistent. Notably, there is continued rise in the transmission and prevalence of pneumonia and typhoid, and no reason has been described to explain the scenario. Suffice it to note that cases of malaria resurgence are also still common despite over use of anti-malarial medicines. This therefore means misdiagnosis of pneumonia and typhoid as malaria. Hence delay in giving appropriate treatment as suggested by studies that showed higher cases of transmission and fatality rates among non- malarial fevers compared to malarial fevers [50].

Given that pneumonia and typhoid are still leading killers in Kenya, the misdiagnosed patients have substantial public health importance which calls for bifurcation analysis to find out the actual impact of misdiagnosis on the transmission and prevalence of these diseases. Bifurcation analysis

is used to prove the existence or none existence of the stable equilibrium states.

Only one out five health care givers knows the danger signs of pneumonia and typhoid [61]. When diagnostic facilities are available, clinicians respond to negative tests by ignoring them and half or more of those with negative test results are still treated for malaria [24, 50]. There is no robust clinical algorithm about what should be followed when the tests are negative.

Several mathematical models have been developed on transmission and spread of malaria starting with Ross' models [53]. A few models have been developed on presumptive treatment of malaria but all these models concentrate on the impact of intermittent presumptive treatment (IPT) and are used to depict its positive impact only. In this study we have developed Mathematical models through ordinary differential equations (ODE) to predict the impact of misdiagnosis and treatment on the dynamics of malaria concurrent and co-infection with other common diseases with similar symptoms.

1.4 Objectives of the study

The general objective of the research is to develop mathematical models that can be used to study the adverse effects of misdiagnosis and treatment of other common malaria concurrent and co-infections that are fatal to human beings.

The specific objectives of this research are:

(i) To investigate the observed epidemiological trends for the prevalence and incidence of each disease considered in the misdiagnosis.

(ii) To investigate backward bifurcation in any of the concurrent and co-infections by analysing the various models.

(iii) To determine if there is a possibility of the stable disease-free equilibrium coexisting with a stable endemic equilibrium when the reproduction number is less than one.

1.5 Scope of the Study

The study was carried out in Kenya Africa and the study station was Maseno University, Kenya, Africa. The required information and data about malaria and the other related diseases were obtained from the government district and provincial hospitals , health centers and Kenya Medical Research Institute (KEMRI).

1.6 Expected outcomes and the research impact

(i) The models constructed will give insight into the impact of the dynamics and effects of misdiagnosis of other infectious diseases that share similar symptoms with malaria.

(ii) The results of the study are relevant and valuable to all stake holders in the health system and more importantly to the health care providers who are going to understand how misdiagnosis errors are made, reduce misdiagnosis and improve patient care.

Chapter 2

Literature review

2.1 Introduction

A multitude of factors have been found to lead to presumptive treatment and these affect various levels at which drugs are handled. Research studies conducted by International health organizations such as World Health Organization (WHO) reveal that factors such as knowledge, attitudes and practice within the community, economic status and promotional practices contribute towards presumptive treatment leading to inappropriate drug use [62]. Mathematical models have been used to provide an explicit understanding of malaria and other infectious diseases transmission dynamics in human for over 100 years. The recent near success of malaria control programs have shown that models can make great pragmatic contribution to intervention programs especially if the modelling is integrated into the overall program.

2.2 Modelling single diseases

Malaria was one of the first infections to which the use of mathematical modelling was applied. An initial model that provided the first accurate representations of the origins of the disease was developed in early 1890s by Ross [52]. While working at the Indian Medical Service, he developed a simple model now known as "the classical Ross model" which explained the relationship between the number of mosquitoes and the incidence of malaria in humans. In 1911 he went ahead to provide quantitative understanding of the dynamics of malaria transmission by creating a model that consisted of a few differential equations to describe the changes in densities of susceptible and infected mosquitoes. He introduced the concept of threshold density depending on biological factors such as the biting rate and vectorial capacity. He concluded that "in order to counteract malaria any where, we need not banish anopheles mosquitoes completely, the numbers need only to be reduced below a certain figure, and that control programs that integrate vector reduction, drug treatment and personal protection are likely to succeed than a mono directed program". Major extensions on Ross' models were described by Macdonald. He showed that at equilibrium the weakest link in the chain of transmission of malaria is the survivorship of the female anopheles mosquito [36]. Macdonald analyzed several factors contributing to malaria transmission and his model suggested that reducing the number of mosquitoes is an inefficient control strategy that would have little effect on the epidemiology of malaria in areas of intense transmission [36]. He came up with the

following model

$$R_0 = \frac{a^2bcm}{r\mu} \tag{2.2.1}$$

where r is the per capita rate of recovery in humans such that $\frac{1}{r}$ is the duration of the disease in humans, μ is the per capita rate of mortality in mosquitoes, $\frac{1}{\mu}$ is the life expectancy of mosquitoes, m is the number of mosquitoes per human host, a is the rate of biting on human by a single mosquito (number of bites per unit time), b is the proportion of infected bites on human that produce an infection, c is the transmission efficiency from human to mosquito. Bailey and Aron et al [3, 4] took into account that acquired immunity to malaria depends on exposure and that immunity is boosted by additional infections.

By 1970s Molineaux et al developed a more sophisticated malaria transmission model at Gorki in Nigeria [41]. Halloran et al in 1980 explicitly considered the population level effects of potential specific vaccines on malaria transmission control [41]. In 1991 Koella et al [30] incorporated the importance of immunity and age structure of the human community in the malaria model. Further work on acquired immunity in malaria was conducted by Aron et al and Bailey [3, 4].

Much has been done on modelling the dynamics of pneumonia and that of typhoid. Siato [56] modelled the dynamics of pneumonia transmission in a given population. Pitt [48] worked on a simple model for treating childhood pneumonia in hard-to-reach areas to estimate the ef-

fectiveness of mobile clinics and fixed community-based health services. Emaline [16] in his dissertation worked on a model to help in understanding of transmission dynamics of pneumonia in the presence of vaccination and treatment [16]. Cvjetanovic [11] developed epidemiological model of typhoid with age structure added to the population dynamics so that the dynamics of the disease in specific age groups could be studied and the effect of interventions in these groups analyzed. More work on typhoid has been done by Guzman [21] on direct and indirect transmission of typhoid fever, malaria, pneumonia and tuberculosis, demographic and geographic distribution, more so in Kenya.

2.3 Co-infections

Incidences of co-infection of malaria and any of the infectious diseases are common. Thus deterministic model of malaria and tuberculosis co-dynamics [55] was developed by Rwezaura et al to determine whether the two diseases will co-exist whenever their reproduction numbers exceed unity. Several other malaria co-infection models have been developed. Malaria-HIV co-infection model was developed by Nannyonga and Mugisha in 2011 in which they showed that both diseases co-exist if prevalence of one is low and that of the other is high. This idea had also been articulated by Bhunu and Mukandavire in their HIV/AIDS and tuberculosis co-infection model in which they incorporated antiretroviral therapy for the AIDS cases and treatment of latent forms of TB. Malaria-Rotavirus

and malaria-pneumonia among children were formulated by Lawi et al [33] in 2011. He deduced that reduction in malaria cases through prompt treatment reduces the number of new co-infections. In 2011 a model on the potential impact of IPT on malaria was developed by Prudhomme et al [49]. The model was used to predict the spread of resistant parasites in low and high transmission areas. The epidemiological impact of IPT against malaria in infants [1] was modeled by Amanda et al.

Most of the mathematical models discussed above are single disease models used to describe their transmission dynamics. While those on co-infection are based on the interaction of the diseases, their prevalence and their progress over time. None of the infection models consider the similarity of their symptoms and hence the misdiagnosis of one of the diseases on the dynamics of the other. This study therefore develops mathematical models on the impact of misdiagnosis and treatment on the dynamics of malaria concurrent and co-infection with pneumonia and typhoid.

Chapter 3

A Model for Misdiagnosis of Pneumonia as Malaria

3.1 Introduction

Pneumonia and malaria, the two leading causes of morbidity and mortality among Kenyans [16], often have overlapping clinical manifestations. Both of these diseases can be treated if diagnosed early, pneumonia with antibiotics and malaria with artemisinin-based combination therapy. However, because pneumonia presents with similar symptoms as malaria, many people are treated inappropriately with anti-malaria drugs [50]. This misdiagnosis is worrying because giving anti-malaria drugs to people with pneumonia delays their treatment with more appropriate drugs, increases morbidity and mortality rates due to pneumonia, and the increased risk of drug resistant malaria emerges. We develop a pneumonia-malaria model to investigate the effect of the dynamics of misdiagnosing pneumonia as malaria. We focus on the transmission trends

of the two diseases on the incidence of pneumonia misdiagnosis.

3.2 Model Description and Formulation

The model subdivides the total human population $N_H(t)$ and the total vector population $N_V(t)$ into various components depending on their disease status. At time t there are $S_H(t)$ and $S_V(t)$ susceptible humans and mosquitoes respectively, individuals infected with malaria $I_M(t)$, those infected with pneumonia but are not misdiagnosed $I_P(t)$ and $I_{MP}(t)$ are the human population who are dually infected with both malaria and pneumonia, $I_V(t)$ are the infectious mosquitoes and $I^d(t)$ are the individuals with pneumonia but have been misdiagnosed as having malaria. The model assumes no partial recovery for both diseases in human and mosquito. $N_H(t) = S_H(t) + I_M(t) + I_{MP}(t) + I^d(t) + I_P(t)$ and $N_V(t) = S_V(t) + I_V(t)$ are respectively the total human and vector populations at time t. The recruitment rate into susceptible humans and mosquito are Λ_H and Λ_V respectively. Susceptible humans become infectious with malaria and pneumonia at rates λ_M and λ_P respectively, while mosquitoes become infectious at rate λ_V. Individuals in the human population experience natural death rate of μ_H and similarly the mosquito natural death rate is μ_V. The proportion of the total number of bites that is infectious to humans is $\frac{I_V(t)}{N_V(t)}$. Let a be the per capita biting rate of mosquito, the number of potentially infectious bites to susceptible humans is $\frac{aI_V(t)}{N_H(t)}$. However the probability that a bite by an infected mosquito on a sus-

ceptible human will transfer the infection to human is c, thus susceptible humans acquire malaria at a rate;

$$\lambda_M = \frac{acI_V(t)}{N_H(t)} \tag{3.2.1}$$

Similarly susceptible individuals acquire pneumonia infection at the rate

$$\lambda_P = \frac{\beta(I_P(t) + \psi I^d(t) + \sigma I_{MP}(t))}{N_H(t)} \tag{3.2.2}$$

where β is the effective contact rate associated with pneumonia infection and the modification parameter ψ accounts for the risk of infectiousness of individuals in $I^d(t)$, while σ accounts for very high infectiousness in the double infected individuals $I_{MP}(t)$ whose pneumonia has been misdiagnosed. We define the force of infection of susceptible mosquito by infected human as

$$\lambda_V = \frac{\vartheta a(I_M(t) + \pi I_{MP}(t))}{N_H(t)} \tag{3.2.3}$$

where ϑ is the transmission probability for mosquito infection, π is modification parameter accounting for increased likelihood of infection of vectors by the highly infectious dually infected individuals. Malaria infectious humans recover at a rate of q (without regaining immunity) to join the susceptible class. Humans with pneumonia that are misdiagnosed progress to $I^d(t)$ class at rate of ρ. All malaria only infected individuals $I_M(t)$ and pneumonia only infected individuals $I_P(t)$ suffer disease induced death at the rate δ_M and δ_P respectively. However individuals in $I^d(t)$ class suffer disease induced death at rate $\varpi\delta_P$ where ϖ accounts for the increased

mortality due to prolonged time taken without the accurate diagnosis and right treatment. Individuals in $I^d(t)$ class acquire malaria infection at a rate $\gamma\lambda_M$ where the parameter γ accounts for increased rate of acquiring malaria due to the reduced immunity caused by prolonged stay with pneumonia. When pneumonia is misdiagnosed as malaria, the patient is given anti-malaria, pneumonia bacteria continue multiplying and the body defense system weakens and leads to easy infection by other parasites or death. In case the pneumonia infected person gets infected with malaria, the body weakens faster and the rate of death increases. Hence individuals in $I_{MP}(t)$ class suffer disease induced death rate of $\theta\delta_{MP}$, where θ accounts for accelerated deaths by malaria and pneumonia together. We assume that individuals in $I_M(t)$ class are treated with anti-malaria and do not get doubly infected with pneumonia. From the above definitions and explanations we have the following model of malaria and pneumonia concurrent and co-infection.

$$
\begin{aligned}
\frac{dS_H(t)}{dt} &= \Lambda_H - \lambda_M S_H(t) - \lambda_P S_H(t) - \mu_H S_H(t) + qI_M(t) \\
\frac{dI_M(t)}{dt} &= \lambda_M S_H(t) - \delta_M I_M(t) - \mu_H I_M(t) - qI_M(t) \\
\frac{dI_P(t)}{dt} &= \lambda_P S_H(t) - \rho I_P(t) - \delta_P I_P(t) - \mu_H I_P(t) \\
\frac{dI^d(t)}{dt} &= \rho I_P(t) + \xi I_{MP}(t) - \gamma\lambda_M I^d(t) - \varpi\delta_P I^d(t) - \mu_H I^d(t) \\
\frac{dI_{MP}(t)}{dt} &= \gamma\lambda_M I^d(t) - \xi I_{MP}(t) - \theta\delta_{MP} I_{MP}(t) - \mu_H I_{MP}(t) \\
\frac{dS_V(t)}{dt} &= \Lambda_V - \mu_V S_V(t) - \lambda_V S_V(t) \\
\frac{dI_V(t)}{dt} &= \lambda_V S_V(t) - \mu_V I_V(t)
\end{aligned}
\tag{3.2.4}
$$

3.3 Analysis of the Model

Based on the fact that model 3.2.4 monitors living populations, all the state variables and parameters are assumed to be nonnegative, $\forall\ t \geq 0$.

$$\Omega = (S_H(t), I_M(t), I_P, I_{MP}(t), I^d(t), I_V(t), S_V(t)) \in \mathbb{R}^7_+$$

is positively invariant domain, and thus, the model is epidemiologically and mathematically well posed. Solutions of the model remain positive for all the time $t \geq 0$ and are uniformly bounded in Ω. Thus we find it sufficient to consider the dynamics of the model (3.2.4) in this positively invariant domain Ω.

