Mathematical Models of Malaria Control with Artificial Feeders, Odorants and Bed Nets

by

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Abstract

Vector behaviour influences the speed of disease spread in populations. The presence of vector bias towards hosts with special characteristics suggests the need for new or tactical disease-control approaches. Malaria parasites produce volatile mosquito attractants. As a result, mosquitoes have bias towards malaria-infected humans. The control of mosquito-borne diseases can be improved by targeting mosquito bias. The attractiveness of humans to mosquitoes can be masked using appropriate odorants. Further, vectors can be artificially blood-fed using simplified devices to prevent infectious bites. In this study, we focus on the use of mosquito feeders, mosquito attractants, repellents and bed nets, knowing that such a multifaceted approach has not been explored previously using mathematical models.

Three models of malaria control are developed using systems of nonlinear differential equations. The models are based on the Ross-Macdonald Theory and recent studies of vector-host interactions. In the artificial-feeder model, all infected humans acquire protective odorants at the onset of the infectious stage. The model is analyzed to examine the effect of repellents and artificial

feeders on disease transmission and spread. The second model is without artificial feeders and assumes that infected individuals are recruited to use protective odorants during the infectious stage. The resulting mosquito-bias model is analyzed to examine how the recruitment rate affects disease spread. The third model combines the use of artificial feeders and protective odorants with the use of bed nets. The resulting bed-net model is analyzed to examine the effect of bed nets and protective odorants on disease transmission and spread in the presence of artificial feeders.

The results of this study suggest that artificial feeders can slow disease spread, but eradication is easily done if mosquito bias is increased towards uninfected individuals. Increasing repellent-usage during the infectious stage decreases disease spread. The disease persists if mosquitoes are less attracted to bed-net users than to non-users. The conclusion is that the transmission and spread of mosquito-borne pathogens can be stopped by using artificial feeders that are attractive to mosquitoes, by increasing repellent-usage throughout the infectious stage, and by ensuring optimal bed-net coverage with protective odorants for all bed-net non-users.

Dedication

I dedicate this dissertation to my wife, Claire Kesande, and my children, Achilles and Albert, who missed me so much and sacrificed a lot for me when I was a PhD student.

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Chapter 1

Introduction

1.1 Introduction

The resurgence of vector-borne diseases presents a global health problem. According to Gubler [37], the problem has come as a result of "changes in public health policy, insecticide and drug resistance, shift in emphasis from prevention to emergency response, demographic and societal changes, and genetic changes in pathogens". Every year there are more than one billion cases and over one million deaths from vector-borne diseases such as malaria, dengue, Chagas disease, yellow fever, plague, human African trypanosomiasis (sleeping sickness), schistosomiasis, leishmaniasis, Japanese encephalitis and onchocerciasis, globally (World Health Organization [112]). Although the diseases are preventable through informed protective measures, the resurgence suggests the need for more effective disease control approaches.

Vectors are living organisms that can transmit infectious diseases from animals to humans or between humans. Many vectors are bloodsucking insects, which ingest disease-producing pathogens during a blood meal from an infected host and later inject them into a new host during a subsequent blood meal. Vectors include mosquitoes, ticks, flies, triatomine bugs, sandflies, fleas and some freshwater aquatic snails. Mosquitoes are the most common disease vectors. Mosquitoes transmit malaria, dengue, Rift Valley fever, yellow fever, Chikungunya, lymphatic filariasis, Japanese encephalitis, and West Nile fever through bites [94, 95, 77, 109, 112].

Vector behaviour influences the speed of disease spread among hosts. Many studies of vector dynamics assume that vector-host interactions are random. Evidence suggests that mosquitoes do not choose hosts randomly [17, 52, 91, 93]. Carey and Carlson [17] suggest that a mosquito relies on its sense of smell (olfaction) for locating food sources, hosts and egg-deposition sites. A mosquito finds a host using chemical, visual, and thermal cues. According to Tauxe et al. [101], a mosquito's cpA neuron detector of skin and carbon dioxide is used to locate humans. This dependence of host-selection on mosquito behaviour and cues is called mosquito bias.

Malaria parasites produce volatile mosquito attractants [27, 45, 52, 93]. In a study by Lacroix et al [52], the presence of gametocytes in malaria-infected children increased mosquito attraction. Considering the difference between the proportions of the mosquitoes attracted to gametocyte carriers before and after treatment, a statistical analysis suggested that mosquito

attraction was approximately 14% less likely after treatment than before treatment. Although the analysis showed that the increased attractiveness was due to the infection status associated with the presence of gametocytes, the mechanism underlying this manipulation was unknown. The conclusion of the study is that mosquitoes are biased towards humans infected by the transmissible gametocyte stage of malaria parasites compared to uninfected humans or carriers of non-transmissible stages.

Shirai et al. [91] found that mosquitoes landed on people with Type O blood, nearly twice as often as those with Type A. There are opinions suggesting that mosquitoes are attracted to people with blood group O, a lot of skin bacteria or body heat, heavy breathers and the pregnant. "Blood type, metabolism, exercise, shirt color and even drinking beer can make individuals especially delicious to mosquitoes" (Stromberg [98]).

A study by Smallegange et al. [93] suggests that malaria-infected mosquitoes express enhanced attraction to human odour. Female mosquitoes were obtained by feeding on gametocytes of the chloroquine-sensitive NF54 strain of *P. falciparum*. All mosquitoes received another human blood meal nine days after the previous meal. From the analysis of experimental data the authors found that infected mosquitoes performed significantly more landings and probing attempts in response to human odour than did uninfected mosquitoes. The authors expressed the need for mathematical models addressing the influence of parasites on vector-host interactions.

In order to stop the spread of mosquito-borne diseases, it is important

to influence mosquito bias. Mosquito bias can be influenced using protective odorants such as mosquito attractants and insect repellents. Following [17], Potter [83] asks whether a mosquito would still be able to target a human host if it lacked its olfactory senses, and if odorants could be used to trick the mosquito into avoiding humans! According to Potter, recent studies by Tauxe et al. [101] and several others have started to address the answers.

The study by Tauxe et al. [101] suggests that a mosquito's cpA dual detector of skin odour and carbon dioxide can be blocked by an inhibitory odorant, thus blocking attraction of mosquitoes to human skin. That said, Potter [83] concludes that host seeking involves multiple sensory modalities, and abolishing one sense might not be sufficient to completely eliminate biting. To improve disease control, there is need to study and identify the mechanisms by which other sensory cues are detected by the mosquito, and the potential strategies to block them.

Insect repellents and other protective odorants (see Figure 1.1) can be used to prevent bites. Further, mosquitoes can be artificially blood-fed to prevent mosquito bites. It is known that animals can be used to blood-feed mosquitoes but the practice has diminished due to the implementation of strict guidelines governing the use of live animals (see Section 2.4.10 of MR4 Staff [72]). Artificial feeders [26, 34] are simplified devices which can be distributed in multiple places to provide blood meals to mosquitoes. They include the recently developed "Glytube" [25] (see Figure 1.2) and membrane feeders such as the Mishra feeder [67], the Mourya feeder [71], and the

Tseng feeder [102]. Further, artificial feeders can be treated with mosquito attractants to increase the attractiveness of the feeders to mosquitoes.

Figure 1.1: Insect repellents. Left-Right: Off Family with aloe vera (cream), Nopikex (square soap with 22% Deet), Off Deep Woods (spray), Bushman Plus Water Resistant (80% Deet with sunscreen), Fly Out (pump spray), Mosquito F.O! (pump spray), and Bugs Lock (wrist/ankle bands).

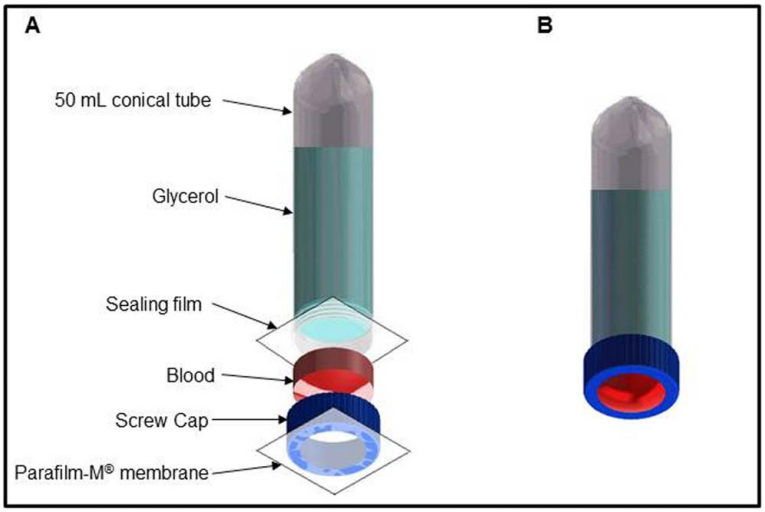

Figure 1.2: Schematic representation of the artificial feeder. Diagram **A** shows the materials used to prepare the device and the order of assembly of the feeder. Diagram **B** shows the assembled Glytube before mosquito feeding. Source: Costa-da-Silva et al. (2013) [25], page 3.

Several studies [2, 15, 22, 40, 111, 112] suggest that people can acquire protection against mosquito bites through regular use of insecticide-treated bed nets (see Figure 1.3). On the other hand, it is challenging to control mosquito-borne diseases using bed nets alone because bed nets are only used for a fraction of each day. It is important to examine how combining bed-net usage with other disease-control approaches affects disease spread.

Photo taken by Tjeerd Wiersma from Amsterdam, The Netherlands.

Figure 1.3: Bed net: Ceiling hung mosquito netting.

To influence mosquito bias requires a combination of disease control strategies, such as artificial feeders, attractants, repellents and bed nets, but the effectiveness of such a multifaceted approach has not been studied previously using mathematical models. In this study, we examine the effect of influencing mosquito bias on disease transmission and spread. To do this

we develop three mathematical models of malaria incorporating a controlled attractiveness of hosts to mosquitoes. The models are analyzed to examine the effect of artificial feeders, attractants, repellents, and bed nets on disease transmission and spread. Throughout this study, and wherever applicable, the following explanation is implied for simplicity.

> Hosts and vectors carrying transmissible stages of malaria parasites are referred to as being '**infectious**', whereas uninfected individuals and carriers of non-transmissible stages are referred to as being '**noninfectious**'. Individuals who successfully recover with immunity to the pathogen are referred to as being '**recovered**'.

Given below are the main objectives of this study.

OB1: To find out if artificial feeders affect disease spread, and if so, find out if they are a viable control measure.

OB2: To assess how the relative attractiveness of infectious humans using protective odorants affects disease transmission and spread.

OB3: To examine how the odorant-acquisition rate during the infectious stage affects disease transmission and spread.

OB4: To assess the effect of bed nets on disease spread and find out if the disease can be eliminated with bed nets alone.

OB5: To examine the combined effect of odorants and bed nets on disease spread in the presence of artificial feeders.

The artificial-feeder model is studied to examine the effect of mosquito feeders and protective odorants or repellents on disease transmission and spread. Mosquito bias is modelled by a dependence of the relative biting rates on the attractiveness of infectious hosts. We show that mosquito bias has a significant (and nonlinear) effect on disease spread.

The artificial-feeder model is modified to study the case without the feeders and where infected humans acquire protective odorants during the infectious stage. The resulting mosquito-bias model assumes that infectious humans are either odorant users or non-users. The odorants are acquired to manipulate the attractiveness of the users. The model is analyzed to examine the effect of the odorant-acquisition rate on disease spread. The effect of the odorant on disease control is also discussed.

Our third model combines the use of artificial feeders and protective odorants with the use of bed nets, where a fraction of the human population accounts for bed-net users. People can use protective odorants or bed nets to prevent mosquito bites. Thus, mosquito bias is modelled by a dependence of the relative biting rates on bed-net usage. The resulting bed-net model is used to examine how the use of odorants or mosquito repellents and bed nets affects disease transmission and spread. The effect of mosquito feeders on disease-control outcomes is also discussed.

