Considering the effect reinfected asymptomatic individuals have on malaria transmission

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Contents

1 Abstract

In this paper we will consider a mathematical model that aims to better describe the transmission of malaria. The transmission model is an interaction model between mosquitoes and humans that describes the progress of the infectious disease malaria in the human population. It accounts for the different stages of the disease, showing how the infection develops in both humans and mosquitoes, together with treatment of both sick and partially immune humans. Partially immune humans, which are termed as asymptomatic, have recovered from the worst stages of the infection, but can still pass on the disease to other humans. I will present a mathematical model that consists of a system of ordinary differential equations that describes the evolution of humans and mosquitoes in a range of different stages of the disease.

A new part of the model that I have added, in what turns out to be a key part of the system, is the consideration of asymptomatic humans that have been reinfected again with malaria. The analysis of the new model will include finding out of the value of the basic reproduction number, R_0, also asymptotic analysis to find out the important timescale of events that leads to malaria moving from a non-endemic state to a endemic state in a region following that specific region gaining a few infected mosquito's. Studying the model I will be able to provide a better timeframe in which possible interventions, in the infected region, may produce better results. From this we will be able to show a better method to control the disease and possibly eradicate the infection from the region.

2 Introduction

2.1 The biology of malaria

One of the most fatal diseases in the world is seen to be malaria. Malaria has many symptoms associated with it however the most common ones, such as a fever, have been observed since the prehistoric ages [1], during the European Renaissance period was when the name malaria was derived, it comes from the Medieval Italian word, *mal aria* which has the meaning "bad air", humans thought that the awful vapours coming from stagnate water and swamps were the main cause of the symptoms associated with malaria, such as chills which is a common symptom of the infection.

Looking at historical records of the disease we can see quickly that there are many occasions documented where descriptions match the symptoms associated with malaria, these descriptions are in the historical records of early civilisations. An ancient Chinese medical text, *Huangdi Neijing* documents the disease as repeated and sudden outburst of fever that leads to an increase in size of the spleen, the document also states that the disease has the potential to become an epidemic. One major treatment that has been adopted by the World Health Organisation is Artemisinin combination treatment, this front line drug used to treat malaria came from a Chinese plant, Qing-hao. The plant was first discovered around 2300 years ago, back then it was used to treat severe fever episodes. One description of the disease is seen in the ancient Hindus of India where in this text they assert that the disease is caused by the bite of a certain insect. Homer, Empedocles and Hippocrates, who lived in ancient Greek times, refer to the disease as having characteristics of acute fever and increased spleen size seen and only seen in humans who live in or near marshy lands. One astonishing fact is that some research accredit malaria as the cause of the fall of the roman empire, the evidence comes from an archaeological dig that discovered a child that had malaria present in their bones and the child was said to have died 1500 years, showing the disease can stay active long after death. Charles Laveran found the cause of malaria, in the later part of the 19th century, when he found a malaria parasite in human blood in Africa. Giovanni Grassi and Raimondo Filetti first coined the word plasmodium to denote the malaria parasite. Ronald Ross in 1897 demonstrated that plasmodium parasite can be transmitted to a female Anopheles mosquito from an infected human, by a bite. Subsequently, this showed how malaria can quickly become endemic in a region, through mosquito human transmission.

This chapter aims to give an insight into biological and historical facts about malaria, also showing some problems with the disease which forms the main part of study, this allows the reader to gain a great depth of knowledge surrounding the infection. The infectious disease malaria normally presents with the most common symptoms been chills, fever, sweating, and anaemia which happen in recurrent episodes, the disease is mostly prevalent in tropical climatic regions which contain a higher density of mosquito's. Malaria is a parasitic infection of red blood cells caused by a protozoan of the genus Plasmodium, which is transmitted from human to human by the bite of an infected female anopheles mosquito [2], which requires a blood meal to mature its eggs. Plasmodium parasites normally come in four types all of which can cause infection, these are: plasmodium falciparum, plasmodium vivax, plasmodium ovale and plasmodium malariae. Falciparum malaria caused by plasmodium falciparum is the often documented to be the most severe type of malaria [3]. During the parasites life cycle it will under go a series of changes that will be documented in a future chapter. WHO have said that roughly 300-600 million people suffer with malaria each year and around 1 million are killed every year [4]. It is also said that climate change may increase this number this is because due to the role of temperature and rainfall in the dynamics of the population of the mosquito vector. [5] [6].

Due to malaria's high mortality rate, it continues to inflict major socio-economic issues in developing countries, which leads to slow economic growth, only increasing by up to 1.3 percent each year [7].

Most epidemiological research into malaria is conducted into the disease transmission, the mosquito vector and how the parasite interacts with the human host. This research has lead to major steps forward in disease elimination, intervention strategies and also total eradication of the disease. Elimination of malaria has been achieved in most of Europe, North America, Australia, North Africa and the Caribbean, and parts of South America, Asia and Southern Africa [8]. However in the Tropical and sub-tropical climates of the world the disease still does remain endemic in certain regions. WHO are leading the fight against this deadly infection one of the important programs implemented by them was the initiation of the Roll-Back Malaria Program which looked at two key areas of prevention and treatment. Eradicating the disease has been more difficult than first thought so the program has had to focus more on disease control rather than disease eradication, this is due to the high mortality rate of children and pregnant women, the most vulnerable group.

Looking to eradicate malaria is a ever more difficult problem as as there is strong evidence that the parasites and mosquito's are becoming resistant to chemicals that they were once vulnerable to [9]. Another challenge that exists is the use of quick fix drugs to treat malaria, without complete clearance of parasites, we create a paradox of asymptomatic parasite carriage. The issue of asymptomatic parasite carriage is crucial in the the transmission of malaria. Intermittent Preventive Treatment (ITP) is instituted by the WHO with the aim of treating and clearing existing malaria parasites and preventing new infections in children and pregnant women. Asymptomatic carriers are not regularly treated so an increased knowledge on the asymptomatic carriage of malaria parasites is needed to assess the cost-benefit ratio of Intermittent Preventive Treatment [10].

Research carried out on the prevalence of asymptomatic carriage of P. *falciparum* in sub-saharan Africa, Ogutu et al. [11] maintains that a disproportionate ratio of P. *falciparum* infections are asymptomatic. Asymptomatic carriage is as high as 39% in children under 10 years old has been reported. From this we can conclude that "if a significant reduction in the malaria parasite pool present in asymptomatic carriers could be achieved this would lend itself to a reduction in the rate of disease transmission across an endemic region". It becomes imperative to understand asymptomatic carriers role in disease transmission of malaria, for which mathematical modelling can play a key role. In this paper, we present a mathematical modelling framework to explicate the dangers that asymptomatic carriers present to the population when they are given a quick treatment rather than a complete cure which leads to an incomplete clearance of malaria parasites in a endemic region.

2.1.1 Structure of this paper

This thesis is made up of 6 chapters. In chapter 1 we present the abstract to the work. In chapter 2, we present an introduction to the work looking at biological issues that surround malaria. In chapter 3, we present a review of some infectious disease models including mathematical models in malaria epidemiology to prepare the background to the transmission model. We present the derivation and analysis of the new transmission model in chapter 4 and round up the chapter with a brief discussion of the numerical simulations and asymptotic analysis. Chapter 5 is the conclusion to the paper with limitations of the new model I created.

2.2 Life cycle of a malaria parasite

In this section we present the life cycle of the plasmodium parasite, which is the parasite that will cause the most severe form of malaria. Seeing the life cycle of this parasite will give us an insight into the modelling that has been used in this paper. The malaria parasite has a complicated life cycle involving a mosquito and a human, which can be identified in four phases these are the sporozoite phase, merozoite or erythrocytic phase and gametocyte phase. The merozoite phase starts and ends within the human host whereas the parasite in the first and third stages need both the mosquito and

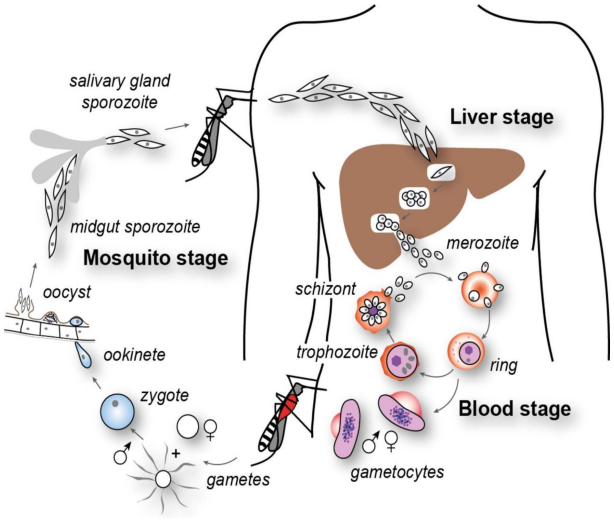


Figure 1: A figure describing the life cycle of P. falciparum, the most deadly parasite causing the most severe malaria [12]

human environments to be sucessful in infecting. The female anopheles mosquito requires blood meal to nurture its eggs and during the process of blood feeding it injects the malaria parasite in form of sporozoites they attach their salivry glands onto the hu,man host wherever the host was bitten by the mosquito. These sporozoites are moved around the body via the circulatory system to the liver before this they envade immune cells, in which they infect hepatic cells. Each of these sporozoites penetrates a liver cell using the liver to asexually reproduce through a process often referred to as exoerythrocytic schizogony which leads to the production of merozoites, which are then released into the bloodstream. During the process of schizogony an infected hepatic cell passes through four metamorphic stages namely young ring, old ring, young trophozoite and old trophozoite to become a schizont. However, this process may vary depending on the plasmodium species. For instance, for some malaria parasites such as Plasmodium vivax and Plasmodium ovale, the development of certain trophozoites is arrested at earlier stages to form some temporarily dormant cells termed hypnozoites, which may reactivate after some weeks, months, or years being responsible for relapses of the disease [13]. Once these merozoites are released into the blood stream, each starts another round of asexual replication using a red blood cell and after approximately 48 hours, except Plasmodium malariae that maintains a 72 hour cycle, each surviving merozoite from any of the other three species produces a second generation of merozoites. Immediately after the erythrocyte invasion, the Plasmodium falciparum parasite has the appearance of a 'ring' and after about 12 hours it gradually adopts a more solid appearance known as a 'young trophozoite', which continues to grow after 24 hours to become a schizont or segmenta and after about 12 hours later ruptures to release daughter parasites that infect other erythrocytes [14]. The production of second and subsequent generations of merozoites increases the level of parasitemia creating the common sysmptoms associated with malaria, due to continuous rupturing of infected erythrocytes. Plasmodium falciparum merozoites attack all red blood cells, not

just the young or old cells, as do other types and a patient with this type of malaria can die within hours of the first symptoms [15]. Prolonged fever destroys so manyred blood cells causing blockage of the blood vessels in vital organs (especially the kidneys), which in some cases culminates in the enlargement of the spleen [16]. When malaria infection is left untreated for a long time, it can lead to many complications including severe anaemia. There may be brain damage, leading to coma and convulsions. The kidneys and liver may also fail [17].

The period starts from an immature ring stage, through trophozoite stage to a mature schizont, and eventually bursts to release merozoites. As an alternative to continuous merozoite replication cycles, some of these merozoites divide into sexual forms of the parasite called gametocyte. These gametocytes, made up of the male form (microgametocytes) and the female form (macrogametocytes) are later picked up by a female anopheles mosquito during blood feeding. Fertilization occurs in the stomach of the mosquito as a microgamete becomes agellated and penetrates a macrogamete to form a zygote. The zygote developed into a mobile form oockinete and penetrates the midgut wall of the mosquito for further development into an asexual form, oocyst. After rounds of multiple replication the oocyst ruptures to release sporozoites, which migrate to the salivary gland of the mosquito waiting to be injected into the skin of the human host.

2.3 Interruption strategies and immunity to malaria

The constant world fight against malaria has been lead by the WHO with support from local governments and charities too. At the current time of writing no vaccination exists against the disease so control and interruption strategies have been put in place to contain it. A Global Partnership program called Roll Back Malaria (RBM) is one of the main control strategies that targeted at reducing the disease where it is most prevalent. The main aims of the program are to reduce the burden of the disease, in particular for the most vulnerable, namely children and pregnant women. To aid the research done in this paper we shall review some of the important interruption strategies that have taken place to fight the disease. The control measures include:

1. Prompt and effective management of the disease through testing, treating and tracking (T3) of every malaria case using antimalarial drug combination (eg. Ateminisinin combination treatments).

2. Using Insecticide-treated bed nets (ITN)

3. Intermitent preventive treatment (IPT) especially, for pregnant women during anti-natal and infants irrespective of disease symptoms

4. Killing the larva of the mosquito and the destruction of breeding sites to reduce the population number

5. Indoor residual spraying (IRS) is been used to kill any infectious mosquitos that may lay indoors

6. Introduction of genetically modified mosquitoes that would produce single sex young ones. Although this has not been implemented but researches are ongoing in this area.

7. Administration of transmission blocking drugs like gametocydal drugs to reduce the transition of merozoites to gametocytes.

With all these measures the WHO have still not been able to establish the desired effect. The greatest challenge that now presents itself is the raise of drug resistance making the infection harder to treat. Similarly, the benefits of intermittent preventive treatment may not be certain since, when a patient goes through repeated treatments the immunity of that patient isn't certain these are the major challenges of intermittent preventive treatment (IPT)[18]. Treatments are designed such that there main aims are to reduce morbidity and mortality and make sure that in severe cases the most extreme symptoms such as chronic anemia are not present in people. Another important design feature of treatments is that they aim to significantly reduce the transmission of the infection.

The World Health Organisation aims at tackling malaria at the community level so as to reduce the intensity of malaria transmission at the local level by protecting people against infected mosquito bites by reducing the density of mosquitoes as well as their life span. The application of indoor and outdoor residual spraying, clearing of home surroundings, good drainage systems, use of treated bed nets, among others are geared towards achieving these objectives. For instance one of the greatest challenges in the fight against malaria is drug resistance which has been on the increase. Single use therapies have been identified as contributing immensely to drug resistance and the recommended use of Ateminisinin combination treatments is a measure to curb this form of drug resistance. This shows us that mono therapies don't fully treat and clear the patient of all parasites meaning that after a patient is treated they become asymptomatic for a while. From what I have documented so far i am looking to create a mathematical model such that we can model the dynamics of malaria in a endemic region focusing on the transmission and control of the infection. Looking ahead i will use methods looking at the potential of eliminating malaria from these regions by using data that very accurately describes malaria transmission.

3 History of modelling

3.1 Infectious disease models

Malaria is an infectious disease hence it would be logical to assume that some other models used to model infections might be helpful. Every model must take into account how the infection is transmitted and whether the disease is contagious or vector transmitted. This is one of the determining factors to whether an infection would turn into an epidemic or whether the disease would just stay prevalent in a region . A disease could be an epidemic, pandemic or endemic. Contagious diseases sometimes turn out to be epidemic especially, when humans are passing the infection around to each other normally this is caused by droplets of infected spit been passed around. Often, an epidemic can be a pandemic in that it spreads and affects a very high proportion of the population across a large region within a continent or between continents, in recent months we have seen the rise of COVID-19 which became a pandemic so quickly due to the availability to travel easily between countries. A disease can be classified as endemic if it is just prevalent in a specific region. Most of the infectious disease models reviewed focus on explicating the dynamics of the disease by investigating its incidence and prevalence through some basic assumptions relating the affected population, the status and spread of the disease, and the mode of recovery. These models are the well known compartmental models SI, SIS, SIR, SEIR and SEIRS, S=Susceptible, I=Infectious, E=incubating, R=Recovered [19, 20, 21]. However, Hethcote [20], discusses two additional models, MSEIR and MSEIRS where M represents child immunity transferred by a mother in form of antibodies through the placenta. Hence a newborn may have temporary passive immunity to an infection and after the antibodies disappear from the body the infant moves to the S class, this only occurs if the mother has experienced that infection

previously. For example measles fits this model however an infant is only in the M category if the mother has had the infection. The SI model describes a simple epidemic in which a susceptible population is exposed to infection. The basic foundation of this model can be found in the following assumptions.

1. It is a contagious disease that is spread only from human to human
2. The rate that susceptible people and infected people interact is proportional to the number of susceptible people and the number of infected people with the rate of proportionality expressed by a infection parameter
3. A human who is susceptible when they get infected they become infectious immediately and will never recover
4. The epidemic is short lived and the number of people remains constant so there is no births or deaths

The SI model constructed with a coupled system of ordinary differential equations (ODEs). The rate of change of the susceptible population with respect to time would be decreasing and the infected population would be increasing at a rate proportional to the infection parameter or precisely, the infectious contact rate. The implication of this is that, if a susceptible population is exposed to an infectious disease with some proportion of the population being infected then the disease would spread exponentially infecting most of the population, the implication of this is that if control strategies are not implicated soon enough an infection can quickly become a very large problem. The SI epidemic model does not describe an epidemic realistically since an infected population will either die or recover and where there is no immunity, then the recovered population become susceptible again. The SIS model describes a disease scenario where infected people have the tendency of recovering from the disease without gaining immunity. Thus, infected people become susceptible again immediately after recovery. It might be appropriate for some sexually transmitted diseases like chlamydia because after recovery, the host is once again susceptible to infection [19]. The SIR model describes an infectious disease in which some infected people recover from the disease then they receive immunity from the infection forever and will never become susceptible to that infection again for example chicken pox infection. This model unlike the SI and SIS models may have some practical implications. The SIR model is a great example of modelling a flu epidemic since once a person has had a particular strain of flu, their immune system prevents them from being reinfected with that strain a second time. The classical SIR model is of the form:

$$\begin{aligned}\frac{dS}{dt} &= -\beta SI,\\ \frac{dI}{dt} &= \beta SI - \alpha I,\\ \frac{dR}{dt} &= \alpha I.\end{aligned}$$

where β is the infection parameter and α, the recovery rate assumed to be proportional to the number of infected people. The system is nonlinear and cannot be solved explicitly, although implicit solutions can be found We note that this form of the SIR model does not involve demography but inclusion of some host demographic factors like birth and deaths may impact the model if the disease is to persist over a long period of time. Although the SIR model does have limitations, it is the basis

for more involved deterministic models in epidemiology. The SEIR model is an improvement on the SIR in most disease cases where an incubation period is relevant. The assumption that once you have recovered you can't catch the disease again still exists in this model. However, once being infected, the person passes through an incubation period E before showing disease symptoms. The SEIRS models describe the dynamics of endemic diseases where individuals who contact the disease progress through a period of incubation before showing disease symptoms and becoming infectious and after recovery from the disease may gain partial immunity and later become susceptible after loss of immunity. Most of the models used initially to model malaria took the form of the SIR model it appears clearly that the SEIRS portrays the dynamics of malaria better as we know that an issue with the disease is the asymptomatic carriers that exist after they have recovered. Malaria transmission is a cyclic relationship between an infectious human population and a susceptible mosquito population also it can be seen as an infectious mosquito population and a susceptible human population. Various mathematical models have been constructed to help understand the dynamics of malaria.

3.2 A review of models in malaria epidemiology

3.2.1 Transmission models

The first to construct a mathematical model of malria was Sir Ronald Ross [22]. He used two equations, one representing the rate of change of infected humans with respect to time and the other that of infected mosquitoes. One important outcome of the analysis of his model is that of threshold density of the Anopheles mosquito, which he said that we did not have to eradicate the mosquitos simply just bring the number below a certain threshold. Based on this, Kermack and McKendrick published a classic paper in 1927 that discovered a a condition where they could predict the size of an epidemic [61]. In 1957, MacDonald made further extensions on the work on the malaria model of Ross [24]. In a systematic historical review of mathematical models in epidemiology, Smith et al. [25] lead to over 70 scientists contributing to the Ross-Macdonald model. This model lead to major devlopments and in 1982 Aron and May wrote the first transmission model.

$$\frac{dx}{dt} = mabz(1-x) - rx, \tag{3.1}$$

$$\frac{dz}{dt} = ax(1-z) - gz. \tag{3.2}$$

where x and z are fractions of infectious humans and adult female mosquitoes respectively. The parameter a represents the number of bites a single female mosquito gives to humans and b is the probability that a bite infects the human. The average number of female mosquitoes is represented by m. The mortality rates of humans and adult female mosquitoes are rx and gz respectively. This model has been extensively discussed in Chitnis [64]. Its assumptions are based on a simplified process-based description of the pathogen life cycle [25], as represented by the biology in section 2.2. The life cycle is simplified to these 4 events.