Lemma 3.1. *Let the initial data be*

$(S_H(0), S_v(0)) > 0, (I_M(0), I^d(0), I_{MP}(0), I_P(0), I_V(0)) \geq 0 \in \Omega.$

Then the solution set $(S_H(0), S_v(0) > 0, (I_M(t), I_{MP}(t), I^d(t), I_P(t), I_V(t))$ *of model* (3.2.4) *is positive for all* $t \geq 0$, *Rwezaura et al [55]*

3.3.1 Local stability of the disease-free equilibrium

In the absence of disease with all the infective classes set to zero the disease-free equilibrium of the system 3.2.4 denoted by D^0 is given by $D^0 = (S_H(t), I_M(t), I_P(t), I^d(t), I_{MP}(t), S_V(t), I_V(t)) = (\frac{\Lambda_H}{\mu_H}, 0, 0, 0, 0, \frac{\Lambda_V}{\mu_V}, 0)$ and the local behaviour of the system at or near the DFE is determined based on the threshold parameter, the basic reproduction number R_0 [12], and in calculating R_0 we use the next generation method [15] and the matrices F and V associated with the next generation method are as given below.

$$F = \begin{pmatrix} 0 & 0 & 0 & 0 & ac \\ 0 & \beta & \beta\psi & \beta\sigma & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ \vartheta cQ & 0 & 0 & \vartheta cQ & 0 \end{pmatrix}$$

and $V = \begin{pmatrix} r_1 & 0 & 0 & 0 & 0 \\ 0 & r_4 & 0 & 0 & 0 \\ 0 & -\rho & r_5 & -\xi & 0 \\ 0 & 0 & 0 & r_3 & 0 \\ 0 & 0 & 0 & 0 & \mu_V \end{pmatrix}$

Where $r_1 = q + \delta_M + \mu_H$, $r_2 = \beta - (\rho + \delta_P + \mu_H)$, $r_3 = \xi + \theta\delta_{MP} + \mu_H$,

$r_4 = \rho + \delta_P + \mu_H$, $r_5 = \varpi\delta_P + \mu_H$, $r_6 = h_P + \delta_P + \mu_H$, $Q = \frac{\Lambda_V \mu_H}{\Lambda_H \mu_V}$. The eigenvalues of the matrix FV^{-1} are $0, 0, \pm\sqrt{\frac{c^2 a\vartheta\Lambda_V\mu_H}{\mu_V^2\Lambda_H(\delta_M+\mu_H+q)}}$ and $\frac{\beta}{\delta_P+\mu_H+\rho} + \frac{\beta\rho\psi}{(\delta_P+\mu_H+\rho)(\mu_H+\varpi\delta_P)}$ The reproduction number for pneumonia R_{MP} which is the spectral radius of matrix FV^{-1} is given by $R_{MP} = \max\{R_M, R_P\}$. The spectral radius is the maximum of the absolute values of the eigenvalues of the square matrix FV^{-1}. Due to the high rates of misdiagnosing pneumonia, reproduction number for pneumonia is likely to be higher and therefore R_{MP} is the spectral radius. Thus

$$R_{MP} = \max\{\sqrt{\frac{c^2 a\vartheta\Lambda_V\mu_H}{\mu_V^2\Lambda_H(\delta_M+\mu_H+q)}}, \frac{\beta}{\delta_P+\mu_H+\rho} + \frac{\beta\rho\psi}{(\delta_P+\mu_H+\rho)(\mu_H+\varpi\delta_P)}\} \tag{3.3.1}$$

where

$R_M = \sqrt{\frac{c^2 a\vartheta\Lambda_V\mu_H}{\mu^2\Lambda_H(\delta_M+\mu_H+q)}}$ and

$R_{MP} = \frac{\beta}{\delta_P+\mu_H+\rho} + \frac{\beta\rho\psi}{(\delta_P+\mu_H+\rho)(\mu_H+\varpi\delta_P)}$

R_M the reproduction number for malaria gives the average number of secondary malaria infectious cases produced by a malaria infectious individual during her/his infectious period when introduced in a completely malaria susceptible population. Likewise R_{MP} gives the average number of new infections generated by a single pneumonia infected individual in a fully susceptible population [15]. The disease free equilibrium D^0 of the model (3.2.4) is locally asymptotically stable (LAS) if $R_{MP} < 1$ and unstable if $R_{MP} > 1$.

3.3.2 Global stability of the disease-free equilibrium

Let us consider a situation where the anti-malarials are in use such that most malaria infections are treated hence the possibility of global stability at DFE for a situation where there is continued misdiagnosis of pneumonia infection but a supposedly more controlled malaria is analyzed. In the study of the global behaviour of the model (3.2.4) we use the theorem by Castillo-chavez et al [7]. The model (3.2.4) is re-written as

$$\begin{aligned} \frac{dX}{dt} &= W(X, Z), \\ \frac{dZ}{dt} &= M(X, Z), M(X, 0) = 0 \end{aligned} \tag{3.3.2}$$

where $X = (S_H, S_V) \in \mathbb{R}^2_+$ denotes the number of uninfected individuals while $Z = (I_M, I_P, I^d, I_{MP}, I_V) \in \mathbb{R}^5_+$ denotes the number of infected individuals. The disease-free equilibrium is denoted by $D^0 = (X^*, 0)$.

$$\text{where } X^* = (\frac{\Lambda_H}{\mu_H}, \frac{\Lambda_V}{\mu_V}) \tag{3.3.3}$$

The conditions in (3.3.4) must be met to guarantee a local asymptotic stability:

$$\begin{aligned} \frac{dX}{dt} &= W(X, 0), X^* \text{ is } \textit{globally asymptotically stable } (GAS) \\ M(X, Z) &= AZ - \widehat{M}(X, Z), \widehat{M}(X, Z) \geq 0 \text{ for } (X, Z) \in \Omega \end{aligned} \tag{3.3.4}$$

where $A = D_z M(X^*, 0)$ is an M-matrix (the off-diagonal elements of A are non-negative). If the system (3.3.2) satisfies the conditions of (3.3.4)

then the theorem below holds.

Theorem 3.2. *The fixed point $D^0 = (X^*, 0)$ is a globally asymptotically stable equilibrium of system* (3.3.2) *if $R_{MP} < 1$ and if the assumptions in* (3.3.4) *are satisfied. Castillo-chavez et al [7].*

Proof. Consider

$$W(X,0) = \begin{pmatrix} \Lambda_H - \mu_H S_H \\ \Lambda_V - \mu_V S_V \end{pmatrix}$$

and

$$M(X,Z) = AZ - \widehat{M}(X,Z)$$

where

$$A = \begin{pmatrix} -r_1 & 0 & 0 & 0 & ac \\ 0 & r_2 & \beta\psi & \beta\sigma & 0 \\ 0 & \rho & -r_4 & \xi & 0 \\ 0 & 0 & 0 & -r_3 & 0 \\ \vartheta c & 0 & 0 & \vartheta cy & -\mu_V \end{pmatrix}$$

and

$$\widehat{M}(X,Z) = \begin{pmatrix} \widehat{M}_1(X,Z) \\ \widehat{M}_2(X,Z) \\ \widehat{M}_3(X,Z) \\ \widehat{M}_4(X,Z) \\ \widehat{M}_5(X,Z) \end{pmatrix} = \begin{pmatrix} acI_V(t)(1-\frac{S_H(t)}{N_H(t)}) \\ \beta(I_P(t) + \psi(I^d(t)) + \sigma I_{MP}(t)(1-\frac{S_H(t)}{N_H(t)})) \\ \gamma\lambda_M I^d(t) \\ -\gamma\lambda_M I^d(t) \\ \vartheta c(I_M(t) + \pi I_{MP}(t))(1-\frac{S_V(t)}{N_H(t)}) \end{pmatrix}$$

Thus $\widehat{M}_1, \widehat{M}_2, \widehat{M}_3, \widehat{M}_5 > 0$, but $\widehat{M}_4 < 0$. The conditions in (3.3.4) are

not satisfied, since $\widehat{M}(X,Z) < 0$ and hence D^0 may not be globally asymptotically stable $\square$

In the case of the misdiagnosed pneumonia, the DFE may not be globally asymptotically stable in the invariant region due to possible occurrence of backward bifurcation at $R_{MP} = 1$ [18]. And particularly in a case like this where there is sufficiently large disease induced death rate [7] because of untreated pneumonia.

3.4 Endemic Equilibrium and Stability analysis

We employ the Center Manifold theorem [6, 7]

Theorem 3.3. *Consider the following general system of ordinary differential equations with a parameter* η

$$\frac{dx}{dt} = f(x,\eta), \text{ with } f \in C^2(\mathbb{R}^n \times \mathbb{R})$$

Where 0 *is an equilibrium point for system* (3.2.4) *for all values of the parameter* η, *that is* $f(0,\eta) \equiv 0$ *and*

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

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

3. *Matrix G 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

$$\varrho^* = \sum_{kij=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0)$$
$$l^* = \sum_{ki=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \rho_B}(0,0)$$

then, the local dynamics of the system around the equilibrium point 0 is entirely determined by the sign of ϱ^* and l^*, and especially if $\varrho^* > 0$ and $l^* > 0$ then a backward bifurcation occurs. Particularly when:

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

2. *$l^* < 0$, $\varrho^* < 0$, when $\rho_B < 0$ with $|\rho_B| \ll 1$, $(0,0)$ is unstable; when $0 < \rho_B \ll 1$, $(0,0)$ is asymptotically stable and there exists a positive unstable equilibrium.*

3. *$l^* > 0$, $\varrho^* < 0$, when $\rho_B < 0$ with $|\rho_B| \ll 1$, $(0,0)$ is unstable, and there exists a negative and locally asymptotically stable equilibrium;*

when $0 < \rho_B \ll 1$, $(0,0)$ *is stable and there exists a positive unstable equilibrium.*

4. $l^* < 0$, $\varrho^* > 0$, *when* ρ_B *changes from negative to positive,* $(0,0)$ *changes its stability from stable to unstable. Correspondingly a negative equilibrium becomes positive and locally asymptotically stable.*

To apply the Center Manifold approach we make the following variable changes. Let $S_H(t) = x_1, I_M(t) = x_2, I_P(t) = x_3, I^d(t) = x_4, I_{MP}(t) = x_5, S_V(t) = x_6, I_V(t) = x_7$ and thus $N_H(t) = x_1 + x_2 + x_3 + x_4 + x_5$ and $N_V = x_6 + x_7$. We can therefore re-write the model system 3.2.4 in the form $\frac{dx}{dt} = F(x)$ where $X = (x_1, x_2, x_3, x_4, x_5, x_6, x_7)$ and $F = (f_1, f_2, f_3, f_4, f_5, f_6, f_7)$ as follows

$$
\begin{aligned}
\frac{dx_1}{dt} &= f_1 = \Lambda_H + qx_2 - \frac{acx_7x_1}{x_1 + \ldots + x_5} - \frac{\beta x_1(x_3 + \psi x_4 + \sigma x_5)}{x_1 + \ldots + x_5} - \mu_H x_1 \\
\frac{dx_2}{dt} &= f_2 = \frac{acx_2x_1}{x_1 + \ldots + x_5} - (q + \delta_M + \mu_H)x_2 \\
\frac{dx_3}{dt} &= f_3 = \frac{\beta(x_3 + \psi x_4 + \sigma x_5)x_1}{x_1 + \ldots + x_5} - (\rho + \delta_P + \mu_H)x_3 \\
\frac{dx_4}{dt} &= f_4 = \rho x_3 - \frac{\gamma acx_7x_4}{x_1 + \ldots + x_5} - (\varpi\delta_P + \mu_H)x_4 + \xi x_5 \\
\frac{dx_5}{dt} &= f_5 = \frac{\gamma acx_7x_4}{x_1 + \ldots + x_5} - (\xi + \theta\delta_{MP} + \mu_H)x_5 \\
\frac{dx_6}{dt} &= f_6 = \Lambda_V - \mu_V x_6 - \frac{\vartheta c(x_1 + yx_5)x_6}{x_1 + \ldots + x_5} \\
\frac{dx_7}{dt} &= f_7 = \frac{\vartheta c(x_2 + yx_5)x_6}{x_1 + \ldots + x_5} - \mu_V x_7
\end{aligned}
\tag{3.4.1}
$$

The Jacobian of the system 3.4.1 at disease free equilibrium is got by differentiating f_i with respect to x_i at DFE, where $i = 1...7$ and is given by

$$\begin{pmatrix} -\mu_H & q & \beta & -\beta\psi & -\beta\sigma & 0 & -ac \\ 0 & -r_1 & 0 & 0 & 0 & 0 & ac \\ 0 & 0 & r_2 & \beta\varphi & \beta\sigma & 0 & 0 \\ 0 & 0 & \rho & -r_4 & \xi & 0 & 0 \\ 0 & 0 & 0 & 0 & -r_3 & 0 & 0 \\ 0 & -\vartheta cQ & 0 & 0 & -\vartheta cyQ & -\mu_V & 0 \\ 0 & \vartheta cQ & 0 & 0 & \vartheta cyQ & 0 & -\mu_V \end{pmatrix}$$

From which it can be shown that the basic reproduction number calculated using the next generation matrix method by Driessche et al[15] is

$$R_{MP} = \frac{\beta(\mu_H + \psi\delta_{MP} + \rho\psi)}{(\delta_P + \mu_H + \rho)(\mu_H + \varpi\delta_P)} \tag{3.4.2}$$

Taking $\rho = \rho_B$ as a bifurcation parameter, then we can solve for ρ from $R_{MP} = 1$ which is also the bifurcation point and get

$$\rho = \rho_B = \frac{\mu_H(\delta_P + \mu_H + \varpi\delta_P - \beta) + \varpi\delta_P(\delta_P - \beta)}{\beta\psi - \mu_H - \varpi\delta_P} \tag{3.4.3}$$

We can show that the Jacobian of the system has a right eigenvector

given by $w = (w_1, w_2, w_3, w_4, w_5, w_6, w_7)^T$ where

$$\begin{aligned}
w_1 &= \frac{w_2(ac^2\vartheta Q) - q}{\mu_V} - \frac{(\psi\mu_H^2 + \beta\psi)\beta w_3}{\psi\mu_H^3} \\
w_2 &= w_2 > 0 \\
w_3 &= \frac{-\beta\psi w_4}{r_2} \\
w_4 &= \frac{\beta w_3}{r_4} \\
w_5 &= 0 \\
w_6 &= -\frac{\vartheta cQ w_2}{\mu_V} \\
w_7 &= \frac{\vartheta cQ w_2}{\mu_V}
\end{aligned}$$

and a left eigenvector $v = (v_1, v_2, v_3, v_4, v_5, v_6, v_7)^T$, where $Q = \frac{\Lambda_V \mu_H}{\mu_V \Lambda_H}$ and

$$\begin{aligned}
v_1 &= 0 \\
v_2 &= v_2 > 0 \\
v_3 &= -\frac{\rho v_4}{r_2} \\
v_4 &= -\frac{r_2 v_3}{\rho} \\
v_5 &= \frac{(\xi r_2 - \beta\psi\rho)v_4}{r_2 r_3} + \frac{ac^2\vartheta Q v_2}{\mu_V} \\
v_6 &= 0 \\
v_7 &= \frac{acv_2}{\mu_V}
\end{aligned}$$

After some manipulation involving the evaluation of the associated non-

vanishing partial derivatives of f it can be shown from

$$\begin{aligned} \varrho^* &= \sum_{kij=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0) \\ l^* &= \sum_{ki=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \rho_B}(0,0) \end{aligned}$$

that

$$l^* = w_3(v_3 + \psi v_4) > 0 \tag{3.4.4}$$

and

$$\varrho^* = \frac{\mu_H}{\Lambda_H}(v_3 + v_7 w_2 ac - v_4) > 0 \tag{3.4.5}$$

thus $\varrho^* > 0$ and $l^* > 0$ and the following result is ascertained

Theorem 3.4. *If ϱ^* and l^* satisfy the inequalities given in* (3.4.4) *and* (3.4.5) *then, the model* (3.2.4) *undergoes a backward bifurcation that occurs at $R_{MP} = 1$*

3.4.1 Sensitivity Analysis

We perform sensitivity analysis in order to determine the parameters which have high impact on R_{MP} that should be targeted for intervention strategies. In order to determine how best to reduce human mortality and morbidity due to pneumonia, it is necessary to know the relative importance of the different factors responsible for its spread and prevalence. The sensitivity indices of the reproduction number are computed using

the approach by Chitnis et al [8] as follows:

$$\Upsilon_B^{R_{MP}} = \frac{\partial R_{MP}}{\partial B}\frac{B}{R_{MP}} \tag{3.4.6}$$

to each of the parameters $\delta_P, \psi, \rho, \varpi$. For example the sensitivity index $\Upsilon^{R_{MP}}$ of R_{MP} to the parameter ρ is given by

$$\Upsilon^{R_{MP}} = \frac{\partial R_{MP}}{\partial \rho}\frac{\rho}{R_{MP}} = \frac{\rho r_4 r_5 \ln r_4 + \psi}{r_5 + \rho\psi}. \tag{3.4.7}$$

Similarly we compute sensitivity indices of the reproduction number R_{MP} to the parameters δ_P, ψ and ϖ, and compare the results to find out the most sensitive parameter. The sensitivity indices to the parameters and the values of the respective parameters used are given in Table 1

Table 1: Sensitivity indices

parameters	value	reference	sensitivity index
δ_P	$7.8335 \times 10^{-4}\text{day}^{-1}$	[61]	-4.938×10^{-4}
ψ	$0.00021\,\text{day}^{-1}$	Assumed	2.0785×10^{-4}
ρ	$0.08\,\text{day}^{-1}$	[16]	1.9255×10^{-1}
ϖ	$1.00005\,\text{day}^{-1}$	[16]	-1.6006×10^{-5}

The most sensitive parameter is the misdiagnosis rate ρ. This suggests that correct diagnosis in treatment of pneumonia has positive impact in

controlling pneumonia in the community. Reducing the rate of misdiagnosis through laboratory tests would have the largest effect on pneumonia transmission. It can also be noted that the moment ρ increases or decreases, ψ also increases or decreases considerably.