Although the three models are designed with a specific focus on malaria control, they are applicable to many vector-borne pathogens. The proposed disease control strategies are applicable to all mosquito-borne diseases.

1.2 Epidemiological Background

Malaria is a vector-borne disease caused by protozoan parasites of the genus *Plasmodium*. According to the World Health Organisation [111], malaria is caused by five parasite species in humans: *Plasmodium falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi*. Of these, *P. falciparum* and *P. vivax* are the most common with *P. falciparum* being the most dangerous. The pathogens are transmitted from host to host by infected female *Anopheles* mosquitoes, which bite mainly between dusk and dawn [94, 77, 109, 111, 112]. Blood is required by the female mosquito for the protein needed to produce eggs [23, 109]. An uninfected mosquito can acquire the pathogen when biting an infected host and infect a new host during a subsequent bite.

The symptoms of malaria in an infected human include bouts of fever and anaemia. On average, the latent period is about ten days in humans [68] and about 11 days in mosquitoes [20]. The presentation may include headache, fever, shivering, joint pain, vomiting, haemolytic anaemia, jaundice, haemoglobin in the urine, retinal damage, and convulsions [11, 20]. If left untreated, malaria can lead to severe complications and death [112].

Malaria is a public health problem causing many deaths around the world. Malaria-related deaths can be reduced through disease control. In 1998, the World Health Organization in conjunction with other main international health agencies launched the Roll Back Malaria Global Partnership with the goal of halving the global burden of malaria by 2010. This was

done by supporting numerous anti-malarial activities and research efforts which can be seen in [111], A.10 of Chitnis [20] and other relevant sources.

The methods used in controlling malaria include larval control, which is the destruction of breeding sites to reduce the number of mosquitoes; indoor residual spraying, which reduces mosquito longevity and fertility; prompt and effective case management to quickly identify and treat malaria cases, and insecticide-treated bed nets. Bed nets are used to reduce mosquito-human contacts. Preventing mosquito-human contacts can lead to mosquitoes biting alternative hosts or not biting at all.

Further, certain disease-control approaches are undergoing research and development. These include insecticide-treated livestock, which involves treating cattle and other livestock with insecticides; intermittent prophylactic treatment, which involves administering antimalarial drugs at regular intervals to reduce parasitemia load; intermittent prophylactic treatment in pregnancy, intermittent prophylactic treatment for infants to reduce infant mortality, and gametocytocidal drugs targeting the reproduction of parasites in humans to reduce human-to-mosquito disease transmission. There are plans to develop transmission-blocking vaccines [70, 100] and genetically manipulated insect vectors [24, 65] to control the disease.

Malaria is endemic and widespread in tropical and subtropical regions, including much of sub-Saharan Africa, Asia, and the Americas. According to the World Health Organization's World Malaria Report 2013 [111], there were around 207 million cases of malaria in 2012 killing around 627 thousand

people. Malaria mortality rates were reduced by about 42% globally within the period 2000-2012. During the same period, malaria incidence declined by 25% around the world. The reductions result from improvements in vector control interventions, diagnostic testing and treatment. This represents a substantial progress towards the World Health Assembly target of reducing malaria mortality rates by 75% by the year 2015 [111].

Malaria transmission still occurs in 97 countries, putting more than 3.4 billion people at risk of illness. Four out of ten people who die of malaria live in the two highest burden countries: the Democratic Republic of the Congo and Nigeria [112]. Challenges such as drug resistance [5, 50, 77, 111], infected travellers [77, 104, 111, 112], mosquito bias [19, 48, 52], and debilitating effects of the disease burden on economic growth [38, 110] make malaria control increasingly difficult. More effective approaches are needed to stop the spread of the disease.

1.3 Mathematics for Malaria control

Although there are historical records[1] suggesting that malaria has been killing humans for thousands of years, the study of malaria using mathematics did not begin until the 20th century. In fact, according to the Roll Back Malaria Partnership [84], mathematical modelling began influencing public health policy in 1766 when Daniel Bernoulli published a model of smallpox. Ronald

[1] Ancient Chinese, Indian, Greek and Roman writings (see A.2 of Chitnis [20]).

Ross began the study of malaria using mathematics at the beginning of the 20th century. A study by Smith et al. [95] gives a historical account in which we see that Ross published his first dynamic malaria model in 1908 and coined the phrase "*a priori pathometry*" to describe the scientific activity of modelling transmission dynamics. As seen in the account [95], the field "*a priori pathometry*", or "constructive epidemiology" [89], is now widely known as mathematical epidemiology.

Following Ross' ideas relating mosquito flight distances and densities to larval control [85, 86], mathematical tools can be used to develop or support malaria control strategies. Ross invented the idea of a threshold condition defining a critical density of mosquitoes below which the malaria parasite would die out. The threshold condition implied that it was not necessary to kill every mosquito to eradicate malaria. Because of his work, malaria control and elimination efforts focused on larval control.

Lotka [59] and Waite [107] further developed the dynamic model [86] leading to a single difference equation model

$$X_{t+1} = \beta_0 X_t(1 - \frac{X_t}{N}) - \alpha_h X_t,$$

where N is the constant human population size; X_t is the number of infected humans at time t; α_h is the recovery rate of each infected human; β_0 is Ross' vectorial capacity describing the potential intensity of transmission by mosquitoes. Ross' time step was one month within which a mosquito made

two bites to complete the transmission cycle, whereas Waite considered the interval between bites. The different time steps led to different results. Ross improved the model to remove the dependency on the time step, and in 1911 he published the famous differential equation model [88].

Mathematicians who contributed to what is called the Ross-Macdonald Theory, played a big role in malaria control. The model by Kermack and McKendrick [46] and its subsequent extensions, which led to developments in mathematical modelling, facilitated developments in malaria modelling. The authors study a mathematical theory of epidemics and set conditions relating population densities to the outcome of the epidemic given a susceptible population. There is a natural removal of infected individuals through various stages and the epidemic vanishes before the susceptible population is exhausted. These developments were applicable to diseases which spread through an intermediate host. More contributions from the paper and its extensions are widely discussed by Brauer [13] and Dietz [31].

In 1950, George Macdonald focused on the mathematical theory of malaria transmission [95] and tested Ross' theory with field data [60, 61]. The World Health Assembly voted in 1955 to eradicate malaria and this was based largely on indoor residual spraying with DDT because the field trials had demonstrated its effectiveness in interrupting malaria transmission [84]. Macdonald's analysis explained that insecticides greatly reduced the number of mosquitoes that would live long enough to survive sporogony and transmit malaria [84].

Macdonald, Irwin and Dietz worked together to develop a model that incorporated immunity acquired after reinfection. A function accounting for superinfection was considered by Macdonald and Irwin, and this was improved later by Dietz. The model was tested in the Garki project [30, 68] and was able to qualitatively reproduce the age-specific patterns in malaria prevalence. With equations similar to Ross' first model, Macdonald's ideas further led to the formulation of the Ross-Macdonald model [63] which has driven much of the recent malaria modelling. The model and its subsequent extensions are available in many forms [3, 7, 95]. We notice that in 1982, Aron and May [7] first wrote the Ross-Macdonald model as

$$\begin{aligned} x_h' &= m_0 p_1 \beta x_m (1 - x_h) - \alpha_h x_h, \\ x_m' &= \beta x_h (1 - x_m) - \mu_m x_m, \end{aligned} \tag{1.1}$$

where x_h is the fraction of infectious humans at time t; x_m is the fraction of infectious female mosquitoes at time t; β is the biting rate per female mosquito; p_1 is the probability a bite by an infected mosquito on a susceptible human host leads to infection of the human; m_0 is the ratio of the total female mosquito population size to the total human population size; α_h is the rate at which each human recovers from infection; and μ_m is the death rate of adult female mosquitoes.

Models of the form (1.1) are widely studied. They are known to admit two kinds of equilibria: a disease-free equilibrium if $x_h = x_m = 0$, and an endemic equilibrium if $x_h, x_m \neq 0$. As a tradition, analysis of the disease-free

equilibrium includes a derivation of the threshold condition. Ross' threshold condition was redefined by Macdonald to become the basic reproduction ratio $\mathcal{R}_0$ for malaria [62]. $\mathcal{R}_0$ for malaria is the expected number of new infected hosts as a result of introducing one infected host in a completely susceptible population. For history of $\mathcal{R}_0$ and its usage, see Heesterbeek and Dietz [41, 42]. Koella [49] studies a Ross-Macdonald model and gives an algebraic derivation of $\mathcal{R}_0$ showing that its threshold value is unity. For the malaria model (1.1), the derivation gives

$$\mathcal{R}_0 = \frac{m_0 p_1 \beta^2}{\alpha_h \mu_m}.$$

$\mathcal{R}_0$ is a measure of transmission intensity. It defines the extent to which a given disease threatens a susceptible population in absence of disease control measures. The larger the value of $\mathcal{R}_0$ the more severe is the disease spread. The disease dies out if $\mathcal{R}_0 < 1$ and spreads in the population if $\mathcal{R}_0 > 1$.

Epidemic models in general divide a population into compartments based on the number in each disease-state: S for susceptible; E for latently infected; I for infectious; and R for recovered individuals. Thus, models are SIS, SIR, SIRS, or SEIRS, where S, E, I, and R denote the numbers of individuals in each of these compartments. Figure 1.4 illustrates a mathematical model with SEIRS for the human population and SEI for the female mosquitoes. Our models are based on this framework with notations such as $S_h E_h I_h R_h$ for the humans and $S_m E_m I_m$ for the mosquitoes.

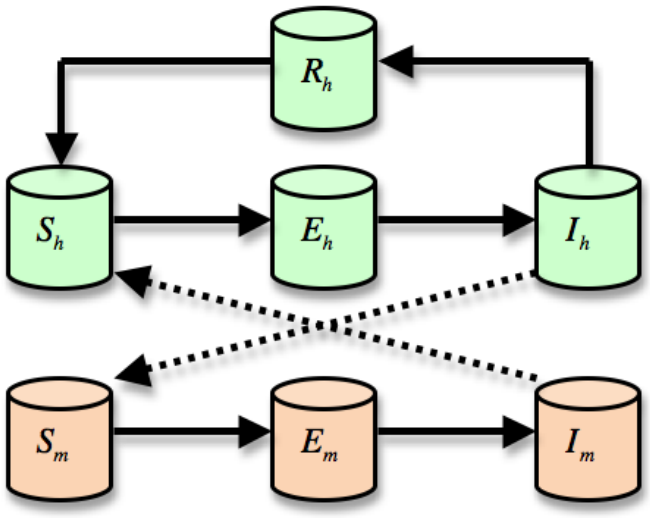

Figure 1.4: A schematic diagram of the dynamics for malaria transmission. Susceptible populations S_h and S_m can acquire malaria pathogens through contacts with infectious groups I_m and I_h respectively.

Extensions and modifications of the Ross-Macdonald model exist with changes in the number of population compartments. We notice that models like (1.1) are SIS. They assume all infected mosquitoes are infectious and ignore a transmission-delay due to the latent period. Aron and May [7] consider a second version of the Ross-Macdonald model which is a delay model with the delay to account for the latent period. In both models, immunity to the disease is boosted as a result of reinfection. The immunity boost acquired by repeated infection was further studied by Aron [8, 9, 10]. Models represented by Figure 1.4 assume that recovered humans become susceptible when the acquired immunity is lost.

Hethcote [43] and Mandal et al. [64] review several models including some extensions of the Ross-Macdonal model. Anderson and May [3, 4] considered (1.1) with changes in its second equation. This led to the equation $x'_m = p_2\beta x_h(1-x_m)-\mu_m x_m$, where p_2 is the probability a bite by a susceptible mosquito on an infected human host leads to infection of the mosquito. They also revisited the delay model and compiled data relating to the latent period, the rate of recovery for humans, the expected adult lifespan of mosquitoes and malaria prevalence across age distributions for humans. The latent period was seen to lower the long term prevalence of the disease. We consider the latent period by including classes for the latently infected E_h and E_m as shown in Figure 1.4. The probability p_2 is also considered.