1. The patheogen is transmitted to the human during mosquito blood feeding
2. The pathogen infects then human then begins to multiply to a high density
3. A susceptible mosquito then lands on the infected human and begins blood feeding hence becoming infected.
4. The pathogen develops in the mosquito moves to the salivary gland ready to infect a human

Further work done on the Ross-Macdonald model by Bailey in 1982, led to the general theory that describes malaria transmission in form of the classical SIR-SI model and since then considerable modifications have been made in the quest for a model that will better describe the mosquito-human interaction process and pathogen transmission.

A more sophisticated model that incorporates acquired immunity in malaria was constructed by Dietz et al. [27], which gave a more realistic description of malaria epidemiology in the Garki area in Nigeria, given entomological input and provided conditional inputs and comparative forecasts for several specific intervention. Many malaria models involving immunity have been reviewed in [28, 76, 30]. The models proposed by Anderson and May [66] and Aron and May [32] use the assumption that acquired immunity does not depend on duration of exposure. While the models of Aron [33, 34] and Bailey [35] are based on the assumption that immunity is boosted by additional infections. A more comprehensive mathematical model typical of a characteristic endemic malaria is the one proposed by Ngwa and Shu [52]. A malaria model with periodic mosquito birth and death rates was proposed in [37]. The paper considers a novel situation where the birth and death rates of mosquitoes and human death rate are periodic. Although the model does not include incubating classes of both human and mosquitoes but they established a basic reproduction number such that the disease will only prevail if this number was greater than unity, otherwise the disease will die out. Another model involving the effects of seasonality and immigration's of infected humans was proposed in [53]. The results show that the strength of seasonality increases the number of infections and it is not possible to achieve a disease free equilibrium in the presence of infected immigrants, signifying that the disease cannot be completely eradicated if there is constant intake of infected immigrants. Most prominent in the models discussed so far is the concept of the basic reproduction number. The basic reproduction number of an infectious disease is a very important concept in epidemiology. This important quantity provides the key to transmission dynamics, indicating the ease by which major epidemics may be eradicated but also showing how quickly an infection may spread throughout a population [**?**]. The symbol R_0 is often used to represent it. If a single infectious case is introduced in a population of susceptibles and assuming the population evolves in a continuum sense, it is expected to generate a chain of subsequent infections for the disease to fully register itself (endemic) or die out eventually. The expected number of cases that would arise from the introduction of a single primary case into a fully susceptible population is referred to as the basic reproduction number of the disease. R_0 is a threshold parameter which determines whether or not an infectious disease will be endemic, such that

- If $R_0 < 1$ then the infection is growing at a slower rate than it can infect other susceptibles hence the infection will eventually die out
- If $R_0 > 1$ successive infection generations are larger than their predecessors, and the number of cases in the population will initially increase, not necessarily indefinitely, but the disease remains endemic.

Using analytic methods we want to produce a model such that we can prove the existence and stability of a disease-free equilibrium point, defining the basic reproduction number and describing the existence and stability of the endemic equilibrium points.

3.2.2 Summary from the review

None of the models discussed above considers the assumption that immune humans being bitten by infectious mosquitoes may be constantly incubating and there is the possibility of some immune humans falling sick immediately after loss of immunity. We incorporate into our model some of the features found in the SEIRS model of Ngwa and Shu [52]. In the next chapter we will present and analyse the proposed model of malaria transmission.

4 The new Transmission model

Here we will derive a new model of malaria transmission. This model extends that of Ngwa and Shu [52] to take into account the various phases of the disease in humans and mosquitoes. The asymptomatic humans have recovered from the worst of the symptoms, but can still transmit the disease. A new feature added is the consideration of re-infected asymptomatic humans leading to an additional incubating class. We first derive the model, then we undertake stability analysis to establish the value of R_0 and finally employ a time scale analysis to gain insight into how an epidemic evolves from a small outbreak from a disease free population. The modelling is relevant for a 0.5 year timescale in which the population is not expected to change too much in the absence of malaria. The model will also take into account the routine treatment of individuals who present with malaria symptoms. In addition, we consider a putative treatment for post symptomatic humans, to limit the capacity for asymptomatic human carriers of the disease.

4.1 Derivation of the model

A population of humans in a region is susceptible to malaria infection if the environmental conditions in that region favour the breeding of the anopheles mosquitos. We recall from Section 2.2, that once an infectious female anopheles mosquito injects parasites into the human at the bite site, these parasites undergo some developmental stages within the host. These stages partition the host into a incubation state,disease state or a non-disease state in the presence of parasites. In order to set the necessary framework for the proposed model, we divide the human population into compartments of susceptible, incubating, incubating asymptomatic, symptomatic and asymptomatic carriers, and that of mosquitoes into susceptible, incubating and infectious compartments. State variables in the model are given in Table 1 and the movement between compartments is summarised in Figure 3, the individual pathways to be discussed below.

Sate Variable	Description
N	Total human population
C	Susceptible human population
I	Incubating human population
I_A	Number of incubating asymptomatic infectious humans
S	Number of symptomatic infectious humans
A	Number of asymptomatic infectious humans
M	Total mosquito (female anopheles) population
X	Number of susceptible mosquitoes
Y	Number of incubating (incubating) mosquitoes
Z	Number of infectious mosquitoes

Table 1: Table to show the state variables in my model

The total population of humans and (female) mosquitoes are simply the sum of their respective state variables, i.e.

$$N = C + I + I_A + S + A,$$
$$M = X + Y + Z.$$

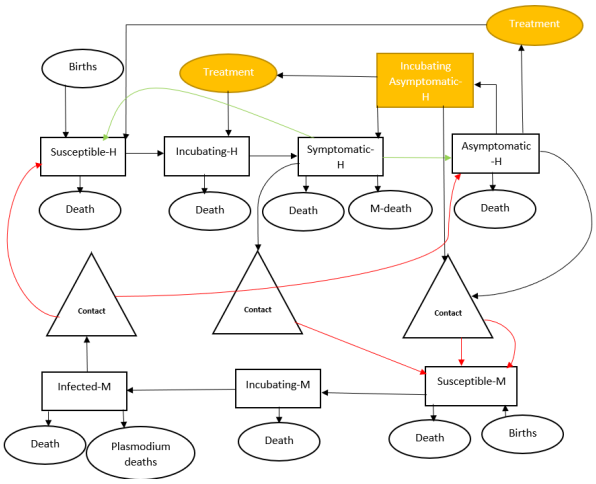


Figure 2: Schematic representation of mosquito human interaction model. The rectangles indicates the state variables, the ovals are actions within humans and mosquitoes and the triangles indicates action between species.

We use C to represent the set of susceptible humans who initially do not have malaria parasites but have natural nonspecific immunity, whilst I represents the collection of humans who have received infectious bites and are within the liver and early erythrocyte stage infection(humans will remain in this state, untreated, for about 7-30 days). The S class involves those in the erythrocyte stage that have developed both disease symptoms and gametocytes. Unlike those in the I class, symptomatic infectious humans require treatment as those in the I class do not know they are infected. Individuals reach a asymptomatic status A when they no longer have symptoms of the disease that would warrant clinical attention but are still infectious to mosquitoes, which may be caused by improper treatment or reinfection (individuals in this class can remain so for a mean time of around 165 days, provided they are not infected again). We use I_A for individuals in the A class being bitten by infectious mosquitoes. Since they carry both gametocytes and asexual parasites, loss of immunity may cause their immediate transition into the S class instead of the C class. A mosquito is said to be in the Y class as soon as it ingests gametocytes from an infectious human until the time (about 12 days) before sporozoites migrate to the salivary gland when the mosquito becomes infectious and proceed to the Z class. The I_A, S and A classes are infectious to X, while the Z class infects C and A.

One of the main benefits of disease modelling is its use to be able to control the disease and even in some circumstances plan for disease eradication. The practical use of such models must rely heavily on the realism put into the model. As usual, this does not mean inclusion of all variables in a environment, but rather the incorporation in the model mechanisms, in as simple a way as possible, that appear to be the major components [39]. The model explains the dynamics of both human and mosquito populations as they progress from susceptible noninfectious states to infectious states. Malaria is transmitted when a susceptible human is bitten by an infected Anopheline mosquito. The

rate at which a susceptible person becomes infected is a function of contact rate with the infected mosquitoes and level of host susceptibility [40]. We assume that mosquito biting vectors are equally susceptible and a humans infectiousness to mosquitoes is determined solely by the gametocyte density level inside the host [41].

Susceptible humans get infected at rate $\alpha_h eZ\frac{C}{N}$ where eZ is the rate at which infected mosquitoes bite (constant e being the biting rate per human per unit time), $\frac{C}{N}$ is the probability that the human bitten is susceptible and α_h is the number of human infections per bite. Likewise the rate of reinfection of an asymptomatic individual is $\alpha_h eZ\frac{A}{N}$. The rate at which uninfected mosquitoes obtain the plasmodium parasite from human carriers is $e(\alpha_s S + \alpha_a A + \alpha_a I_A)\frac{X}{N}$, noting that humans in class I are in the incubating stage of infection and are not infectious to mosquitoes.

Susceptible mosquitoes are recruited into the mosquito population through a constant birth rate λ_m. Assuming that each mosquito has the same biting behaviour, there will be a total of eM bites by mosquitoes on humans. But only $\frac{C}{N}$ of these bites will be made on susceptible humans. The probability that a bite is made by an infectious mosquito is $\frac{Z}{M}$. It is important to note here that the parameter α_h assumes that not all bites by an infectious mosquito on a susceptible human can lead to infection. The parameter $\alpha_h \in [0, 1]$ is the proportion of bites by an infectious mosquito that passes on the infection, where $\alpha_h = 1$ means all bites transmits the disease. However, $\alpha_h = 0.086$ in the data, so this means there is only a 10% chance of an infected mosquito passing on its infection. The cross infection rate is $\alpha_h e\frac{Z}{N}$ between the human and mosquito populations depends on the average number of mosquito bites per unit time and the transmission probability normalised by the human population [68, 43]. We also assume that the recruitment of humans into the susceptible population occurs at a constant per capita birth rate λ_h and apart from asymptomatic individuals no human in the incubating and symptomatic infectious classes would be affected by a bite from an infectious mosquito. This assumption becomes necessary since we are primarily concerned about how infectious bites from mosquitoes can lead to the disease. Those in the I class are already in the process of transition into the S class who are entitled to treatment. Incubating humans become infectious after a mean latency time $\frac{1}{\sigma_h}$. All human classes die "naturally" at per capita rate μ_h while some individuals in the S class die at an additional rate $\beta_h S$ from the disease. The survivors receive treatment and either recover with complete clearance of parasites to join the susceptible class at a rate $r_s S$ (individuals undergo a 14-day treatment), or only recover from symptoms (after a 3-day monotherapy) without parasite clearance to join the A class at a rate $r_a S$. The asymptomatic class, A still carry merozoites and produce gametocytes, so can infect biting mosquitoes. A human can be in this state for several weeks or months and hence play an important part in sustaining an epidemic, noting that symptomatic individuals are in this state for 3-14 days [44, 45, 74]. It seems that if there exists some treatment to target post infected humans, then the pool of people who infect mosquitoes will be reduced. We then consider in our model a assumed treatment which removes individuals from the A and I_A class down to C and I respectively. The effect of the treatment parameter, $\phi\theta_h$ (ϕ are being treated) in R_0 will be an important part of the analysis.

Susceptible mosquitoes get infected through infectious contacts with infectious humans at a rate $e(\alpha_s S + \alpha_a A + \alpha_a I_a)\frac{X}{N}$ and then move to the incubating compartment. Although there are some conflicting findings on whether or not the plasmodium parasite reduces the life span of infectious mosquitoes, direct laboratory results of [47, 48, 49, 50] suggest that the malaria parasite reduces mosquito survival. Since mosquitoes do not recover from infection it follows that the infectiousness of mosquitoes end in their death [68, 52]. We assume that mosquitoes in the incubating class die naturally at a rate $\mu_m Y$ and the rest get infectious at a rate $\sigma_m Y$ to join the infectious compartment which they remain until their death either naturally, or through the carriage of infectious parasites in their body [53] at a rate $\beta_m Z$. Using the above assumptions, then the system of equations for the human classes are

$$\frac{dC}{dt} = \lambda_h N + r_s S + i_a A - \alpha_h e \frac{Z}{N} C - \mu_h C + \phi\theta_h A, \tag{4.1}$$

$$\frac{dI}{dt} = \alpha_h e \frac{Z}{N} C - \sigma_h I - \mu_h I + \phi\theta_h I_A, \tag{4.2}$$

$$\frac{dS}{dt} = \sigma_h I + \sigma_h I_A - \beta_h S - r_s S - r_a S - \mu_h S, \tag{4.3}$$

$$\frac{dA}{dt} = r_a S - \alpha_h e \frac{Z}{N} A - i_a A - \mu_h A - \phi\theta_h A, \tag{4.4}$$

$$\frac{dI_A}{dt} = \alpha_h e \frac{Z}{N} A - \sigma_h I_A - \mu_h I_A - \phi\theta_h I_A. \tag{4.5}$$

The mosquito class equations are

$$\frac{dX}{dt} = \lambda_m M - \alpha_s e \frac{S}{N} X - \alpha_a e \frac{A}{N} X - \alpha_a e \frac{I_A}{N} X - \mu_m X, \tag{4.6}$$

$$\frac{dY}{dt} = \alpha_s e \frac{S}{N} X + \alpha_a e \frac{A}{N} X + \alpha_a e \frac{I_A}{N} X - \sigma_m Y - \mu_m Y, \tag{4.7}$$

$$\frac{dZ}{dt} = \sigma_m Y - \beta_m Z - \mu_m Z. \tag{4.8}$$

The total population equations are

$$\frac{dN}{dt} = \lambda_n N - \beta_h S - \mu_h N, \tag{4.9}$$

$$\frac{dM}{dt} = \lambda_m M - \beta_m Z - \mu_m M. \tag{4.10}$$

where (4.9) is derived from adding (4.1) through to (4.5) and (4.10) is the sum of (4.6) through to (4.8). To close this system we need a set of initial conditions for each of the state variables. A suitable set depends on the context of the study. In section 4.7 we will consider the evolution of the disease in a disease free human population with a small number of infected mosquitoes. Nevertheless, we impose

$$t = 0,\ N = N_0,\ M = M_0.$$

as initial population values for humans and mosquitoes.

4.2 Values of the parameters

Symbol	Representation	Value	Dimension	Cite
λ_h	human birth rate per capita	0.00014	day^{-1}	[57]
e	mean number of bites a human receives per unit time	0.55	day^{-1}	[58]
i_a	Rate at which asym infectious humans loose immunity	0.006061	day^{-1}	[57]
α_h	Proability a bite from a infectious mosquito infects a susceptible human	0.086	N/A	[59]
μ_h	human death rate per capita	0.0000356	day^{-1}	[57]
σ_h	rate at which incubating humans pass into the symptomatic class per unit time	0.00670	day^{-1}	[60]
β_h	Death rate due to malria per capita	0.0006061	day^{-1}	[61]
r_s	Drug recovery rate of symptomatic humans	0.07	day^{-1}	[74]
r_a	Transition rate from symptomatic to asymptomatic infectious class	0.33	day^{-1}	Calculated from [44, 45, 63]
λ_m	mosquito birth rate per capita	0.13	day^{-1}	[64]
μ_m	mosquito death rate per capita	0.125	day^{-1}	[65]
σ_m	Transition rate of incubating mosquitoes into the infectious class per unit time	0.0830	day^{-1}	[66]
α_s	The probability that a susceptible mosquito gets infected after biting a symptomatic infectious human	0.1	N/A	[67]
α_a	probability that a bite by a susceptible mosquito on an asymptomatic infectious human transfers the infection to the mosquito	0.53	N/A	[67]
β_m	Per capita death rate of mosquitoes due to gametocyte carriage per unit time	0.03152	day^{-1}	[68]
θ_h	Recovery rate of asymptomatic infectious humans due to treat- ment per unit time		day^{-1}	
ϕ	fraction that continue treatment after malaria		N/A	

4.3 Non-dimensionalisation of the model

Since the variables N and M are the sum of the relevant compartment values, it is convenient to re-express the compartment values as population fractions using

$$\hat{C} = \frac{C}{N}, \hat{I} = \frac{I}{N}, \hat{I_A} = \frac{I_A}{N}, \hat{S} = \frac{S}{N}, \hat{A} = \frac{A}{N}, \hat{X} = \frac{X}{M}, \hat{Y} = \frac{Y}{M}, \hat{Z} = \frac{Z}{M}$$

So that

$$\hat{C} + \hat{I} + \hat{I_A} + \hat{S} + \hat{A} = 1 \tag{4.11}$$

$$\hat{X} + \hat{Y} + \hat{Z} = 1. \tag{4.12}$$

The time derivatives for the variables will become, using variable C as an example

$$\frac{dN\hat{C}}{dt} = N\frac{d\hat{C}}{dt} + \hat{C}\frac{dN}{dt} = N\frac{d\hat{C}}{dt} + (\lambda_h - \beta_h\hat{S} - \mu_h)N\hat{C}.$$

There are a number of time scales in the system, mosquito life cycle (weeks), incubation and symptom (weeks), population turnover (tens of years), asymptomatic clearance $\approx$ 6 months), and the most suitable choice for the scaling depends on the context. We are focusing on an endemic area and year time scale, in which the total population change is negligible in the absence of the disease, hence we scale time with the asymptomatic susceptible transmission parameter i_a, and write

$$t = \frac{\hat{t}}{\hat{i_a}}$$

so that $\hat{t} = 1$ is about 165 days. Recalling that M_0 and N_0 are the initial populations of humans and mosquitoes respectively, we write

$$N = N_0\hat{N}, M = M_0\hat{M}$$

and define the following dimensionless parameters:

$$\alpha = \frac{\alpha_h e M_0}{i_a N_0}, b = \frac{\alpha_s e}{i_a}, d = \frac{\alpha_a e}{i_a}, \sigma = \frac{\sigma_h}{i_a}, \mu = \frac{\mu_h}{i_a}, \lambda = \frac{\lambda_h}{i_a}, \beta = \frac{\beta_h}{i_a},$$

$$\gamma = \frac{r_s}{i_a}, \rho = \frac{r_a}{i_a}, \theta = \frac{\phi\theta_h}{i_a}, f = \frac{\sigma_m}{i_a}, q = \frac{\lambda_m}{i_a}, g = \frac{\mu_m}{i_a}, h = \frac{\beta_m}{i_a}$$

and by substituting these new parameters into (4.1) to (4.10) and dropping the hats for clarity we get for the new human classes are

$$\frac{dC}{dt} = \lambda + \gamma S + A - \beta ZC\frac{M}{N} - \lambda C + \beta CS + \theta A, \tag{4.13}$$

$$\frac{dI}{dt} = \alpha ZC\frac{M}{N} - \sigma I - \lambda I + \beta IS + \theta I_A, \tag{4.14}$$

$$\frac{dI_A}{dt} = \alpha ZA\frac{M}{N} - \sigma I_a - \lambda I_A + \beta I_A S - \theta I_A, \tag{4.15}$$

$$\frac{dS}{dt} = \sigma I + \sigma I_a - (\beta + \gamma + \rho + \lambda)S + \beta S^2, \tag{4.16}$$

$$\frac{dA}{dt} = \rho S - A - \alpha ZA\frac{M}{N} - \lambda A + \beta AS - \theta A. \tag{4.17}$$

The new mosquito class equations are

$$\frac{dX}{dt} = q(1-X) - bSX - dAX - dI_aX + hXZ, \tag{4.18}$$
$$\frac{dY}{dt} = bSX + dAX + dI_AX - (f+q)Y + hYZ, \tag{4.19}$$
$$\frac{dZ}{dt} = fY - (h+q)Z + hZ^2. \tag{4.20}$$

The new total population equations are

$$\frac{dN}{dt} = -\beta SN + (\lambda - \mu)N, \tag{4.21}$$
$$\frac{dM}{dt} = -hZM + (q-g)M. \tag{4.22}$$

In solving the problem we can use (4.11) and (4.12) to reduce the number of ODEs. We solve the system together with (4.11) and (4.12).