3.5 A case of prompt and accurate diagnosis of pneumonia, $\rho \simeq 0$

3.5.1 Local Stability of Disease-Free Equilibrium

After analyzing the model system of misdiagnosis it is in order to gain insight into the dynamics of the pneumonia-malaria concurrent and co-infection model in which pneumonia is promptly and accurately diagnosed and treatment given in time. We have the model where $I^d(t) = I_{MP}(t) = 0$ given by

$$\begin{aligned}
\frac{dS_H(t)}{dt} &= \Lambda_H - \lambda_M S_H(t) - \lambda_P S_H(t) - \mu_H S_H(t) + qI_M(t) \\
\frac{dI_M(t)}{dt} &= \lambda_M S_H(t) - \delta_M I_M(t) - \mu_H I_M(t) - qI_M(t) \\
\frac{dI_P(t)}{dt} &= \lambda_P S_H(t) - h_P I_P(t) - \delta_P I_P(t) - \mu_H I_P(t) \\
\frac{dS_V(t)}{dt} &= \Lambda_V - \mu_V S_V(t) - \lambda_V S_V(t) \\
\frac{dI_V(t)}{dt} &= \lambda_V S_V(t) - \mu_V I_V(t)
\end{aligned} \tag{3.5.1}$$

Where

$$\begin{aligned}\lambda_M &= \frac{acI_V(t)}{N_H(t)} \\ \lambda_P &= \frac{\beta I_P(t)}{N_H(t)} \\ \lambda_V &= \frac{\vartheta a I_M(t)}{N_H(t)}\end{aligned}$$

and the total population of humans and the vector are given by $N_H(t) = S_H(t) + I_M(t) + I_P(t)$ and $N_V = S_V(t) + I_V(t)$ respectively. h_P is the rate at which those pneumonia infectious persons get healed on receiving treatment and join the susceptible.

The region $\phi_T = (S_H(t), I_M(t), I_V(t), I_P(t), S_V(t)) \in \mathbb{R}^5_+$ is positively invariant and attracting and the solution starting in ϕ_T approach, enter or stay in ϕ_T. Thus the dynamics of the model (3.5.1) is analyzed in ϕ_T. The DFE is given as

$$D^0 = (S_H(t), I_M(t), I_P(t), I_V(t), S_V(t)) = (\tfrac{\Lambda_H}{\mu_H}, 0, 0, 0, \tfrac{\Lambda_V}{\mu_V})$$

The basic reproduction number R^+_{MP} when there is accurate diagnosis of pneumonia is determined by using the next generation approach. Thus we have;

$$F = \begin{pmatrix} 0 & 0 & ac \\ 0 & \beta & 0 \\ \vartheta cT & 0 & 0 \end{pmatrix}$$

and

$$V = \begin{pmatrix} r_1 & 0 & 0 \\ 0 & r_6 & 0 \\ 0 & 0 & \mu_H \end{pmatrix}$$

The eigenvalues of the matrix FV^{-1} are $\frac{\beta}{h_P+\delta_p+\mu_H}$ and $\pm\sqrt{\frac{ac^2\Lambda_V\mu_H}{\mu_V^2\Lambda_V(\delta_M+\mu_H+q)}}$ Therefore the reproduction number R_{MP}^+ which is the spectral radius of matrix FV^{-1} is given by $R_{MP}^+ = \max\{R_M, R_P\}$. Where the reproduction number of malaria

$R_M = \sqrt{\frac{ac^2\Lambda_V\mu_H}{\mu_V^2\Lambda_V(\delta_M+\mu_H+q)}}$ and the reproduction number of pneumonia

$R_{MP}^+ = \frac{\beta}{h_P+\delta_p+\mu_H}$.

Consequently the reproduction number associated with pneumonia is $R_{MP}^+ = \frac{\beta}{h_P+\delta_p+\mu_H}$.

The reproduction number R_{MP}^+ measures the number of infections generated by a single pneumonia infected individual during his or her infectious period when introduced in a susceptible population.
We observe that $R_{MP}^+ = \frac{\beta}{h_P+\delta_p+\mu_H} \ll R_{MP} = \frac{\beta}{\delta_P+\mu_H+\rho} + \frac{\beta\rho\psi}{(\delta_P+\mu_H+\rho)(\mu_H+\varpi\delta_P)}$.
It can be noted that as ρ increases, the rate at which susceptible individuals are infected with pneumonia also increases.

3.5.2 Global Stability of DFE

Theorem 3.5. *The DFE $[D^0]$ of model 3.5.1 is globally asymptotically stable (GAS) whenever $R_{MP}^+ < 1$ and unstable if $R_{MP}^+ > 1$*

Proof. The proof is based on using comparison theorem [32]

The equation of the infected components in the model 3.5.1 can be written as

$$\begin{pmatrix} \frac{dI_M(t)}{dt} \\ \frac{dI_P(t)}{dt} \\ \frac{dI_V(t)}{dt} \end{pmatrix} = (F-V)\begin{pmatrix} I_M(t) \\ I_P(t) \\ I_V(t) \end{pmatrix} - (1-\frac{S_H(t)}{N_H(t)})\begin{pmatrix} ac & 0 & 0 \\ 0 & \beta & 0 \\ \vartheta cQ & 0 & 0 \end{pmatrix}$$

Where F and V are as defined in section 3.3 and

$$F-V = \begin{pmatrix} -r_1 & 0 & ac \\ 0 & \beta - r_6 & 0 \\ \vartheta cT & 0 & -\mu_H \end{pmatrix}$$

Since $S \leq N \; \forall \; t \geq 0$ in ϕ_T then

$$\begin{pmatrix} \frac{dI_M(t)}{dt} \\ \frac{dI_P(t)}{dt} \\ \frac{dI_V(t)}{dt} \end{pmatrix} \leq (F-V)\begin{pmatrix} I_M(t) \\ I_P(t) \\ I_V(t) \end{pmatrix}$$

From the fact that eigenvalues of the matrix $F-V$ all have negative real parts, it follows that the linearized differential inequality above is stable whenever $R^+_{MP} < 1$. Negative eigenvalues is an indication of the disease being driven back to steady state. Consequently there is no more infection and $(I_M(t), I_P(t), I_V(t)) \to (0,0,0)$ as $t \to \infty$. Substituting $I_M(t) = I_P(t) = I_V(t) = 0$ in the first equation of system (3.5.1) gives $S(t) \to S^0$ as $t \to \infty$. Thus $(S(t), I_M(t), I_P(t), I_V(t)) \to (S^0, 0, 0, 0)$ as $t \to \infty$, where S^0 is the population of susceptible individuals at $t = 0$ and hence D^0 is globally asymptotically stable if $R^+_{MP} < 1$. This is

contrary to the case of misdiagnosis of pneumonia where the DFE is globally asymptotically unstable and a backward bifurcation occcurs. The above result shows that in the absence of misdiagnosis, pneumonia will be eliminated if the threshold R^{+}_{MP} can be brought to a value less than unity. □

3.5.3 Global stability of endemic equilibrium

In this section we study the global stability of the endemic equilibrium of (3.5.1) using the Lyapunov second method also known as Lyapunov direct method. We use the Lyapunov function $L_\varepsilon(x_1, x_2, x_3, ...x_n) = \sum_{i=1}^{n} C_i(x_i - x_i^* - x_i^* log\frac{x_i}{x_i^*})$ to prove the global stability of the endemic equilibrium $E^*(S_H^*(t), I_M^*(t), I_P^*(t), S_V^*(t), I_V^*(t))$.

Theorem 3.6. *If $R_0 > 1$ then the unique endemic steady state E^* of 3.5.1is Globally Asymptotically stable in the interior of ϕ_T.*

Define Lyapunov function

$L_e : (S_H, I_M, I_P, S_V, I_V) \in \phi_T : S_H, I_M, I_P, S_V, I_V > 0 \to \mathbb{R}$

by

$L_e : (S_H(t), I_M(t), I_P(t), S_V(t), I_V(t)) = \lambda_V(S_H - S_H^* - S_H^* log\frac{S_H}{S_H^*}) + \lambda_V(I_M - I_M^* - I_M^* log\frac{I_M}{I_M^*}) + \lambda_V(I_P - I_P^* - I_P^* log\frac{I_P}{I_P^*}) + \lambda_M(S_V - S_V^* - S_V^* log\frac{S_V}{S_V^*}) + \lambda_M(I_V - I_V^* - I_V^* log\frac{I_V}{I_V^*})$

L_e is C^1 on the interior of ϕ_T, E^* is the global minimum of L_e on ϕ_T and $L_e : (S_H^*, I_M^*, I_P^*, S_V^*, I_V^*) = 0$. The time derivative of L_e computed

along the solution of system (3.5.1) is

$\frac{dL_e}{dt} = \lambda_V(1 - \frac{S_H^*}{S_H})\frac{dS_H}{dt} + \lambda_V(1 - \frac{I_M^*}{I_M})\frac{dI_M}{dt} + \lambda_V(1 - \frac{I_P^*}{I_P})\frac{dI_P}{dt} + \lambda_M(1 - \frac{S_V^*}{S_V})\frac{dS_V}{dt} + \lambda_M(1 - \frac{I_V^*}{I_V})\frac{dI_V^*}{dt}$

$\frac{dL_e}{dt} = \lambda_V(1 - \frac{S_H^*}{S_H})(\Lambda_H - (\lambda_M + \lambda_P + \mu_H)S_H + qI_M) + \lambda_V(1 - \frac{I_M^*}{I_M})(\lambda_M S_H - (\delta_M + \mu_H + q)I_M)) + \lambda_V(1 - \frac{I_P^*}{I_P})(\lambda_P S_H - (h_P + \delta_P + \mu_H)I_P)) + \lambda_M(1 - \frac{S_V^*}{S_V})(\Lambda_V - (\mu_V + \lambda_V)S_V)) + \lambda_M(1 - \frac{I_V^*}{I_V})(\Lambda_V S_V - \mu_V I_V)$

Using $\Lambda_H = (\lambda_M + \lambda_P + \mu_H)S_H^* + qI_M^*$, $\Lambda_V = (\mu_V + \lambda_V)S_V^*$ to rewrite this, we get

$\frac{dL_e}{dt} = -\lambda_V\frac{(S_H - S_H^*)^2}{S_H}(\lambda_M + \lambda_P + \mu_H) + \lambda_V\frac{(I_M - I_M^*)}{I_M}(\lambda_M S_H - r_1 I_M) + \lambda_V\frac{(I_P - I_P^*)}{I_P}(\lambda_P S_H - (h_P + \delta_P + \mu_H)I_P) - \lambda_M(\frac{(S_V - S_V^*)^2}{S_V})(\lambda_V^* - \lambda_V) + \lambda_M\frac{I_V - I_V^*}{I_V}(\lambda_V S_V - \mu_V I_V) \leq 0$

$\lambda_V\frac{(I_P - I_P^*)}{I_P}(\lambda_P S_H - (h_P + \delta_P + \mu_H)I_P)$ is negative since due to correct diagnosis $h_p \to \infty$ as $\lambda_P \to 0$. Which is the same case with $\lambda_V\frac{(I_M - I_M^*)}{I_M}(\lambda_M S_H - r_1 I_M)$, as $q \to \infty$ due to the availability of anti-malaria $\lambda_M \to 0$. $\frac{dL_e}{dt}$ is less or equal to zero, with equality only if $S_H = S_H^*$, $I_M = I_M^*$, $I_P = I_P^*$, $S_V = S_V^*$ and $I_V = I_V^*$. Hence the largest compact invariant set in $(S_H, I_M, I_P, S_V, I_V) \in \phi_T : \frac{dL_e}{dt} = 0$ is only E^*, where E^* is the endemic equilibrium point. This implies that by the asymptotic stability theorem [35], the endemic steady state E^* is globally asymptotically stable in the interior of ϕ_T which proves theorem 3.6.

3.6 Numerical simulations

In this section we use numerical simulation in order to give graphical projection of the results of the model 3.2.4. Some of the parameters were obtained from literature, some were assumed or made varying for realistic simulation results. The simulations are done with varying initial conditions. The parameter values used are in Table2.