Recent mathematical models of malaria incorporate recruitment to the susceptible class and infectiousness of individuals in various forms with an assumption that mosquitoes choose and bite hosts randomly. Cai et al. [16], Chitnis [20], Chitnis et al. [21], Mukandavire et al. [73], Ngwa and Shu [74], Niger and Gumel [75], Okosun et al. [78], Olaniyi and Obabiyi [79], Tumwiine et al. [103, 104] and several others study malaria dynamics with recruitment to the susceptible class to reflect population-change as a result of birth and immigration. There is need to use mathematical models to find out how nonrandom feeding by mosquitoes affects disease dynamics.

It is important to mention that the disease-induced death of infectious individuals, which is ignored in numerous studies, has received attention in some recent works. Studies with SIS models like (1.1) ignore the death to

simplify analysis. This can also be seen in Koella and Antia [50] where deaths are balanced by births into the susceptible class and the disease-induced death is ignored to simplify analysis of disease control options. In some cases, such as [16, 20, 75, 78, 79], the additional death may facilitate a backward bifurcation leading to subcritical endemic equilibria for $\mathcal{R}_0 < 1$.

Ngwa and Shu [74] proposed a compartmental model for malaria with varying population size. The SEIRS model was later studied and analyzed by Chitnis [20] in a Ph.D. dissertation. The density-dependent and density-independent death rates assumed in [20] led to the existence of two disease-free equilibria: one in absence of mosquitoes and another in presence of both populations. A unique endemic equilibrium was confirmed. Two reasonable sets of baseline values for the parameters in the model were compiled, for high and for low transmission regions. The sets were used to compute sensitivity indices of $\mathcal{R}_0$. It was found out that the mosquito biting rate was the most sensitive parameter in both high and low transmission regions, making it a possible target for control with bed nets.

The model of Niger and Gumel [75] extends some earlier models of malaria by including multiple infected and recovered classes to account for the effect of reinfection. A backward bifurcation arises due to reinfection or the use of standard incidence, and this cannot be averted by interchanging standard incidence with a mass action incidence. The backward bifurcation region increases with decreasing average life span of mosquitoes. However, the phenomenon can be averted if reinfection does not occur, acquired immu-

nity is not lost, and the standard incidence function is replaced with a mass action incidence to model the rate of infection. In the absence of reinfection and loss of acquired immunity, the model with mass action incidence has a globally asymptotically stable endemic equilibrium when $\mathcal{R}_0 > 1$.

The model of Tumwiine et al. [104] assumes recruitment with infected humans as a result of immigration. The model is an extension of the model proposed in [103]. There is no disease-free equilibrium in presence of infective immigrant humans and the model exhibits a unique endemic equilibrium. The results agree with conclusions from a general SIR model of Brauer and van den Driessche [12]. The epidemiological implication is that reductions in $\mathcal{R}_0$ have negligible effects towards disease eradication except when the fraction of infective immigrants approaches zero. If $\mathcal{R}_0 > 1$, the unique endemic equilibrium is globally stable and the disease remains in the population.

Mathematical models with mosquito bias present new options for disease control. Numerous studies have assumed that mosquitoes choose and feed on hosts randomly, but several experiments and analyses of vector dynamics give evidence suggesting that vector feeding follows a nonrandom pattern. This feature and the absence of its exploitation in various disease control methods could be responsible for the emergence and resurgence of vector-borne diseases globally. For mosquito-borne diseases, there is need to target mosquito attraction to improve disease control.

To exploit mosquito bias, Kingsolver [48] developed an SIS model of mosquito host choice and analyzed it with three types of mosquito prefer-

ence for infected hosts: consistent preference, increasing preference, and a switching behaviour with preference depending on the relative abundance of infected and uninfected hosts. Kingsolver followed the results of Edman et al. [33] showing that nonrandom feeding is expressed at three stages: attraction and penetration, probing and the location of blood, and blood intake. The author [48] discussed several laboratory experiments suggesting that mosquitoes prefer infected hosts to ones that are not infected. Thus, nonrandom feeding was incorporated in the model to study how such feeding behaviour could alter the conditions for the existence, stability, and levels of infection at equilibrium. The author suggested that a more detailed study was needed to better understand the dynamics of malaria.

Mosquito bias can influence the impact of bed-net usage on disease spread. Agusto et al. [2] and Buonomo [15] model bed nets by a mosquito-human contact rate, which is a linearly decreasing function of bed-net usage. The models [2, 15] ignore bites during the day, which implies that bed nets are 100% effective at all times. The bed-net model in [15] assumes mosquito bias, where the bias refers to the enhanced relative attractiveness of infectious humans to mosquitoes. The model suggests that mosquito bias may negatively affect disease control as bed-net usage increases.

Bed nets can be used with other approaches to influence disease-control outcomes. According to Lengeler [56], bed-net usage reduced malaria cases by 50%. Bed nets provide complete protection from mosquitoes, but they are only used by a fraction of the human population for a fraction of each day.

Protection from mosquito bites can be acquired through regular use of bed nets [22, 40, 111, 112]. It is important to mention that there are no previous studies showing how the use of bed nets together with repellents [1, 69, 93] or artificial feeders could affect disease transmission and spread.

1.4 Mathematical Background

1.4.1 Basic system properties

Consider an infectious-disease model with n population compartments X_1, X_2, ..., X_n presented as a system of nonlinear differential equations:

$$\begin{aligned} X_1' &= f_1(X_1, X_2, \ldots, X_n), \\ X_2' &= f_2(X_1, X_2, \ldots, X_n), \\ &\vdots \\ X_n' &= f_1(X_1, X_2, \ldots, X_n). \end{aligned}$$

Using vector notation, let $X = (X_1, X_2, \ldots, X_n)$. The above system can be written as

$$X' = f(X), \tag{1.2}$$

where $f = (f_1, ..., f_n) : U \to \mathbb{R}^n$ is continuous on set U, that is, $f \in C(U)$. In this case U is an open subset of $\mathbb{R}^n$.

Definition 1.4.1 ([81], A solution of a system)**.** *A function X is a solution*

of System (1.2) *on an interval* $\mathcal{T} \ni 0$ *if* X *is differentiable on* $\mathcal{T}$ *and if for all* $t \in \mathcal{T}$, $X \in U$ *satisfying* (1.2). *Given* $X_0 \in U$, X *is a solution of the initial value problem*

$$X' = f(X), \quad X(0) = X_0, \tag{1.3}$$

on an interval $\mathcal{T} \ni 0$ *if* $X(0) = X_0$ *and* X *is a solution of* (1.2) *on the interval* $\mathcal{T}$; $X(0) = X_0$ *is then called an initial condition of System* (1.2).

Definition 1.4.2 ([81], The flow of a system)**.** *Let* $\phi(t, X_0)$ *denote the solution of the initial value problem* (1.3) *defined on its maximal interval of existence,* $\mathcal{T}(X_0)$, *then for* $t \in \mathcal{T}(X_0)$, *the set of mapping* ϕ_t *defined by*

$$\phi_t(X_0) = \phi(t, X_0)$$

is called the flow of System (1.2); ϕ_t *is also referred to as the flow of the vector field* $f(X)$.

Definition 1.4.3 ([81], Invariant Set)**.** *A set* $D \subset U$ *is called invariant with respect to the flow* ϕ_t *if* $\phi_t(D) \subset D$ *for all* $t \in \mathbb{R}^n$. *Further,* D *is called positively invariant with respect to the flow* ϕ_t *if* $\phi_t(D) \subset D$ *for all* $t \geq 0$.

Theorem 1.4.1 ([81], The Fundamental Existence-Uniqueness Theorem)**.** *Let* $U \ni X_0$ *be an open subset of* $\mathbb{R}^n$ *and assume that* f *is continuously differentiable on* U, *then there exists* $\tau > 0$ *such that the initial value problem* (1.3) *has a unique solution* X *on the interval* $[-\tau, \tau]$.

Theorem 1.4.2 ([80], Theorem 2.2.2, Comparison Theorem)**.** *Let $f(t,x)$ be continuous in an open set U containing a point (τ_0, x_0), and suppose that the initial value problem*

$$z'(t) = f(t, z(t)), \quad z(\tau_0) = x_0,$$

has a maximal solution $z = z(t)$ with domain $\tau_0 \leq t \leq \tau_1$. If x is any differentiable function on $[\tau_0, \tau_1]$ such that $(t, x(t)) \in U$ for $t \in [\tau_0, \tau_1]$ and

$$x'(t) \leq f(t, x(t)), \quad \tau_0 \leq t \leq \tau_1, \quad x(\tau_0) \leq x_0, \tag{1.4}$$

then

$$x(t) \leq z(t), \quad \tau_0 \leq t \leq \tau_1. \tag{1.5}$$

Moreover, the result remains valid if 'maximal' is replaced by 'minimal' and $<$ is replaced by $>$ in both (1.4) *and* (1.5)*.*

Definition 1.4.4 ([108], Equilibrium solution)**.** *An equilibrium solution of System* (1.2) *is a particular point $X^* \in \mathbb{R}^n$ such that $f(X^*) = 0$.*

Theorem 1.4.3 ([82], Descartes Theorem)**.** *The number of positive roots (counted according to their multiplicity) of a polynomial $P_n(x)$ with real coefficients is either equal to the number of sign alterations in the sequence of its coefficients or is by an even number less.*

Definition 1.4.5 ([108], Definition 1.2.1, Liapunov stability)**.** *An equilibrium solution X^* is said to be Liapunov stable if for $\epsilon > 0$, there exists a $\delta = \delta(\epsilon) > 0$, such that, for any solution $X(t, X_0)$ of (1.3), $||X_0 - X^*|| < \delta$ implies $||X - X^*|| < \epsilon$ for $t > 0$. An equilibrium which is not stable is called unstable. In this case $||\cdot||$ denotes a norm in $\mathbb{R}^n$.*

Definition 1.4.6 ([108], Definition 1.2.2, Asymptotic stability)**.** *An equilibrium solution X^* is said to be asymptotically stable if it is Liapunov stable and if there exists a constant $\delta > 0$ such that $||X_0 - X^*|| < \delta$ implies*

$$\lim_{t \to \infty} ||X - X^*|| = 0.$$

Definition 1.4.7 ([97], Basin of attraction)**.** *The basin of attraction of an equilibrium solution X^* is the set of initial conditions X_0 such that $X \to X^*$ as $t \to \infty$.*

1.4.2 Stability analysis

The stability of an equilibrium solution tells whether small perturbations that start away from the solution decay or grow larger with time. For an equilibrium solution, stability analysis is done by linearising $f(X)$ using the Jacobian matrix evaluated at the solution.

Theorem 1.4.4 ([108], Theorem 1.2.5)**.** *Suppose all of the eigenvalues of $J(X^*)$ have negative real parts. Then the equilibrium solution $X = X^*$ of the nonlinear vector field $X' = f(X)$ is asymptotically stable.*

From (1.3), the Jacobian matrix of $f(X)$ is defined as

$$J = \begin{pmatrix} \frac{\partial f_1}{\partial X_1} & \frac{\partial f_1}{\partial X_2} & \cdots & \frac{\partial f_1}{\partial X_n} \\ \frac{\partial f_2}{\partial X_1} & \frac{\partial f_2}{\partial X_2} & \cdots & \frac{\partial f_2}{\partial X_n} \\ \vdots & \vdots & \ddots & \vdots \\ \frac{\partial f_n}{\partial X_1} & \frac{\partial f_n}{\partial X_2} & \cdots & \frac{\partial f_n}{\partial X_n} \end{pmatrix}.$$

Let X^0 denote a disease-free equilibrium solution of (1.3). It follows that the disease-free equilibrium is locally asymptotically stable if all eigenvalues of $J(X^0)$ have negative real parts. If applicable, the decomposition method of van den Driessche and Watmough [106] is equivalent to checking the eigenvalues of the Jacobian and is always sufficient.