Dimensional form	Non-dimensional parameter	Value	Value in terms of ϵ
$\frac{\alpha_h e M_0}{i_a N_0}$	α	62.43	$O(1/\epsilon^2)$
$\frac{\sigma_h}{i_a}$	σ	11.1	$1/\epsilon$
$\frac{\mu_h}{i_a}$	μ	0.0056	$O(\epsilon^2)$
$\frac{\beta_h}{i_a}$	β	0.01	$O(\epsilon^2)$
$\frac{\lambda_h}{i_a}$	λ	0.017	$O(\epsilon^2)$
$\frac{r_s}{i_a}$	γ	11.5	$O(1/\epsilon)$
$\frac{r_a}{i_a}$	ρ	54.45	$O(1/\epsilon^2)$
$\frac{\alpha_s e}{i_a}$	b	7.2	$O(1/\epsilon)$
$\frac{\alpha_a e}{i_a}$	d	38.2	$O(1/\epsilon)$
$\frac{\sigma_m}{i_a}$	f	14	$O(1/\epsilon)$
$\frac{\lambda_m}{i_a}$	q	21.45	$O(1/\epsilon)$
$\frac{\mu_m}{i_a}$	g	20.62	$O(1/\epsilon)$
$\frac{\beta_m}{i_a}$	h	1.45	$O(1)$
$\frac{\phi\theta_h}{i_a}$	θ		

Table 2: List of dimensionless parameters and their definitions in terms of the original parameters, the dimensional values. In the final column we express the size of the parameter in terms of the small parameter $\epsilon = \sigma^{-1} \approx 0.09$, this being relevant for section 4.7.

The dimensionless parameter values are shown in Table 2 and the parameters in relation to the small parameter $\epsilon = \sigma^{-1}$ are also included. We note from the rescalings that the population of humans, N_0, and mosquitoes, M_0, need not be presented but only $\frac{M_0}{N_0}$. We do not have data for malaria vectors/human populations, but we assume that the initial female mosquito population M_0

is ten times that of humans N_0 due to the claim that in an endemic area of dengue fever the ratio of female Aedes aegypti (the main vector of the virus) population to human population is $10:1$ [54]. Though the main vector in our case is the female Anopheles mosquito, we expect that in an endemic malaria region, the distribution of female An. gambiae mosquito will be well compared with that of Aedes aegypti. But the rescalings are such that $\frac{M_0}{N_0}$ only affects the parameter α. By definition, ϵ is the ratio of σ_h and i_a (i.e. the proportion of time for the incubation period compared to the mean asymptomatic state timescale) and $\epsilon << 1$, means that asymptomatic humans remain infectious for a longer time compared to the incubation period of humans. Analysing the model using ϵ as a small parameter provides a convenient basis for the application of asymptotic methods in understanding the effect of partial immunity on the spread of malaria.

4.4 R_0 of the new transition model

The application of approaches like the traditional or intuitive method used in [52] or the next generation matrix method used in [28, 64] may be used in the determination of the basic reproduction number, R_0. Here we use the next generation operator approach, which approximates the number of secondary infections due to one infected individual and express R_0 in the traditional form as suggested by van den Driessche and Watmough [55]. As usual we consider a small perturbation of the disease free state ($C = 1; X = 1; I = I_A = S = A = X = Y = Z = 0$) and assume that growth and decay is much faster than population change, i.e. M = N = 1, we consider the linearised system expressed in the form

$$R' = FR - VR \tag{4.23}$$

where, $R' = \frac{dR}{dt}$ and

$$F = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & \alpha \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & d & b & d & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix} V = \begin{bmatrix} a_1 & -\theta & 0 & 0 & 0 & 0 \\ 0 & a_0 & 0 & 0 & 0 & 0 \\ -\sigma & -\sigma & a_2 & 0 & 0 & 0 \\ 0 & 0 & -\rho & a_3 & 0 & 0 \\ 0 & 0 & 0 & 0 & a_4 & 0 \\ 0 & 0 & 0 & 0 & -f & a_5 \end{bmatrix} R = \begin{bmatrix} I \\ I_A \\ S \\ A \\ Y \\ Z \end{bmatrix}$$

here, FR represents the emergence of new infections, V R the transition of these infections between compartments and R the reservoir of infection". The constants a_i are are expressed in terms of the model parameters as follows:

$$a_0 = \sigma + \lambda + \theta, a_1 = \sigma + \lambda, a_2 = \alpha + \gamma + \rho + \lambda \tag{4.24}$$

$$a_3 = 1 + \lambda + \theta, a_4 = f + q, a_5 = h + q$$

This method assumes that there is a non-negative matrix $G = FV^{-1}$ that guarantees a unique, positive and real eigenvalue strictly greater than all others. Computing the inverse of V yields

$$G = \frac{1}{b_0} \begin{bmatrix} 0 & 0 & 0 & 0 & \alpha b_{11} & \alpha b_{12} \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ f_1 & f_2 & f_3 & f_4 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix} \tag{4.25}$$

where,

$$b_0 = a_0a_1a_2a_3a_4a_5, b_{11} = fa_0a_1a_2a_3, b_{12} = a_0a_1a_2a_3a_4, f_1 = bb_2 + db_3, f_2 = db_4 + bb_5 + db_6$$
$$f_3 = bb_7 + db_8, f_4 = db_9, b_2 = \sigma a_0a_3a_4a_5, b_3 = \sigma\rho a_0a_4a_5, b_4 = a_1a_2a_3a_4a_5, b_5 = \sigma a_1a_2a_3a_4a_5.$$
$$b_6 = \sigma\rho a_1a_4a_5, b_7 = a_0a_1a_3a_4a_5, b_8 = \rho a_0a_1a_4a_5, b_9 = a_0a_1a_2a_4a_5$$

The characteristic equation of (4.25) in terms of the eigenvalue, η, shows that four of the eigenvalues vanish leaving the expression

$$\eta^2 = \frac{\alpha(bb_2 + db_3)b_{11}}{b_0^2} \tag{4.26}$$

which expressed in terms of the model parameters gives

$$\eta^2 = \frac{\alpha\sigma f(b(1+\lambda+\theta)+\rho d)}{(\sigma+\lambda)(\beta+\gamma+\rho+\lambda)(1+\lambda+\theta)(f+q)(h+q)} \tag{4.27}$$

Although the next generation matrix demands that $R_0 = \eta$ is the basic reproduction number, in practice η^2 is often taken as R_0 (indeed this was the assumption used in the original work applying this method). We note from the numerator of (4.27) that the basic reproduction number is proportional to the square of mosquito biting rate (e^2) as expected.

4.5 Model analysis and the steady state solution

Consider the domain

$$\Gamma \in \mathbb{R}^{10} = \{C, I, I_A, S, A, X, Y, Z, N, M \tag{4.28}$$
$$: C, I, I_A, S, A, X, Y, Z, M \geq 0, N > 0,$$
$$C + I + I_A + S + A = 1, X + Y + Z = 1\}$$

and suppose $t = 0$ all variables are positive, the $C(0) + I(0) + I_A(0) + S(0) + A(0) = 1$ and $X(0) + Y(0) + Z(0) = 1$. if $C = 0$ and all other variables in Γ, then $\frac{dC}{dt} \geq 0$. This is also the case for all other variables in (4.11-4.22). If $N = 0$, then $\frac{dN}{dt} = 0$ and $M = 0$ implies $\frac{dM}{dt} = 0$. But if $N > 0$ and $M > 0$, assuming $\lambda > \mu$ and $q > g$, then with appropriate initial conditions, $\frac{dN}{dt} > 0$ and $\frac{dM}{dt} > 0$. Note the right hand side of (4.11-4.22) is continuous with continuous partial derivatives, so solutions exist and are unique. The model is therefore mathematically and epidemiologically well posed with solutions in Γ for all $t \in [0, \infty)$. The disease free state $(C, I, I_A, S, A, X, Y, Z) = (1, 0, 0, 0, 0, 1, 0, 0)$ is locally and globally asymptotically stable when $R_0 < 1$ and unstable for $R_0 > 1$, where

$$R_0 = \frac{\alpha\sigma f(b(1+\lambda+\theta)+\rho d)}{(\sigma+\lambda)(\beta+\gamma+\rho+\lambda)(1+\lambda+\theta)(f+q)(h+q)} \tag{4.29}$$

is the expected number of secondary infection cases that would arise from the introduction of a single primary case into a fully susceptible population. We note that $R_0 = 1$ is a bifurcation surface in which the system changes its stability status, but we will only show proof of stability for the disease free state. Since $R_0 >> 1$ using previopus table and the infectiousness of asymptomatic humans to mosquitoes is significantly large, a good target for treatment is to reduce the infectivity of asymptomatic humans (reduce d) and that of symptomatic humans (reduce b) by increasing the treatment parameters θ and γ An important task is to determine an amount of treatment that can bring R_0 to a safe level. For instance, for R_0 to be brought down to unity, we will expect θ to be

$$\theta_c = \frac{(\sigma+\lambda)(\alpha+\rho+\lambda)(f+q)(h+q)(1+\lambda) - \alpha\sigma f(b(1+\lambda)+\rho d)}{\alpha\sigma fb - (\sigma+\lambda)(\beta+\gamma+\rho+\lambda)(h+q)} \tag{4.30}$$

in terms of parameters.

4.6 Stability analysis of the transition model

Here we derive sufficient conditions for global stability of the disease free state from all initial conditions $\in \Gamma$. The Jacobian matrix obtained by linearising system (4.13)-(4.20) about the disease free equilibrium point, $(C, I, I_A, S, A, X, Y, Z) = (1, 0, 0, 0, 0, 1, 0, 0)$ is

$$J_{df} = \begin{bmatrix} -\lambda & 0 & 0 & a_6 & 1+\theta & 0 & 0 & -\alpha \\ 0 & -a_1 & \theta & 0 & 0 & 0 & 0 & \alpha \\ 0 & 0 & -a_0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \sigma & \sigma & -a_2 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \rho & -a_3 & 0 & 0 & 0 \\ 0 & 0 & -d & -b & -d & -q & 0 & h \\ 0 & 0 & d & b & d & 0 & -a_4 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & f & a_5 \end{bmatrix} \tag{4.31}$$

Where the a_i are as defined above and $a_6 = \beta + \gamma$. The characteristic polynomial with eigenvalues (τ) is

$$(\tau + \lambda)(\tau + a_0)(\tau^5 + H_1\tau^4 + H_2\tau^3 + H_3\tau^2 + H_4\tau + H_5) = 0 \tag{4.32}$$

$$H_1 = a_1 + a_2 + a_3 + a_4 + a_5$$

$$H_2 = a_2a_5 + a_3a_4 + a_4a_5 + a_1a_2 + a_1a_3 + a_1a_4 + a_3a_5 + a_2a_3 + a_2a_4 + a_1a_5$$

$$H_3 = a_1a_2a_3 + a_1a_2a_4 + a_2a_3a_4 + a_2a_3a_5 + a_2a_4a_5 + a_3a_4a_5 + a_1a_4a_5 + a_1a_2a_5 + a_1a_3a_4 + a_1a_3a_5$$

$$H_4 = a_1a_2a_4a_5 + a_1a_3a_4a_5 + a_2a_3a_4a_5 + a_1a_2a_3a_4 + a_1a_2a_3a_5 - \alpha\sigma fb$$

$$H_5 = a_1a_2a_3a_4a_5 - \alpha\sigma f(ba_3 + \rho d)$$

We note the linear factorisation of (4.31) clearly yields negative real eigenvalues, however, from the quintic equation, no such deduction can immediately be made.

Lemma: The disease free equilibrium is asymptotically stable if $R_0 < 1$ and is unstable if $R_0 > 1$

Proof. From the definition of the $a_i's$ in (4.24), R_0 is given by

$$R_0 = \frac{\alpha\sigma f(ba_3 + \rho d)}{a_1a_2a_3a_4a_5}$$

if $R_0 < 1$ then

$$a_1a_2a_3a_4a_5 > \alpha\sigma f(ba_3 + \rho d)$$

The the coefficients of the quintic polynomial of (3.6.2) are all positive and non zero; so by the Descartes' rule of signs there are no positive real eigenvalues, this means there are 1, 3 or 5 negative real eigenvalues with the remaining being complex conjugate pairs. We need to show that Routh Hurwitz stability conditions for a fifth order polynomial as stated in [79] and given in this case by

$$H_1H_2H_3 > H_3^2 + H_1^2H_4$$

$$(H_1H_4 - H_5)(H_1H_2H_3 - H_3^2 - H_1^2H_4) > H_5(H_1H_2 - H_3)^2 + H_1H_5^2$$

are both satisfied. By letting $D = H_1H_2H_3 - H_3^2 - H_1^2H_4$ we express the above conditions as $F > 0$ *implies* $T > 0$ where $T = (H_1H_4 - H_5)D - H_5(H_1H_2 - H_3)^2 - H_1H_5^2$ Need to express T as

a finite sum of positive terms involving the model parameters. We can show that D and T_1 are sums of positive terms and

$$T = T_1 + [(a_3^2F_1 + a_1F_2 + F_3 + F_4 + F_5 + F_6)(Q_1 + E_2)]$$

$$+a_1^2(F_7 + F_8) + a_1F_9 + F_{10})](Q_1 - E_2) + [a_3^2E_2 + Q_2(b_4 + E_1)](b_4 - E_1)$$

The expressions for $Q_i's, F_i's, E_i's$ and b_4 in A1 Since $b_4 > E_1$ and $Q_1 > E_2$ it follows that $Q > 0$. Thus the disease disease-free equilibrium is locally and asymptotically stable if $R_0 < 1$. The coefficients H_1, H_2, H_3 are positive and we observe that if $R_0 > 1$,

$$a_1a_2a_3a_4a_5 < \alpha\sigma f\rho d + \alpha\sigma fba_3$$

in which H_5 is negative. Therefore the sequence of coefficients $1, H_1, H_2, H_3, H_4, H_5$ has only one sign change irrespective of the sign of H_4. By using Descartes' rule of sign there must exist at least one positive real eigenvalue, we conclude that the disease free state is unstable if $R_0 > 1$ □

Lemma: The disease-free equilibrium is globally asymptotically stable in Γ if

Proof.

$$\frac{\sigma\alpha}{\sigma+\alpha} \leq (h+q), \frac{fd}{f+q} \leq \gamma + \lambda, \frac{fd}{f+q} \leq \frac{\lambda(\sigma+\theta+\lambda)}{\sigma+\lambda}$$

Consider the function $\phi : [(C, I_A, S, A, X, Y, Z) \in \Gamma : C, X > 0] \to \mathbb{R}$, where

$$\phi = \frac{\sigma}{\sigma+\lambda}(1-C) + \frac{\lambda}{\sigma+\lambda}(I_A + S + A) + \frac{f}{f+q}(1-X) + \frac{q}{f+q}Z \tag{4.33}$$

We note that $\phi \geq 0$ and is continuously diferentiable on the interior of Γ We shall show that the disease free equilibrium is a global minimum of ϕ on Γ if (4.35) holds. The derivative of ϕ computed along solutions of the system is

$$\frac{d\phi}{dt} = (\frac{\sigma\alpha}{\sigma+\lambda} - q)Z + [\frac{fb}{f+q} - (\gamma+\lambda)]S + [\frac{fd}{f+q} - (1+\theta+\lambda)]A$$

$$+[\frac{fd}{f+q} - \frac{\lambda(\sigma+\theta+\lambda)}{\sigma+\lambda}]I_A - \frac{\sigma\alpha}{\sigma+\lambda}(I_A + S + A)ZS$$

$$-\beta(C + \frac{\lambda}{\sigma+\lambda}I_A) - \frac{1}{f+q}[fbS + fd(A + I_A + qhZ)]YS$$

$$-\frac{1}{f+q}(fbS + fdA + fdI_A + qhX)Z \tag{4.34}$$

We can see that $\frac{d\phi}{dt} \leq 0$ whenever

$$\frac{\sigma\alpha}{\sigma+\alpha} \leq (h+q), \frac{fd}{f+q} \leq \gamma + \lambda, \frac{fd}{f+q} \leq \frac{\lambda(\sigma+\theta+\lambda)}{\sigma+\lambda} \tag{4.35}$$

In fact, for $(I_A, S, A, Y, Z) = (0, 0, 0, 0, 0)$, $\frac{d\phi}{dt} \leq 0$ and (I_A, S, A, Y, Z) is the largest positively invariance subset in the interior of Γ and by LaSalle's invariant principle [56], $(I_A, S, A, Y, Z) \to (0, 0, 0, 0, 0)$ as $t \to \infty$, while $(C, X) \to (1, 1)$ on the boundary of Γ Some calculations given in Appendix A.2, using the inequalities in (4.35) show that the basic reproduction number is less than unity. The disease free state is globally stable if (4.35) are true, noting (4.35) $R_0 < 1$. □

4.7 Time scale analysis

In this section we present the time scale analysis of the model. Asymptotic analysis on the M and N equations show that M changes on the time scale t = O(ϵ), while N changes on t = O($\frac{1}{\epsilon^2}$). Thus we assume M N to be constant over the time scale of our analysis. By letting $\theta = 0$, we present the time scale analysis of the dimensionless system

$$\epsilon^2\frac{dC}{dt} = \epsilon^4\hat{\lambda} + \epsilon\hat{\gamma}S + \epsilon^2 A - \hat{\alpha}ZC - \epsilon^4\hat{\lambda}C + \epsilon^4\hat{\beta}CS, \tag{4.36}$$

$$\epsilon^2\frac{dI}{dt} = \hat{\alpha}ZC - \epsilon\hat{\sigma}I - \epsilon^4\hat{\lambda}I + \epsilon^4\hat{\beta}IS, \tag{4.37}$$

$$\epsilon^2\frac{dI_A}{dt} = \hat{\alpha}ZA - \epsilon\hat{\sigma}I_A - \epsilon^4\hat{\lambda}I_4 + \epsilon^4\hat{\beta}I_A S \tag{4.38}$$

$$\epsilon^2\frac{dS}{dt} = \epsilon\hat{\sigma}I + \epsilon\hat{\sigma}I_A - (\hat{\rho} + \epsilon\hat{\gamma} + \epsilon^4\hat{\beta} + \epsilon^4\hat{\lambda})S + \epsilon^4\hat{\beta}S^2, \tag{4.39}$$

$$\epsilon^2\frac{dA}{dt} = \hat{\rho}S - (\epsilon^2 + \epsilon^4\hat{\lambda})A - \hat{\alpha}ZA + \epsilon^4\hat{\beta}AS, \tag{4.40}$$

$$\epsilon\frac{dX}{dt} = \hat{q}(1 - X) - \hat{b}SX - \hat{d}AX - \hat{d}I_A X + \epsilon\hat{h}YZ, \tag{4.41}$$

$$\epsilon\frac{dY}{dt} = \hat{b}SX + \hat{d}AX + \hat{d}I_A X - (\hat{f} + \hat{q})Y + \epsilon\hat{h}YZ \tag{4.42}$$

$$\epsilon\frac{dZ}{dt} = \hat{f}Y - (\epsilon\hat{h} + \hat{q})Z + \epsilon\hat{h}Z^2. \tag{4.43}$$

subject to

$$C(0) = 1, I(0) = 0, I_A(0) = 0, S(0) = 0, A(0) = 0$$
$$Y(0) = y_0, X(0) = 1 - y_0, Z(0) = 0.$$

The definitions of the parameters with hats are given as

$$\alpha = \frac{1}{\epsilon^2}\hat{\alpha}, \sigma = \frac{1}{\epsilon}\hat{\sigma}, \mu = \epsilon^2\hat{\mu}, \lambda = \epsilon^2\hat{\lambda}, \gamma = \frac{1}{\epsilon}\hat{\gamma}, \rho = \frac{1}{\epsilon^2}\hat{\rho}. \tag{4.44}$$
$$b = \frac{1}{\epsilon}\hat{b}, d = \frac{1}{\epsilon}\hat{d}, f = \frac{1}{\epsilon}\hat{f}, g = \frac{1}{\epsilon}\hat{g}, h = \hat{h}, q = \frac{1}{\epsilon}\hat{q}.$$

where we have assumed for simplicity all parameters to be equal (not proportional) to the powers of ϵ as indicated in Table 2. We will carry out the analysis in the limit, $\epsilon \to 0$, $y_0 \to 0$ and $y_0 << \epsilon$. We note $R_0 \sim \frac{1}{\epsilon}$ in this limit so endemic outbreak is guaranteed. The time scale analysis reveals the endemic equilibrium for the human population as

$$C \sim \epsilon^2\frac{\hat{\gamma}\hat{\sigma}(\hat{q} + \hat{d})(\hat{q} + \hat{f})}{\hat{\rho}\hat{\alpha}\hat{f}\hat{d}}$$

$$I \sim \epsilon \frac{\hat{\gamma}}{\hat{\rho}}$$

$$I_A \sim 1$$

$$S \sim \epsilon \frac{\hat{\sigma}}{\hat{\rho}}$$

$$A \sim \frac{\hat{\sigma}(\hat{q}+\hat{d})(\hat{q}+\hat{f})}{\hat{\alpha}\hat{f}\hat{d}}$$

and for mosquitoes

$$X \sim \frac{\hat{q}}{\hat{q}+\hat{d}}$$

$$Y \sim \frac{\hat{d}\hat{q}}{(\hat{q}+\hat{d})(\hat{q}+\hat{f})}$$

$$Z \sim \frac{\hat{f}\hat{d}}{(\hat{q}+\hat{d})(\hat{q}+\hat{f})}$$

Details of the analysis are presented below in which there is evolution from an introduction of infected mosquitoes (population fraction ($y(0) = y_0$) to an uninfected area. The left-hand side of equations (4.36)-(4.43) seem to provide an initial guess of two time scales (i.e $t = O(\epsilon^2)$ and $t = O(\epsilon)$) but quite interestingly it happens to be a multi-scale problem. The method we use is that of formal asymptotics, namely singular perturbation methods whose application to problems in mathematical biology and classical mechanics is well established. The report does not include all the technical details involved as we are only interested in the leading-order behaviour of the system. There are a number of timescales but the six main timescales as predicted by the model are

$t = O(\epsilon^2), \approx 1-3$ **days:** A small amount of infected mosquitoes introduced into the system become infectious after passing through the incubation period. Susceptible humans bitten by these mosquitoes get infected. The early infection registers itself in the human compartments. However the effect of this early infection remains unnoticeable ($O(\epsilon y_0)$) in the incubating asymptomatic class. The amount of susceptible mosquitoes increases linearly due to natural birth.