Table 2: Parameter Values

Parameter Description	Symbol	Value	Source
Human recruitment rate	Λ_H	$8.748 \times 10^{-3}\,\text{day}^{-1}$	[9]
Mosquito recruitment rate	Λ_V	$0.071\,\text{day}^{-1}$	[33]
Human natural mortality rate	μ_H	$2.740 \times 10^{-3}\,\text{day}^{-1}$	[9]
Mosquito natural mortality rate	μ_V	$0.1429\,\text{day}^{-1}$	[8]
Transmission probability for malaria in humans	a	$0.5\,\text{day}^{-1}$	[8]
Biting rate of mosquito	c	$0.125\,\text{day}^{-1}$	Assumed
Transmission probability for malaria in mosquitoes	ϑ	$Variable\,\text{day}^{-1}$	Variable
Pneumonia contact rate	β	$Variable\,\text{day}^{-1}$	Variable
Rate of misdiagnosis	ρ	$0.08\,\text{day}^{-1}$	Estimate
Malaria induced death rate	δ_M	$4.49312 \times 10^{-4}\,\text{day}^{-1}$	[33]
Pneumonia induced death rate	δ_P	$7.8335 \times 10^{-4}\,\text{day}^{-1}$	[66]
Pneumonia and malaria induced death rate	δ_{MP}	$9.6445 \times 10^{-4}\,\text{day}^{-1}$	
Recovery rate from malaria	q	$0,00655\,\text{day}^{-1}$	Assumed
Modification parameters	ψ, σ, π	$0.00021, 0.00025, 0.007$	Assumed
Modification parameters	ϖ, θ, γ	$1.00005, 0.05, 0.8883$	Assumed

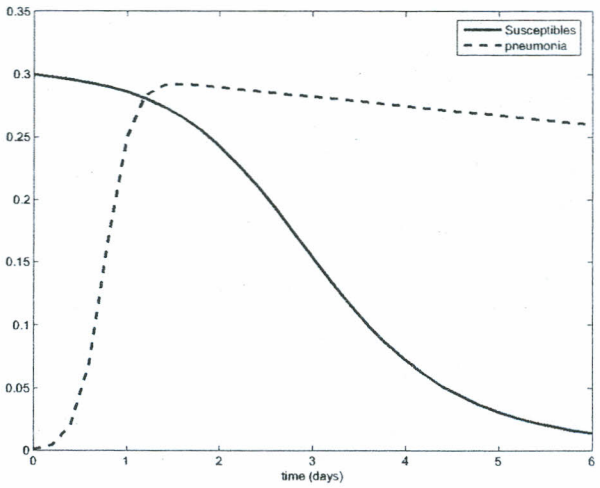

Figure 3.6.1: misdiagnosing pneumonia as malaria sharply increases the population of pneumonia infectives, which only stablizes at high level of infection, and the susceptible decrease

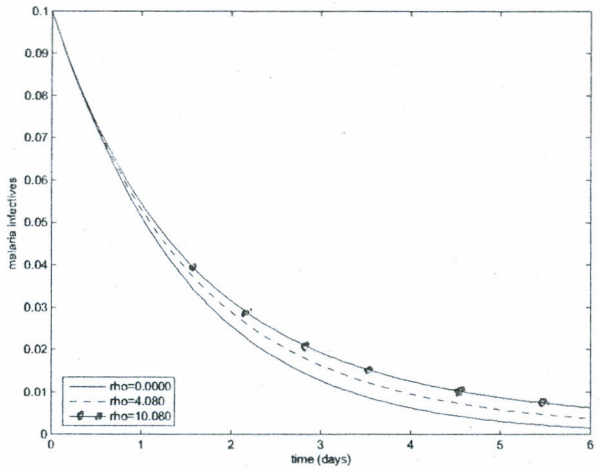

Figure 3.6.2: Simulation showing the effect of misdiagnosing pneumonia as malaria. Despite the overuse of anti-malaria, malaria persists and rises with rise in rate of misdiagnosis

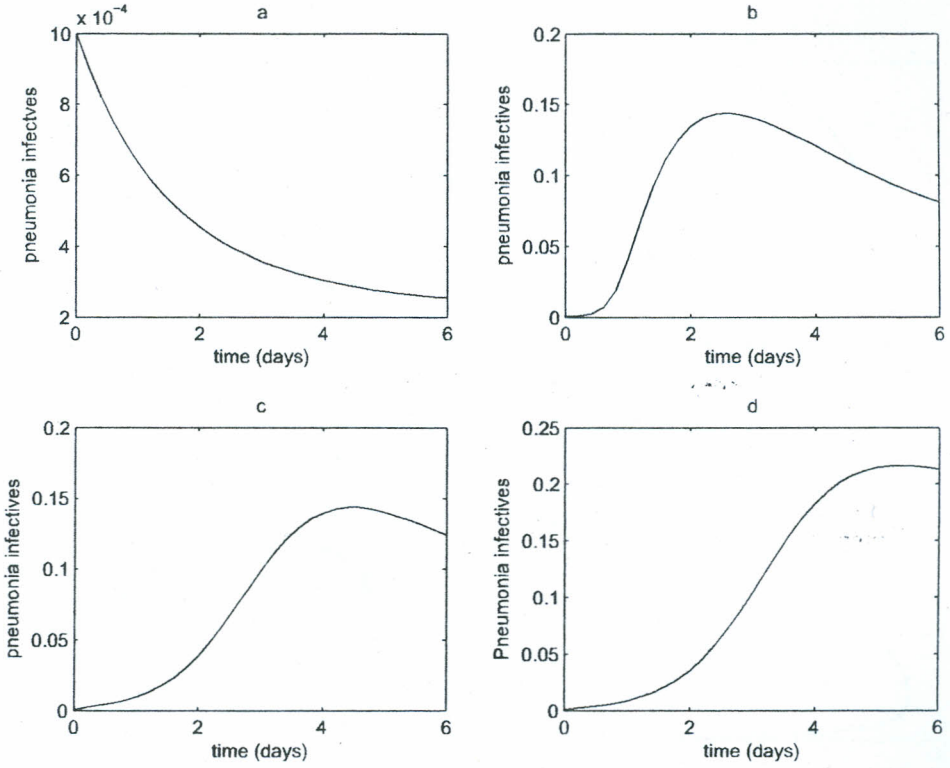

Figure 3.6.3: Simulations of model 3.2.4 with increasing levels of misdiagnosis to show the effect of increasing misdiagnosis on pneumonia transmission, with $\rho = 0.000$, $\rho = 0.080$, $\rho = 1.080$, $\rho = 2.080$

It is evident that increasing rates of misdiagnosis of pneumonia result into increased pneumonia infection. At no misdiagnosis, $\rho = 0$, the pneumonia infection decreases towards zero. But once there is misdiagnosis pneumonia infection incredibly increases

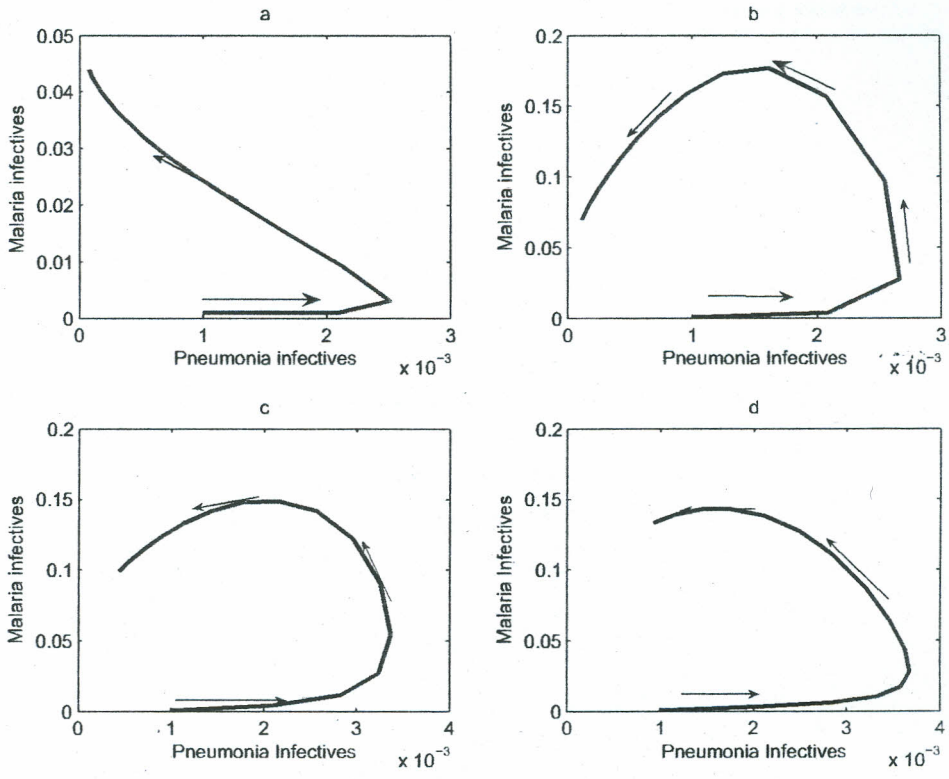

Figure 3.6.4: Simulations of malaria and pneumonia with increasing misdiagnosis, with$\rho = 0.0800$, $\rho = 1.080$, $\rho = 2.080$, $\rho = 4.080$

In the presence of pneumonia malaria persists despite malaria treatment. And since misdiagnosis of pneumonia leads to increased pneumonia transmission, malaria transmission equally rises as is evident from figure 'a' to 'd'.

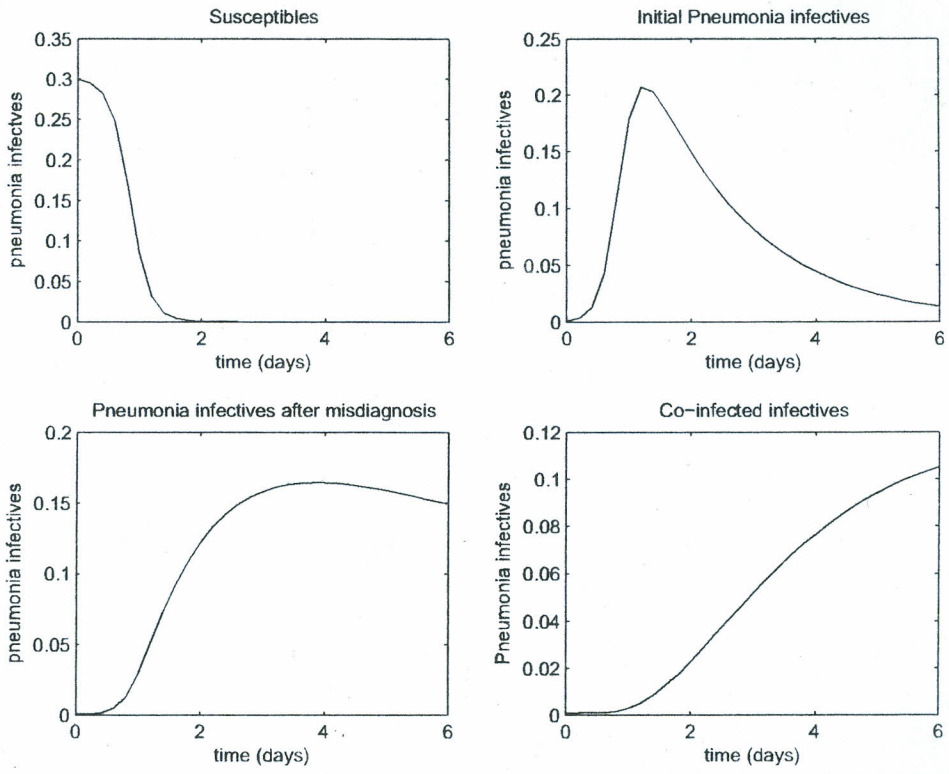

Figure 3.6.5: Simulation of model 3.2.4 showing the plots of the dynamical evolution of pneumonia in the different classes against time

. In the susceptibles pneumonia reduces to zero infection, in the initially infected, pneumonia infection rises then decreases overtime. when there is pneumonia misdiagnosis and co-infection, there is an exponential increase in pneumonia.

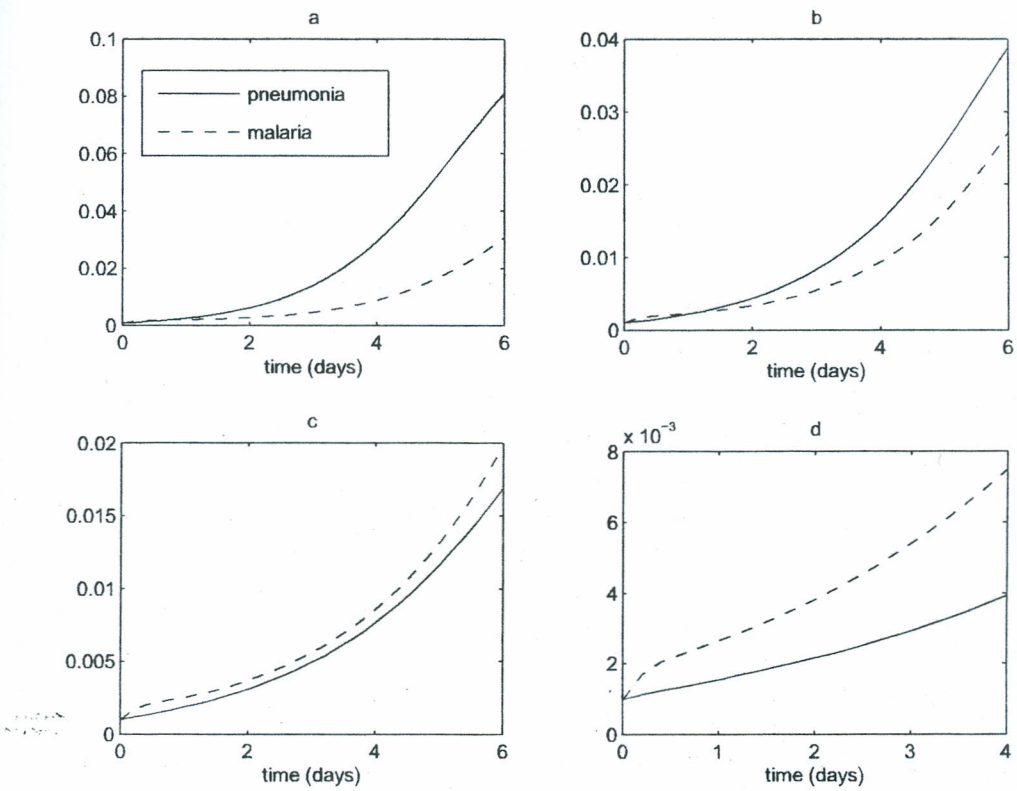

Figure 3.6.6: Simulation of model 3.2.4 comparing Pneumonia and malaria in the presence of increasing misdiagnosis of pneumonia
The diagram depicts that misdiagnosis of pneumonia concomitantly leads to increasing levels of malaria.

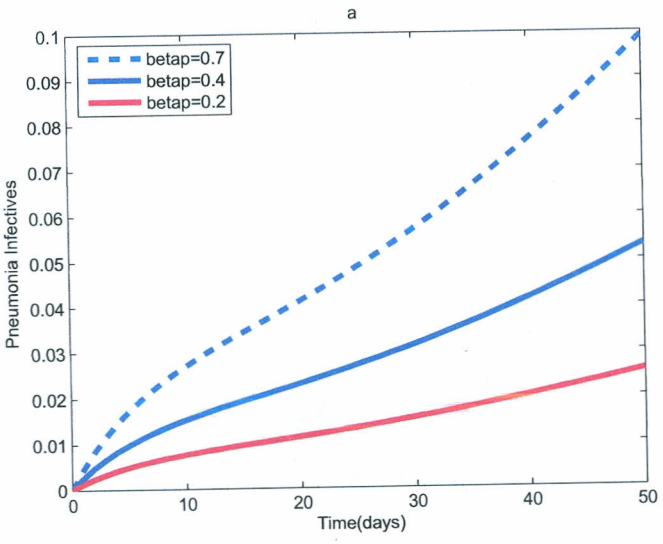

Figure 3.6.7: This is a simulation showing the effect of varying the pneumonia contact rate β: A higher contact rate greatly increases pneumonia infectives, and the more the misdiagnosis, the higher the rate of contact $.\beta_p$

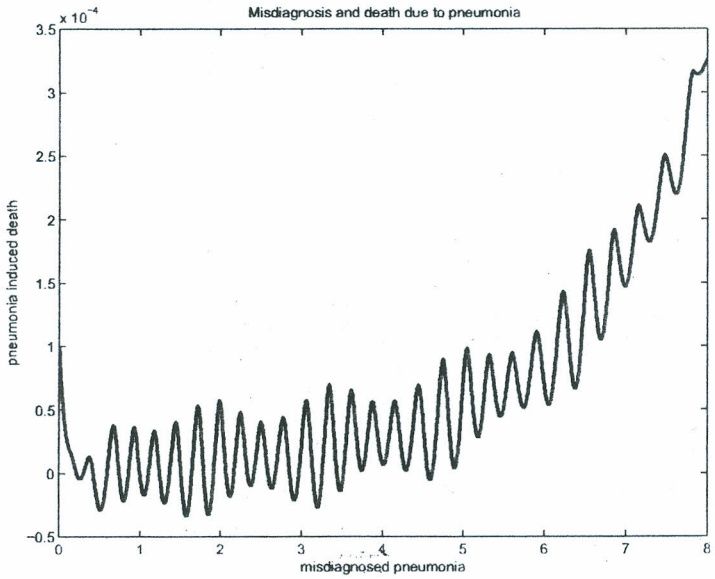

Figure 3.6.8: Death increases with misdiagnosis

3.7 SUMMARY

In many health facilities especially peripheral health centers, a diagnosis of malaria is based solely on clinical features such as fevers [38]. Although the approach may reduce morbidity, many infectious diseases mimic malaria and this strategy leads to high rates of over-diagnosis and over-treatment of malaria with consequent under-diagnosis of other fever causing disorders such as pneumonia and typhoid. Pneumonia accounts for extensive personal suffering and death which has been elevated more by the high prevalence of HIV that renders the body weak and is easily attacked by pneumonia causing bacteria. The recent commissioned pneumonia vaccine may not benefit the majority of Kenyans due to its exorbitant cost and no equipment for its delivery and storage in the more easily accessible health centers. This translates to increased susceptibility to pneumonia. And since pneumonia is highly infectious and fatal, which is elevated by the nature of our habitat(highly dusty and never disinfected), many more lives continue to be lost particularly due to it being misdiagnosed as malaria. Yet the pneumonia treating drugs are quite affordable.