Following [106], (1.3) can be written in terms of new functions as

$$X' = f(X) = g(X) - v(X), \tag{1.6}$$

with $v(X) = v^-(X) - v^+(X)$, where $g(X)$ is the rate at which new infections come into the system; $v^+(X)$ is the rate of transfer of individuals into the system by all other means; and $v^-(X)$ is the rate of transfer of individuals out of the system. Sort the compartments so that $X = (X_a, X_b)$, where X_a is a vector of compartments with infected individuals and X_b corresponds to compartments with uninfected individuals. Similarly, define $f = (f_a, f_b)$ with $f_a = g_a - v_a$ and $f_b = g_b - v_b$.

If System (1.3) admits a disease-free equilibrium X^0 and the functions

in (1.6) satisfy Lemma 1 of [106], then $J(X^0)$ admits the partitions below.

$$J(X^0) = \frac{\partial f}{\partial X}(X^0) = \left[\frac{\partial g}{\partial X}(X^0) - \frac{\partial v}{\partial X}(X^0)\right] = \begin{bmatrix} F & 0 \\ 0 & 0 \end{bmatrix} - \begin{bmatrix} V & 0 \\ V_a & V_b \end{bmatrix},$$

where F and V are square matrices with entries from X_a. F is nonnegative, V is nonsingular and all eigenvalues of V_b have positive real parts.

$$F = \left[\frac{\partial g_a}{\partial X_a}(X^0)\right], \quad V = \left[\frac{\partial v_a}{\partial X_a}(X^0)\right],$$

and we can see that $J(X^0)$ admits a submatrix $J_{aa}(X^0)$ of the structure

$$J_{aa}(X^0) = F - V. \tag{1.7}$$

The product FV^{-1} is called the model's next generation matrix. It follows that all eigenvalues of $J(X^0)$ have negative real parts if all eigenvalues of $J_{aa}(X^0)$ have negative real parts. According to [106], all eigenvalues of $J_{aa}(X^0)$ have negative real parts if and only if $\rho(FV^{-1}) < 1$, where ρ denotes the spectral radius. We square $\rho(FV^{-1})$ and define a reproduction number

$$\mathcal{R}_c = \left(\rho(FV^{-1})\right)^2. \tag{1.8}$$

We refer to $\mathcal{R}_c$ as the control reproduction number for (1.3) in the presence of disease control methods. The square is introduced for $\mathcal{R}_c$ to be consistent with Macdonald's definition of the reproduction number [62]. $(\rho(FV^{-1}))^2$ is

used if the cycle of infection has two generations, whereas $\rho(FV^{-1})$ applies to the case with one generation. If the controls are absent, then $\mathcal{R}_c = \mathcal{R}_0$.

Theorem 1.4.5 ([106], Theorem 2)**.** *Consider the disease transmission model given by* (1.6)*. If X^0 is a disease-free equilibrium of the model, then it is locally asymptotically stable if $\rho(FV^{-1}) < 1$, but unstable if $\rho(FV^{-1}) > 1$.*

By Theorem 1.4.5, the $\mathcal{R}_c$-definition (1.8) can be used to claim the local stability status of the disease-free equilibrium. In fact X^0 is locally asymptotically stable if $\mathcal{R}_c < 1$ and unstable if $\mathcal{R}_c > 1$.

1.4.3 Backward bifurcation

Although the $\mathcal{R}_c$-condition tells that the disease dies out if $\mathcal{R}_c < 1$ and grows if $\mathcal{R}_c > 1$, some models admit subcritical endemic equilibria for $\mathcal{R}_c < 1$ and a bistability arises whereby a stable endemic equilibrium co-exists with the stable disease-free equilibrium. This is because of a backward bifurcation [18, 97, 105, 106] at the critical value $\mathcal{R}_c = 1$. It is important to find a subcritical value, denoted $\mathcal{R}_c^*$, below which the stable disease-free equilibrium exists alone in its neighbourhood. We do this using the centre manifold theory of bifurcation analysis found in [18, 81, 106] and several other texts.

First, choose a bifurcation parameter, say c, whose critical value c^1 satisfies $\mathcal{R}_c = 1$. The Jacobian $J(X^0)$ computed at the disease-free equilibrium is recomputed with $c = c^1$ giving $J(X^0, c^1)$ whose eigenvalues have negative real parts except for a simple zero eigenvalue. Let $u = (u_1, u_2, \ldots, u_n)$ and

$r = (r_1, r_2, \ldots, r_n)$ be the left and right eigenvectors respectively corresponding to the simple zero eigenvalue. The eigenvectors satisfy

$$uJ(X^0, c^1) = J(X^0, c^1)r = 0.$$

The direction of the bifurcation at $\mathcal{R}_c = 1$ is determined by the signs of the bifurcation coefficients a_B and b_B computed as follows:

$$\begin{aligned} a_B &= \sum_{k,i,j=1}^{n} u_k r_i r_j \frac{\partial^2 f_k}{\partial X_i \partial X_j}(X^0, c^1), \\ b_B &= \sum_{k,i=1}^{n} u_k r_i \frac{\partial^2 f_k}{\partial X_i \partial c}(X^0, c^1). \end{aligned}$$

If $b_B > 0$ and $a_B > 0$, then the model (1.6) exhibits a subcritical bifurcation at $\mathcal{R}_c = 1$. The direction of the bifurcation at $\mathcal{R}_c = 1$ is backward, hence backward bifurcation. The curve $a_B = 0$ corresponds to $\mathcal{R}_c - \mathcal{R}_c^* = 0$, giving the stricter threshold below which the stable disease-free equilibrium exists alone in its neighbourhood. At $\mathcal{R}_c = \mathcal{R}_c^*$, the bifurcation is forward.

Chapter 2

A mathematical model of Malaria control with artificial feeders and protective odorants

2.1 Introduction

The transmission and spread of vector-borne diseases such as malaria, dengue, West Nile virus and several others, is greatly influenced by vector behaviour. Evidence suggests that mosquitoes do not choose hosts randomly [17, 52, 91, 93]. Carey and Carlson [17] suggest that a mosquito relies on its sense of smell (olfaction) for locating food sources, hosts and egg-deposition sites. In a study by Lacroix et al [52], the presence of gametocytes in malaria-infected children increased mosquito attraction. In a controlled setting, Shirai et

al. [91] found that mosquitoes landed on people with Type O blood nearly twice as often as those with Type A. This dependence of host-selection on behaviour and cues is called mosquito bias.

Many mathematical models of vector-borne diseases incorporate several features of population dynamics with the assumption that vectors bite hosts randomly. For a survey of malaria models and their features, see recent works by Cai et al. [16], Chitnis [20], Chitnis et al. [21], Mukandavire et al. [73], Ngwa and Shu [74], Niger and Gumel [75], Okosun et al. [78], Olaniyi and Obabiyi [79], Tumwiine et al. [104] and many others. The basic reproduction number, which depends on disease-specific parameters, is used to analyze and assess options for disease control without considering the effect of mosquito bias on disease transmission and spread.

Following Kingsolver [48] and Lacroix et al [52] (reviewed in Chapter 1), Chamchod and Britton [19] model mosquito bias towards infected humans and measure mosquito attraction in terms of differing probabilities depending on disease-status of the host. A mosquito arrives at a human host depending on whether the human is infected or susceptible. The model is later studied by Buonomo and Vargas-De-Leon [14] incorporating a disease induced death rate. The studies [14, 19] suggest that the increased preference of humans infected with malaria over uninfected individuals favours the high prevalence of the parasites. This indicates the need to control mosquito bias.

From Chapter 1, mosquito bias can be influenced using odorants such as mosquito attractants and repellents. A mosquito's detector of a host can

be targeted using attractants (Potter [83] and Tauxe et al. [101]) to lure mosquitoes away or into traps. Infected humans can use mosquito repellents for protection against bites. Further, simplified devices–such as "glytube" (Costa-da-Silva et al. [25]) and other simple membrane feeders–can be used to artificially blood-feed mosquitoes.

We develop and analyze an artificial-feeder model to study the effect of artificial feeders, mosquito attractants and repellents on disease transmission and spread. Humans and mosquitoes with parasites in the infectious stage are said to be infectious, whereas uninfected individuals and carriers of non-transmissible stages are referred to as noninfectious. The model is used to examine if artificial feeders affect disease spread, and if so, find out if the feeders present a viable control measure. A disease control reproduction number is derived to examine epidemiological conditions governing disease spread. Analysis is done to assess the effect of repellents and attractants on disease transmission and spread. The centre manifold theory of bifurcation analysis is used to explore the existence of subcritical endemic equilibria and bistability. We also examine the dependence of the direction of bifurcation on the control parameters. Numerical simulations are done to support analytical results which are also discussed.

2.2 The artificial-feeder model

2.2.1 Model formulation

The human population is divided into compartments depending on disease-states S_h, E_h, I_h, R_h, where S_h is the number of susceptible humans, E_h is the number of humans latently infected (not infectious), I_h is the number of infectious humans, and R_h is the number of recovered humans with immunity to the disease. Let $N_h(t)$ be the total human population at time t; thus

$$N_h(t) = S_h(t) + E_h(t) + I_h(t) + R_h(t).$$

People are recruited to the susceptible class through birth at a constant rate $\mu_h\lambda_h$, which is assumed to be balanced by deaths, where μ_h is the per capita natural death rate and λ_h is the constant human population in the absence of the disease. Susceptible individuals may become infected through contacts with infectious mosquitoes. It is assumed that only infectious mosquitoes can transmit infection to susceptible humans through bites. Infected individuals go through a latent period, during which they do not transmit infection. They progress from the latent stage to the infectious stage at the rate γ_h. Infectious individuals recover at the rate α_h with temporary immunity to the disease or leave the population through an additional disease-induced death rate, δ_h. Recovered humans lose the immunity and return to the susceptible class at the rate ρ_h.

Let N_m be the total mosquito population with three compartments where S_m is the number of susceptible mosquitoes, E_m is the number of latently infected mosquitoes, and I_m is the number of infectious mosquitoes. At time t,

$$N_m(t) = S_m(t) + E_m(t) + I_m(t).$$

Mosquitoes enter the susceptible class through birth at a constant rate $\mu_m\lambda_m$, which is assumed to be balanced by deaths, where μ_m is the per capita natural death rate and λ_m is the constant mosquito population in the absence of the disease. It is probable that the parasite enters the mosquito through biting an infectious human. It is assumed that only infectious humans can transmit infection to susceptible mosquitoes through bites. Infected mosquitoes go through a latent period, during which they do not transmit infection. Mosquitoes progress from the latent stage to the infectious stage at the rate γ_m, and remain infectious for life. It is not clear if there are disease-induced deaths among infectious mosquitoes. We assume that mosquitoes leave the population through natural death.

From Smallegange et al. [93], malaria-infected mosquitoes express increased attraction to human odour. Let β_1 be the increased biting rate of an infected mosquito and β_2 denote the average biting rate of a susceptible mosquito, where $\beta_1 \geq \beta_2$. A mosquito approaches the vicinity of a host, but this does not always translate into biting. In the presence of artificial feeders, mosquito attraction to the feeder depends on the lure.

The formulation of the incidence function follows the conservation law, that is, the total number of bites made by mosquitoes balances those received by the hosts. Let N_a be the number of feeders. Let $c_i, i = 1, 2, 3$ be the probability of a mosquito biting a noninfectious human, an infectious human or an artificial feeder, respectively, given an encounter with such a host. In this case, the distribution of bites depends on the probabilities c_i. Given an encounter rate θ (per day), a mosquito is likely to bite

$$\theta(c_1(S_h + E_h + R_h) + c_2 I_h + c_3 N_a)$$

hosts per day. The probability a host bitten by a mosquito is a susceptible human is $\dfrac{c_1 S_h}{(c_1(S_h + E_h + R_h) + c_2 I_h + c_3 N_a)}$. Similarly, the probability a host bitten is an infectious human is $\dfrac{c_2 I_h}{(c_1(S_h + E_h + R_h) + c_2 I_h + c_3 N_a)}$.