$t = O(\epsilon^{\frac{4}{3}}), \approx 7-8$ **days:** In this time scale susceptible mosquitoes get infected by biting asymptomatic infectious humans. The amount of mosquitoes converting to the infectious class is also balanced by the amount of mosquitoes becoming infected by biting people in the asymptomatic infectious class. This behaviour is expected because individuals with clinical malaria have low level of gametocytes. Thus the early infection of susceptible mosquitoes is likely to come through contact with asymptomatic infectious humans since they have high gametocyte density. Infected humans are still negligible, $O(\epsilon^{1/3} y_0)$.

$t = O(\epsilon^{\frac{5}{4}}), \approx 9-10$ **days:** As more mosquitoes get infected through contact with asymptomatic infectious humans, the amount of susceptible mosquitoes reaches its maximum and starts decreasing. Whereas the feedback from infectious humans offsets the linear growth effect of the initial small amount of infected mosquitoes introduced, eventually causing the amount of incubating mosquitoes to grow exponentially. Human infected $= O(\epsilon^{-\frac{1}{2}} y_0)$:

4.7.1 $t = O(\epsilon^2)$

Using a hat to denote variables in this time scale we write

$$t = \epsilon^2 \hat{t},$$

and with appropriate balancing of terms in each of the equations exploring the idea that out of a small amount y_0 of infected mosquitoes introduced into the population only a smaller proportion ϵy_0 becomes infectious, we seek leading order solution of the form

$$C \sim 1 + \epsilon y_0 \hat{C}_1, I \sim \epsilon y_0 \hat{I}_0, I_A \sim \epsilon^3 y_0^2 \hat{I}_{A_0}, S \sim \epsilon^2 y_0 \hat{S}_0$$

$$A \sim \epsilon^2 y_0 \hat{A}_0, X \sim 1 - y_0 + \epsilon y_0 \hat{X}_1, Y \sim y_0 + \epsilon y_0 \hat{Y}_1, Z \sim \epsilon y_0 \hat{Z}_0.$$

On substitution of these rescalings into (4.36)-(4.43), we obtain the leading order system

$$\frac{d\hat{C}_1}{d\hat{t}} = -\hat{\alpha}\hat{Z}_0, \frac{d\hat{I}_0}{d\hat{t}} = \hat{\alpha}\hat{Z}_0, \frac{d\hat{I}_{A_0}}{d\hat{t}} = \hat{\alpha}\hat{A}_0\hat{Z}_0 \tag{4.45}$$

$$\frac{d\hat{S}_0}{d\hat{t}} = \hat{\sigma}\hat{I}_0 - \hat{\rho}\hat{S}_0, \frac{d\hat{A}_0}{d\hat{t}} = \hat{\rho}\hat{S}_0, \frac{d\hat{X}_1}{d\hat{t}} = \hat{q}, \tag{4.46}$$

$$\frac{d\hat{Y}_1}{d\hat{t}} = -(\hat{f} + \hat{q}), \frac{d\hat{Z}_0}{d\hat{t}} = \hat{f} \tag{4.47}$$

recalling $y_0 << \epsilon << 1$, satisfying the initial conditions

$$\hat{C}_1(0) = 0, \hat{I}_0(0) = 0, \hat{I}_{A_0}(0) = 0, \hat{S}_0(0) = 0,$$

$$\hat{A}_0(0) = 0, \hat{Y}_1(0) = 0, \hat{X}_1(0) = 0, \hat{Z}_0(0) = 0.$$

By doing direct integration we get the following leading order solutions

$$\hat{C}_1 \sim -\frac{1}{2}\hat{\alpha}\hat{f}\hat{t}^2, \hat{I}_0 \sim \frac{1}{2}\hat{\alpha}\hat{f}\hat{t}^2, \hat{I}_{A_0} \sim \frac{1}{30}\hat{\alpha}^2\hat{\sigma}\hat{f}^2\hat{t}^5, \hat{S}_0 \sim \frac{\hat{\alpha}\hat{\sigma}\hat{f}}{2\hat{\rho}}\hat{t}^2,$$

$$\hat{A}_0 \sim \frac{1}{6}\hat{\alpha}\hat{\sigma}\hat{f}\hat{t}^3, \hat{X}_1 \sim \hat{q}\hat{t}, \hat{Y}_1 \sim -(\hat{f} + \hat{q})\hat{t}, \hat{Z}_0 \sim \hat{f}\hat{t}.$$

We observe that susceptible humans (C) and incubating mosquitoes (Y) are decaying linearly in time from their initial values due to incubating mosquitoes converting to the infectious class and susceptible humans becoming infected as a consequence of infectious contact with mosquitoes in the Z class. With $\hat{A}_0 = O(t^3)$ there is a balance shift in (4.42), when $\hat{A}_0 = O(\epsilon^{-2})$ i.e. at a timescale $t = O(\epsilon^{-\frac{2}{3}})$, as susceptible mosquitoes become infected by biting asymptomatic humans. It is interesting to note that I and S equilibrate such that $\frac{S}{I} \sim \frac{\epsilon\sigma}{\rho}$ in this time scale 6and remain so as we will see in all the following timescales.

4.7.2 $t = O(\epsilon^{\frac{4}{3}})$

Denoting variables with over-bars in this time scale we write

$$t = \epsilon^{4/3}\bar{t}$$

and obtain the variable rescalings

$$C \sim 1 + \epsilon^{-1/3}y_0\bar{C_1}, I \sim \epsilon^{-1/3}y_0\bar{I_0}, I_A \sim \epsilon^{-1/3}y_0^2 I_{A_0}, S \sim \epsilon^{2/3}y_0\bar{S_0},$$

$$A \sim y_0\bar{A_0}, X \sim 1 - y_0 + \epsilon^{1/3}y_0\bar{X_1}, Y \sim y_0 + \epsilon^{1/3}y_0\bar{Y_1}, Z \sim \epsilon^{1/3}y_0\bar{Z_0}.$$

On substitution of these rescalings into (4.36)-(4.43) and considering the leading order terms we found that all the other equations remain the same as (4.45)-(4.47) in the previous time scale but the X and the Y equations both have an additional term, $\hat{d}\bar{A_0}$, given by

$$\frac{d\bar{X_1}}{d\bar{t}} = \hat{q} - \hat{d}\bar{A_0}, \frac{d\bar{Y_1}}{d\bar{t}} = \hat{d}\bar{A_0} - (\hat{f} + \hat{q})$$

marking the advent of feedback of infection from asymptomatic individuals to susceptible mosquitoes due to the initial small amount of infected mosquitoes introduced into the totally susceptible human population. This creates a balancing effect between the amount of mosquitoes converting to the infectious class and the amount becoming infected by biting people in the asymptomatic infectious class. We use the initial conditions

$$\bar{C_1}(0) = 0, \bar{I_0}(0) = 0, \bar{I}_{A_0}(0) = 0, \bar{S_0}(0) = 0,$$

$$\bar{A_0}(0) = 0, \bar{Y_1}(0) = 0, \bar{X_1}(0) = 0, \bar{Z_0}(0) = 0.$$

to obtain following solutions

$$\bar{C_1} \sim -\frac{1}{2}\hat{\alpha}\hat{f}\bar{t}^2, \bar{I_0} \sim \frac{1}{2}\hat{\alpha}\hat{f}\bar{t}^2, \bar{I}_{A_0} \sim \frac{1}{30}\hat{\alpha}^2\hat{\sigma}\hat{f}^2\bar{t}^5, \bar{S_0} \sim \frac{\hat{\alpha}\hat{\sigma}\hat{f}}{2\hat{\rho}}\bar{t}^2,$$

$$\bar{A_0} \sim \frac{1}{6}\hat{\alpha}\hat{\sigma}\hat{f}\bar{t}^3, \bar{X_1} \sim -\frac{1}{24}\hat{\alpha}\hat{\sigma}\hat{f}\hat{d}\bar{t}^4, \bar{Y_1} \sim \frac{1}{24}\hat{\alpha}\hat{\sigma}\hat{f}\hat{d}\bar{t}^4, \bar{Z_0} \sim \hat{f}\bar{t}.$$

The only notable difference between these and the earlier time scale is in X and Y with an accelerated rate of mosquito infection from asymptomatic infectious humans. The implication of this is that the flow of the solution may change direction especially when the amount of mosquitoes getting infected becomes more than the in ow of new born mosquitoes. This happens at the point of breakdown

$$\bar{t} = O(\epsilon^{-1/12})$$

where $\bar{Y_1}$ becomes $O(y_0)$. The dynamics of the system in the next time scale is a consequence of the change in the order of $\bar{Y_1}$.

4.7.3 $t = O(\epsilon^{\frac{5}{4}})$

Using a tilde to denote variables in this time scale where,

$$t = \epsilon^{5/4}\tilde{t}$$

the rescalings are

$$C \sim 1 + \epsilon^{-1/2} y_0 \tilde{C_1}, I \sim \epsilon^{-1/2} y_0 \tilde{I_0}, I_A \sim \epsilon^{-3/4} y_0^2 \tilde{I}_{A_0}, S \sim \epsilon^{1/2} y_0 \tilde{S_0}$$

$$A \sim \epsilon^{-1/4} y_0 \tilde{A_0}, X \sim 1 + y_0 \tilde{X_1}, Y \sim y_0 \tilde{Y_1}, Z \sim \epsilon^{1/4} y_0 \tilde{Z_0}$$

On substitution of these into (4.36)-(4.43) we find (at leading order) that the equations representing the human compartments are unchanged, but due to the dominant contribution of asymptomatic infectious humans on the infection of mosquitoes, the rate of change of $\tilde{Y_1}$ and $\tilde{X_1}$ are proportional to the amount of asymptomatic humans with that of $\tilde{Z_0}$ proportional to $\tilde{Y_1}$. The system in full is

$$\frac{d\tilde{C_1}}{d\tilde{t}} = -\hat{\alpha}\tilde{Z_0}, \frac{d\tilde{I_0}}{d\tilde{t}} = \hat{\alpha}\tilde{Z_0}, \frac{d\tilde{I}_{A0}}{d\tilde{t}} = \tilde{A_0}\hat{\alpha}\tilde{Z_0}, \hat{\sigma}\tilde{I_0} = \hat{\rho}\tilde{S_0},$$

$$\frac{d\tilde{A_0}}{d\tilde{t}} = \hat{\rho}\tilde{S_0}, \frac{d\tilde{X_1}}{d\tilde{t}} = -\hat{d}\tilde{A_0}, \frac{d\tilde{Y_1}}{d\tilde{t}} = \hat{d}\tilde{A_0}, \frac{d\tilde{Z_0}}{d\tilde{t}} = \hat{f}\tilde{Y_1}.$$

Successive differentiation of $\frac{d\tilde{Z_0}}{d\tilde{t}}$ we find that $\frac{d^4\tilde{Z_0}}{d\tilde{t}^4} = K\tilde{Z_0}$ and matching the solution with section (4.7.2) as $\tilde{t} \to \infty$ we have

$$\tilde{C_1}(0) = \tilde{I_0}(0) = \tilde{I}_{A0}(0) = \tilde{S_0}(0) = \tilde{A_0}(0) = \tilde{Z_0} = 0, \tilde{X_1}(0) = -1,$$

$$\tilde{Y_1}(0) = 1, \frac{d\tilde{Z_0}}{d\tilde{t}}(0) = \hat{f}, \frac{d^2\tilde{Z_0}}{d\tilde{t}^2}(0) = 0, \frac{d^3\tilde{Z_0}}{d\tilde{t}^3}(0) = 0, \tilde{Z_0}(0) = 0,$$

where $K = \hat{\alpha}\hat{\sigma}\hat{f}\hat{d}$. Large time solutions are

$$\tilde{C_1} \sim -\frac{\hat{\alpha}\hat{f}}{4K^{1/2}}e^{K^{1/4}\tilde{t}}, \tilde{I_0} \sim \frac{\hat{\alpha}\hat{f}}{4K^{1/2}}e^{K^{1/4}\tilde{t}}, \tilde{I}_{A0} \sim \frac{\hat{\alpha}\hat{f}}{32\hat{d}K^{1/4}}e^{2K^{1/4}\tilde{t}}, \tilde{S_0} \sim \frac{\hat{\alpha}\hat{\sigma}\hat{f}}{4\hat{\rho}K^{1/2}}e^{K^{1/4}\tilde{t}}$$

$$\tilde{A_0} \sim \frac{\hat{\alpha}\hat{\sigma}\hat{f}}{4K^{3/4}}e^{K^{1/4}\tilde{t}}, \tilde{X_1} \sim -\frac{1}{4}e^{K^{1/4}\tilde{t}}, \tilde{Y_1} \sim \frac{1}{4}e^{K^{1/4}\tilde{t}}, \tilde{Z_0} \sim \frac{\hat{f}}{4K^{1/4}}e^{K^{1/4}\tilde{t}}$$

shows that both the mosquito and human compartments are growing exponentially. For $K_0 = K^{1/4}$ the approximations for this timescale become poor when $\tilde{C_1} = O(e^{K_0\tilde{t}}) = O(\epsilon^{1/2}/y_0)$ i.e $\tilde{t} = ln(\epsilon^{1/2}/y_0/K_0)$ when asymptomatic humans become infected with new asexual parasites due to contact with infectious mosquitoes.

4.7.4 $t = \epsilon^{\frac{5}{4}} ln(\epsilon\frac{1}{2}/y_0)/K_0 + O(\epsilon^{\frac{5}{4}})$

In order to describe events captured on this time scale we translate in time from the former time scale and write

$$t = \epsilon^{\frac{5}{4}} ln(\epsilon^{\frac{1}{2}}/y_0)/K_0 + \epsilon^{\frac{5}{4}}\check{t}$$

where the check is the symbol for variable representation. The initial small amount of infection has been totally distributed and whose effect has developed into the beginnings of a full blown epidemic with C and I becoming O(1) and no dependence on y_0, to leading order as we can see in the following rescalings

$$C \sim \check{C_0}, I \sim \check{I_0}, I_A \sim \epsilon^{1/4}\check{I}_{A0}, S \sim \epsilon\check{S_0}, A \sim \epsilon^{1/4}\check{A_0},$$

$$X \sim 1 + \epsilon^{1/2}\check{X_1}, Y \sim \epsilon^{1/2}\check{Y_1}, Z \sim \epsilon^{3/4}\check{Z_0}.$$

Following the usual substitution procedure we find that at leading order, some equations remain the same as in the preceding time scale whereas the C, L, A, X and Y equations are now being expressed as

$$\frac{d\check{C}_0}{d\check{t}} = -\hat{\alpha}\check{C}_0\check{Z}_0, \frac{d\check{I}_0}{d\check{t}} = \hat{\alpha}\check{C}_0\check{Z}_0, \frac{d\check{I}_{A0}}{d\check{t}} = \hat{\alpha}\check{A}_0\check{Z}_0. \tag{4.48}$$

$$S_0 = \frac{\hat{\sigma}}{\hat{\rho}}\check{I}_0, \frac{d\check{A}_0}{d\check{t}} = \hat{\rho}S_0 - \hat{\alpha}\check{A}_0\check{Z}_0, \frac{d\check{X}_1}{d\check{t}} = -\hat{d}\check{A}_0 - \hat{d}\check{I}_{A0}, \tag{4.49}$$

$$\frac{d\check{Y}_1}{d\check{t}} = \hat{d}\check{A}_0 + \hat{d}\check{I}_{A0}, \frac{d\check{Z}_0}{d\check{t}} = \hat{f}\check{Y}_1.$$

where by matching with the long time solution of section 4.7.3

$$\check{t} \to -\infty$$

$$\check{C}_0 \to 1^-, \check{I}_0 \to 0^+, \check{I}_{A0} \to 0^+, \check{S}_0 \to 0^+, \check{A}_0 \to 0^+, \check{X}_1 \to 0^+, \check{Y}_1 \to 0^+, \check{Z}_0 \to 0^+$$

the situation where asymptomatic humans become infected with new asexual parasites due to their contact with infectious mosquitoes, which eventually reduces the size of A as asymptomatic humans leave for the I_A class. Consequently, more susceptible mosquitoes get infected as incubating asymptomatic humans transfer infection. In order to obtain a solution of the system, we note

$$\frac{d\check{C}_0}{d\check{t}} + \frac{d\check{I}_0}{d\check{t}} = 0, \frac{d(\check{I}_{A0} + \check{A}_0)}{d\check{t}} = \hat{\sigma}\check{I}_0, \frac{d^3\check{Z}_0}{d\check{t}^3} = \hat{\sigma}\hat{f}\hat{\check{I}}_0.$$

First equation gives us, $\check{C}_0 + \check{I}_0 = 1$. Substituting this into the differential equation for $\check{C}_0$, leads to the fourth-order nonlinear ode, which is the main equation that drives the dynamics of the system on this time scale given by

$$\frac{d^4\check{F}}{d\check{t}^4} = -K(1 - e^{\check{F}})$$

Where K is defined above and $\check{F} = ln(\check{C}_0)$ This equation does not seem to have an analytical solution but we can extract some key information by investigating its behaviour. It is easy to show that $F = 0(\check{C}_0 = 1)$ is an unstable steady state. Considering $g(F) = -K(1 - e^{\check{F}}), F = 0 \to g = 0, F < 0 \to g < 0$ and $F > 0 \to g > 0$. Thus $F = 0$ is unstable. By matching we have $F \to 0^-$, or $\check{C}_0 \to 1^-$, as $\check{t} \to -\infty$ hence $\frac{d\check{F}}{d\check{t}} < 0$ as $\check{t}$ increases i.e. a non-negligible amount of humans are becoming infected. For large, negative $\check{F}$ we have

$$\frac{d^4\check{F}}{d\check{t}^4} \sim -K,$$

as the homogenous ODE whose general solution is,

$$\check{F} = -\frac{1}{24}K\check{t}^4 + \frac{1}{6}\alpha_1\check{t}^3 + \frac{1}{2}\alpha_2\check{t}^2 + \alpha_3\check{t} + \alpha_4$$

as $\check{t} \to +\infty$ where $\alpha_1, \alpha_2, \alpha_3, \alpha_4$ are unresolved constants depending on the solution as $\check{t} \to -\infty$. The solutions for the susceptible and incubating human compartments are

$$\check{C}_0 \sim B_0 exp(\frac{a_1}{6}\check{t}^3 + \frac{a_2}{2}\check{t}^2 + a_3\check{t})e^{-\frac{K}{24}\check{t}^4}, \check{I}_0 \sim 1 - B_0 exp(\frac{a_1}{6}\check{t}^3 + \frac{a_2}{2}\check{t}^2 + a_3\check{t})e^{-\frac{K}{24}\check{t}^4}$$

indicating a very rapid exchange from the C to the I class describe how the force of infection generated by infectious mosquitoes, Z drastically reduces the size of C and increases that of I. As $\check{C}_0 \to 0$ and by applying dominant balancing of terms we obtain large time behaviour of other variables as

$$\check{I}_{A0} \sim \hat{\sigma}\check{t}, \check{S}_0 \sim \frac{\hat{\sigma}}{\hat{\rho}}, \check{A}_0 \sim \frac{6\hat{\sigma}}{K}\check{t}^{-3}, \check{X}_1 \sim -\frac{1}{2}\hat{d}\hat{\sigma}\check{t}^2, \check{Y}_1 \sim \frac{1}{2}\hat{d}\hat{\sigma}\check{t}^2, \check{Z}_0 \sim \frac{K}{6\hat{\alpha}}\check{t}^3$$

as $\check{t} \to \infty$. Due to the rapid drop in the C class, there are series of minor transition timescales in which $C = O(1)$ falls to $C = O(\epsilon^2)$, in several very small timescale stages. We shall omit the details and move on to the next major rebalance of the system, at $\check{t} = O(\epsilon^{-1/4})$, where the infected mosquito classes become non-negligible and the incubating classes dominate the human population.