The work has addressed the co-dynamics between malaria and pneumonia using deterministic mathematical model which incorporates the intricate issue of misdiagnosing pneumonia as malaria.An important epidemic threshold parameter R_0, the basic reproduction number which indicates the population level impact of an infectious disease classifies the long term progression of the disease. When $R_0 < 1$ and when $R_0 > 1$,

the DFE is stable and unstable respectively.

From the results of subsection 3.3.2 there is evidence that the basic reproduction number being less than unit $R_{MP} < 1$ alone does not guarantee the global dynamics of the disease transmission. The global stability of the DFE steady state does not hold due to the model undergoing backward bifurcation. A backward bifurcation occurs when the delayed effect for treatment is strong. Therefore driving R_{MP} value below one is not enough to eradicate the disease.

When pneumonia is not diagnosed the infected continue to mingle with the susceptible and continue infecting them. Worse still the concentration of the bacteria in the pneumonia infected persons rises and this makes the misdiagnosed persons even more infectious, infecting a large number of people. The increased frequency of cough easily contaminates the environment thus infecting many more people as seen in figure 3.6.2. Those admitted with misdiagnosed pneumonia are even a greater risk because they are put together with other sick people who have a weak immune response and are highly predisposed to pneumonia infection. If pneumonia develops in people who are already hospitalized for other conditions death rates can be much higher. Hospital acquired pneumonia is particularly difficult to identify in the hospitalized patients because many already have similar symptoms including fever or signs of lung infection which makes it more difficult for the health care worker to guess that there is another new infection [66]. Incidences of hospital pneumonia are much greater and fatal.

The backward bifurcation in a disease model has important qualitative implications. Small changes in certain parameters can produce large changes in equilibrium behaviour. In backward bifurcation when the R_{MP} just gets greater than one the disease can invade to relatively high endemic level. In R_{MP} the most sensitive parameter after an individual has got into contact with pneumonia is the rate of misdiagnosis ρ, increasing or decreasing ρ also increases or decreases R_{MP}. Despite extensive use of anti-malarials, the presence of pneumonia enhances the existence of malaria. The compromised immunity of the pneumonia infectives makes them easy to be infected as seen in figure 3.6.3 and figure 3.6.4. Also pneumonia induced increase in susceptibility to malaria infection significantly increases the number of new cases of the dual malaria pneumonia co-infection. A double infection with malaria worsens the condition and makes the individual even more infectious with malaria and pneumonia. Comparing the reproduction number $R_{MP} = \frac{\beta}{\delta_P+\mu_H+\rho} + \frac{\beta\rho\psi}{(\delta_P+\mu_H+\rho)(\mu_H+\varpi\delta_P)}$ with the one where there is accurate diagnosis, R^{+}_{MP}, the time an individual takes with pneumonia $\frac{1}{\delta_P+\mu_H+\rho} + \frac{\rho\psi}{(\delta_P+\mu_H+\rho)(\mu_H+\varpi\delta_P)}$ has increased thus raising the probability of infecting more people, consequently increasing β the effective contact rate with pneumonia infectious person, which continues to increase R_{MP} and causes pneumonia to reach high endemic level.

Pneumonia can evolve rapidly and become severe even in previously fit people. And mortality becomes high despite availability of effective antibiotics. A slight increase in β, (figure 3.6.7), which is occasioned

by the increase of ρ increases R_{MP} to a value greater than unity, and consequently pneumonia rises to high endemic levels. And since there is a high percentage of misdiagnosing pneumonia as malaria, the level of pneumonia infection rises, and also the longer one stays with pneumonia the more infectious one becomes. And because of no treatment δ_P and δ_{MP} increase compounded by the fact that pneumonia is a fast killer.

A major conclusion from our study is that if there is accurate diagnosis of the disease then all the diseases can be reduced if the basic reproduction number is reduced below unity. If there is any degree of misdiagnosis then $R_{MP} < 1$ alone is not sufficient for the diseases to be eliminated since there are high chances of backward bifurcation occurring.

Chapter 4

A model for Misdiagnosis of Typhoid as Malaria

4.1 Introduction

In endemic areas most cases of malaria are diagnosed on clinical grounds without laboratory confirmation of parasitaemia. The diagnosis is based on the presence of fever, or history of fever. Since fever is a symptom of many illnesses, many people treated for malaria are not actually infected with malaria parasites. There are always delays in establishing the correct diagnosis as a result of the clinical status, accounting to high morbidity and mortality due to typhoid. further more, a large proportion of typhoid fever infection take the form of carriers. These are those people who are infected but do not show any signs of infection, but are equally infectious as the symptomatic infectives. Because of delays in treating typhoid, it is a major killer in this combination.

4.2 Model Description and Formulation

The total human population $N_H(t)$ is sub-divided into compartments, namely susceptible $S_H(t)$, those infectious with malaria $I_M(t)$, individuals with symptoms of typhoid but have not misdiagnosed $I_T(t)$, those dually infected with symptomatic malaria and Typhoid $I_{MT}(t)$, those infected with typhoid but are misdiagnosed for malaria $I^d(t)$, and carriers of the typhoid bacteria who do not show the typhoid symptoms $I^C(t)$ [64]. For the vector, S_V represent the susceptible and I_V are the infectious class. The susceptible humans and mosquitoes are recruited into their populations at the rates of Λ_H and Λ_V respectively. $N_H(t) = S_H(t) + I_M(t) + I_{MT}(t) + I_T(t) + I^C(t) + I^d(t)$ is the total human population, while $N_V(t) = S_V(t) + I_V(t)$ represent the total vector population, at time t. Susceptible humans acquire malaria infection at the rate of λ_M and typhoid at the rate of λ_T, while mosquitoes become infectious with malaria at the rate λ_V. q is the rate of human recovery into the susceptible from being infectious with malaria. Our model excludes partial immunity. All individual humans and mosquitoes in different human and vector subgroups suffer natural death rates of μ_H and μ_V respectively. Individuals in classes $I_T(t)$ and $I_{MT}(t)$ can have their typhoid status misdiagnosed as malaria and progress to $I^d(t)$ class at the rate of ρ and ξ correspondingly. Typhoid infected individuals who have been misdiagnosed develop a much weaker immunity due to the rise in bacteria concentration thus can easily get malaria infection at the rate of $\gamma\lambda_M$, where γ is the modification parameter accounting for increased rate of malaria infection. ζ accounts for

the people who become carriers on infection [64] and g accounts for the the individuals who get typhoid infection, are misdiagnosed and as the body fights the bacteria, the bacteria hides in the gallbladder [64]. These people also become carriers and keep shedding the bacteria for years, unless they get accurately diagnosed and treated. Otherwise these people can cause high endemic disease levels or even epidemic situations [11]. L is the rate at which those who happen to be treated rejoin the susceptible individuals. Individuals in the $I_M(t)$ and $I_T(t)$ classes suffer disease induced deaths at the rates δ_M and δ_T respectively. However those in $I^d(t)$ class suffer disease induced death at rate $\varpi\delta_T$, where ϖ accounts for increased mortality due to prolonged time taken without the right diagnosis and treatment. Individuals in $I_{MT}(t)$ class suffer disease induced death at the rate $\theta\delta_{MT}$ where θ accounts for accelerated deaths due to immunosuppression by the untreated typhoid and the newly acquired malaria in dual infection. Susceptible humans acquire malaria at a rate

$$\lambda_M = \frac{abI_M(t)}{N_H(t)} \tag{4.2.1}$$

where a is the transmission probability per bite and b is the biting rate of mosquito. The rate of infection of susceptibles with typhoid is

$$\lambda_T = \frac{\beta(I_T(t) + \eta I^d(t) + \sigma I_{MT}(t) + \alpha I^C(t))}{N_H(t)} \tag{4.2.2}$$

Where β is the effective transmission rate of typhoid on contact and η, σ and α account for increased infection by a misdiagnosed, dually infected

individual, and a carrier respectively. The rate of infection of susceptible mosquito by infected human is given as

$$\lambda_V = \frac{\kappa b(I_M(t) + \pi I_{MT}(t))}{N_H(t)}. \tag{4.2.3}$$

κ is the transmission probability for mosquito infection and b is the biting rate of mosquito, π is the modification parameter accounting for increased likelihood of infection of vectors by people in $I_{MT}(t)$ class. We assume no simultaneous infection. With the above definitions and assumptions, we have the following model

$$\begin{aligned}
\frac{dS_H(t)}{dt} &= \Lambda_H + qI_M(t) + LI_T(t) - \lambda_M S_H(t) - \lambda_T S_H(t) - \zeta\lambda_T S_H(t) - \mu_H S_H(t) \\
\frac{dI_M(t)}{dt} &= \lambda_M S_H(t) - qI_M(t) - \delta_M I_M(t) - \mu_H I_M(t) \\
\frac{dI_T(t)}{dt} &= \lambda_T S_H(t) - \rho I_T(t) - LI_T(t) - \delta_T I_T(t) - \mu_H I_T(t) \\
\frac{dI^d(t)}{dt} &= \rho I_T(t) + \xi I_{MT}(t) - \gamma\lambda_M I^d(t) - \varpi\delta_T I^d(t) - gI^d - \mu_H I^d(t) \\
\frac{dI_{MT}(t)}{dt} &= \gamma\lambda_M I^d(t) - \xi I_{MT}(t) - \theta\delta_{MT} I_{MT}(t) - \mu_H I_{MT}(t) \\
\frac{dI^C(t)}{dt} &= \zeta\lambda_T S_H(t) + gI^C(t) - \mu_H I^C(t) \\
\frac{dS_V(t)}{dt} &= \Lambda_V - \mu_V S_V(t) - \lambda_V S_V(t) \\
\frac{dI_V(t)}{dt} &= \lambda_V S_V(t) - \mu_V I_V(t)
\end{aligned} \tag{4.2.4}$$

4.3 Analysis of the Model

Since the model monitors living populations, all the state variables and parameters are assumed to be non-negative, $\forall t \geq 0$. This shows that the biologically feasible region

$$\phi_{TM} = (S_H(t), I_M(t), I_T(t), I_{MT}(t), I^d(t), I^C(t), I_V(t), S_V(t)) \in \mathbb{R}^8_+$$

is positively-invariant domain, and thus the model system (4.2.4) is epidemiologically and Mathematically well posed.

4.3.1 Local stability of the disease-free equilibrium

The (DFE) of the Model (4.2.4) is given by $E^0 = (\frac{\Lambda_H}{\mu_H}, 0, 0, 0, 0, 0, \frac{\Lambda_V}{\mu_V}, 0)$ and the local behaviour of the model at or (near) the DFE is determined based on an important quantity, the threshold parameter, the basic reproduction number R_0 [12], which measures the average number of new infections generated by a single infectious individual in a population of completely susceptible individuals. The conditions under which the disease will prevail is determined by this parameter at DFE. In calculating R_0 we use the next generation matrix method [15] and the matrices F and V associated with the next generation method are as given below.

$$F = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & ab \\ 0 & \beta & \beta\eta & \beta\sigma & \beta\alpha & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \beta\zeta & \beta\zeta\eta & \beta\zeta\sigma & \beta\zeta\alpha & 0 \\ \kappa bQ & 0 & 0 & \kappa ybQ & 0 & 0 \end{pmatrix}$$

and $V = \begin{pmatrix} r_1 & 0 & 0 & 0 & 0 & 0 \\ 0 & r_2 & 0 & 0 & 0 & 0 \\ 0 & -\rho & r_3 & -\xi & 0 & 0 \\ 0 & 0 & 0 & r_4 & 0 & 0 \\ 0 & 0 & -g & 0 & \mu_H & 0 \\ 0 & 0 & 0 & 0 & 0 & \mu_V \end{pmatrix}$

Where $r_1 = q + \delta_M + \mu_H$, $r_2 = \rho + \delta_T + \mu_H + L$, $r_3 = \varpi\delta_T + \mu_H + g$, $r_4 = \xi + \varpi\delta_{MT} + \mu_H$, $r_5 = \beta - (\rho + \delta_T + \mu_H + L)$, and $Q = \frac{\Lambda_V \mu_H}{\Lambda_H \mu_V}$. The eigenvalues of the matrix FV^{-1} are $0, 0, 0, \pm\frac{\sqrt{abQ\kappa}}{\sqrt{\mu_V(\delta_M+\mu_H+q)}}, \frac{\alpha\beta\zeta}{\mu_H} + \frac{\beta}{\delta_T+\mu_H+\rho+L} + \frac{\beta\eta\rho}{(\mu_H+q+\varpi\delta_T)(\delta_T+\mu_H+\rho+L)} + \frac{\alpha\beta\rho g}{\mu_H(\mu_H+\varpi\delta_T+g)(\delta_T+\mu_H+\rho+L)}$ The reproduction number R_{MT} which is the spectral radius of matrix FV^{-1} is given by $R_{MT} = \max\{R_M, R_T\}$. Thus

Where

$R_M = \frac{\sqrt{abQ\kappa}}{\sqrt{\mu_V(\delta_M+\mu_H+q)}}$ and

$R_{MT} = \frac{\alpha\beta\zeta}{\mu_H} + \frac{\beta}{\delta_T+\mu_H+\rho+L} + \frac{\beta\eta\rho}{(\mu_H+g+\varpi\delta_T)(\delta_T+\mu_H+\rho+L)} + \frac{\alpha\beta\rho g}{\mu_H(\mu_H+\varpi\delta_T+g)(\delta_T+\mu_H+\rho+L)}$

The reproduction number R_{MT} is the average number of secondary typhoid infections generated by a single infectious individual in the whole

course of her/his infectious period, when introduced in a completely susceptible population [15].

The disease-free equilibrium E^0 of the model 4.2.4 is locally asymptotically stable (LAS) if $R_{MT} < 1$ and unstable if $R_{MT} > 1$. $R_{MT} < 1$ generally implies that the disease is eradicated.

4.3.2 Global stability analysis

We determine whether the population can attain global stability after misdiagnosis of typhoid as malaria using the approach by Castillo-Chavez et al. [7]. We re-write the system 4.2.4

$$\begin{aligned} \frac{dX}{dt} &= F(X,Z), \\ \frac{dZ}{dt} &= G(X,Z), G(X,0) = 0 \end{aligned} \tag{4.3.1}$$

Where $X = (S_H(t), S_V(t)) \in \mathbb{R}^2$ denotes the number of uninfected individuals and $Z = (I_M(t), I_T(t), I^d(t), I_{MT}(t), I^C(t), I_V(t)) \in \mathbb{R}^6$ denotes the number of infected individuals, including the typhoid bacteria carriers. The disease-free equilibrium is denoted thus by $E^0 = (X^*, 0)$

Theorem 4.1.

$$E^0 = (X^*, 0) where\, X^* = (\frac{\Lambda_H}{\mu_H}, \frac{\Lambda_V}{\mu_V}) \tag{4.3.2}$$

is a globally asymptotically stable equilibrium for this system if $R_{MT} < 1$ *(locally asymptotically stable) and if the following two conditions are*

satisfied.