The daily number of potentially infectious bites from mosquitoes is $\beta_1 I_m$. Let p_1 be the probability a bite by an infectious mosquito on a susceptible human leads to infection of the human. Thus, $\dfrac{c_1 p_1 \beta_1 S_h I_m}{c_1(S_h + E_h + R_h) + c_2 I_h + c_3 N_a}$ is the incidence of new human infections. The daily number of bites from susceptible mosquitoes is $\beta_2 S_m$. Let p_2 be the probability a bite by a susceptible mosquito on an infectious human leads to infection of the mosquito. The incidence of new mosquito infections is $\dfrac{c_2 p_2 \beta_2 S_m I_h}{c_1(S_h + E_h + R_h) + c_2 I_h + c_3 N_a}$. We introduce the following parameters to simplify the incidence terms.

$$\beta_h = p_1 \beta_1; \quad \beta_m = p_2 \beta_2; \quad c = \frac{c_2}{c_1}; \quad A = \frac{c_3}{c_1} N_a. \tag{2.1}$$

It is clear that if we set $\beta_1 = \beta_2 = \beta$, we can compensate for the actual differences between β_1 and β_2 by choosing appropriate values for p_1 and p_2.

With the above description, our mathematical model consists of the following system of differential equations.

$$\begin{aligned}
S_h' &= \mu_h(\lambda_h - S_h) - \frac{\beta_h S_h I_m}{S_h + E_h + cI_h + R_h + A} + \rho_h R_h, \\
S_m' &= \mu_m(\lambda_m - S_m) - \frac{c\beta_m S_m I_h}{S_h + E_h + cI_h + R_h + A}, \\
E_h' &= \frac{\beta_h S_h I_m}{S_h + E_h + cI_h + R_h + A} - (\gamma_h + \mu_h)E_h, \\
E_m' &= \frac{c\beta_m S_m I_h}{S_h + E_h + cI_h + R_h + A} - (\gamma_m + \mu_m)E_m, \\
I_h' &= \gamma_h E_h - (\alpha_h + \mu_h + \delta_h)I_h, \\
I_m' &= \gamma_m E_m - \mu_m I_m, \\
R_h' &= \alpha_h I_h - (\rho_h + \mu_h)R_h.
\end{aligned} \tag{2.2}$$

Using vector notation $X = (S_h, S_m, E_h, E_m, I_h, I_m, R_h)$, System (2.2) can be studied as an initial value problem $X' = f(X)$ with nonnegative initial data X_0, where $X_0 = X(0) = (S_{h0}, S_{m0}, E_{h0}, E_{m0}, I_{h0}, I_{m0}, R_{h0})$.

The malaria model (2.2) is based on the following set of assumptions.

A1: There is a constant recruitment to the susceptible human population as a result of birth, which is balanced by natural deaths.

A2: There is a constant recruitment to the susceptible mosquito population as a result of birth, which is balanced by natural deaths.

A3: Transmission takes place only from infectious mosquitoes to susceptible humans and from infectious humans to susceptible mosquitoes.

A4: Infected mosquitoes do not live long enough to recover from infection.

A5: Recovered humans have full immunity to the disease for a few years after which the individuals become susceptible.

A6: Artificial feeders do not harbour or preserve disease parasites.

The parameters for the Artificial-feeder model are outlined in Table 2.1. All parameters are positive. A and c are the control parameters.

Table 2.1: Parameters for the artificial-feeder model

Parameter	**Description**
λ_h	Human population size at disease-free equilibrium.
λ_m	Female mosquito population size at disease-free equilibrium.
μ_h	Natural death rate of humans.
μ_m	Natural death rate of female mosquitoes.
β_h	Mosquito biting rate leading to infection of the human host.
β_m	Mosquito biting rate leading to infection of the mosquito.
γ_h	Rate at which a human becomes infectious after infection.
γ_m	Rate at which a mosquito becomes infectious after infection.
α_h	Rate at which a human recovers from infection.
ρ_h	Rate at which a recovered human loses partial immunity.
δ_h	Rate at which infectious humans die from the disease.
A	Adjusted number of artificial feeders.
c	Controlled relative attractiveness of infectious humans.

The parameter A is the adjusted number of artificial feeders for the case where noninfectious humans and artificial feeders are equally attractive to

mosquitoes. c is the controlled relative attractiveness of infectious humans to mosquitoes. The attractiveness is measured relative to that of noninfectious individuals. Previous mosquito-bias models [14, 19, 48] are SIS, hence they assume bias to all infected humans, with $c > 1$. Based on experimental studies [52], the bias is towards humans who can transmit the parasite, and these belong to the infectious class of the SEIRS model such as System (2.2). For this study, c takes the following cases.

$c > 1$: A mosquito is more likely to bite an infected human in the infectious stage than a noninfectious individual upon encounter.

$c = 1$: A mosquito is equally likely to bite an infected human in the infectious stage and a noninfectious individual upon encounter.

$c < 1$: A mosquito is less likely to bite an infected human in the infectious stage than a noninfectious individual upon encounter.

2.2.2 Well-posedness

A mathematical model is well-posed (in the sense of Hadamard), if a solution exists, the solution is unique, and the solution depends continuously on initial data. By the basic theory of ordinary differential equations (Theorem 1.4.1), the right hand side of (2.2) is differentiable on $\mathbb{R}^7$, which implies that a unique solution X exists for every initial condition in $\mathbb{R}^7$.

Further, the model is epidemiologically well-posed if the solution is always positive and bounded given nonnegative initial data. Thus, there

exists a domain of attraction for all positive solutions. All solutions with $E_h = E_m = I_h = I_m = 0$ exist in the $S_h - S_m - R_h$ plane, which we refer to as a disease-free plane.

The following theorems and proofs show that the malaria model (2.2) is epidemiologically well-posed with a solution which is always positive and bounded given nonnegative initial data.

Theorem 2.2.1. *For Model* (2.2)*, the disease-free plane is invariant. All solutions starting with* $E_h = E_m = I_h = I_m = 0$ *remain in the disease-free plane for all time* $t > 0$ *with* $S_h > 0$*,* $S_m > 0$*, and* $R_h \geq 0$*.*

Proof. With $E_h = E_m = I_h = I_m = 0$, System (2.2) gives
$S_h' = \mu_h(\lambda_h - S_h) + \rho_h R_h$, $S_m' = \mu_m(\lambda_m - S_m)$, $R_h' = -(\rho_h + \mu_h)R_h$, and $E_h' = E_m' = I_h' = I_m' = 0$. Solving these yields $E_h = E_m = I_h = I_m = 0$, $S_h = \lambda_h - S_{h0}e^{-\mu_h t} - R_{h0}e^{-(\rho_h+\mu_h)t} > 0$, $S_m = \lambda_m + (S_{m0} - \lambda_m)e^{-\mu_m t} > 0$, and $R_h = R_{h0}e^{-(\rho_h+\mu_h)t} \geq 0$. The solutions exist in the disease-free plane. □

Theorem 2.2.2 (Positivity of solutions)**.** *Model* (2.2) *is mathematically and epidemiologically well-posed with a unique solution. Given nonnegative initial data* X_0*, the solution* X *is positive for all time* $t \geq 0$*.*

Proof. Consider System (2.2) with $X = (S_h, S_m, E_h, E_m, I_h, I_m, R_h)$.
Suppose $X_0 > 0$ and that at least one component of X is negative at some time $t > 0$. By continuity and differentiability of X, there must be some time t_0 such that $X(t) > 0 \; \forall t \in [0, t_0)$ and one or more components of $X(t_0)$ are zero with nonpositive derivatives. By the equation for S_h', if $S_h(t_0) = 0$

and $\mu_h\lambda_h + \rho_h R_h(t_0) \leq 0$, then $R_h(t_0) < 0$ and R_h must be zero somewhere on $(0, t_0)$. Hence $S_h(t_0) > 0$. By the equation for S'_m, if $S_m(t_0) = 0$, then $S'_m(t_0) = \mu_m\lambda_m$, $S'_m(t_0) > 0$ and hence $S_m(t_0) > 0$. If $R_h(t_0) = 0$ with $R'_h(t_0)$ nonpositive, then $I_h(t_0)$ must be nonpositive. Similarly, if $I_h(t_0) = 0$ and $I'_h(t_0) \leq 0$, then $E_h(t_0) \leq 0$; if $E_h(t_0) = 0$ and $E'_h(t_0) \leq 0$, then $I_m(t_0) \leq 0$ because $S_h(t_0) > 0$; if $I_m(t_0) = 0$ and $I'_m(t_0) \leq 0$, then $E_m(t_0) \leq 0$; and if $E_m(t_0) = 0$ with $E'_m(t_0) \leq 0$, then $I_h(t_0) \leq 0$ because $S_m(t_0) > 0$. Hence, if $X(t) > 0$ on $[0, t_0)$ and any component of $X(t_0)$ is zero, then it must be that at t_0, $E_h, E_m, I_h, I_m = 0$ with $E'_h, E'_m, I'_h, I'_m = 0$. From the invariance of the disease-free set (Theorem 2.2.1) and the uniqueness of solutions, having $E_h, E_m, I_h, I_m = 0$ at t_0 implies that $\forall t > 0$, $E_h, E_m, I_h, I_m = 0$, $S_h > 0$, $S_m > 0$, and $R_h \geq 0$, contradicting the supposition that $X(t) > 0\ \forall t \in [0, t_0)$. □

Theorem 2.2.3 (Boundedness of solutions)**.** *Model* (2.2) *is mathematically and epidemiologically well-posed. The solution X is bounded given nonnegative initial data X_0.*

Proof. By the definitions of N_h and N_m, and Equations (2.2),
$N'_h = (S_h + E_h + I_h + R_h)' = S'_h + E'_h + I'_h + R'_h \leq \mu_h\lambda_h - \mu_h N_h$; and
$N'_m = (S_m + E_m + I_m)' = S'_m + E'_m + I'_m = \mu_m\lambda_m - \mu_m N_m$.
By the Comparison Theorem (see Theorem 1.4.2), integration gives

$$\begin{cases} N_h \leq \lambda_h + (N_{h0} - \lambda_h)e^{-\mu_h t}, \\ N_m = \lambda_m + (N_{m0} - \lambda_m)e^{-\mu_m t}, \end{cases} \tag{2.3}$$

$\forall t \geq 0$, where N_{h0} and N_{m0} are initial values. By positivity, N_h and N_m are bounded between 0 and the solutions of (2.3), hence so are all components of X (by positivity of each component). □

Corollary 2.2.4 (Domain of attraction)**.** *For Model* (2.2) *with nonnegative initial data* X_0*, there exists a domain attracting all solutions* $X \in \mathbb{R}^7_+$*.*

Proof. Let the domain be denoted by D. From Equations (2.3), as $t \to \infty$, $N_h \leq \lambda_h$ and $N_m = \lambda_m$. $N_h < \lambda_h$ and $N_m < \lambda_m$ for all time if this holds at any time. Hence D is positive invariant and attracts all solutions. □

By Theorem 2.2.2, if $S_h = 0$, then $S_h' > 0$; if $S_m = 0$, then $S_m' > 0$; if $E_h = 0$, then $E_h' \geq 0$; if $E_m = 0$, then $E_m' \geq 0$; if $I_h = 0$, then $I_h' \geq 0$; if $I_m = 0$, then $I_m' \geq 0$; and if $R_h = 0$, then $R_h' \geq 0$. Thus, the solutions are bounded below by 0. Theorem 2.2.3 guarantees that the solutions are bounded above. Given $X_0 \in \mathbb{R}^7_+$, the components of X are always contained in the bounded domain given as follows.

$$D = \left\{ \begin{array}{l|c} X \quad \in \mathbb{R}^7_+ & \begin{array}{c} S_h > 0, S_m > 0, \\ E_h \geq 0, E_m \geq 0, \\ I_h \geq 0, I_m \geq 0, R_h \geq 0 \\ S_h + E_h + I_h + R_h \leq \lambda_h \\ S_m + E_m + I_m = \lambda_m \end{array} \end{array} \right\}.$$

Consequently, System (2.2) has no orbits leaving D and all solutions are attracted to this domain.