4.7.5 $t = O(\epsilon)$

We will use the $*$ symbol to denote variables on this time scale. By expressing time as

$$t = \epsilon t^*$$

The variable rescalings are as follows:

$$C \sim \epsilon^2 C_0^*, I \sim I_0^*, I_A \sim I_{A0}^*, S \sim \epsilon S_0^*, A \sim \epsilon A_0^*, X \sim X_0^*, Y \sim Y_0^*, Z \sim Z_0^*,$$

noting the susceptible class is now $O(\epsilon^2)$ and that most of human population are in the incubating classes. On substitution of these into the full system as usual, yields a situation where some of the variables have assumed quasi-steady states, i.e. they are expressed in terms of the other variables, especially,

$$C_0^* = \frac{\hat{\gamma}}{\hat{\rho}}A_0^*, S_0^* = \frac{\hat{\sigma}}{\hat{\rho}}(I_0^* + I_{A0}^*), A_0^* = \frac{\hat{\rho}S_0^*}{\hat{\alpha}Z_0^*}$$

The remaining variables are described by the system

$$\frac{dI_0^*}{dt^*} = -\sigma I_0^*, \frac{dI_{A0}^*}{dt^8} =_0^*, \frac{dX_0^*}{dt^*} = \hat{q} - (\hat{q} + \hat{d}I_{A0}^*)X_0^*,$$

$$\frac{dY_0^*}{dt^*} = \hat{d}I_{A0}^* - (\hat{f} + \hat{q})Y_0^*, \frac{dZ_0^*}{dt^*} = \hat{f}Y_0^* - \hat{q}Z_0^*.$$

subject to

$$I_0^*(0) = 1, I_{A0}^*(0) = 0, Y_0^*(0) = 0, X_0^*(0) = 1, Z_0^*(0) = 0.$$

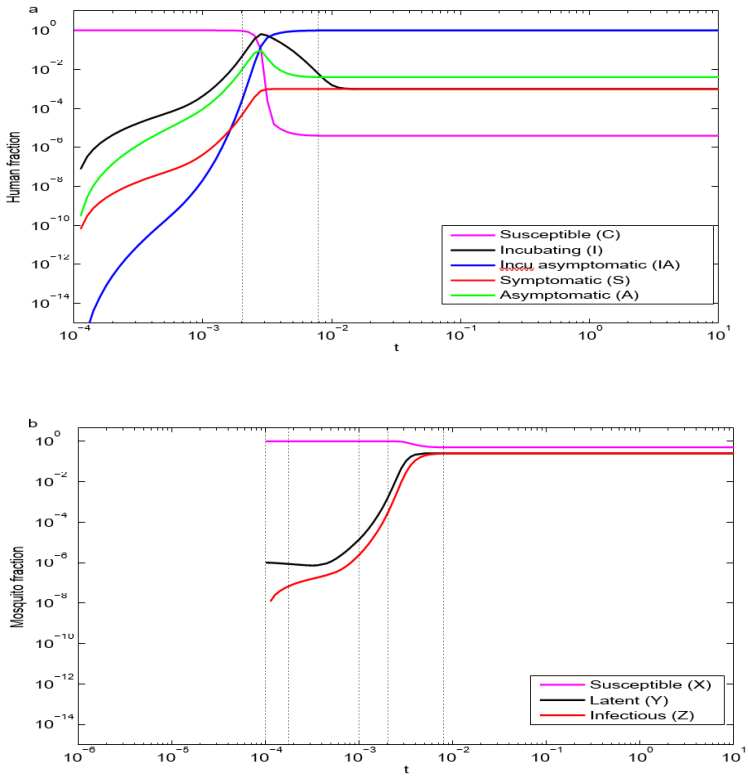
The straightforward solutions are

$$I_0^* \sim e^{-\sigma t^*}, I_{A0}^* \sim 1 - e^{-\sigma t^*}$$

and consequently, $S_0^* = \frac{\hat{\sigma}}{\hat{\rho}}$ We cannot solve for the other variables, but it is useful to note that the leading behaviour as $t^* \to \infty$, are the steady states

$$C_0^* \sim \epsilon^2 \frac{\hat{\gamma}\hat{\sigma}(\hat{q} + \hat{d})(\hat{q} + \hat{f})}{\hat{\rho}\hat{\alpha}\hat{f}\hat{d}}, A_0^* \sim \epsilon \frac{\hat{\sigma}(\hat{q} + \hat{d})(\hat{q} + \hat{f})}{\hat{\alpha}\hat{f}\hat{d}},$$

$$X_0^* \sim \frac{\hat{q}}{\hat{q} + \hat{d}}, Y_0^* \sim \frac{\hat{d}\hat{q}}{(\hat{q} + \hat{d})(\hat{q} + \hat{f})}, Z_0^* \sim \frac{\hat{f}\hat{d}}{(\hat{q} + \hat{d})(\hat{q} + \hat{f})}$$



We note that while other variables are in their steady states, the amount of incubating humans decays rapidly causing the amount of incubating asymptomatic humans to grow due to massive inflow of asymptomatic humans being infected with asexual parasites. Although not apparent from the solutions we can show that approximation to I will no longer be $O(1)$ when

$$t^* = \frac{1}{\hat{\sigma}} ln(1/\epsilon) + O(1)$$

which gives us our final time scale

4.7.6 $t = (1/\epsilon)/\sigma + O(\epsilon)$

Variables on this time scale will be denoted using "$'$" so that;

$$t = (1/\epsilon)/\hat{\sigma} + \epsilon t^{'}$$

and

$$C \sim \epsilon^2 C_0^{'}, I \sim \epsilon I_0^{'}, I_A \sim 1, S \sim \epsilon S_0^{'}, A \sim \epsilon A_0^{'}, X \sim X_0^{'}, Y \sim Y_0^{'}, Z \sim Z_0^{'}$$

On substitution of these into (4.36-4.43) we find that the variables in their steady states remain unchanged and $I_A \sim 1$. Only $I^{'}$ is evolving at leading order according to,

$$\frac{dI_0^{'}}{dt^{'}} = \frac{\hat{\gamma}\hat{\sigma}}{\hat{\rho}} - \hat{\sigma} I_0^{'}.$$

The graphs below show that the rapid drop of susceptible humans as shown in the fourth timescale of the analysis follows immediately after a sharp increase in the number of infectious mosquitoes. The fraction of Incubating humans, I increases as C drops. Above is the solution of the dimensionless system (4.36-4.43) using $\epsilon = 0.001$ and all other dimensionless parameters set to unity. The top

graph represents the various compartments in the human population and the bottom graph shows the fractions of mosquito population. Note the time axes are the log10 values for time and that the human and mosquito fractions are also been logged. The vertical dotted lines indicate different timescales, marking conspicuous event. We only present the 4th and the 5th time scale for the human population where the 3rd class is omitted for the mosquito class.
The number of incubating asymptomatic humans had been of low order from the beginning of the analysis and I had always dominated the infection classes. But immediately after the disease fully established itself, we observe that in the fifth timescale, I is no longer O(1) as I_A grows to overtake I, which culminates in the final state of the disease showing about 90% of the human population in the incubating asymptomatic class as predicted by the analysis. Different stages of events in the mosquito population as predicted by the analysis are also well represented by the simulations. By matching with the previous timescale we have $I_0^{'} \sim e^{\sigma t^{'}}$ as $t \to -\infty$ hence the solution

$$I_0^{'} = \frac{\hat{\gamma}}{\hat{\rho}} - e^{\hat{\sigma} t^{'}}$$

which decays to $\frac{\hat{\gamma}}{\hat{\rho}}$ as $t \to -\infty$. Thus we reach the complete equilibrium state at leading order namely

$$C \sim \epsilon^2 \frac{\hat{\gamma}\hat{\sigma}(\hat{q}+\hat{d})(\hat{q}+\hat{f})}{\hat{\rho}\hat{\alpha}\hat{f}\hat{d}}, I \sim \epsilon\frac{\hat{\gamma}}{\hat{\rho}}, I_A \sim 1, S \sim \epsilon\frac{\hat{\sigma}}{\hat{\rho}}, A \sim \epsilon\frac{\hat{\sigma}(\hat{q}+\hat{d})(\hat{q}+\hat{f})}{\hat{\alpha}\hat{f}\hat{d}},$$

$$X \sim \frac{\hat{q}}{\hat{q}+\hat{d}}, Y \sim \frac{\hat{d}\hat{q}}{(\hat{q}+\hat{d})(\hat{q}+\hat{f})}, Z \sim \frac{\hat{f}\hat{d}}{(\hat{q}+\hat{d})(\hat{q}+\hat{f})}$$

4.7.7 Conclusion from the analysis

Through our timescale analysis we have provided insight into the transmission of the disease as shown by the numerical simulations. Six main time scales as predicted by the model are used with appropriate rescalings to explicate the dynamics of the disease in relation to events as they evolve from early incidence to endemic state. There are important concluding remarks about the spread of the disease:

- Throughout the analysis, S has been proportional to I showing that the level of the disease depends very much on non-immune individuals becoming infected. We also find that C remained at O(1) from the first timescale until the fourth time scale

  $$t = \epsilon^{\frac{5}{4}} ln(\epsilon\frac{1}{2}/y_0)/K_0 + O(\epsilon^{\frac{5}{4}})$$

  when it suddenly dropped to $O(\epsilon^2)$, which suggests that intervention programs may yield better results if implemented before this time scale, preferably by the time $t = O(\epsilon^{5/4})$, during which the feedback from infectious humans osets the linear growth effect of the initial small amount of infected mosquitoes. This equates to about 2-3 weeks from the initial infection.

- The contribution of asymptomatic infectious humans has a significant effect on the dynamics of the disease. This becomes evident in the time scale $t = O(\epsilon^{4/3})$ and influences the mode of infection throughout the period of analysis. This is due to our choice of the values of the model parameters, which we have assumed that asymptomatic humans are far more infectious than symptomatic humans. We recall that disease symptoms are associated with the erythroctye cycle, a period characterised by incursion and invasion of the red blood cells by asexual parasites.

- The noticeable build-up of Incubating asymptomatic humans at steady state is a clear characteristic of the dynamics of malaria in an endemic region. This portends a dangerous scenario and creates adverse effect on public policies aimed at control or eradication of the disease. It appears adults get partial immunity at the expense of children and women (who may likely loose immunity) during pregnancy. The condition $\epsilon << 1$, or precisely $i_a << \sigma_h$, on which our analysis is based, represents a situation where humans spend a very long time in the asymptomatic class potentially, but they get infected almost immediately harbouring infection without remarkable symptom of the disease and from known results, this is reinforced through continuous infection as shown in our analysis.

- In order to use our model to achieve effective control or eradication of the disease we will perform some more simulations in the future to ascertain if it is worth considering an option of reducing the time humans spend in the asymptomatic class through treatment so that we can recommend and promote the simple slogan, check your 'Malaria Infection Status' (MIS) and get treated. Another option is to ascertain whether or not prompt treatment of sick people would guarantee a disease free state by considering γ as a treatment parameter.

- The scenario in which the analysis is based has $R_0 > 1$ so an endemic situation is guaranteed. It is interesting to note that the dominant human class is the I_A class who are both incubating and infectious to mosquitoes. This class is absent in all other models to our knowledge, yet, this model suggests, it is by far the most important class in sustaining the disease. Throughout this analysis, $S = O(\epsilon)$ which means that the amount of death due to the disease is negligibly small, and, together with a negligible natural birth and death rate, $N \approx 1$ throughout this analysis. The scalings for mosquitoes suggest that death by the disease is negligible compared to natural death, and hence $\frac{dM}{dt} \sim (\hat{q} - \hat{g})M/\epsilon$ so that M will change in a t = O() timescale. In reality there will be limitation to population growth.

4.8 Numerical Simulations

In section 4.6 we analysed the transition model by adducing good conditions to show that the disease free state is locally and asymptotically stable if $R_0 < 1$ and unstable for $R_0 > 1$. We studied the disease based on $R_0 > 1$ using timescale analysis in section 4.7 to demonstrate the existence of an endemic state. Here we will use numerical analysis to verify the results we have derived. We will also demonstrate numerically that the endemic state is globally and asymptotically stable if $R_0 > 1$ using a set of initial conditions defined by Γ (4.28).
Due to the asymptotic analysis, we assume that $\frac{M}{N}$ is constant throughout the simulations. The numerical solution is obtained using MATLAB'S ODE45, a variable order Runge-Kutta. The parameters used are defined in Table 2 are $\alpha = 62.43, \sigma = 11.1$ (i.e $\epsilon = 0.09$), $\mu = 0.0056, \lambda = 0.017, \beta = 0.01, \gamma = 11.5, \rho = 54.45, \theta = 0, b = 7.2, d = 38.2, f = 14, g = 21.12, h = 1.45, q = 21.45$. The inital conditons at t=0 are: $C = 1, I = 0, I_A = 0, S = 0, A = 0, X = 0.9999, Y = y_0 = 0.0001, Z = 0, N = 1, M = 1$. This is a situation where the entire susceptible human population is exposed to a small fraction of infected mosquitoes. The program was run in MATLAB with different sets of initial conditions. In Figure 3 a,c, the proportion of susceptible human population drops. This is more pronounced in Figure 3 a, in which we have used $\theta = 0$ to represent non-treatment of asymptomatic humans leading to more infection of susceptible humans.

The incubating human fraction peaks and later drops to a steady state. There is a high proportion of incubating asymptomatic humans showing that the asymptomatic state is being preserved in continuous infection. In Figure 3 b, more than half of the mosquito population are infected indicating

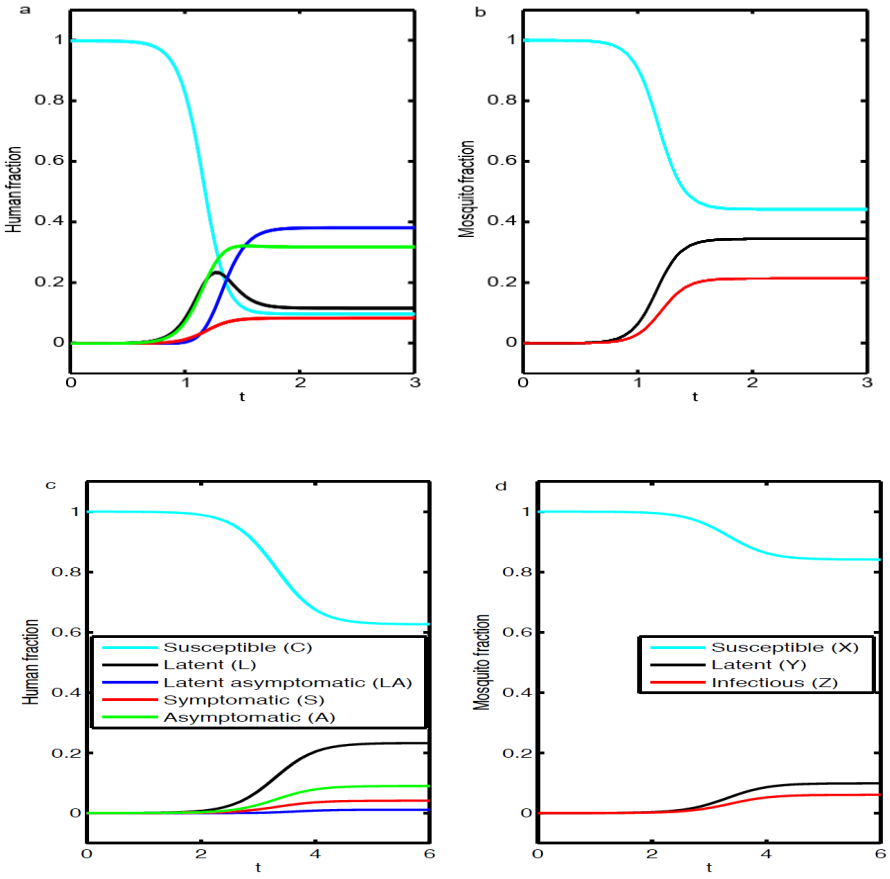


Figure 3: Results showing the effect of the initial infected mosquito population on evolution of endemic infection where t = 1, represents 165 days in real time. The initial conditions used are $C = 1, I = 0, I_A = 0, S = 0, A = 0, X = 0.9999, Y = 0.0001, Z = 0, N = 1, M = 1$ and the parameter values are given in Table 2. In Figure 3 c,d, there is some level of post disease treatment ($\theta = 20$), whilst we have used $\theta = 0$ in Figure 3 a,b to explicate the dynamics of endemic malaria in which asymptomatic humans are not treated

high level of disease prevalence. However, a smaller proportion of mosquitoes become infected when $\theta = 20$ as shown in Figure 3 d.

In Figure 4 a,b, the population of humans and mosquitoes are gradually increasing. Figure 4 c,d,e,f show the effect of different values of y_0 on the various fractions of human population. We investigate each of the human sub-populations as y_0 varies from 0.00001 to 0.1 and the results show that there is a unique steady state for each human compartment irrespective of the value of y_0 except that it takes a longer time to reach the steady state with a smaller y_0. We note that the delay increases linearly as y_0 decreases exponentially as predicted by the analysis of section 4.74.

The results demonstrate the typical behaviour of rapid infection of susceptible individuals in a malaria endemic region. Figure 5 a, b shows the relationship between the basic reproduction number and the disease profile as it affects both mosquito and human populations. The disease establishes itself for values of $R_0 > 1$ and dies out if $R_0 < 1$. The values of R_0 were obtained by varying α and $R_0 = 1$ corresponds to $\alpha = 1.87$. Figure 6 is a bifurcation diagram showing a switch from a disease free state to an endemic state. The result is obtained by drawing the steady states of symptomatic humans against different values of R_0.