- *(I)* $\frac{dX}{dt} = F(X,0), X^*$ *is globally asymptotically stable (GAS)*
- *(II)* $G(X,Z) = BZ - \widehat{G}(X,Z), \widehat{G}(X,Z) \geq 0 \, for \, (X,Z) \in \phi_{TM}$

where $B = D_z G(X^*,0)$ *is an M-matrix (the off-diagonal elements of* B *are non-negative) and* ϕ_{MT} *is the region where the model makes biological sense. Castillo-Chavez et al [7]*

Proof. We consider

$$F(X,0) = \begin{pmatrix} \Lambda_H - \mu_H S_H \\ \Lambda_V - \mu_V S_V \end{pmatrix}$$

and

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

where

$$B = \begin{pmatrix} -r_1 & 0 & 0 & 0 & 0 & ab \\ 0 & \beta - r_2 & \beta\eta & \beta\sigma & \beta\alpha & 0 \\ 0 & \rho & -r_3 & \xi & 0 & 0 \\ 0 & 0 & 0 & -r_4 & 0 & 0 \\ 0 & \beta\zeta & \beta\zeta\eta + g & \beta\zeta\sigma & \beta\zeta\alpha - \mu_H & 0 \\ \kappa b & 0 & 0 & \kappa b y & 0 & -\mu_V \end{pmatrix}$$

and

$$\widehat{G}(X,Z) = \begin{pmatrix} \widehat{G}_1(X,Z) \\ \widehat{G}_2(X,Z) \\ \widehat{G}_3(X,Z) \\ \widehat{G}_4(X,Z) \\ \widehat{G}_5(X,Z) \\ \widehat{G}_6(X,Z) \end{pmatrix} = \begin{pmatrix} abI_V(t)(1-\frac{S_H(t)}{N_H(t)}) \\ \beta(I_T(t)+\eta(I^d(t))+\sigma I_{MT}(t)+\alpha I^C(t))(1-\frac{S_H(t)}{N_H(t)}) \\ \gamma\lambda_M I^d(t) \\ -\gamma\lambda_M I^d(t) \\ \kappa b(I_M(t)+\pi I_{MT}(t))(1-\frac{S_V(t)}{N_H(t)}) \end{pmatrix}$$

□

We notice that $\widehat{G}(X,Z) < 0$, the conditions in I and II are not satisfied, and hence E^0 may not be globally asymptotically stable. Backward bifurcation occurs at $R_{MT} = 1$.

assuming that there is no misdiagnosis and the typhoid cases are accurately diagnosed and given appropriate treatment $\rho = 0$ then the system 4.2.4 is reduced as shown below

$$\begin{aligned}
\frac{dS_H(t)}{dt} &= \Lambda_H + qI_M(t) + LI_T(t) - \lambda_M S_H(t) - \lambda_T S_H(t) - \zeta\lambda_T S_H(t) - \mu_H S_H(t) \\
\frac{dI_M(t)}{dt} &= \lambda_M S_H(t) - \delta_M I_M(t) - \mu_H I_M(t) \\
\frac{dI_T(t)}{dt} &= \lambda_T S_H(t) - LI_T(t) - \delta_T I_T(t) - \mu_H I_T(t) \\
\frac{dI^C(t)}{dt} &= \zeta\lambda_T S_H(t) - \mu_H I^C(t) \qquad (4.3.3) \\
\frac{dS_V(t)}{dt} &= \Lambda_V - \mu_V S_V(t) - \lambda_V S_V(t) \\
\frac{dI_V(t)}{dt} &= \lambda_V S_V(t) - \mu_V I_V(t)
\end{aligned}$$

We see that when $\rho = 0$ the matrix $\widehat{G}^D(X,Z)$ the matrix without misdiagnosis is given by

$$\widehat{G}(X,Z) = \begin{pmatrix} \widehat{G}_1(X,Z) \\ \widehat{G}_2(X,Z) \\ \widehat{G}_3(X,Z) \\ \widehat{G}_4(X,Z) \\ \widehat{G}_5(X,Z) \\ \widehat{G}_6(X,Z) \end{pmatrix} = \begin{pmatrix} abI_V(t)(1-\frac{S_H(t)}{N_H(t)}) \\ \beta(I_T(t)+\sigma I_{MT}(t)+\alpha I^C(t))(1-\frac{S_H(t)}{N_H(t)}) \\ 0 \\ 0 \\ \beta\zeta(I_T(t)+\sigma I_{MT}(t)+\alpha I^C(t))(1-\frac{S_H(t)}{N_H(t)}) \\ \kappa b(I_M(t)+\pi I_{MT}(t))(1-\frac{S_V(t)}{N_H(t)}) \end{pmatrix}$$

In this case $(\widehat{G}^D(X,Z) > 0)$; this means there is global stability. Hence we have the following theorem:

Theorem 4.2. *In the event of accurate diagnosis and prompt treatment, the disease-free equilibrium is globally asymptotically stability.*

4.4 Bifurcation analysis

to investigate the possibility of occurrence of backward bifurcation we use the center manifold theorem in Castillo-Chavez [7, 6]. In order to apply the theorem, we first redefine our model by making the following changes of variables; $S_H(t) = x_1, I_M(t) = x_2, I_T(t) = x_3, I^d(t) = x_4, I_{MT}(t) = x_5, I^C(t) = x_6, S_V(t) = x_7, I_V(t) = x_8$ and thus $N_H(t) = x_1 + x_2 + x_3 + x_4 + x_5 + x_6$ and $N_V(t) = x_7 + x_8$

The forces of infection are thus

$$\lambda_M = \frac{abx_2}{x_1 + x_2 + x_3 + x_4 + x_5 + x_6}$$

$$\lambda_T = \frac{\beta(x_3 + \eta x_4 + \sigma x_5 + \alpha x_6)}{x_1 + x_2 + x_3 + x_4 + x_5 + x_6}$$

$$\lambda_V = \frac{\kappa b(x_2 + y x_5)}{x_1 + x_2 + x_3 + x_4 + x_5 + x_6}.$$

And now, $N_H = x_1 + x_2 + x_3 + x_4 + x_5 + x_6$ and $N_V = x_7 + x_8$

Theorem 4.3. *Consider the following general system of ordinary differential equations with a parameter* Υ

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

Where 0 *is an equilibrium point for system* (4.1.4) *for all values of the parameter* Υ, *that is* $f(0, \Upsilon) \equiv 0 \forall \Upsilon$ *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* Υ *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

$$\varrho^* = \sum_{kij=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0)$$

$$l^* = \sum_{ki=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \rho_B}(0,0)$$

, then, the local dynamics of the system around the equilibrium point 0 is entirely determined by the sign of ϱ^* and l^*, and especially if $\varrho^* > 0$ and $l^* > 0$ then a backward bifurcation occurs. Particularly when:

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

2. *$l^* < 0$, $\varrho^* < 0$, when $\rho_B < 0$ with $|\rho_B| \ll 1$, $(0,0)$ is unstable; when $0 < \rho_B \ll 1$, $(0,0)$ is asymptotically stable and there exists a positive unstable equilibrium.*

3. *$l^* > 0$, $\varrho^* < 0$, when $\rho_B < 0$ with $|\rho_B| \ll 1$, $(0,0)$ is unstable, and there exists a negative and locally asymptotically stable equilibrium; when $0 < \rho_M \ll 1$, $(0,0)$ is stable and there exists a positive unstable equilibrium.*

4. *$l^* < 0$, $\varrho^* > 0$, when ρ_B changes from negative to positive, $(0,0)$*

changes its stability from stable to unstable. Correspondingly a negative equilibrium becomes positive and locally asymptotically stable.

To apply the Center Manifold approach we make the following variable changes as mentioned earlier, let $S_H(t) = x_1, I_M(t) = x_2, I_T(t) = x_3, I^d(t) = x_4, I_{MT}(t) = x_5, I^C(t) = x_6, S_V(t) = x_7, I_V(t) = x_8$ and thus $N_H(t) = x_1 + x_2 + x_3 + x_4 + x_5 + x_6$ and $N_V(t) = x_7 + x_8$. We can therefore re-write the model system 4.1.4 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 follows

$$
\begin{aligned}
\frac{dx_1}{dt} &= f_1 = \Lambda_H + qx_2 - \frac{abx_8x_1}{x_1 + ... + x_6} - \frac{r_6(\zeta + 1)}{x_1 + ... + x_6} - \mu_H x_1 + Lx_3 \\
\frac{dx_2}{dt} &= f_2 = \frac{abx_8x_1}{x_1 + ... + x_6} - (q + \delta_M + \mu_H)x_2 \\
\frac{dx_3}{dt} &= f_3 = \frac{\beta(x_3 + \eta x_4 + \sigma x_5 + \alpha x_6)x_1}{x_1 + ... + x_6} - (\rho + \delta_T + \mu_H + L)x_3 \\
\frac{dx_4}{dt} &= f_4 = \rho x_3 - \frac{\gamma abx_8x_4}{x_1 + ... + x_6} - (\varpi\delta_T + \mu_H + g)x_4 + \xi x_5 \\
\frac{dx_5}{dt} &= f_5 = \frac{\gamma abx_8x_4}{x_1 + ... + x_6} - (\xi + \theta\delta_{MT} + \mu_H)x_5 \qquad (4.4.1) \\
\frac{dx_6}{dt} &= f_6 = \frac{\zeta\beta x_1(x_3 + \eta x_4 + \sigma x_5 + \alpha x_6)}{x_1 + ... + x_6} - \mu_H x_6 + gx_4 \\
\frac{dx_7}{dt} &= f_7 = \Lambda_V - \mu_V x_7 - \frac{\kappa b(x_2 + yx_5)x_7}{x_1 + ... + x_6} \\
\frac{dx_8}{dt} &= f_8 = \frac{\kappa b(x_2 + yx_5)x_7}{x_1 + ... + x_6} - \mu_V x_8
\end{aligned}
$$

$\beta x_1(x_3 + \eta x_4 + \sigma x_5 + \alpha x_6 = r_6$

From the Jacobian of the Model 4.4.1 which is derived by differentiating f_i with respect to x_i at disease free equilibrium as given below. $i = 1...8$

$$\begin{pmatrix} -\mu_H & q & -h_1 & -h_2 & -h_3 & -h_4 & 0 & -ab \\ 0 & -r_1 & 0 & 0 & 0 & 0 & 0 & ab \\ 0 & 0 & r_5 & \beta\eta & \beta\sigma & \beta\alpha & 0 & 0 \\ 0 & 0 & \rho & -r_3 & \xi & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -r_4 & 0 & 0 & 0 \\ 0 & 0 & \beta\zeta & \beta\zeta\eta + g & \beta\zeta\sigma & h_5 & 0 & 0 \\ 0 & -\kappa bQ & 0 & 0 & 0 & 0 & -\mu_V & 0 \\ 0 & \kappa bQ & 0 & 0 & \kappa b\eta Q & 0 & 0 & -\mu_V \end{pmatrix}$$

Where $h_1 = \beta(1+\zeta) + L$, $h_2 = \beta\eta(1+\zeta)$, $h_3 = \beta\sigma(1+\zeta)$, $h_4 = \beta\alpha(1+\zeta)$ and $h_5 = \beta\zeta\alpha - \mu_H$ From which it can be shown that the basic reproduction number [15] is

$$R_{MT} = \frac{\beta}{r_2} + \frac{\alpha\beta\zeta}{\mu_H} + \frac{\beta\eta\rho}{(r_2)(r_3)} + \frac{\alpha\beta\rho g}{\mu_H r_2 r_3} \tag{4.4.2}$$

Taking $\rho = \rho_B$ as the bifurcation parameter, we can obtain a right eigenvector for the Jacobian of the system given by $w = (w_1, w_2, w_3, w_4, w_5, w_6, w_7, w_8)^T$.

Where

$$\begin{aligned}
w_1 &= \frac{h_1 w_3 + h_2 w_4 + h_4 w_6 + a b w_8}{\mu_H} \\
w_2 &= w_2 > 0 \\
w_3 &= \frac{r_3 w_4}{\rho} \\
w_4 &= \frac{\rho w_3}{r_3} \\
w_5 &= 0 \\
w_6 &= -\frac{r_5 r_3 w_4 + \beta\eta w_4}{\beta\alpha} \\
w_7 &= -\frac{\kappa b Q w_2}{\mu_V} \\
w_8 &= \frac{\kappa b Q w_2}{\mu_V}
\end{aligned}$$

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

$$\begin{aligned}
v_1 &= 0 \\
v_2 &= v_2 > 0 \\
v_3 &= -\frac{(\beta\alpha\zeta + g - \mu_H) v_6}{\beta\alpha} \\
v_4 &= -\frac{\beta\eta v_3 (\beta\alpha\zeta)}{r_3 h_5} + 1 \\
v_5 &= \frac{\beta\sigma v_3 + \beta\zeta\sigma v_6 + \xi v_4 + \kappa b Q v_8}{r_4} \\
v_6 &= -\frac{\beta\alpha v_3}{h_5} \\
v_7 &= 0 \\
v_8 &= \frac{r_1 v_2}{\kappa b Q}
\end{aligned}$$

We show from $\varrho^* = \sum_{kij=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0)$ that

$$\varrho^* = \frac{\mu_H(\gamma a b w_4 w_8(v_5 - v_4) + \kappa b w_2 w_7 v_8}{\Lambda_H}) > 0 \tag{4.4.3}$$

and from $l^* = \sum_{ki=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \rho_B}(0,0)$ we get

$$l^* = -v_3 w_3 + v_4 w_3 > 0 \tag{4.4.4}$$

Since $\varrho^* > 0$ and $l^* > 0$ the following theorem holds

Theorem 4.4. *If ϱ^* and l^* satisfy the inequalities given in* (4.3.4) *and* (4.3.5) *then, the model* (4.2.4) *undergoes a backward bifurcation that occurs at $R_{MT} = 1$*

The significance of this result is that although the initial state is locally asymptotically stable when $R_{MT} < 1$ misdiagnosis of even a small magnitude can cause the endemic to explode into epidemic.