2.3 Equilibria and their stability

2.3.1 Disease-free equilibrium

A constant solution to a system of equations is referred to as an equilibrium solution. A disease-free equilibrium refers to the equilibrium that exists in the absence of the disease. For System (2.2), the equilibrium solutions satisfy the following equations:

$$\mu_h(\lambda_h - S_h) - \frac{\beta_h S_h I_m}{S_h + E_h + cI_h + R_h + A} + \rho_h R_h = 0, \tag{2.4a}$$

$$\mu_m(\lambda_m - S_m) - \frac{c\beta_m S_m I_h}{S_h + E_h + cI_h + R_h + A} = 0, \tag{2.4b}$$

$$\frac{\beta_h S_h I_m}{S_h + E_h + cI_h + R_h + A} - (\gamma_h + \mu_h)E_h = 0, \tag{2.4c}$$

$$\frac{c\beta_m S_m I_h}{S_h + E_h + cI_h + R_h + A} - (\gamma_m + \mu_m)E_m = 0, \tag{2.4d}$$

$$\gamma_h E_h - (\alpha_h + \mu_h + \delta_h)I_h = 0, \tag{2.4e}$$

$$\gamma_m E_m - \mu_m I_m = 0, \tag{2.4f}$$

$$\alpha_h I_h - (\rho_h + \mu_h)R_h = 0. \tag{2.4g}$$

Theorem 2.3.1 (Boundary equilibria)**.** *System* (2.2) *has a unique disease-free equilibrium and no other equilibria on the boundary of* D*.*

Proof. Consider Equations (2.4). Suppose X^* is a nonnegative equilibrium solution of (2.4). By Equation (2.4a), $X^* \geq 0 \Rightarrow S_h^* > 0$. Similarly, (2.4b) $\Rightarrow S_m^* > 0$, (2.4c) $\Rightarrow E_h^* \geq 0$, (2.4d) $\Rightarrow E_m^* \geq 0$, (2.4e) $\Rightarrow I_h^* \geq 0$, (2.4f) $\Rightarrow I_m^* \geq 0$, and (2.4g) $\Rightarrow R_h^* \geq 0$. In addition, if $R_h^* = 0$, then $I_h^* = 0$; if

$I_h^* = 0$, then $E_h^* = 0$; if $E_h^* = 0$, then $I_m^* = 0$; if $I_m^* = 0$, then $E_m^* = 0$; if $E_m^* = 0$, then $I_h^* = 0$; and if $I_h^* = 0$, then $R_h^* = 0$. Thus, at equilibrium, if any of E_h, E_m, I_h, I_m, R_h is zero, then $E_h = E_m = I_h = I_m = R_h = 0$, and hence the solution is on the disease-free set. Setting $E_h, E_m, I_h, I_m, R_h = 0$ in equations (2.4a) and (2.4b) proves uniqueness. □

Theorem 2.3.1 implies that if X^* is an equilibrium solution of System (2.2) in the boundary of D, then $E_h = E_m = I_h = I_m = R_h = 0$. Let X^0 denote the disease-free equilibrium solution. It follows that

$$X^0 = (\lambda_h, \lambda_m, 0, 0, 0, 0, 0).$$

Stability of an equilibrium solution is investigated using linearization of the system at the equilibrium. By Theorem 1.4.4, X^0 is locally asymptotically stable if all eigenvalues of the Jacobian matrix, evaluated at X^0, have negative real parts. Let $\mathcal{R}_c$ be the control reproduction number for System (2.2). The following definition for $\mathcal{R}_c$ is used to describe the stability of X^0.

Definition 2.3.1. *For the malaria model* (2.2)*, the control reproduction number* $\mathcal{R}_c$ *is defined as*

$$\mathcal{R}_c = \frac{c\beta_h\beta_m\lambda_h\lambda_m\gamma_h\gamma_m}{(\lambda_h + A)^2(\gamma_h + \mu_h)(\alpha_h + \mu_h + \delta_h)(\gamma_m + \mu_m)\mu_m}. \tag{2.5}$$

From the definition, $\mathcal{R}_c$ is a function of disease-specific parameters and control parameters. $\beta_h\lambda_h$ and $\beta_m\lambda_m$ are the rates of infection, $1/(\alpha_h+\mu_h+\delta_h)$

and $1/\mu_m$ are the life expectancies, $\gamma_h/(\gamma_h+\mu_h)$ and $\gamma_m/(\gamma_m+\mu_m)$ are the fractions of the populations that progress to the infectious stage, whereas $c/(\lambda_h+A)^2$ is the control factor. Thus, $\mathcal{R}_c$ is the expected number of new infected hosts as a result of introducing one infected host in a completely susceptible population in the presence of mosquito bias and artificial feeders.

Theorem 2.3.2. *For System* (2.2), *the disease-free equilibrium is locally asymptotically stable if* $\mathcal{R}_c < 1$ *and unstable if* $\mathcal{R}_c > 1$.

Proof. Let $J(X^0)$ denote the Jacobian matrix at X^0. It follows that $J(X^0)$ has the block structure

$$J(X^0) = \begin{bmatrix} J_{11} & J_{12} & J_{13} \\ 0 & J_{22} & 0 \\ 0 & J_{32} & -(\rho_h+\mu_h) \end{bmatrix},$$

with submatrices

$$J_{11} = \begin{bmatrix} -\mu_h & 0 \\ 0 & -\mu_m \end{bmatrix}, \quad J_{12} = \begin{bmatrix} 0 & 0 & 0 & -\dfrac{\beta_h\lambda_h}{\lambda_h+A} \\ 0 & 0 & -\dfrac{c\beta_m\lambda_m}{\lambda_h+A} & 0 \end{bmatrix},$$

$$J_{22} = \begin{bmatrix} -\gamma_h-\mu_h & 0 & 0 & \dfrac{\beta_h\lambda_h}{\lambda_h+A} \\ 0 & -\gamma_m-\mu_m & \dfrac{c\beta_m\lambda_m}{\lambda_h+A} & 0 \\ \gamma_h & 0 & -\alpha_h-\mu_h-\delta_h & 0 \\ 0 & \gamma_m & 0 & -\mu_m \end{bmatrix},$$

$$J_{32} = [\ 0 \quad 0 \quad \alpha_h \quad 0\ ], \quad \text{and} \quad J_{13} = [\ \rho_h \quad 0\ ]^T.$$

By the block structure of $J(X^0)$, X^0 is locally asymptotically stable if all eigenvalues of J_{11} and J_{22} have negative real parts. This is obvious for J_{11}. Note that J_{22} arises from the linear subsystem involving the infected compartments. Hence, we can apply the decomposition method of van den Driessche and Watmough [106] to derive a threshold condition for stability involving the control reproduction number for the system. By equation (1.7), the submatrix J_{22} admits the partition $J_{22} = F - V$, with

$$F = \begin{bmatrix} 0 & 0 & 0 & \dfrac{\beta_h \lambda_h}{\lambda_h + A} \\ 0 & 0 & \dfrac{c\beta_m \lambda_m}{\lambda_h + A} & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix},$$

and

$$V = \begin{bmatrix} \gamma_h + \mu_h & 0 & 0 & 0 \\ 0 & \gamma_m + \mu_m & 0 & 0 \\ -\gamma_h & 0 & \alpha_h + \mu_h + \delta_h & 0 \\ 0 & -\gamma_m & 0 & \mu_m \end{bmatrix}.$$

Let $\rho(\cdot)$ denote the spectral radius of a matrix. Following [106], all eigenvalues of J_{22} have negative real parts iff $\rho(FV^{-1}) < 1$. There are two generations in the cycle of infection. Thus, we square $\rho(FV^{-1})$ and define a reproduction number $\mathcal{R}_c = (\rho(FV^{-1}))^2$, yielding the formula (2.5). The conclusion of

the proof follows from the fact that $\rho(FV^{-1}) < 1$ implies $(\rho(FV^{-1}))^2 < 1$ (Theorem 1.4.5). □

The product FV^{-1} is called the model's next generation matrix. The spectral radius $\rho(FV^{-1})$ is also referred to as the dominant eigenvalue of the matrix. Squaring $\rho(FV^{-1})$ gives the traditional reproduction number for vector-host models (Macdonald [62]). $\mathcal{R}_c$ is a function of the the control parameters. In the absence of the controls, $\mathcal{R}_c$ gives the basic reproduction number, $\mathcal{R}_0$, which is independent of mosquito bias and artificial feeders. It is computed from $\mathcal{R}_c$ by setting $c = 1$ and $A = 0$, which yields

$$\mathcal{R}_0 = \frac{\beta_h \beta_m \lambda_m \gamma_h \gamma_m}{\lambda_h(\gamma_h + \mu_h)(\alpha_h + \mu_h + \delta_h)(\gamma_m + \mu_m)\mu_m}. \tag{2.6}$$

$\mathcal{R}_0$ is the expected number of new infected hosts as a result of introducing one infected host in a completely susceptible population in the absence of mosquito bias and artificial feeders.

Equations (2.5) and (2.6) give the $\mathcal{R}_c$-$\mathcal{R}_0$ relation:

$$\mathcal{R}_c = \mathcal{R}_0 \frac{c\lambda_h^2}{(\lambda_h + A)^2}. \tag{2.7}$$

If $\mathcal{R}_c < 1$, then each infected human produces, on average, less than one new infected human over the course of their infectious period in the presence of malaria control methods, and the disease cannot invade the population. Conversely, if $\mathcal{R}_c > 1$, then each infected human produces, on average, more

than one new infected human in the presence of malaria control methods and the disease can invade the population.

Equation (2.7) shows that $\mathcal{R}_c$ increases linearly with c and decreases with A. Reducing mosquito bias towards infectious hosts reduces the control reproduction number. In addition, $\mathcal{R}_c$ is decreasing with the number of artificial feeders, A. Therefore, $\mathcal{R}_c$ can be reduced by reducing vector bias for infectious hosts or increasing the number of artificial feeders until $\mathcal{R}_c < 1$. If this condition is not achieved, then $\mathcal{R}_c \geq 1$ and the disease persists.