Each curve in Figure 7a represents the effect of θ on S for a given γ. The red curve in particular shows

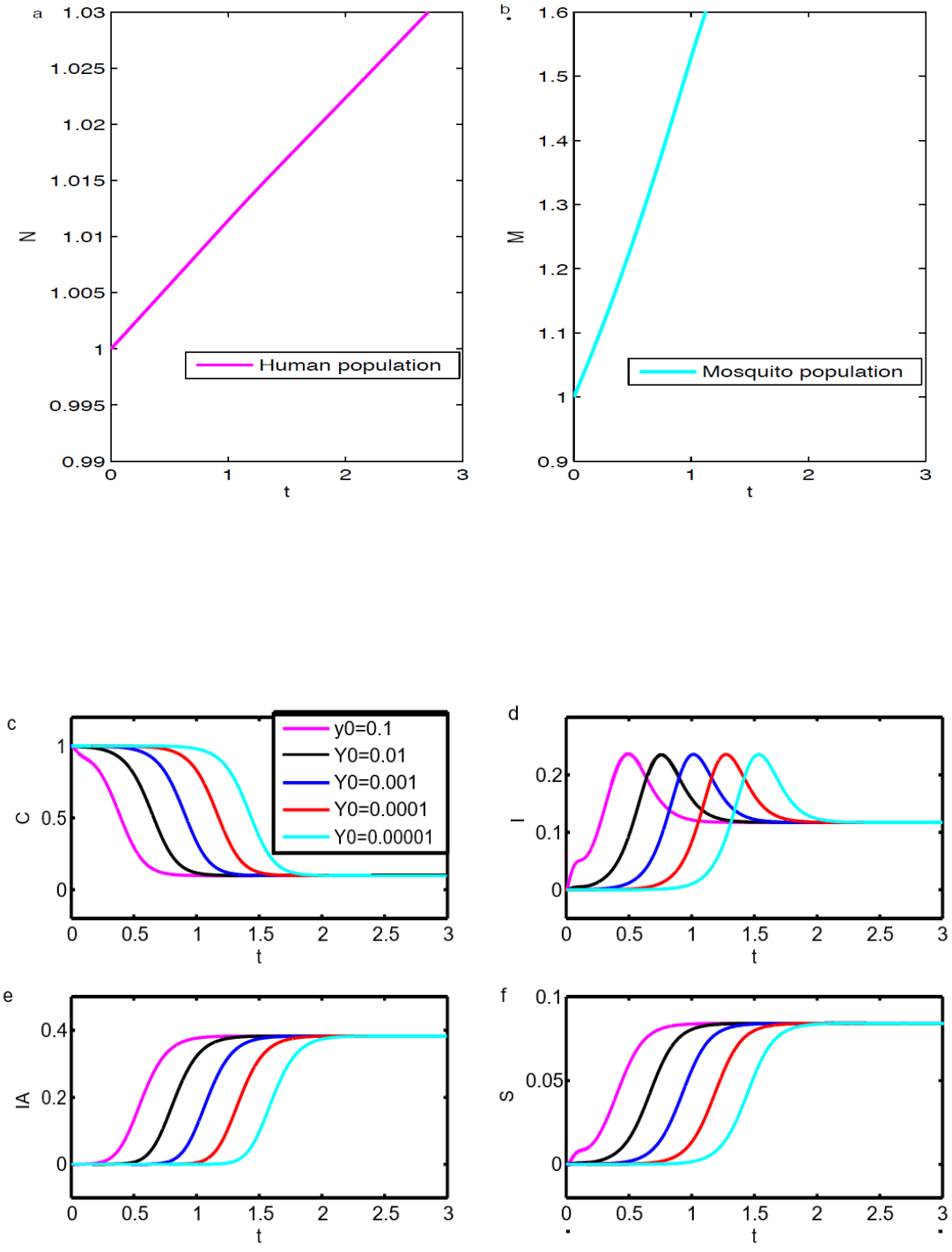


Figure 4: Results showing the human and mosquito populations (Figure 4 a,b) and the effect of introducing different amount of infected mosquitoes on the various fractions of human population (Figure 4 c,d,e,f). The values used for the simulations are the same as those in (Figure 3 c,d) except that for Figure 4 a,b we used g = 21.02 and for (Figure 4 c,d,e,f) we have used the initial conditions, $C = 1, I = 0, I_A = 0, S = 0, A = 0, X = 1 - y_0, Y = y_0, Z = 0, N = 1, M = 1$ with different values of y_0 as shown in the graphs

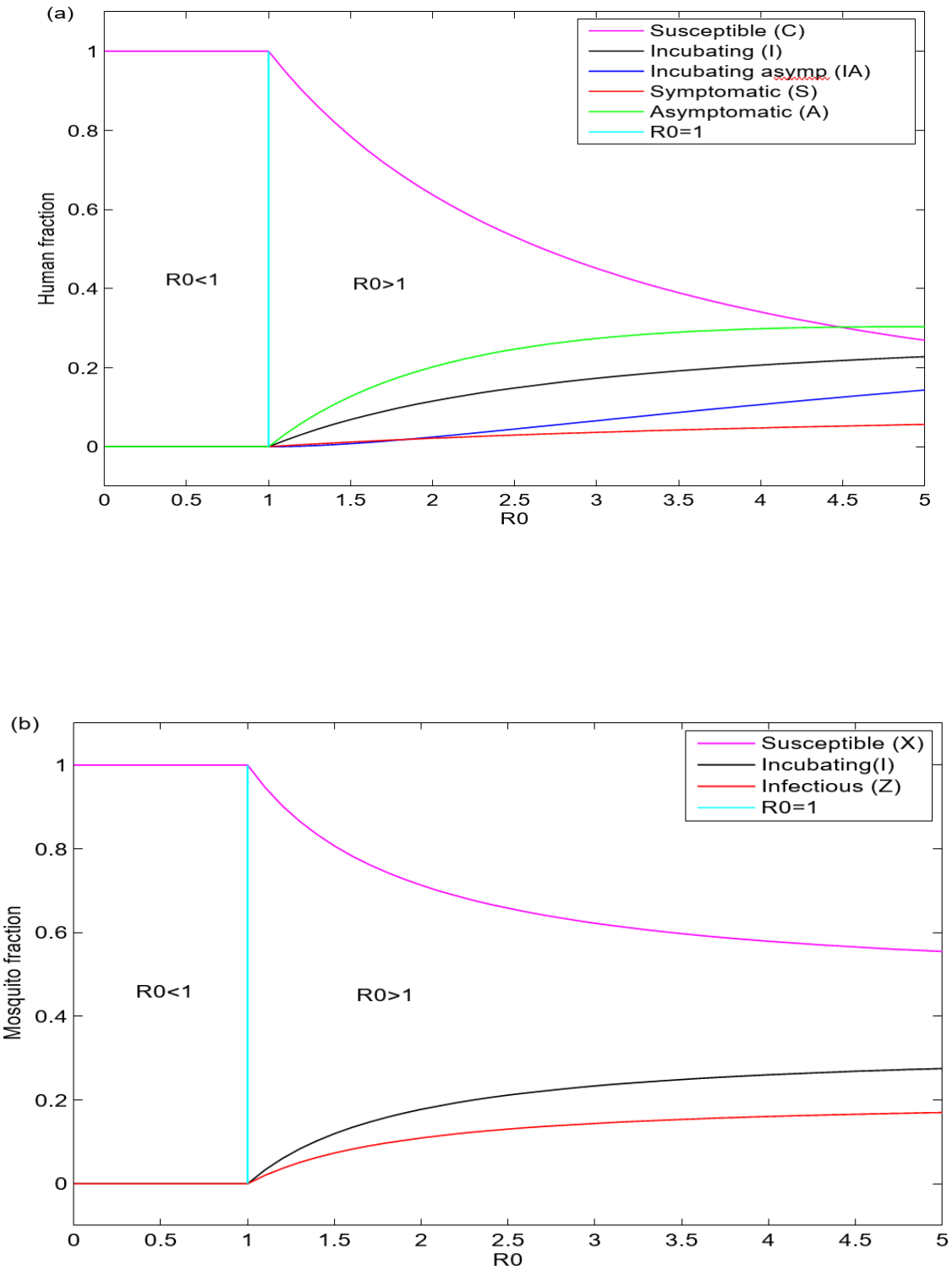


Figure 5: Results showing the disease free state when $R_0 < 1$ and the endemic state for $R_0 > 1$ by varying the value of R_0 from 0 to 5. The parameter values used to obtain these results are given in Table 2 except $\theta = 4.13$. We used the parameter, α to change R_0 where $R_0 = 5$ corresponds to $\alpha = 9.35$.

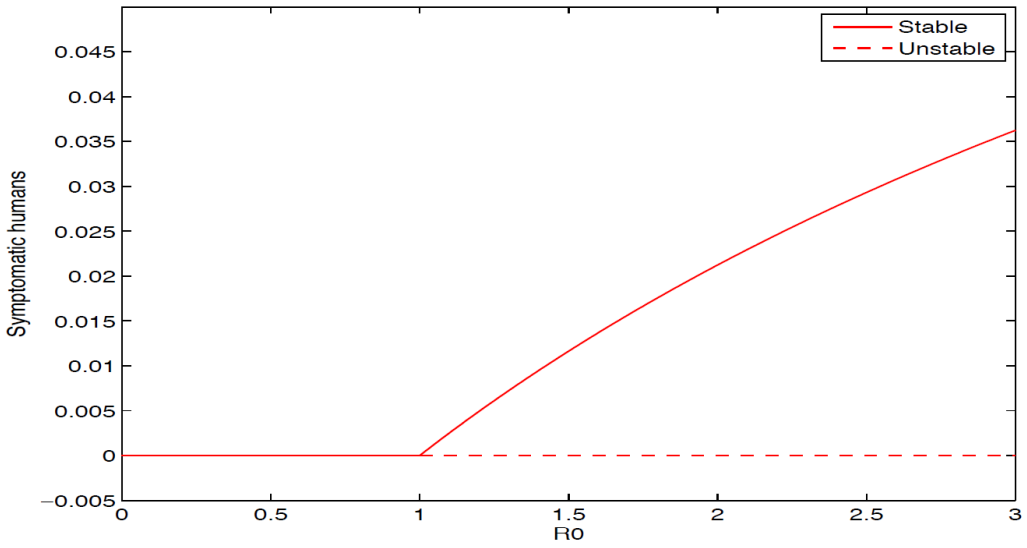


Figure 6: Basic reproduction number (R_0) bifurcation diagram. The curve shows a transcrital bifurcation obtained by drawing the steady states of symptomatic humans against different values of R_0 ranging from 0 to 3. Parameter values are the same as those in Figure5

that for a certain level of symptomatic treatment, $\gamma = 60$ people require a post disease treatment, $\theta = 21$ to drive the disease to extinction. Treatment of both symptomatic and asymptomatic humans can easily lead to a disease free state. Figure 7b gives the variation of the amount of symptomatic humans as gradually it increases from zero in the absence of post disease treatment.

In order to demonstrate the impact of the basic reproduction number on the dynamics of the system, we plot the steady states of the various human and mosquito compartments against the basic reproduction number (R_0). Figures 5a,b show the disease free state when R_0 is less than unity and for $R_0 > 1$ the disease invades both the human and mosquito populations. The plot shows a transcritical bifurcation in the vicinity of $R_0 = 1$, as is expected from the analysis. Although some uncertainty still surrounds our quest on whether or not the disease invades the population at $R_0 = 1$ the disease free state is stable for values of $R_0 < 1$, but becomes unstable when $R_0 > 1$ whereas, the endemic state becomes stable as expected.

The disease free state assumes that the entire mosquito and human populations are free from the disease. Any simulation leading to S = 0, by varying the model parameters will not be valid if it does not target C = 1 and X = 1. Hence we also demonstrate the effect of θ and γ on C and X in Figure 8. The results show that as $S \to 0$, there is the indication that with various combinations of symptomatic and asymptomatic treatment, humans and mosquitoes will likely become free from the disease.

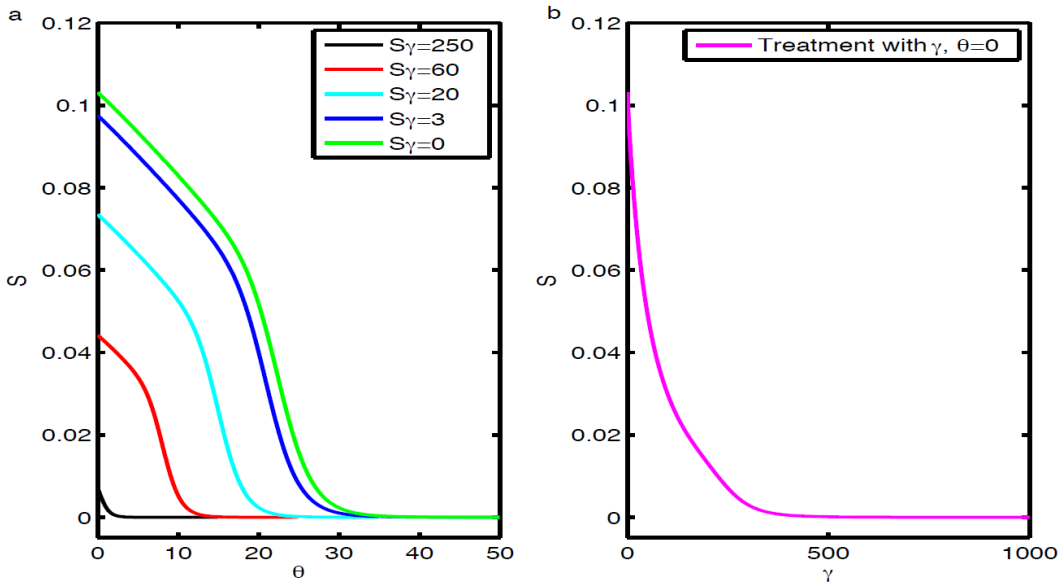


Figure 7: Plot of symptomatic humans against drug strength showing impact of clinical and post disease treatment on malaria control. In Figure 7b, $\theta = 0$, Whilst each curve in Figure 7a represents a plot of symptomatic humans with a given level of treatment against different values of θ. Initial conditions and parameter values are the same as those in Figure 3

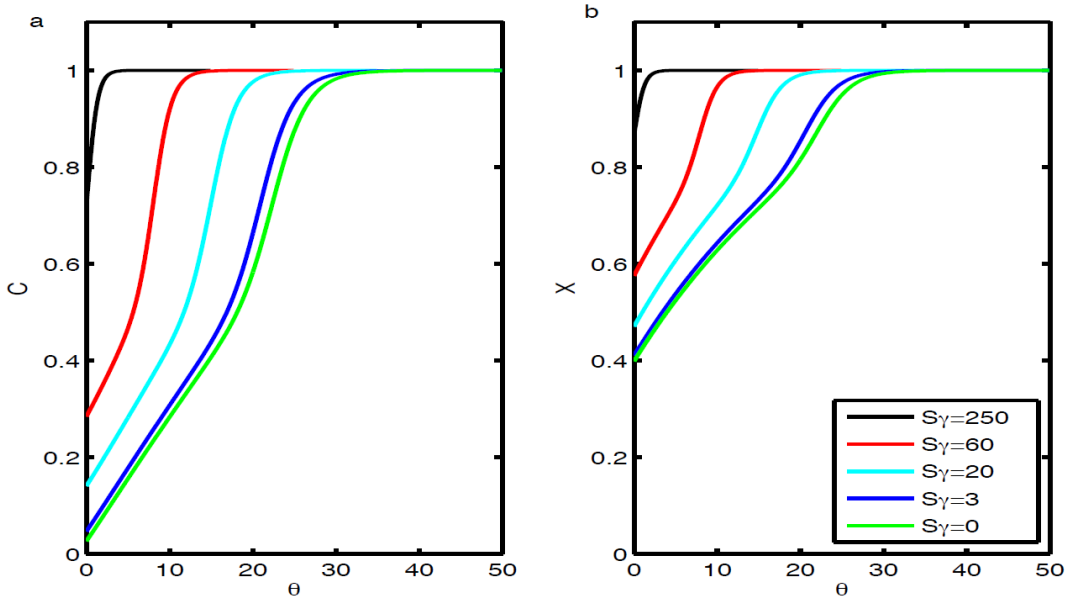


Figure 8: Plot of susceptible humans and mosquitoes against drug strength. Parameter values and initial conditions are the same as those in Figure 7. The disease dies out for different combined values of γ and θ.

4.9 Discussion

Our model describes a typical situation of an endemic malaria. This is supported by the value of R_0 for $\theta = 0$, given as 33.4, obtained from data using (4.29). There is a high proportion of Incubating asymptomatic humans since they require a longer time to loose infection before experiencing disease symptoms. The numerical solution (Figure 3.3) shows that about 90% of the entire population will be engulfed by the disease within a period of one year out of which about 8% will be sick and would require medical attention in the hospital resulting in loss of man-hours. Although those mostly affected by the disease are usually children and pregnant women [69]. This line of work is definitely an extension for the future differentiating between adults and children to see the effects on both different groups of people. The results also show that about 38% of the population would be carrying a greater number of gametocytes without showing symptoms of the disease within the period whilst approximately 32% of the population is asymptomatic and equally harbouring some levels of asexual parasites due to their being infected from infectious mosquitoes despite their partial immunity. We assume an equal transmission rate σ_h into the symptomatic compartment for both incubating and incubating asymptomatic classes but the latter keeps on building up instead of moving into the symptomatic class. Although, the asymptotic analysis shows approximately 90% of humans in the incubating asymptomatic class, this does not in any way show that the results are not correct. The reason for this disparity is that the analysis is based on the assumption that $\epsilon << 1$ and we have presented a simulation in this regard in section 4.7.6 that agrees well with the results of the analysis.

The model prediction seems plausible since immunity to malaria has always been associated with continuous exposure to infection. In particular, [70] has shown that the rate of development of clinical immunity to malaria correlates with the length of infection and that asymptomatic status is reached sooner when the infections are longer. Although we expect this behaviour since incubating asymptomatic individuals have partial immunity and are not expected to show disease symptoms until they loose immunity, it rather portends a dangerous scenario which could pose serious threats to the control of the disease especially if there happens to be a sudden upsurge of the disease in the population if more of these individuals loose immunity within a short interval of time. This is expected since, asymptomatic carriage may represent a mode of entry to symptomatic malaria especially in young children [71] and in regions of high malaria transmission, every member of the community might be chronically infected and as such there could be a high prevalence of sub-clinical malaria [72].

A good mathematical model of epidemiology can be assesed on it's application to disease control. We consider γ as a treatment parameter due to the results of our time scale analysis. γ is the ratio of r_h and i_a where r_h is the recovery rate of symptomatic humans due to treatment and i_a is the loss of asymptomatic infection or simply, the recovery rate of asymptomatic humans. The duration of untreated or inadequately treated P. falciparum infection ranges from 197 to 480 days [73] and due to epidemiological observation of populations under treatment, the average duration of infection reduces from 270 days to 14 days [74]. From results obtained by Tumwiine et al. [75], early, prompt and proper treatment of symptomatic humans reduces the duration of infection to as low as 3 days.

In order to determine the effect of γ we consider an ideal situation where the duration of infection can be reduced to zero through effective administration of treatment to symptomatic infectious human on the first day of the observation of the disease symptoms such that the gametocytes are destroyed or made inactive to the extent that they would not infect susceptible mosquitoes, i.e, $r_h \in [0, \infty)$. We deduce that increasing the duration of partial immunity increases R_0. Acquisition of partial immunity

is beneficial to the individual who has it but could be detrimental to the entire population because it increases the reservoir of infection. A strict suggestion by [76] demands that in order to bring a disease under control in a population of varying size, we need to reduce the reservoir of infection to zero with increasing time. We note that a faster way of reducing R_0 is by reducing α, σ or f. The only way of reducing γ is by increasing i_a, the rate of immunity loss or the duration of asymptomatic infection. We deduce that reducing the duration of asymptomatic infection reduces R_0, which agrees with the findings of [76]. We also introduce a post disease parameter $\theta \in [0, \infty)$ aimed at reducing the time partially immune humans spend in the asymptomatic and incubating asymptomatic classes. An asymptotic analysis on the model with the treatment parameters shows that for $\theta = 0$, the model can only predict a disease free state when γ is of $O(\epsilon^{-3})$. In order to assess treatement success we consider the distinguished limit case

$$\gamma = \frac{\gamma_0}{\epsilon}, \epsilon \to 0, \gamma \to \infty. \tag{4.50}$$

with an assumption that for successful treatment to take place, $S \sim O(small), C \sim 1 + O(small)$ and $X \sim 1 + O(small)$. The results suggest that treatment of symptomatic humans alone cannot lead to the eradication of malaria but could only help in the management and control of the disease. We deduce from our analysis that at leading order

$$R_0 = \frac{1}{\gamma_0} \frac{\hat{\alpha}\hat{f}\hat{\rho}\hat{d}}{\hat{q}(\hat{f} + \hat{q})} \tag{4.51}$$

where $\gamma_0 = O(\epsilon^2)$ compares well with the one obtained using the next generation matrix. We also consider the cases $\gamma = 0$ with treatment of asymptomatic humans and treatment of both sick and partially immune individuals. The results show that there is the possibility of eradicating the disease by treating both symptomatic and asymptomatic infectious humans. The key information we derive from the treatment analysis is that if for instance, a particular drug of reasonable efficiency administered on sick people requires $O(\epsilon^{-3}$ to bring the disease under control, then less effort of $O(\epsilon^{-1})$ is required to achieve the same objective when combined with asymptomatic treatment effort of $O(\epsilon^{-1})$.

Malaria transmission is a cyclic process of parasite transfer between human and mosquito populations. While there is the likelihood of humans avoiding the irritating bites from mosquito's, there seems to be a natural or ecological demand from the female anopheles mosquito to feed on humans in order to reproduce. Although the origin of the parasite is yet to be known, considering the process in one direction, it seems the mosquito deposits young parasites during blood meal and later comes back to ingest the matured form of the parasite and provide a conducive environment for its reproduction, since it lacks the ability to reproduce sexually in the human host. The parasite spends a longer time in the human host than in the vector and its within-host occupation apart from causing disease pathology and mortality, also sets the pace for transmission to another host. If the host has a hash environment inimical to the survival of the parasite then disease morbidity, mortality and transmission will be greatly reduced. The immune system plays a great role in defending the host's system against foreign pathogens. This is an area that should be explored in greater detail at a later. Especially looking at the differences between adult and child immune systems especially since children are the ones that suffer the most from this disease.