4.4.1 Sensitivity analysis and model simulations

Here the reproduction number R_{MT} is analyzed to determine whether or not the rate of misdiagnosis ρ, leads to large epidemics of typhoid and thus it's control would lead to effective control or even elimination of typhoid fever. A distinctive feature of typhoid is the existence of a large number of asymptomatic carriers, and since carriers also shed bacteria and infect others with active bacteria, we also determine the extent to which

the rate of becoming carrier on infection ζ and rate of becoming carrier after misdiagnosis g affects the level of transmission of typhoid fever in the community. And we also find out the effect of the rate of treatment L in this environment of high likeliness of misdiagnosis. Equation 3.4.6 and the parameter values in table 3 are used to calculate the sensitivity indices, the same values will be used for the model simulations. Table 3: Parameter Values

Parameter Description	Symbol	Value	Source
Human recruitment rate	Λ_H	$8.748 \times 10^{-3}\,\text{day}^{-1}$	[9]
Mosquito recruitment rate	Λ_V	$0.071\,\text{day}^{-1}$	[33]
Human natural mortality rate	μ_H	$2.740 \times 10^{-3}\,\text{day}^{-1}$	[9]
Mosquito natural mortality rate	μ_V	$0.1429\,\text{day}^{-1}$	[8]
Transmission probability for malaria in humans	a	$0.5\,\text{day}^{-1}$	[8]
Biting rate of mosquito	b	$0.125\,\text{day}^{-1}$	Assumed
Transmission probability for malaria in mosquitoes	κ	$Variable\,\text{day}^{-1}$	Variable
Typhoid contact rate	β	$Variable\,\text{day}^{-1}$	Variable
Rate of misdiagnosis	ρ	$0.08\,\text{day}^{-1}$	Estimate
Rate of becoming carrier	g, ζ	$0.1, 0.1\,\text{day}^{-1}$	Estimates
Malaria induced death rate	δ_M	$4.49312 \times 10^{-4}\,\text{day}^{-1}$	[33]
Typhoid induced death rate	δ_T	$5.479 \times 10^{-4}\,\text{day}^{-1}$	[66]
Recovery rate from typhoid	L	$0,00075\,\text{day}^{-1}$	Assumed
Recovery rate from malaria	q	$0,00655\,\text{day}^{-1}$	Assumed
Modification parameters	η, σ, α	$0.09, 1.0001, 1.0007$	Assumed
Modification parameters	ϖ, θ, γ	$1.0005, 1.000, 0.8$	Assumed

The sensitivity indices of R_{MT} to the parameters ρ, g, ζ and L are given in Table 4

Table 4: Sensitivity indices

parameters	value	sensitivity index
ρ	$0.08, \text{day}^{-1}$	0.7914
L	$0.00075, \text{day}^{-1}$	-2.709×10^{-2}
g	$0.1, \text{day}^{-1}$	0.6351
ζ	$0.1\,\text{day}^{-1}$	0.4945

The most sensitive parameter is the rate of misdiagnosis ρ. The high sensitivity is mainly due to the high concentration of the bacteria that accumulates as a result of the long time taken with the bacteria due to misdiagnosis thus a carrier easily sheds off a lot of bacteria.. Other important parameters are the rates of becoming carriers on misdiagnosis g and on infection ζ, more so, g which is the rate of becoming carrier after misdiagnosis is more sensitive parameter. Due to the high level of misdiagnosis, the rate of recovery L from typhoid has very little effect on R_{MT}. This is a clear indication that carriers cause high incidences of typhoid infection in the community. A carrier easily sheds off a lot of bacteria. This situation is made worse by the fact that the carriers are not aware of the fact that they are infectious [66]. It has been noted that the ultimate source of salmonella-typhi in most cases is the asymptomatic or

recently symptomatic carriers [59]. The carriers are able to infect others with acute bacteria. Worse still the likelihood of becoming a carrier increases with age, and more women than men become carriers [66]. More woman than men handle and prepare food, and more women than men live in rural areas where there are no affordable programs to assure safe water and good sanitation, the consequences are that a very big number of people get infected by the carriers.

In this section we simulate our model using the estimations of the model parameters as described and defined in table 3 above

.

4.5 Summary

The DFE is stable if $R_{MT} < 1$ and unstable if $R_{MT} > 1$, but it is shown that in the presence of misdiagnosis it is not possible to eradicate malaria and typhoid despite $R_{MT} < 1$. In the event of the absence of misdiagnosis ($\rho = 0$), $R_{MT} = \max\{R_M^0, R_{MT}^0\} = \max\{\frac{\sqrt{ab\zeta_K}}{\sqrt{\mu_V(\delta_M+\mu_H+q)}}, \frac{\alpha\beta\zeta}{\mu_H} + \frac{\beta}{(\delta_T+\mu_H+L)}\}$. It is noted that $R_{MT}^0 \ll R_{MT}$ which implies that the right diagnosis can greatly reduce the burden of typhoid fever[11]. R_{MT} is also greatly dependent on ζ and g, the probabilities of becoming a typhoid bacteria carrier. In the situation of the right diagnosis g is greatly reduced and consequently $I^C(t)$ is reduced [21]. In the absence of carriers $R_{MT}^{-C} = \frac{\beta}{(\delta_T+\mu_H+L)} \ll R_{MT}$. In the event of no misdiagnosis at all, which may

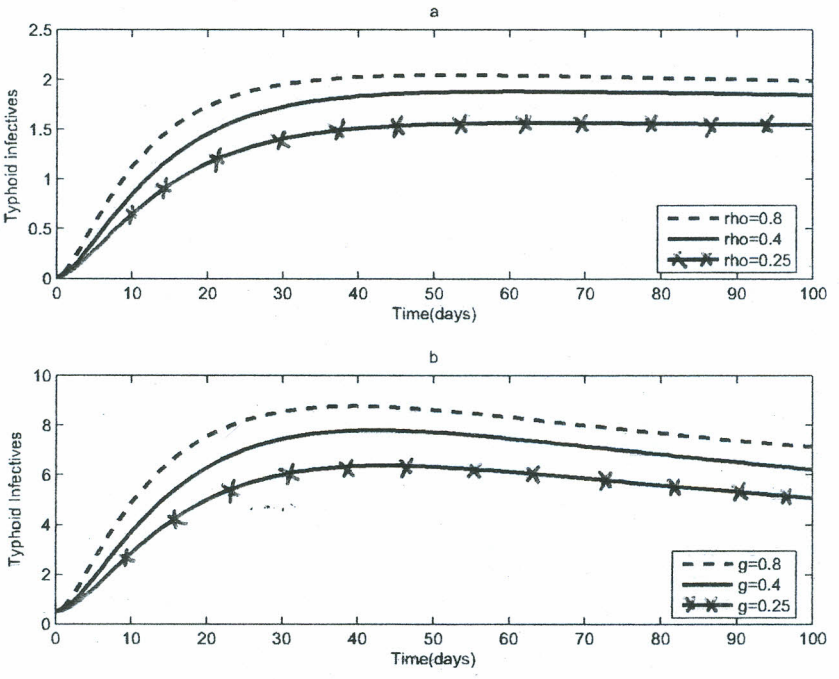

Figure 4.4.1: Simulation of model 4.2.4 with rho = 0.25, 0.4, 0.8 and g = 0.25, 0.4, 0.8

comparing rate of transmission in the presence of misdiagnosis and when there are carriers.

not be practical in real life situation, $R_{MT} = \frac{\beta}{(\delta_T+\mu_H+L)}$. We observe that $R_{MT} \to 0$ since $L \to \infty$ and $\beta \to 0$, a situation of no typhoid in the population. The two reproduction numbers are the same, which is an indication that both misdiagnosis and carriers increase transmission of typhoid equally.

From the numerical simulations we observe that misdiagnosis of typhoid as malaria increases the transmission of typhoid fever by increasing

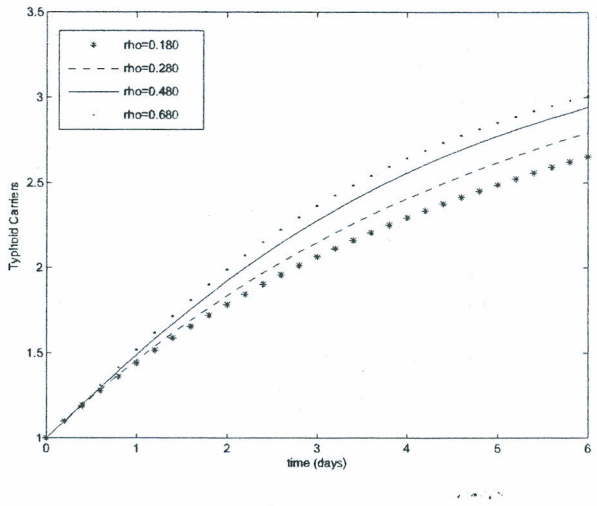

Figure 4.4.2: Simulation of model 4.2.4 showing an increase in the number of typhoid carriers with increase in the rate of misdiagnosis, ρ.

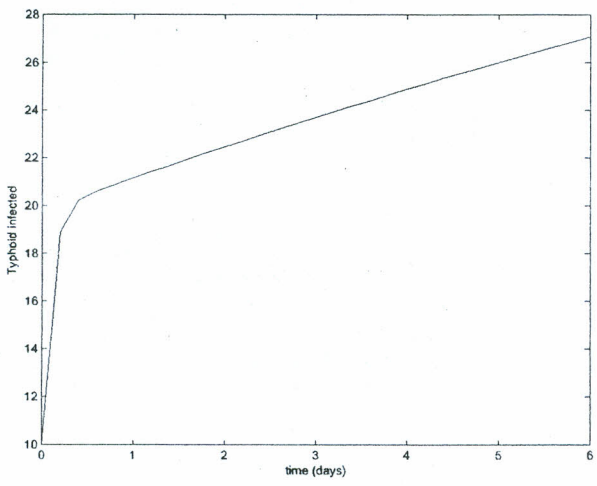

Figure 4.4.3: Simulation of model 4.2.4 on the effect of typhoid bacteria carriers on the typhoid infection transmission. As g increases, typhoid infection greatly increases.

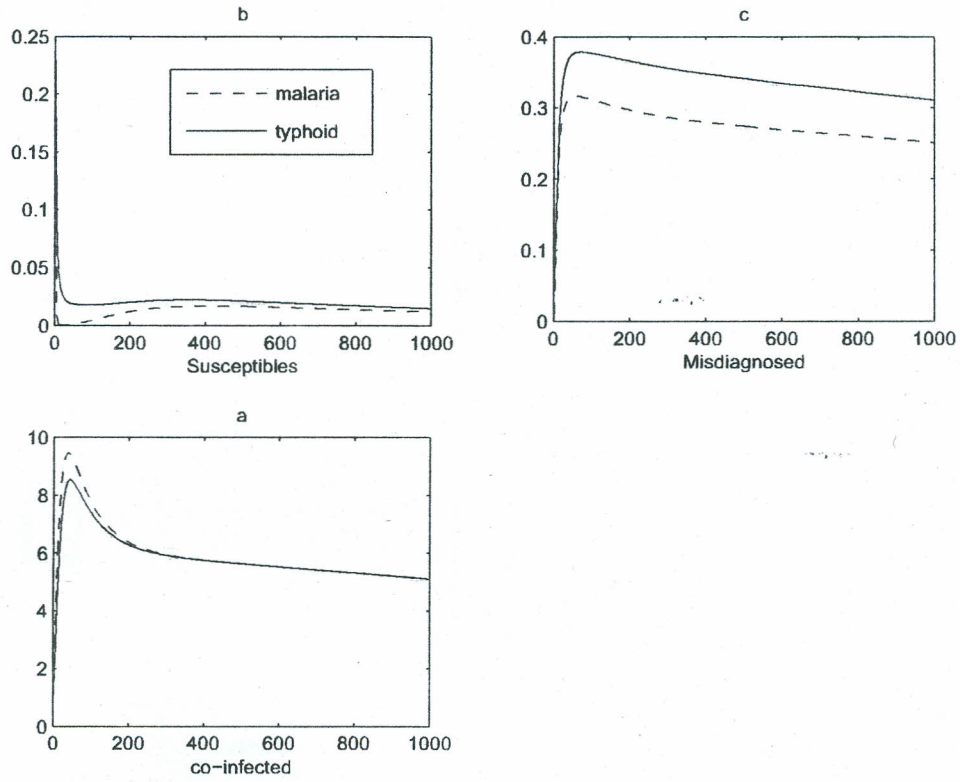

Figure 4.4.4: simulation of model 4.2.4. fig *a* compares malaria and typhoid in the absence of misdiagnosis, figure *b*, when there is misdiagnosis and figure *c*, compares typhoid with increasing co-infection

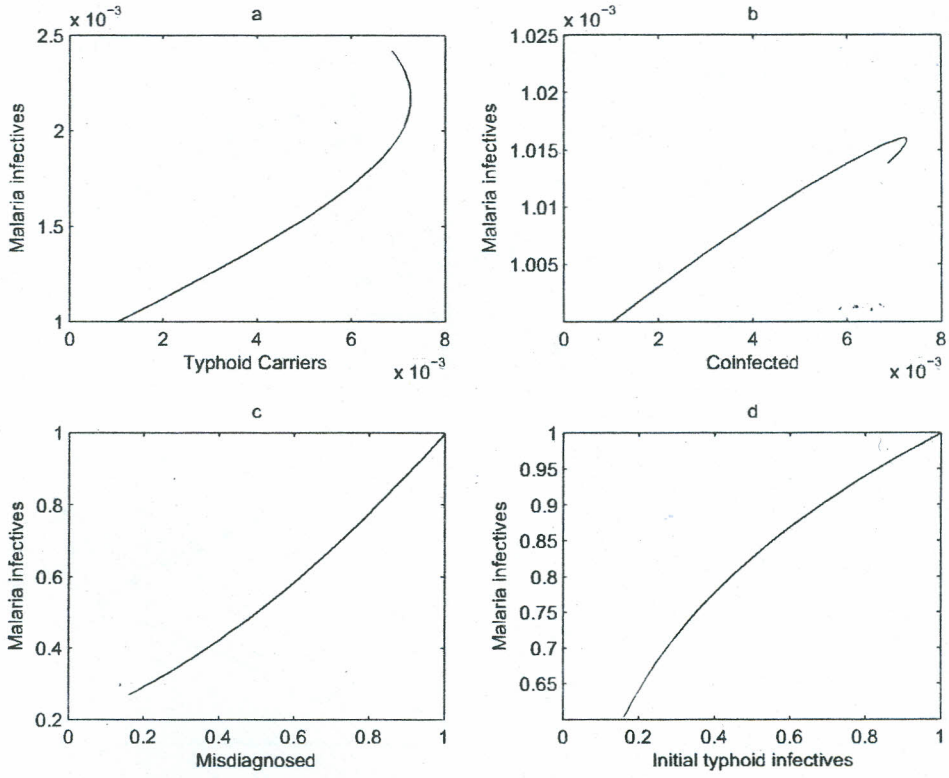

Figure 4.4.5: Simulation results for malaria infectives against typhoid bacteria carriers, co-infected people, misdiagnosed and initial typhoid infectives It is observed that malaria transmission is greatly increased by typhoid infection.