2.3.2 Endemic equilibria

For System (2.2), any equilibrium solution in the interior of D is referred to as an endemic equilibrium. Let X^* denote the endemic equilibrium solution for System (2.2) with $S_h = S_h^*$, $S_m = S_m^*$, $E_h = E_h^*$, $E_m = E_m^*$, $I_h = I_h^*$, $I_m = I_m^*$, and $R_h = R_h^*$. Solve for E_h^*, E_m^* and R_h^* directly from equations (2.4e), (2.4f) and (2.4g), respectively, in terms of I_h^* and I_m^*.

$$E_h^* = \frac{(\alpha_h + \mu_h + \delta_h)I_h^*}{\gamma_h}, \quad E_m^* = \frac{\mu_m I_m^*}{\gamma_m}, \quad R_h^* = \frac{\alpha_h I_h^*}{\rho_h + \mu_h}. \tag{2.8}$$

Further, $S_h^* + E_h^* + I_h^* + R_h^* = \lambda_h - \delta_h I_h^*/\mu_h$, and $S_m^* + E_m^* + I_m^* = \lambda_m$.
It follows that

$$S_h^* = \lambda_h - \eta_h I_h^* \quad \text{and} \quad S_m^* = \lambda_m - \frac{(\gamma_m + \mu_m)I_m^*}{\gamma_m}, \tag{2.9}$$

where

$$\eta_h = 1 + \frac{\delta_h}{\mu_h} + \frac{\alpha_h + \mu_h + \delta_h}{\gamma_h} + \frac{\alpha_h}{\rho_h + \mu_h}. \tag{2.10}$$

Solve for I_m^* in terms of I_h^* from (2.4a) using (2.8) and (2.9) and obtain

$$I_m^* = \frac{(\lambda_h + A - (1 + \frac{\delta_h}{\mu_h} - c)I_h^*)(\gamma_h + \mu_h)(\alpha_h + \mu_h + \delta_h)I_h^*}{\beta_h \gamma_h (\lambda_h - \eta_h I_h^*)}. \tag{2.11}$$

Solve for I_m^* in terms of I_h^* from (2.4b) using (2.8) and (2.9) and obtain

$$I_m^* = \frac{c\beta_m \lambda_m \gamma_m I_h^*}{(\gamma_m + \mu_m)[c\beta_m I_h^* + \mu_m(\lambda_h + A - (1 + \frac{\delta_h}{\mu_h} - c)I_h^*)]}. \tag{2.12}$$

Notice that (2.11) and (2.12) can be equated and solved to give $I_h^* = 0$, for the disease-free equilibrium, which is obtained by factoring out I_h^*. For the endemic equilibria, let g_1 and g_2 be functions of I_h^* derived from equations (2.11) and (2.12), respectively, by dividing the equations by I_h^*, where $I_h^* \neq 0$. The following are the resulting simultaneous equations.

$$\begin{aligned} g_1 &= \frac{I_m^*}{I_h^*} = \frac{(\lambda_h + A - (\xi_2 - c)I_h^*)(\gamma_h + \mu_h)(\alpha_h + \mu_h + \delta_h)}{\beta_h \gamma_h (\lambda_h - \eta_h I_h^*)}, \\ g_2 &= \frac{I_m^*}{I_h^*} = \frac{c\beta_m \lambda_m \gamma_m}{(\gamma_m + \mu_m)(\mu_m(\lambda_h + A) - (\mu_m + \beta_m)(\xi_1 - c)I_h^*))}, \end{aligned}$$

where

$$\xi_1 = \frac{\mu_m}{\mu_m + \beta_m}\left(1 + \frac{\delta_h}{\mu_h}\right), \quad \text{and} \quad \xi_2 = \left(1 + \frac{\delta_h}{\mu_h}\right). \tag{2.13}$$

By inspection, $\xi_2 > \xi_1$, and g_1 and g_2 give rectangular hyperbolas whose properties change as c passes ξ_1 and ξ_2. The endemic equilibria are positive solutions satisfying $g_1 - g_2 = 0$. Later we show that both g_1 and g_2 have to be positive for the endemic equilibria to exist. Equating g_1 and g_2 leads to a quadratic equation. The equation is written by making use of the formulae for $\mathcal{R}_c$ and $\mathcal{R}_0$ to give

$$q_2 I_h^{*2} + q_1 I_h^* + q_0 = 0, \tag{2.14}$$

where

$$\begin{aligned} q_2 &= (\mu_m + \beta_m)(\xi_1 - c)(\xi_2 - c), \\ q_1 &= c\mu_m \eta_h \lambda_h \mathcal{R}_0 + (\lambda_h + A)[c\beta_m + 2\mu_m(c - \xi_2)], \\ q_0 &= \mu_m(\lambda_h + A)^2(1 - \mathcal{R}_c). \end{aligned}$$

The endemic equilibria satisfy Equation (2.14). The solutions,

$$I_h^* = \frac{-q_1 \pm \sqrt{q_1^2 - 4q_2 q_0}}{2q_2},$$

correspond to the endemic equilibria of System (2.2) if $I_h^* \in D$. The number of positive solutions depends on the signs of the coefficients q_2, q_1 and q_0. By expansion, $q_0 = \mu_m((\lambda_h + A)^2 - c\mathcal{R}_0\lambda_h^2)$, and it is obvious that the solutions are nonlinear functions of the control parameters A and c. As a result, it is not clear how c affects I_h^*.

Given $-q_1/q_2 > 0$, there exists a critical value of c below which, or above which, c gives two positive values of I_h^*. Let the value be denoted by c^*; we compute it from the discriminant. Thus, c^* is the solution of the equation

$q_1^2 - 4q_2q_0 = 0$, and the two positive solutions exist if c satisfies $q_1^2 - 4q_2q_0 > 0$.

Theorem 2.3.3. *System* (2.2) *has no endemic equilibria if* $c = 0$.

Proof. $c = 0 \Rightarrow \mathcal{R}_c = 0$ and Equation (2.14) gives

$$I_h^{*2} - 2\frac{(\lambda_h + A)}{(1 + \delta_h/\mu_h)} I_h^* + \frac{(\lambda_h + A)^2}{(1 + \delta_h/\mu_h)^2} = 0.$$

The result is a perfect square with $I_h^* = (\lambda_h + A)/(1 + \delta_h/\mu_h) > (\lambda_h + A)/\eta_h$. Consequently, equation (2.9) gives $S_h^* < 0$, which nullifies the solution. □

Although the quadratic equation (2.14) has two positive solutions for $c = 0$ (or as $c \to 0$), the solutions are neither in D nor positive. By definition, endemic equilibria have all components positive. All solutions that do not satisfy this criterion are void, giving no corresponding endemic equilibria.

Thus, c^* is the minimum value of c that gives two positive solutions. It is still not clear if the two positive solutions exist for all $c \geq c^*$. We study the properties of g_1 and g_2 to examine how increasing c affects the number of endemic equilibrium solutions. For the endemic equilibria, $I_h^*, I_m^* > 0$, which implies that $I_m^*/I_h^* > 0$, hence $g_1, g_2 > 0$. Further, the denominator of g_1 must be positive, since it is $\beta_h\gamma_h S_h^*$, with S_h^* from (2.9). Also, g_1 and g_2 must both be positive, hence the numerator of g_1 and the denominator of g_2 must be positive. Furthermore, $S_h^* > 0 \Rightarrow I_h^* < \lambda_h/\eta_h$. Thus, I_h^* must be in the interval $(0, \lambda_h/\eta_h)$. For $0 \leq c < \xi_1$, both the vertical and the horizontal asymptotes of g_1 are positive; the vertical asymptote of g_2 is positive; and

the horizontal asymptote of g_2 is at zero. In the positive quadrant with $0 < I_h^* < \lambda_h/\eta_h$, g_1 and g_2 intersect once or twice or never intersect.

For $\xi_1 \leq c < \xi_2$, both the vertical and the horizontal asymptotes of g_1 are positive; and either g_2 is a horizontal line or a rectangular hyperbola with a negative vertical asymptote and a horizontal asymptote at zero. In the positive quadrant with $0 < I_h^* < \lambda_h/\eta_h$, the functions intersect only once or never intersect.

For $\xi_2 \leq c < \infty$, the vertical asymptote of g_1 is positive; the horizontal asymptote of g_1 is nonpositive; the vertical asymptote of g_2 is negative; and the horizontal asymptote of g_2 is at zero. In the positive quadrant with $0 < I_h^* < \lambda_h/\eta_h$, the functions intersect only once or never intersect.

Thus, System (2.2) has two or no endemic equilibria or exactly one endemic equilibrium for $0 \leq c < \xi_1$, and the system has exactly one endemic equilibrium or no endemic equilibria for $\xi_1 \leq c < \infty$. It is now clear that $c^* < \xi_1$, and there must exist a minimum value of c for which the system has exactly one endemic equilibrium. Let the value be denoted by c^1. It is clear that $c^* \leq c^1 < \xi_1$. In the special case if $c^* = c^1$, then the system has no endemic equilibria (below c^1) or exactly one endemic equilibrium (above c^1). By inspecting the quadratic equation (2.14), we conjecture on the existence of endemic equilibria for the system.

Definition 2.3.2. *Let c^1 be a value of c satisfying $\mathcal{R}_c = 1$. For System (2.2),*

$$c^1 = \frac{1}{\mathcal{R}_0}\left(1 + \frac{A}{\lambda_h}\right)^2. \tag{2.15}$$

Since $\mathcal{R}_c < 1 \Leftrightarrow c < c^1$ and $\mathcal{R}_c > 1 \Leftrightarrow c > c^1$, we conjecture using c^1.

Conjecture 2.3.4. *Let c^1 be a value of c satisfying $\mathcal{R}_c = 1$. For System (2.2), there exists a subcritical value $c^* \leq c^1$ such that,*

(i) if $0 \leq c < c^*$, then the system has no endemic equilibria;

(ii) if $c^* < c < c^1$, then the system has two endemic equilibria; and

(iii) if $c^1 \leq c < \infty$, then the system has exactly one endemic equilibrium.

In the special case if $c^* = c^1$, then there are no endemic equilibria for $c < c^1$ and there is exactly one endemic equilibrium for $c \geq c^1$.

From the stability analysis of the disease-free equilibrium, the disease can invade the population if $c > c^1$. Conjecture 2.3.4 can be extended by suggesting that the system (2.2) has exactly one endemic equilibrium which is globally stable if $\mathcal{R}_c > 1$. This leads to the following conjecture on the stability of the endemic equilibrium.

Conjecture 2.3.5 (Stability of the endemic equilibrium)**.** *Let c^1 be a value of c satisfying $\mathcal{R}_c = 1$. If $c > c^1$, then the endemic equilibrium of System (2.2) is globally asymptotically stable.*

Conjectures 2.3.4 and 2.3.5 claim that if the system has exactly one endemic equilibrium in addition to the disease-free equilibrium, then the disease-free equilibrium is unstable and the endemic equilibrium is globally stable for $c > c^1$, that is, if $\mathcal{R}_c > 1$. Analytic-global stability results are

not available for SEIRS vector-bias models. For the SIS vector-bias model of Buonomo and Vargas-De-Leon [14], the geometric method due to Li and Muldowney [57] is used to show that the endemic equilibrium is globally asymptomatically stable in the interior of the domain of attraction if $\mathcal{R}_0 > 1$. For vector-borne diseases with bilinear incidence terms, Lashari and Zaman [54], Xiao [113] and Yang et al. [114] analyzed global stability for SEIR, SEI, SI, and SIR models in which it is concluded that the endemic equilibrium is globally stable if $\mathcal{R}_0 > 1$. Later we use numerical simulations to illustrate the stability properties of the equilibria.

2.3.3 Bifurcation analysis

Several studies [16, 20, 75, 78, 79] show that the disease-induced death rate δ_h facilitates a backward bifurcation by which at least two endemic equilibria exist for $\mathcal{R}_c < 1$. Later, we examine if the same effect of δ_h applies to System (2.2). Conjecture 2.3.4 states that the system admits two endemic equilibria if $c^* < c < c^1$. Since the disease-free equilibrium is stable for $0 \leq c < c^1$ (Theorem 2.3.2), a bistability may arise as a result of one of the two endemic equilibria being stable for $c^* < c < c^1$. This means that, with $c^* < c^1$, reducing c below c^1 may not necessarily guarantee disease eradication.

There exists exactly one endemic equilibrium for $c \geq c^1$, and $c = c^1$ gives $\mathcal{R}_c = 1$, which is a bifurcation point. The bifurcation point is when the Jacobian of the system, evaluated at the equilibrium solution, has a simple eigenvalue with zero real part. We examine the bifurcation and find out if

the direction of the bifurcation is forward or backward, and if the direction really depends on any of the control parameters A and c or δ_h. A backward bifurcation at $c = c^1$ refers to the slope at the bifurcation point, and implies that subcritical endemic equilibria may coexist with the stable disease-free equilibrium if $c < c^1$. In the following calculations, we use the centre manifold theory of bifurcation analysis (discussed in [18, 81, 105, 106]) to show that a subcritical bifurcation exists for some values of A and c or δ_h.