5 Conclusion

Malaria is an infectious disease with a dangerous global burden in which the quest for regional elimination and entire global eradication cannot be over emphasized. In this work we have constructed and analysed a mathematical model investigating a major area involving the transmission of the disease between human and mosquito populations. Our transmission model describes human-mosquito interaction on malaria epidemiology. Susceptible and asymptomatic humans get infected when they are bitten by an infectious mosquito. They then progress through the incubating, symptomatic and asymptomatic classes, before joining the the susceptible class again. Susceptible mosquitoes can become infected when they bite symptomatic, asymptomatic or incubating asymptomatic humans, once infected they move through the incubating and infectious mosquito classes. We used both numerical simulations and analytical methods to obtain solutions to the system. The numerical results show the model can predict an endemic malaria situation but for some values of the model parameters a disease free state can be achieved.

Single dose malaria drugs do not completely clear parasites but temporarily create asymptomatic malaria and this has not been considered in previous models. Another area of novelty is the second class of incubating humans resulting from the reinfection of asymptomatic humans. We have proposed and analysed a new transmission model incorporating these ideas. The methods of analysis employed in previous malaria models have mainly focused on stability analysis. In our case we have used in addition, asymptotic analysis to track the dynamics of disease transmission starting from an initial introduction of a small amount of infected mosquitos into a malaria free human population. Through our asymptotic analysis we have provided insight into the transmission of the disease as shown by the numerical simulations. There are important remarks about the transmission of the disease, which we have highlighted. The noticeable build-up of incubating asymptomatic humans at coexisting steady state confirms previous experimental results that asymptomatic status is maintained through continuous infection. This is a clear characteristic of the dynamics of malaria in an endemic region. It portends a dangerous scenario and creates adverse effect on public policies aimed at control or eradication of the disease. Although Ross [22] posits that to remove malaria in a region, the number of mosquitos needs to be reduced below a particular threshold. Ngwa et al. [52] contend that this approach would only be a temporary measure, especially in a malaria endemic region claiming that the disease will resurface as the mosquito population recovers. My findings suggest that Ngwa's claim may hold in a situation whjere there is a high proportion of asymptomatic carriers. But if they are treated then the disease will not resurface despite recovery of the mosquito population. If the attainment of asymptomatic status is an advantage then it appears adults are gaining at the expense of children and women (who may likely loose immunity during pregnancy). This gain may not be sustained for a long time as the analysis demonstrates that asymptomatic individuals will rapidly become incubating when the epidemic takes hold.

During the treatment analysis we considered options of transmitting treated incubating asymptomatic humans to either the susceptible or incubating class but the basic reproduction number remains unchanged in both cases. This suggests that partially immune individuals may be treated by gametocyte destroying drugs only, or by drugs that act on both asexual parasites and gametocytes. We recall from our previous discussion that the basic reproduction number R_0 plays a vital role in the dynamics of a disease. It is a threshold value that determines whether or not a disease will fully establish itself. Comparing the R_0 of our transmission model with that obtained in [37], we found that there are additional parameters in our R_0, namely $\sigma, \beta, \rho, f, h, d$ which is due to the additional

compartments found in our model. When the putative drug parameter, $\theta \neq 0$, the term $1 + \lambda + \theta$ replaces $1 + \lambda$ and taking the limit as $\theta \to \infty$ does not drive R_0 to 0 but only reduces it to less than unity depending on the values of the model parameters. This suggest that treating only asymptomatic individuals, apart from being a mere epidemiological paradox would not guarantee disease eradication except it is done with some form of vector control keeping the parameter α at a reasonable level. Our result is a deterministic approach to the hypothesis given in [77]. Past and present policies of the WHO for the elimination and eradication of malaria have been geared towards vector control and treatment of symptomatic humans and despite the huge amount of money spent there are still reports of greater part of the world population affected by the disease. The old Global Malaria Programme's initiative, T3, urged malaria-endemic countries to ensure that every suspected malaria case is tested, that every confirmed case is treated with a quality-assured antimalarial medicine, and that the disease is tracked through timely and accurate surveillance systems to guide policy and operational decisions [78]. Our results suggest that testing, treating and tracking of suspected symptomatic cases without considering the asymptomatic group that forms a greater part of the reservoir of infection will thwart the global effort on the elimination and eradication of malaria. Although the issue of treating asymptomatic humans may be difficult to control, in that it would take a lot of sensitisation and enlightenment campaigns to be able to persuade people who are not having the symptoms of a disease to take treatment. However, we suggest that 'Check Your Malaria Status' (CYMS) be introduced along with T3 having a relaunch in the countries most savaged by malaria.

5.1 Limitations of the model

Models are generally simplifications of reality and therefore subject to limitations. For instance in an attempt to construct models to curb the shortcomings of previous models, we end up having a model with other limitations. For example we have not considered the potential that many people with a good immune system may go into the asymptomatic infectious state without being treated. Also as the model stands we currently force people to pass through treatment to join back into their respective classes this area could also do with improvement.

5.2 Suggestions for future work

The model we have developed in this study are aimed at describing the dynamics of malaria transmission with the aim of assessing possible elimination strategies. The model can be relevant in areas where malaria has been persistently prevalent and regions that have achieved malaria elimination. However, the model is a mere simplification of reality and some modifications are required for improvement, which will provide directions for further studies. The following areas are included for consideration.

- Numerical simulations of the transmission model suggest that combined treatment of both symptomatic and asymptomatic individuals will lead to malaria elimination. We propose pilot studies in malaria endemic regions using this model as a theoretical framework.
- Environmental factors favourable to mosquito breeding also contribute to the pattern of disease transmission. These factors may vary seasonally within a region or between regions. We propose a model modification that will incorporate temperature and rainfall so as to ensure regional specific results.
- An asymptotic expansion of R_0 shows that the putative drug, θ, used for the treatment of asymptomatic humans is not as effective as γ the full treatment parameter. Whilst in the numerical simulations, θ appears to be much more effective in killing of the disease. The mechanism for this behaviour is not yet known, and hence the need for further investigation.
- The immune systems are different for both adults and children, whilst the numerical simulations gave us an indication towards who gains from an epidemic. I would like to take this further and see how much of a difference the immune system will play in controlling malaria.
- I would also like to consider the scenario that not all humans will pass through the treatment compartment as it may be that some may not receive the formal treatment they require. I feel separating the two dynamics from those that pass through the treatment compartment and those that don't would add an interesting element to the paper.

This list is not exhaustive and it has not in any way invalidated the results of our work but we hope that these suggestions will help to extend the frontier of knowledge and create a better direction in the quest for malaria eradication.

A APPENDIX A

A.1 Expressions for important constants in the stability analysis of transition model

$$b_4 = a_1a_2a_3a_4a_5, Q_1 = a_1a_2a_4a_5, Q_2 = a_1 + a_2 + a_3 + a_4 + a_5$$

$$Q_3 = a_1a_5^2[a_5(4a_2^2 + 5a_2a_4) + 4a_2^3 + 8a_2^2a_4 + 8a_2a_4^2]$$

$$Q_4 = a_1[a_5(5a_2^3a_4 + 8a_2^2a_4^2 + 5a_2a_4^3) + 4a_2^3a_4^2 + 4a_2^2a_4^3 + a_2a_4^4]$$

$$Q_5 = a_1a_5[a_5^3(a_2 + a_4) + 4a_4^2a_5^2 + 4a_4^3a_5 + a_4^4 + 2a_2^3a_5^2 + 4a_5(a_2^4 + 5a_2^2a_4^3)]$$

$$Q_6 = a_2a_4(a_2^2a_4 + a_2^2a_5 + 2a_2a_4^2 + 5a_2a_4a_5 + a_4^3 + 5a_4^2a_5)$$

$$Q_7 = a_1a_5^3[a_5(a_2^2 + a_2a_4 + a_4^2) + 5a_2^2a_4 + 5a_2a_4^2 + 2a_4^3]$$

$$Q_8 = a_1a_5^2(8a_2^2a_4^2 + 5a_2a_4^3 + a_4^4) + a_1a_2a_4^4a_5 + a_2^4a_4^2a_5$$

$$Q_9 = a_5^3[a_5(a_2^2a_4 + a_2a_4^2) + 2a_2^3a_4 + 4a_2^2a_4^2 + 2a_2a_4^3]$$

$$Q_{10} = a_5[a_5(a_2^4a_4 + 4a_2^3a_4^2 + 4a_2^2a_4^3 + a_2^2a_4^4$$

$$F_1 = a_3 + 2(a_1 + a_2 + a_4 + a_5)$$

$$F_2 = a_1(a_1 + 3a_2 + 2a_3 + 3a_4 + 3a_5) + 3a_2^2 + 4a_2a_3$$

$$F_3 = a_1(6a_2a_4 + 6a_2a_5 + 4a_3a_4 + 4a_3a_5 + 3a_4^2)$$

$$F_4 = 6a_1a_4a_5 + 3a_1a_5^2 + a_2^3 + 2a_2^2a_3 + 3a_2^2a_4$$

$$F_5 = a_4(a_4^2 + 3a_2a_4 + 3a_4a_5 + 2a_3a_4 + 3a_5^2 + 4a_3a_5 + 6a_2a_5$$

$$F_6 = 4a_2a_3a_4 + a_5^3 + 2a_3a_5^2 + 3a_2a_5^2 + 3a_2^2a_5 + 4a_2a_3a_5$$

$$F_7 = Q_1^2(a_2a_4 + a_5^4)(a_2 + a_4) + Q_1^2a_5(a_2^2 + a_2a_4 + a_4^2) + Q_8$$

$$F_8 = 2Q_1a_2a_4a_4^5(a_2 + a_4) + Q_1a_2a_4a_5^3(5a_2a_5 + 4a_2^2 + 4a_4^2) + Q_3$$

$$F_9 = a_2^2a_4^2(a_4 + a_2)^2 + a_1a_4^2a_5(8a_2^2 + 5a_2a_4 + a_4^2) + Q_4 + Q_5$$

$$F_{10} = a_2^2Q_1 + Q_6Q_7, F_{11} = a_2a_4a_5(a_4^3 + 2a_4^2a_5 + a_4a_5^2 + 4a_2a_4a_5 + a_2a_5^2)$$

$$E_1 = \alpha\sigma f\rho d, E_2 = \alpha\sigma fb$$

A.2 Demonstrating the effect of inequalities obtained in 4.35 on R_0

$$R_0 = \frac{\alpha\sigma f[b(1+\lambda+\theta)+\rho d]}{(\sigma+\lambda)(\beta+\gamma+\rho+\lambda)(1+\lambda+\theta)(f+q)(h+q)} \tag{A.1}$$

$$\frac{\sigma\alpha}{\sigma+\lambda} \leq q \tag{A.2}$$

$$\frac{fb}{f+q} \leq \gamma+\lambda \tag{A.3}$$

$$\frac{fd}{f+q} \leq \frac{\lambda(\sigma+\theta+\lambda}{\sigma+\lambda} \tag{A.4}$$

We can show that if (A.2-A.4) hold, then $R_0 \leq 1$.

$$Numerator\ \ of\ \ A.1 = \alpha\sigma[fb(1+\lambda+\theta)+f\rho d] \tag{A.5}$$

$$\begin{aligned} Denominator\ \ of\ \ A.1 = (\sigma+\lambda)(h+q)[(\lambda+\gamma)(1+\lambda+\theta)(f+q) \\ +[\rho(1+\lambda+\theta)(f+q)+\beta(1+\lambda+\theta)(f+q)]] \end{aligned} \tag{A.6}$$

Comparing A.5 and A.6, from A.2 we can observe that

$$\alpha\sigma \leq (\sigma+\lambda)q \leq (\sigma+\lambda)(h+q) \tag{A.7}$$

and from A.3 that

$$fb \leq (\gamma+\lambda)(f+q) \tag{A.8}$$

and hence

$$fb(1+\lambda+\theta) \leq (\gamma+\lambda)(f+q)(1+\theta+\lambda). \tag{A.9}$$

Also, from A.4,

$$fd \leq \frac{\lambda(f+q)(\sigma+\lambda+\theta)}{\sigma+\lambda} \rightarrow fd \leq (f+q)(1+\lambda+\theta),\ \ since\ \ 1+\lambda+\theta > \frac{\lambda(\sigma+\lambda+\theta)}{\sigma+\lambda} \tag{A.10}$$

Thus the numerator of A.1 is less than the denominator, meaning $R_0 < 1$.

B APPENDIX B

B.1 Time-scale analysis

By letting $\theta = 0$, we present the time scale analysis of the dimensionless system

$$\epsilon^2\frac{dC}{dt} = \epsilon^4\hat{\lambda} + \epsilon\hat{\gamma}S + \epsilon^2 A - \hat{\alpha}ZC - \epsilon^4\hat{\lambda}C + \epsilon^4\hat{\beta}CS, \tag{B.1}$$

$$\epsilon^2\frac{dI}{dt} = \hat{\alpha}ZC - \epsilon\hat{\sigma}I - \epsilon^4\hat{\lambda}I + \epsilon^4\hat{\beta}IS, \tag{B.2}$$

$$\epsilon^2\frac{dI_A}{dt} = \hat{\alpha}ZA - \epsilon\hat{\sigma}I_A - \epsilon^4\hat{\lambda}I_4 + \epsilon^4\hat{\beta}I_A S \tag{B.3}$$

$$\epsilon^2\frac{dS}{dt} = \epsilon\hat{\sigma}I + \epsilon\hat{\sigma}I_A - (\hat{\rho} + \epsilon\hat{\gamma} + \epsilon^4\hat{\beta} + \epsilon^4\hat{\lambda})S + \epsilon^4\hat{\beta}S^2, \tag{B.4}$$

$$\epsilon^2\frac{dA}{dt} = \hat{\rho}S - (\epsilon^2 + \epsilon^4\hat{\lambda})A - \hat{\alpha}ZA + \epsilon^4\hat{\beta}AS, \tag{B.5}$$

$$\epsilon\frac{dX}{dt} = \hat{q}(1-X) - \hat{b}SX - \hat{d}AX - \hat{d}I_A X + \epsilon\hat{h}YZ, \tag{B.6}$$

$$\epsilon\frac{dY}{dt} = \hat{b}SX + \hat{d}AX + \hat{d}I_A X - (\hat{f} + \hat{q})Y + \epsilon\hat{h}YZ \tag{B.7}$$

$$\epsilon\frac{dZ}{dt} = \hat{f}Y - (\epsilon\hat{h} + \hat{q})Z + \epsilon\hat{h}Z^2. \tag{B.8}$$

subject to

$$C(0) = 1, I(0) = 0, I_A(0) = 0, S(0) = 0, A(0) = 0$$
$$Y(0) = y_0, X(0) = 1 - y_0, Z(0) = 0, \epsilon << 1, y_0 << \epsilon$$

in which all parameters are expressed in terms of their size as a power of ϵ indicated in table 2, namely

$$\alpha = \frac{1}{\epsilon^2}\hat{\alpha}, \sigma = \frac{1}{\epsilon}\hat{\sigma}, \mu = \epsilon^2\hat{\mu}, \lambda = \epsilon^2\hat{\lambda}, \gamma = \frac{1}{\epsilon}\hat{\gamma}, \rho = \frac{1}{\epsilon^2}\hat{\rho}. \tag{B.9}$$

$$b = \frac{1}{\epsilon}\hat{b}, d = \frac{1}{\epsilon}\hat{d}, f = \frac{1}{\epsilon}\hat{f}, g = \frac{1}{\epsilon}\hat{g}, h = \hat{h}, q = \frac{1}{\epsilon}\hat{q}.$$

We analyse this system for the case of newly introduced infected mosquitoes to a previously uninfected region.

B.2 Time scale 1: $t = O(\epsilon^2)$

- Scaling: $t = \epsilon^2 \hat{t}$,

$$C \sim 1 + \epsilon y_0 \hat{C_1}, I \sim \epsilon y_0 \hat{I_0}, I_A \sim \epsilon^3 y_0^2 \hat{I}_{A_0}, S \sim \epsilon^2 y_0 \hat{S_0}$$
$$A \sim \epsilon^2 y_0 \hat{A_0}, X \sim 1 - y_0 + \epsilon y_0 \hat{X_1}, Y \sim y_0 + \epsilon y_0 \hat{Y_1}, Z \sim \epsilon y_0 \hat{Z_0}.$$

Substituting these scaling's into the dimensionless system leads to the following equations:

$$\frac{d\hat{C_1}}{d\hat{t}} = -\hat{\alpha}\hat{Z_0}(1 + \epsilon y_0 \hat{C_1}) + \epsilon^2(\hat{\gamma}\hat{S_0} + \hat{A_0}) - \epsilon^4 \hat{\lambda}\hat{C_1} + \epsilon^5 \hat{\beta}(1 + \epsilon y_0 \hat{C_1})\hat{S_0}$$

$$\frac{d\hat{I_0}}{d\hat{t}} = \hat{\alpha}\hat{Z_0}(1 + \epsilon y_0 \hat{C_1}) - \epsilon\hat{\sigma}\hat{I_0} - \epsilon^4\hat{\lambda}\hat{I_0} + \epsilon^6 y_0 \hat{\beta}\hat{I_0}\hat{S_0}$$

$$\frac{d\hat{I}_{A0}}{d\hat{t}} = \hat{\alpha}\hat{A_0}\hat{Z_0} - \epsilon\hat{\sigma}\hat{I}_{A0} - \epsilon^4\hat{\lambda}\hat{I}_{A0} + \epsilon^6 y_0 \hat{\beta}\hat{I}_{A0}\hat{S_0}$$

$$\frac{d\hat{S_0}}{d\hat{t}} = \hat{\sigma}\hat{I_0} - \hat{\rho}\hat{S_0} + \epsilon^2 y_0 \hat{\sigma}\hat{I}_{A0} - (\epsilon\hat{\gamma} + \epsilon^4\hat{\beta} + \epsilon^4\hat{\lambda})\hat{S_0} + \epsilon^6 y_0 \hat{\beta}\hat{S_0}^2$$

$$\frac{d\hat{A_0}}{d\hat{t}} = \hat{\rho}\hat{S_0} - (\epsilon^2 + \epsilon^4\hat{\lambda})\hat{A_0} - \epsilon y_0 \hat{\alpha}\hat{Z_0}\hat{A_0} + \epsilon^6 y_0 \hat{\beta}\hat{A_0}\hat{S_0}$$

$$\frac{d\hat{X_1}}{d\hat{t}} = \hat{q}(1 - \epsilon\hat{X_1}) - \epsilon^2\hat{b}\hat{S_0}(1 - y_0 + \epsilon y_0 \hat{X_1}) - \epsilon^2\hat{d}\hat{A_0}(1 - y_0 + \epsilon y_0 \hat{X_1}$$
$$+\epsilon^2\hat{h}(1 - y_0 + \epsilon y_0 \hat{X_1})\hat{Z_0} - \epsilon^3 y_0 \hat{d}\hat{I}_{A0}(1 - y_0 + \epsilon y_0 \hat{X_1})$$

$$\frac{d\hat{Y_1}}{d\hat{t}} = -(\hat{f} + \hat{q})(1 + \epsilon\hat{Y_1}) + \epsilon^2\hat{b}\hat{S_0}(1 - y_0 + \epsilon y_0 \hat{X_1}) + \epsilon^2\hat{d}\hat{A_0}(1 - y_0 + \epsilon y_0 \hat{X_1}$$
$$+\epsilon^2\hat{h}(1 - y_0 + \epsilon y_0 \hat{Y_1})\hat{Z_0}) + \epsilon^3 y_0 \hat{d}\hat{I}_{A0}(1 - y_0 + \epsilon y_0 \hat{X_1}$$

$$\frac{d\hat{Z_0}}{d\hat{t}} = \hat{f}(1 + \epsilon\hat{Y_1}) - \epsilon(\hat{q} + \epsilon\hat{h})\hat{Z_0} + \epsilon^3 y_0 \hat{h}\hat{Z_0}^2$$

We see the system changes balance at $\hat{t} = O(\epsilon^{-2/3})$ This happens in the Y equation as the lower order term $\epsilon\hat{d}\hat{A_0}$ catches up with the $O(1)$ term $\hat{f} + \hat{q}$ We observe from the solution in this timescale that $\hat{A_0} = O(t^3)$. Thus $\epsilon^2\hat{t}^3 = O(1)$ implies that $\hat{t} = O(\epsilon^{-2/3})$. We note that $y_0 << \epsilon$ and $\hat{t} = O(\epsilon^{-2/3})$ is the smallest time in which the asymptotic expansion will no longer be valid.