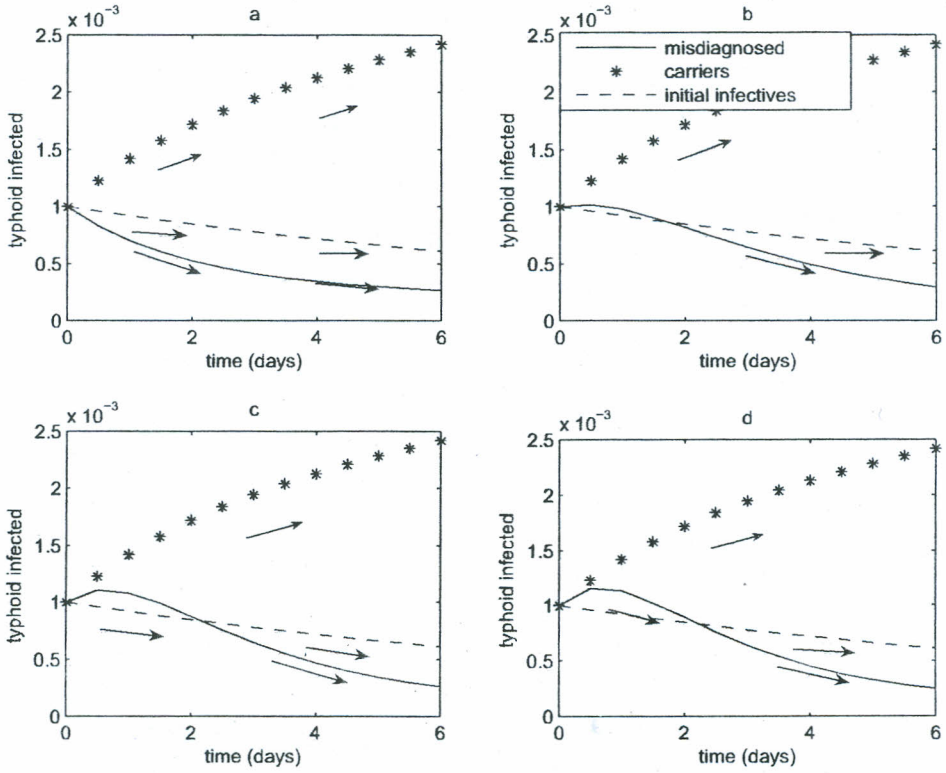

Figure 4.4.6: The simulation results for I_T, I^d and I^C with $\rho = 0.0800, \rho = 0.5800, \rho = 0.8800 and \rho = 1.0800$. As long as there is misdiagnosis, typhoid exists at high levels and the carriers remain at high levels

the rate of contact with salmonella typhi and the number of typhoid bacteria carrier. Carriers are a group of people who in our setup, we are not able to associate them with typhoid bacteria and this greatly increases their chances of spreading the bacteria. Untreated typhoid kills 20 percent of those it infects and many who survive become carriers for life e.g. typhoid Mary who infected several people with typhoid before it was discovered that she was a carrier [59]. This explains why increase in carriers increases the population of those with typhoid as seen in figure 4.4.1. Carriers cause the greatest number of infection especially in the rural setup where there are poor sanitation systems and people use largely untreated water from wells and ponds.

Chapter 5

Research study

A study was carried out to try and corroborate the ideas with the real practiced situation and the research was done as explained below.

5.1 Study design:

The health care delivery system in Kenya includes a national referral hospital, provincial and district hospitals as well as health centers, which are graded according to the administrative zones and the services provided.There are also privately owned health institutions. National, provincial and district hospitals provide both out and in-patient services, while health centers mainly provide out-patient services. Our study adopted descriptive survey where data was collected from carefully selected sample group of a total population in order to establish the effect of misdiagnosis. This involves simple random sampling of the target population and getting the required information. Purposive sampling was used to select

Nyanza Provincial hospital and a health center that is at leased equipped with a malaria diagnosing equipment. Random selection was used in selecting the district hospital. The district hospital serves both the rural and the urban folks, and the health centers serve mainly the rural poor. Patients data was analyzed from the patients files from the patients record office for the retrospective study.For the prospective study the data was analyzed from the medical wards for the ongoing treatment and from the outpatient books for the outpatients.

study population: A total of 240 patients were recruited on a continuous process. Thirty from the adult medical wards, thirty from the paediatric ward and thirty from the outpatient from both the district and the provincial hospitals. sixty patients were also recruited from the health center. Thirty patients data was retrospectively analyzed from the patient files from the records office. All the recruited patients initially presented with malaria symptoms. The data collected includes:

1. Date of reporting.
2. Results of the initial test done
3. Medication administered.
4. The response to treatment.
5. If no response to treatment, results of second test done
6. Medication administered

7. Response to new treatment

8. Hospital discharged and discharge date on cure or death

9. If death, what is the cause of death

The data collected (prospectively and retrospectively) was analyzed descriptively. The data was coded, tallies made and frequencies determined for each factor and generalized for the rest of the study population. The outpatients were asked to come back for review after three days on two occasions, unless the situation became bad then they could seek medical attention at any time.

5.2 Results of the collected data:

The results were as given in the tables below

Table 5: Initial treatment in all the hospitals

Hospital	Russia	District	Health centre
Malaria $+ve$	42	38	
Malaria $-ve$	30	30	
No test done	18	22	60
Given anti-malaria	78	80	56
Antibiotics+malaria	9	7	4
Antibiotics alone	3	3	0
Healed from anti-malaria	33	32	28
Healed from antibiotics	2	2	0
Healed from anti(bio+malaria)	9	7	4

From the analysis of the data we observe that in the provincial and district hospital where malaria tests were done, anti-malaria drugs were administered even to those who tested malaria negative. In the provincial hospital (Russia), it is shown that only 48.7% tested malaria positive but 86.7% were given anti-malarials, which means that about 40% of the patients were misdiagnosed and mistreated with anti-malaria drugs. In the district hospital 42.2% were declared malaria positive but the anti-malaria medicine was given to 88.9%, and this implies that about 46.7% were misdiagnosed and wrongly given anti-malaria drugs. In the health centre, no test is done to those who have symptoms similar to those of malaria, 93.3% got malaria treatment and only 6.7% patients who had some other symptoms that pointed towards pneumonia or typhoid were given antibiotics but still with anti-malaria.

Table 6: Second treatment procedure

Hospital	Russia	District	Health centre
Not healed first time	46	47	28
Malaria +ve	10	17	5
Malaria -ve	36	30	23
pneumonia +ve	14	9	7
typhoid +ve	12	113	6
Malaria+pneu/typhoid	10	9	10
Given anti-malaria	18	21	13
Antibiotics+malaria	18	21	7
Antibiotics alone	10	7	8
Healed from anti-malaria	7	9	4
Healed from antibiotics	8	10	6
Healed from anti(bio+malaria)	16	17	7

Our analysis shows that in the provincial hospital 21.7% tested malaria positive but 39.1% were given anti-malaria. Most of them were advised to buy a stronger anti-malaria than the one they used in the first treatment. Many of those who were pneumonia or typhoid positive were given antibiotic but still with anti-malaria. During the second treatment those who got healed after taking anti-malaria alone in Russia, District and the health centre were 15.2%,19.1% and 14.3% respectively and these are very low healing rates. While those who healed after taking antibiotics (antibiotic + anti-malaria inclusive) in the three hospitals were 52.2%, 57.4% and 60.7% respectively. The percentage of the malaria negative patients who healed after taking antibiotics in the three hospitals were

66.7%, 90% and 56.5%.

This analysis reaffirms that there is over treatment with anti-malarials, such that even those who test malaria negative are still given anti-malarials. Yet from the good response by those who tested malaria negative to antibiotics on second treatment, we can conclude that had the antibiotic treatment been given in the first treatment, then more people would have got well without suffering for a long time and fewer lives would have been lost.

Chapter 6

Discussion, Conclusion, Recommendation

6.1 Discussion

Deterministic Ordinary Differential Equations (ODE) based compartmental model for malaria-pneumonia and that for malaria-typhoid that incorporates misdiagnosis of pneumonia and typhoid respectively have been presented and analyzed. The results show that both models have no globally stable DFE despite their associated reproduction numbers being less than unity due to the possible occurrence of backward bifurcation at $R_{MP} = 1$ and $R_{MT} = 1$. Locally stable endemic equilibrium is supposed to exist when $R_0 > 1$ but it has been shown using Center Manifold theory [7] that the two models, malaria-pneumonia and malaria-typhoid undergo the phenomena of backward bifurcation thus local asymptomatic stability of the the endemic equilibrium does not exist. However the model for prompt accurate diagnosis of pneumonia exhibits local and global stabil-

ity for the DFE and even the endemic state is globally asymptotically stable as proved by the Lyapunov direct method [35] in section 3.4.3.

We evaluated the sensitivity indices with respect to the model parameters of the reproductive numbers. The indices help in determining the relative importance of different parameters in malaria-pneumonia and malaria-typhoid transmission. The results of the sensitivity analysis show that the rate of misdiagnosis ρ is the most sensitive parameter in terms of the disease transmission in both models, followed by the rate of increase in the number of carriers for the malaria-typhoid model. These results suggests that the prompt accurate diagnosis of pneumonia and typhoid infected individuals can be used as an intervention strategy to deter the spread of pneumonia or typhoid and even malaria. Treatment of the disease is most effective when started early in the disease. A more accurate diagnosis is possible when a complete history can be taken early in the disease process, better still when the patient is still able to answer questions and recall the order of the symptoms. Obtaining accurate diagnosis becomes quite difficult once the disease progresses and other infections come in.

As has been earlier shown in section 3.4 prompt and accurate diagnosis of pneumonia elicits asymptotic stability of DFE, global stability and endemic equilibrium stability. Treating pneumonia or typhoid promptly leaves the body immunity still strong enough to defend itself against any malaria infection thus lowering occurrences of malaria-pneumonia or malaria-typhoid double infection. Numerical simulation results suggest that any amount of misdiagnosis results in a rise of pneumonia or typhoid transmission, therefore increase in rate of misdiagnosis means in-

crease in the number of those infected with pneumonia and typhoid. The misdiagnosed persons accumulate more bacteria and go ahead to infect more people.

We expected malaria to be eradicated due to overuse of anti-malaria drugs, but as shown in figures 3.6.4 and 4.4.5 malaria is not only present, but there is increase in its transmission. We can therefore conclude that although the provision of anti-malarials is a bright idea to curtailing malaria, it is not enough. Pneumonia and the typhoid enhance malaria infection by weakening the immune system and inspite of over-treatment of malaria, malaria persists and the number of new cases of malaria increases exponentially with increased rate of pneumonia and typhoid misdiagnosis. The impaired immunity also leaves patients vulnerable to serious life-threatening pneumonia and typhoid known as opportunistic infection which are caused by organisms such as pneumocytis jiroveci and candida albicans which would otherwise be harmless to people with healthy immune system. When the pneumonia bacteria reach the lungs or the typhoid bacteria reach the intestines the immune system sends many cells to attack the germs, but because of malnutrition due to lack of appetite, the body is not able to manufacture enough of the protective cells to replace the used ones and with no treatment less and less of these cells are produced and the immune system gets weaker making it increasingly easier to be infected by malaria parasites, and in some cases by another pneumonia or typhoid parasite. Thus the dually-infected cases shoot up. A co-infected individual is highly likely to infect another person with both diseases further increasing the number of the dually infected per-

sons. They are also capable of infecting two different individuals each with either disease and therefore raising the level of the two diseases in the community. The two diseases continue co-existing, with malaria levels even bypassing the levels of pneumonia or typhoid at high rates of misdiagnosis, as can be observed in figure 3.6.6.

In many health facilities a diagnosis of malaria is based solely on clinical features such as fevers and joint pains [38]. Although the approach may reduce morbidity, many infectious diseases mimic malaria and this strategy leads to high rates of over-diagnosis and over-treatment of malaria with consequent under-diagnosis of fever causing disorders such as pneumonia and typhoid leading to prolonged and more infectious illness due to the disease becoming more severe. Many of our health facilities lack trained human resource and diagnostic equipment which contributes adversely to inaccurate diagnosis. And as has been observed in the results of the research, even those who are diagnosed with negative malaria are still treated for malaria.

6.2 Conclusion

Treating all fevers as malaria masks underlying potential fatal conditions. Individuals wrongly diagnosed with malaria are exposed to unnecessary side effects and the true cause of the fever is not treated leading to suffering and worsening illness. Health facilities are therefore overburdened by incurable diseases. Over-treatment also causes drug resistance, wastage of

drugs and increased costs of treating malaria. The effect of misdiagnosis falls most heavily on the poor who are least able to withstand prolonged ill health and cannot subsequently afford expensive drugs. Such misdiagnosis thus contributes to vicious cycle of ill-health and deepened poverty. People therefore lose faith in health services and opt for traditional healers and herbal drugs which is a threat to the liver and other organs of the body. Loss of earnings increase due to the expenses on more consultations, drugs, healers, and transport. Continuous sickness results into loss of jobs leading to inability to sustain family and educate the children and hence reduced economic growth to the nation. There are high losses of agricultural manpower especially in the rural areas leading to low food production which leads to a malnourished community that is vulnerable to disease infection. Deficiency in pneumonia typhoid diagnosis also makes health facilities data unreliable for monitory trends in pneumonia, typhoid, and malaria morbidity and spread

We are therefore right to say that as much as there is over-treatment of malaria, because of existence of pneumonia and typhoid, malaria cannot be eliminated or even reduced to low endemic levels. No wonder malaria and pneumonia still accounts for 40% of deaths worldwide. Most of these deaths are in developing countries like Kenya.

We can conclude that, misdiagnosis continues to hinder the control of malaria, pneumonia and typhoid in Kenya. This is due to a combination of factors; non-specific presentation of the disease, high prevalence asymptomatic infections, lack of resources and insufficient access to trained health care providers and health facilities and widespread practice

of self treatment for clinically suspected malaria. We can also conclude that accurate diagnosis and treatment of typhoid and pneumonia results in decreased malaria transmission as the weak immune response caused by pneumonia and typhoid enables ease of malaria infection. Misdiagnosis has become so common in the kenyan hospitals that figures put together by medical layers and independent pathologists [Nation newspaper May 11th 2013] show that three out of ten patients that walk into a hospital get the wrong diagnosis. Deficiency in pneumonia and typhoid diagnosis makes health facilities data unreliable for monitory trends in pneumonia, typhoid and even malaria morbidity and fatality and for evaluating the impact of intervention of these diseases.Therefore accurate diagnosis should top priority to curtail the suffering of the patient and the high transmission levels.

6.3 Recommendation

Malaria is a disease that presents with symptoms that are confused with those of pneumonia and typhoid. The accurate diagnosis is made by finding the symptoms and doing accurate laboratory diagnosis as per the guidelines of diagnosis i.e. doing blood slide for microscopy four times within twenty hours. Simultaneously the health care provider must be cognisant that pneumonia and typhoid present like malaria. The patient must be examined in details to identify the symptoms and signs specific

for pneumonia and typhoid.

Specific laboratory tests which are sensitive to pneumonia and typhoid must be done. These include chest X-ray, blood and sputum tests for pneumonia and stool and blood tests specific for typhoid. The health care providers should be adequately trained to accurately diagnose pneumonia and typhoid using the current diagnostic methods. In malaria, pneumonia and typhoid endemic areas, the health care worker should be equipped with adequate knowledge in diagnosis to discern each of the diseases accurately.

Misdiagnosis can be reduced by informing clinicians of the extent of their own errors and urging them to personally take steps to reduce their own errors [2]. Medical practitioners should always use the systems designed to aid their diagnostic decision making. clinicians have under utilized decision support systems [2] hence misdiagnosis rates remain high. The government should try and equip the health centers, which are the facilities that are easily available to the poor, with simple effective diagnostic equipment.

Immunization is one of the most effective medical interventions and there should be routine vaccinations of the high risk population like the children under six and the elderly in the case of pneumonia.Vaccination against pneumonia and typhoid can be encouraged by the health ministry making the vaccine affordable and accessible to the poor since they are the ones who account for the biggest burden of pneumonia and typhoid. This will lower the infection and reduce the transmission.

6.3.1 Future work

There are several ways by which this study could be improved. These include long time efforts through vaccines, prophylactic drugs to the most vulnerable groups as well as environmental and social aspects. The environment/social is an aspect of the infectious diseases that has received relatively little attention yet our environmental set up accelerates a lot of pathogen traffic and should be given prominence in infectious disease models. For a long time there has been over emphasis in public awareness on malaria treatment and prevention and not on pneumonia and typhoid both of which are as fatal as malaria if not diagnosed in time. The manner in which the advertisement for anti-malarials is done in both print and electronic media is inappropriate. This is because they encourage people to take anti-malarials when they have the symptoms. unfortunately these symptoms are also shared by pneumonia and typhoid. There is urgent need to enlighten people on the dangers of pneumonia and typhoid also. For public health interest there should be more clarity and emphasis on seeing the health care worker immediately the symptoms appear and not "When symptoms persist".

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