B.3 Time scale 2: $t = O(\epsilon^{4/3})$

- Scalings: $t = \epsilon^{4/3}\bar{t}$

$$C \sim 1 + \epsilon^{-1/3} y_0 \bar{C_1}, I \sim \epsilon^{-1/3} y_0 \bar{I_0}, I_A \sim \epsilon^{-1/3} y_0^2 I_{A_0}, S \sim \epsilon^{2/3} y_0 \bar{S_0},$$
$$A \sim y_0 \bar{A_0}, X \sim 1 - y_0 + \epsilon^{1/3} y_0 \bar{X_1}, Y \sim y_0 + \epsilon^{1/3} y_0 \bar{Y_1}, Z \sim \epsilon^{1/3} y_0 \bar{Z_0}.$$

On substitution into the dimensionless system we have

- Equations

$$\frac{d\bar{C}_1}{d\bar{t}} = -\hat{\alpha}\bar{Z}_0(1+\epsilon^{-1/3}y_0\bar{C}_1) + \epsilon^{4/3}(\hat{\gamma}\bar{S}_0 + \epsilon^{1/3}\bar{A}_0) - \epsilon^4\hat{\lambda}\bar{C}_1 + \epsilon^{13/3}\hat{\beta}(1+\epsilon^{-1/3}y_0\bar{C}_1)\bar{S}_0$$

$$\frac{d\bar{I}_0}{d\bar{t}} = \hat{\alpha}\bar{Z}_0(1+\epsilon^{-1/3}y_0\bar{C}_1) - \epsilon^{1/3}\hat{\sigma}\bar{I}_0 - \epsilon^{10/3}\hat{\lambda}\bar{I}_0 + \epsilon^4 y_0\hat{\beta}\hat{I}_0\hat{S}_0$$

$$\frac{d\bar{I}_{A0}}{d\bar{t}} = \hat{\alpha}\bar{A}_0\bar{Z}_0\epsilon^{1/3}\hat{\sigma}\bar{I}_{A0} - \epsilon^{10/3}\hat{\lambda}\bar{I}_{A0} + \epsilon^4 y_0\hat{\beta}\hat{I}_{A0}\hat{S}_0$$

$$\epsilon^{2/3}\frac{d\bar{S}_0}{d\bar{t}} = \hat{\sigma}\bar{I}_0 - \hat{\rho}\bar{S}_0 + y_0\hat{\sigma}\bar{I}_{A0} - (\epsilon\hat{\gamma} + \epsilon^4\hat{\beta} + \epsilon^4\hat{\lambda})\bar{S}_0 + \epsilon^{-14/3}y_0\hat{\beta}\bar{S}_0^{\,2}$$

$$\frac{d\bar{A}_0}{d\bar{t}} = \hat{\rho}\bar{S}_0 - \frac{y_0}{\epsilon^{1/3}}\hat{\alpha}\bar{Z}_0\bar{A}_0 - (\epsilon^{4/3} + \epsilon^{10/3}\hat{\lambda})\bar{A}_0 + \epsilon^4 y_0\hat{\beta}\hat{A}_0\hat{S}_0$$

$$\frac{d\bar{X}_1}{d\bar{t}} = \hat{q}(1-\epsilon^{1/3}\bar{X}_1) - \hat{d}\bar{A}_0(1-y_0+\epsilon^{1/3}y_0\bar{X}_1) - \epsilon^{2/3}\hat{b}\bar{S}_0(1-y_0+\epsilon^{1/3}y_0\bar{X}_1)$$
$$-\frac{y_0}{\epsilon^{1/3}}\hat{d}\bar{I}_{A0}(1-y_0+\epsilon^{1/3}y_0\bar{X}_1) + \epsilon^{4/3}\hat{h}(1-y_0+\epsilon^{1/3}y_0\bar{X}_1)\bar{Z}_0$$

$$\frac{d\bar{Y}_1}{d\bar{t}} = -(\hat{f}+\hat{q})(1+\epsilon^{1/3}\bar{Y}_1) + \hat{d}\bar{A}_0(1-y_0+\epsilon^{1/3}y_0\bar{X}_1) + \epsilon^{2/3}\hat{b}\bar{S}_0(1-y_0+\epsilon^{1/3}y_0\bar{X}_1)$$
$$+\frac{y_0}{\epsilon^{1/3}}\hat{d}\bar{I}_{A0}(1-y_0+\epsilon^{1/3}y_0\bar{X}_1) + \epsilon^{4/3}y_0\hat{h}(1+\epsilon^{1/3}y_0\bar{Y}_1)\bar{Z}_0$$

$$\frac{d\bar{Z}_0}{d\bar{t}} = \hat{f}(1+\epsilon^{1/3}y_0\bar{Y}_1) - \epsilon^{1/3}(\epsilon\hat{h}+\hat{q})\bar{Z}_0 + \epsilon^{5/3}y_0\hat{h}\bar{Z}_0^{\,2}$$

Solutions in this timescale suggest that $X_1 = O(\bar{t}^4)$ and the approximations become poor when the second term $\epsilon^{1/3}\bar{t}^4$ becomes $O(1)$, i.e $\bar{t}^4 = O(\epsilon^{-1/3})$. This leads to a breakdown in the X equation when $\bar{t} = O(\epsilon^{-1/12})$.

B.4 Time Scale 3: $t = O(\epsilon^{5/4})$

- Scaling: $t = \epsilon^{5/4}\tilde{t}$

$$C \sim 1 + \epsilon^{-1/2}y_0\tilde{C}_1, I \sim \epsilon^{-1/2}y_0\tilde{I}_0, I_A \sim \epsilon^{-3/4}y_0^2\tilde{I}_{A_0}, S \sim \epsilon^{1/2}y_0\tilde{S}_0$$
$$A \sim \epsilon^{-1/4}y_0\tilde{A}_0, X \sim 1 + y_0\tilde{X}_1, Y \sim y_0\tilde{Y}_1, Z \sim \epsilon^{1/4}y_0\tilde{Z}_0$$

By substituting the scalings into the dimensionless system and carrying out some simplifications we get the following

- Equations

$$\frac{d\tilde{C}_1}{d\tilde{t}} = -\tilde{\alpha}\tilde{Z}_0(1+\epsilon^{-1/2}y_0\tilde{C}_1) + \epsilon^{3/2}(\tilde{A}_0 + \epsilon^{1/4}\hat{\gamma}\tilde{S}_0) - \epsilon^{13/4}\hat{\lambda}\tilde{C}_1 + \epsilon^{9/2}\hat{\beta}(1+\epsilon^{-1/2}y_0\tilde{C}_1)\tilde{S}_0$$

$$\frac{d\tilde{I}_0}{d\tilde{t}} = \tilde{\alpha}\tilde{Z}_0(1+\epsilon^{-1/2}y_0\tilde{C}_1) - \epsilon^{1/2}\hat{\sigma}\tilde{I}_0 + \epsilon^{15/4}y_0\hat{\beta}\tilde{I}_0\tilde{S}_0$$

$$\frac{d\tilde{I_{A0}}}{d\tilde{t}} = \hat{\alpha}\tilde{A}_0\tilde{Z}_0 - \epsilon^{1/4}\hat{\sigma}\tilde{I_{A0}} - \epsilon^{13/4}\hat{\lambda}\tilde{I_{A0}} + \epsilon^{15/4}y_0\hat{\beta}\tilde{I}_0\tilde{S}_0$$

$$\epsilon^{1/2}\frac{d\tilde{S}_0}{d\tilde{t}} = \hat{\sigma}\tilde{I}_0 - \hat{\rho}\tilde{S}_0 + \frac{y_0}{\epsilon^{1/4}}\hat{\sigma}\tilde{I_{A0}} - (\epsilon\hat{\gamma} + \epsilon^4\hat{\beta} + \epsilon^4\hat{\lambda})\tilde{S}_0 + \epsilon^4 y_0\hat{\beta}\tilde{S}_0^{\,2}$$

$$\frac{d\tilde{A}_0}{d\tilde{t}} = \hat{\rho}\tilde{S}_0 - \frac{y_0}{\epsilon^{1/3}}\hat{\alpha}\tilde{Z}_0\tilde{A}_0 - (\epsilon^{5/4} + \epsilon^{13/4}\hat{\lambda})\tilde{A}_0 + \epsilon^{15/4}y_0\hat{\beta}\tilde{A}_0\tilde{S}_0$$

$$\frac{d\tilde{X}_1}{d\tilde{t}} = -\hat{d}\tilde{A}_0(1 + y_0\tilde{X}_1) - \epsilon^{1/4}\hat{q}\tilde{X}_1 - \epsilon^{3/4}\hat{b}\tilde{S}_0(1 + y_0\tilde{X}_1) - \epsilon^{1/2}y_0\hat{d}\tilde{I}_{A0}(1 + y_0\tilde{X}_1)$$

$$\epsilon^{3/2}\hat{h}(1 + y_0\tilde{X}_1)\tilde{Z}_0$$

$$\frac{d\tilde{Y}_1}{d\tilde{t}} = \hat{d}\tilde{A}_0(1 + y_0\tilde{X}_1) - \epsilon^{1/4}(\hat{f} + \hat{q})\tilde{Y}_1 + \epsilon^{3/4}\hat{b}\tilde{S}_0(1 + y_0\tilde{X}_1) + \epsilon^{1/2}y_0\hat{d}\tilde{I}_{A0}(1 + y_0\tilde{X}_1)$$

$$+\epsilon^{3/2}y_0\hat{h}\tilde{Y}_1\tilde{Z}_0$$

$$\frac{d\tilde{Z}_0}{d\tilde{t}} = \hat{f}\tilde{Y}_1 - \epsilon^{1/4}(\hat{q} + \epsilon\hat{h})\tilde{Z}_0 + \epsilon^{3/2}y_0\hat{h}\tilde{Z}_0{}^2$$

The governing equation of the system is $\frac{d^4\tilde{Z}_0}{d\tilde{t}^4} = K\tilde{Z}_0$ obtained by successive differentiation of $\frac{d\tilde{Z}_0}{d\tilde{t}}$ where $K = \hat{\alpha}\hat{\sigma}\hat{f}\hat{d}$ and for $K_0 = K^{1/4}$, change in balance occurs in the C solution when $\tilde{t} = ln(\epsilon^{1/2}/y_0)/K_0$.

B.5 Time scale 4: $t = \epsilon^{5/4}ln(\epsilon^{1/2}/y_0)/K_0 + O(\epsilon^{5/4})$

- Scalings: $t = \epsilon^{\frac{5}{4}}ln(\epsilon^{\frac{1}{2}}/y_0)/K_0 + \epsilon^{\frac{5}{4}}\check{t}$

$$C \sim \check{C}_0, I \sim \check{I}_0, I_A \sim \epsilon^{1/4}\check{I}_{A0}, S \sim \epsilon\check{S}_0, A \sim \epsilon^{1/4}\check{A}_0,$$
$$X \sim 1 + \epsilon^{1/2}\check{X}_1, Y \sim \epsilon^{1/2}\check{Y}_1, Z \sim \epsilon^{3/4}\check{Z}_0.$$

- Equations

$$\frac{d\check{C}_0}{d\check{t}} = -\hat{\alpha}\check{C}_0\check{Z}_0 + \epsilon^{3/2}(\check{A}_0 + \epsilon^{1/4}\hat{\gamma}\check{S}_0) - \epsilon^{13/4}\hat{\lambda}(1 - \check{C}_0 + \epsilon^{17/4}\hat{\beta}\check{C}_0\check{S}_0$$

$$\frac{d\check{I}_0}{d\check{t}} = \hat{\alpha}\check{C}_0\check{Z}_0 - \epsilon^{1/4}\hat{\sigma}\check{I}_0 - \epsilon^{13/4}\hat{\lambda}\check{I}_0 + \epsilon^{17/4}\hat{\beta}\check{I}_0\check{S}_0$$

$$\frac{d\check{I}_{A0}}{d\check{t}} = \hat{\alpha}\check{A}_0\check{Z}_0 - \epsilon^{1/4}\hat{\sigma}\check{I}_{A0} - \epsilon^{13/4}\hat{\lambda}\check{I}_{A0} + \epsilon^{17/4}y_0\hat{\beta}\check{I}_{A0}\check{S}_0$$

$$\epsilon^{3/4}\frac{d\check{S}_0}{d\check{t}} = \hat{\sigma}\check{I}_0 - \hat{\rho}\check{S}_0 + \epsilon^{1/4}\hat{\sigma}\check{I}_{A0} - (\epsilon\hat{\gamma} + \epsilon^4\hat{\beta} + \epsilon^4\hat{\lambda})\check{S}_0 + \epsilon^5\hat{\beta}\check{S}_0{}^2$$

$$\frac{d\check{A}_0}{d\check{t}} = \hat{\rho}\check{S}_0 - \hat{\alpha}\check{Z}_0\check{A}_0 - (\epsilon^{5/4} + \epsilon^{13/4}\hat{\lambda})\check{A}_0 + \epsilon^{17/4}\hat{\beta}\check{A}_0\check{S}_0$$

$$\frac{d\check{X}_1}{d\check{t}} = -\hat{d}\check{A}_0(1 + \epsilon^{1/2}\check{X}_1) - \hat{d}\check{I}_{A0}(1 + \epsilon^{1/2}\check{X}_1) - \epsilon^{1/2}\hat{q}\check{X}_1 - \epsilon^{3/4}\hat{b}\check{S}_0(1 + \epsilon^{1/2}\check{X}_1)$$

$$\epsilon^{3/2}\hat{h}(1 + \epsilon^{1/2}\check{X}_1)\check{Z}_0$$

$$\frac{d\check{Y}_1}{d\check{t}} = \hat{d}\check{A}_0(1 + \epsilon^{1/2}\check{X}_1) + \hat{d}\check{I}_{A0}(1 + \epsilon^{1/2}\check{X}_1) + \epsilon^{3/4}\hat{b}\check{S}_0(1 + \epsilon^{1/2}\check{X}_1) - \epsilon^{1/2}(\hat{f} + \hat{q})\check{Y}_1$$

$$+\epsilon^2\hat{h}\check{Y}_1\check{Z}_0$$

$$\frac{d\check{Z}_0}{d\check{t}} = \hat{f}\check{Y}_1 - \epsilon^{1/4}(\hat{q} + \epsilon\hat{h})\check{Z}_0 + \epsilon^2\hat{h}\check{Z}_0{}^2$$

Some simplification leads to the following fourth order nonlinear ordinary differential equation that determines the dynamics of the system

$$\frac{d^4\check{F}}{d\check{t}^4} = -K(1 - e^{\check{F}})$$

$$\check{F} = ln(\check{C_0})$$

Major breakdown of the solutions occur in the X equation where the X_1 term becomes $O(1)$, i.e when $\check{t} = O(\epsilon^{-1/4})$

B.6 Time scale 5: $t = O(\epsilon)$

- Scalings: $t = \epsilon t^*$

$$C \sim \epsilon^2 C_0^*, I \sim I_0^*, I_A \sim I_{A0}^*, S \sim \epsilon S_0^*, A \sim \epsilon A_0^*, X \sim X_0^*, Y \sim Y_0^*, Z \sim Z_0^*,$$

- Equations

$$\epsilon\frac{dC_0^*}{dt^*} = \hat{\alpha}C_0^*Z_0^* + \hat{\gamma}S_0^* + \epsilon, A_0^* - \epsilon^2\hat{\lambda}(1 - \epsilon^2 C_0^*) + \epsilon^4\hat{\beta}C_0^*S_0^*$$

$$\frac{dI_0^*}{dt^*} = -\hat{\sigma}I_0^* + \epsilon\hat{\alpha}Z_0^*C_0^* - \epsilon^3\hat{\lambda}I_0^* + \epsilon^4\hat{\beta}I_0^*S_0^*$$

$$\frac{dI_{A0}^*}{dt^*} = \hat{\alpha}Z_0^*A_0^* - \hat{\sigma}I_{A0}^* - \epsilon^3\hat{\lambda}I_{A0}^* + \epsilon^4\hat{\beta}I_{A0}^*S_0^*$$

$$\epsilon\frac{dS_0^*}{dt^*} = \hat{\sigma}(I_0^* + I_{A0}^*) - \hat{\rho}S_0^* - (\epsilon\hat{\gamma} + \epsilon^4\hat{\beta} + \epsilon^4\hat{\lambda})S_0^* + \epsilon^5\hat{\beta}S_0^{2*}$$

$$\epsilon\frac{dA_0^*}{dt^*} = \hat{\rho}S_0^* - \hat{\alpha}Z_0^*A_0^* - (\epsilon^2 + \epsilon^4\hat{\lambda})A_0^* + \epsilon^4\hat{\beta}A_0^*S_0^*$$

$$\frac{dX_0^*}{dt^*} = \hat{q}(1 - X_0^*) - \hat{d}I_{A0}^*X_0^* - \epsilon(\hat{b}S_0^*X_0^* + \hat{d}A_0^*X_0^* - \hat{h}X_0^*Z_0^*)$$

$$\frac{dY_0^*}{dt^*} = \hat{d}I_{A0}^*X_0^* - (\hat{f} + \hat{q})Y_0^* + \epsilon(\hat{b}S_0^*X_0^* + \hat{d}A_0^*X_0^* - \hat{h}X_0^*Z_0^*)$$

$$\frac{dZ_0^*}{dt^*} = \hat{f}Y_0^* - \hat{q}Z_0^* - \epsilon\hat{h}(1 - Z_0^{2*})$$

The approximation to I will no longer be $O(1)$ when $t = ln(1/\epsilon)/\sigma$.

B.7 Time scale 6: $t = \epsilon ln(1/\epsilon)/\sigma + O(\epsilon)$

- Scalings: $t = (1/\epsilon)/\hat{\sigma} + \epsilon t'$

$$C \sim \epsilon^2 C_0', I \sim \epsilon I_0', I_A \sim 1, S \sim \epsilon S_0', A \sim \epsilon A_0', X \sim X_0', Y \sim Y_0', Z \sim Z_0'$$

- Equations

$$\epsilon\frac{dC_0^{'}}{dt^{'}} = -\hat{\alpha}C_0^{'}Z_0^{'} + \hat{\gamma}S_0^{'} + \epsilon A_0^{'} - \epsilon^2\hat{\lambda}(1-\epsilon^2 C_0^{'}) + \epsilon^4\hat{\beta}C_0^{'}S_0^{'}$$

$$\frac{dI_0^{'}}{dt^{'}} = -\hat{\sigma}I_0^{'} + \hat{\alpha}Z_0^{'}C_0^{'} - \epsilon^3\hat{\lambda}I_0^{'} + \epsilon^4\hat{\beta}I_0^{'}S_0^{'}$$

$$\frac{dI_{A0}^{'}}{dt^{'}} = \hat{\alpha}Z_0^{'}A_0^{'} - \hat{\sigma}I_{A0}^{'} - \epsilon^3\hat{\lambda}I_{A0}^{'} + \epsilon^4\hat{\beta}I_{A0}^{'}S_0^{'}$$

$$\epsilon\frac{dS_0^{'}}{dt^{'}} = \hat{\sigma}I_{A0}^{'} - \hat{\rho}S_0^{'} + \epsilon\hat{\sigma}I_0^{'} - (\epsilon\hat{\gamma} + \epsilon^4\hat{\beta} + \epsilon^4\hat{\lambda})S_0^{'} + \epsilon^5\hat{\beta}S_0^{2'}$$

$$\epsilon\frac{dA_0^{'}}{dt^{'}} = \hat{\rho}S_0^{'} - \hat{\alpha}Z_0^{'}A_0^{'} - (\epsilon^2 + \epsilon^4\hat{\lambda})A_0^{'} + \epsilon^4\hat{\beta}A_0^{'}S_0^{'}$$

$$\frac{dX_0^{'}}{dt^{'}} = \hat{q}(1-X_0^{'}) - \hat{d}I_{A0}^{'}X_0^{'} - \epsilon(\hat{b}S_0^{'}X_0^{'} + \hat{d}A_0^{'}X_0^{'} - \hat{h}X_0^{'}Z_0^{'})$$

$$\frac{dY_0^{'}}{dt^{'}} = \hat{d}I_{A0}^{'}X_0^{'} - (\hat{f}+\hat{q})Y_0^{'} + \epsilon(\hat{b}S_0^{'}X_0^{'} + \hat{d}A_0^{'}X_0^{'} - \hat{h}X_0^{'}Z_0^{'})$$

$$\frac{dZ_0^{'}}{dt^{'}} = \hat{f}Y_0^{'} - \hat{q}Z_0^{'} - \epsilon\hat{h}(1-Z_0^{2'})$$

Other variables maintain their steady status and $I_{A0} \sim 1$, and the only remaining equation is

$$\frac{dI_0^{'}}{dt^{'}} = \frac{\hat{\gamma}\hat{\sigma}}{\hat{\rho}} - \hat{\sigma}I_0^{'}.$$

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