Let c be the bifurcation parameter. At the bifurcation point, set $c = c^1$, which is given in (2.15). Let $J(X^0, c^1)$ be the Jacobian matrix computed at the disease-free equilibrium X^0, where c^1 is the bifurcation value. The eigenvalues of $J(X^0, c^1)$ have negative real parts except for the simple zero eigenvalue. Let $u = (u_1, u_2, \ldots, u_7)$ and $r = (r_1, r_2, \ldots, r_7)$ be the left and right eigenvectors respectively corresponding to the simple zero eigenvalue, that is, $uJ(X^0, c^1) = J(X^0, c^1)r = 0$.

Solving for u and r in terms of u_3 and r_3 gives

$$\begin{aligned} r_1 &= -\frac{[(\gamma_h + \mu_h)(\alpha_h + \mu_h + \delta_h)(\rho_h + \mu_h) - \gamma_h \alpha_h \rho_h] r_3}{(\alpha_h + \mu_h + \delta_h)(\rho_h + \mu_h)\mu_h}, \\ r_2 &= \frac{(\lambda_h + A)(\gamma_h + \mu_h)(\gamma_m + \mu_m) r_3}{\beta_h \gamma_m \lambda_h}, \end{aligned}$$

$$u_1 = 0,\ u_2 = 0,\ u_7 = 0,\ u_4 = \frac{\beta_h \gamma_m \lambda_h u_3}{(\lambda_h + A)(\gamma_m + \mu_m)\mu_m},\ u_5 = \frac{(\gamma_h + \mu_h) u_3}{\gamma_h},$$
$$u_6 = \frac{\beta_h \lambda_h u_3}{(\lambda_h + A)\mu_m},\ r_4 = \frac{(\lambda_h + A)(\gamma_h + \mu_h)\mu_m r_3}{\beta_h \gamma_m \lambda_h},\ r_5 = \frac{\gamma_h r_3}{(\alpha_h + \mu_h + \delta_h)},$$
$$r_6 = \frac{(\gamma_h + \mu_h)(\lambda_h + A) r_3}{\beta_h \lambda_h}, \text{ and } r_7 = \frac{\alpha_h \gamma_h r_3}{(\rho_h + \mu_h)(\alpha_h + \mu_h + \delta_h)}.$$

Evaluate second-order partial derivatives of the system at (X^0, c^1) and use them to compute the bifurcation coefficients a_B and b_B given by

$$\begin{aligned} a_B &= \sum_{k,i,j=1}^{7} u_k r_i r_j \frac{\partial^2 f_k}{\partial X_i \partial X_j}(X^0, c^1), \\ b_B &= \sum_{k,i=1}^{7} u_k r_i \frac{\partial^2 f_k}{\partial X_i \partial c}(X^0, c^1). \end{aligned}$$

The second-order partial derivatives of f_5, f_6 and f_7 give zeros when evaluated at (X^0, c^1), and the products with u_1, u_2 and u_7 vanish because $u_1, u_2, u_7 = 0$. Further, it is important to note that

$$\frac{\partial^2 f_k}{\partial X_i \partial X_4} = 0 : \quad 1 \leq k, i \leq 7.$$

The surviving components of the calculations are given below:

$$\frac{\partial^2 f_3}{\partial X_1 \partial X_6} = \frac{\partial^2 f_3}{\partial X_6 \partial X_1} = \frac{\beta_h A}{(\lambda_h + A)^2};$$

$$\frac{\partial^2 f_3}{\partial X_3 \partial X_6} = \frac{\partial^2 f_3}{\partial X_6 \partial X_3} = \frac{\partial^2 f_3}{\partial X_6 \partial X_7} = \frac{\partial^2 f_3}{\partial X_7 \partial X_6} = -\frac{\beta_h \lambda_h}{(\lambda_h + A)^2};$$

$$\frac{\partial^2 f_3}{\partial X_5 \partial X_6} = \frac{\partial^2 f_3}{\partial X_6 \partial X_5} = -c^* \frac{\beta_h \lambda_h}{(\lambda_h + A)^2};$$

$$\frac{\partial^2 f_4}{\partial X_1 \partial X_5} = \frac{\partial^2 f_4}{\partial X_5 \partial X_1} = \frac{\partial^2 f_4}{\partial X_5 \partial X_3} = \frac{\partial^2 f_4}{\partial X_3 \partial X_5} = -c^{*2} \frac{\beta_m \lambda_m}{(\lambda_h + A)^2};$$

$$\frac{\partial^2 f_4}{\partial X_5 \partial X_7} = \frac{\partial^2 f_4}{\partial X_7 \partial X_5} = -c^{*2} \frac{\beta_m \lambda_m}{(\lambda_h + A)^2};$$

$$\frac{\partial^2 f_4}{\partial X_2 \partial X_5} = \frac{\partial^2 f_4}{\partial X_5 \partial X_2} = c^{*2}\frac{\beta_m}{\lambda_h + A};$$
$$\frac{\partial^2 f_4}{\partial X_5 \partial X_5} = -2c^{*2}\frac{\beta_m \lambda_m}{(\lambda_h + A)^2}.$$

The partial derivatives of the Jacobian with respect to c vanish except for

$$\frac{\partial^2 f_2}{\partial X_5 \partial c} = -\frac{\beta_m \lambda_m}{\lambda_h + A}; \quad \text{and} \quad \frac{\partial^2 f_4}{\partial X_5 \partial c} = \frac{\beta_m \lambda_m}{\lambda_h + A}.$$

Computing a_B and b_B with $u_3 = r_3 = 1$ gives

$$\begin{aligned} a_B &= \lambda_h^2(-(A/\lambda_h)^2 - 2(A/\lambda_h) + \eta_1(1 - A/\lambda_h) + \eta_0), \\ b_B &= \frac{\beta_h \beta_m \gamma_h \gamma_m \lambda_h \lambda_m}{(\lambda_h + A)^2(\alpha_h + \mu_h + \delta_h)(\gamma_m + \mu_m)\mu_m}, \end{aligned}$$

where

$$\begin{aligned} \eta_1 &= \frac{\mu_m \mathcal{R}_0}{2\mu_m + \beta_m}\left[\frac{(\gamma_h + \mu_h)(\alpha_h + \mu_h + \delta_h)(\rho_h + \mu_h) - \gamma_h \alpha_h \rho_h}{\gamma_h \mu_h (\rho_h + \mu_h)}\right], \\ \eta_0 &= \frac{2\mu_m \mathcal{R}_0}{2\mu_m + \beta_m}\left(1 + \frac{\delta_h}{\mu_h}\right) - 1. \end{aligned}$$

$\eta_1 > 0$ by inspection. Since $b_B > 0$, a backward bifurcation exists if $a_B > 0$. Given that c is the bifurcation parameter, consider a_B as a function of A. Notice that $a_B(A)$ is decreasing with A, and $a_B(0) = \lambda_h^2(\eta_1 + \eta_0)$. Further, $a_B(0)$ is increasing with δ_h, which gives support to the aforementioned effect of δ_h on backward bifurcation. If $\alpha_h >> \delta_h$, then $\mathcal{R}_0$ and η_1 are approximately independent of δ_h and the only dependence of a_B on δ_h is through η_0. It is

now easy to see the effect of A and δ_h on the direction of the bifurcation. Solving $a_B = 0$ gives

$$A_{min} = \frac{\lambda_h}{2}\left(-2 - \eta_1 + \sqrt{4 + 8\eta_1 + \eta_1^2 + 4\eta_0}\right), \tag{2.16}$$

which is the minimum value of A required for the switch from $a_B > 0$ to $a_B < 0$. A large value of δ_h/μ_h gives a large η_0, which leads to $a_B > 0$, hence δ_h facilitates a backward bifurcation. $A > A_{min}$ gives $a_B < 0$, which leads to a forward bifurcation. Thus, given $a_B > 0$, the direction of bifurcation can be switched from backward to forward by increasing A beyond A_{min}.

2.4 Parameter values

The artificial-feeder model is studied with the following parameter values. There are no special restrictions on the parameter values except that they should be positive and reasonable for mosquito-borne pathogens. Thus, the values presented below are selected from literature or randomly assigned for numerical simulations and to illustrate theoretical results from this study. Included is the source or description of how each parameter value is obtained.

λ_h : Human population size in the absence of the disease. Assume 20,000 people. Reasonable range: $0 < \lambda_h < \infty$.

λ_m : Female-mosquito population size in the absence of the disease. Assume 40,000 mosquitoes. Reasonable range: $0 < \lambda_m < \infty$.

μ_h : Natural death rate of humans. Let the life expectancy be 70 years or 70×365 days. This gives $\mu_h = 1/25550 = 0.00004$ per day. Reasonable range: $0.000001 < \mu_h < 0.001$.

μ_m : Natural death rate of female mosquitoes. Several values have been compiled by Chitnis [20] from different sources. Life expectancy for *Anopheles gambiae* is 15.4 days (Garrett-Jones and Shidrawi (1969)). $\mu_m = 1/15.4 = 0.065$ per day. Reasonable range: $0.001 < \mu_m < 0.1$.

β_h : Mosquito biting rate leading to infection of the human ($p_1\beta$). β is the average biting rate of a mosquito, and p_1 is the probability a bite by an infected mosquito on a susceptible human leads to infection of the human. $\beta = 0.4$ (Peters and Standfast (1960) in [20]). $p_1 \in [0.05, 0.13]$ (Krafsur and Armstrong (1978) in [20]). Suppose $p_1 = 0.05$. It follows that $\beta_h = 0.02$ per day. Reasonable range: $0.001 < \beta_h < 0.2$.

β_m : Mosquito biting rate leading to infection of the mosquito ($p_2\beta$). p_2 is the probability a bite by a susceptible mosquito on an infected human leads to infection of the mosquito. With $p_2 = 0.48$ (Boyd (1941) and Nedelman (1984) in [20]), $\beta_m = 0.192$ per day. Reasonable range: $0.005 < \beta_m < 0.4$.

γ_h : Rate at which a human becomes infectious after infection. Latent period for *P. falciparum* is $9 - 10$ days in humans (Molineaux and Gramiccia [68]). Using 10 days, $\gamma_h = 1/10 = 0.10$ per day. Reasonable range: $0.06 < \gamma_h < 0.2$.

γ_m : Rate at which a mosquito becomes infectious after infection. Latent period for *P. falciparum* is 11 days in mosquitoes (Baker (1966) in [20]). $\gamma_m = 1/11 = 0.09$ per day. Reasonable range: $0.02 < \gamma_m < 0.4$.

α_h : Rate at which a human recovers from infection. Estimated recovery period for each human with *P. falciparum* is 9.5 months [68]. Using 30 days for each month, $\alpha_h = 1/(9.5 \times 30) = 0.0035$ per day. Reasonable range: $0.001 < \alpha_h < 0.02$.

ρ_h : Rate at which a recovered human loses partial immunity. Use 5 years for the duration of acquired immunity and 365 days for each year. Thus $\rho_h = 1/(5 \times 365) = 0.0005$ per day. Reasonable range: $0 < \rho_h < 0.01$.

δ_h : Rate at which infectious humans die from the disease. Assume 220 deaths per year per 1000 infected people. $\delta_h = 0.0006$ per day. If disease-induced deaths are ignored, then $\delta_h = 0$ per day. Reasonable range: $0 < \delta_h < 0.001$.

A : Adjusted number of artificial feeders depending on the attractiveness of artificial feeders to mosquitoes relative to that of humans. This is a control parameter with $A \in [0, \infty)$. Reasonable range: $0 < A < \infty$.

c : Relative attractiveness of infectious humans to mosquitoes. This is a control parameter with $c \in [0, \infty)$. Reasonable range: $0 < c < \infty$.

2.5 Discussion of results

In this section, the theoretical results are discussed with supporting figures. All numerical simulations are done using parameter values in Table 2.2. A discussion of the values and range can be found in Section 2.4.

Table 2.2: Parameter values used for simulations

Parameter	**Value**	**Range**	**Source**
λ_h	20,000 people	$(0, \infty)$	§2.4
λ_m	40,000 mosquitoes	$(0, \infty)$	§2.4
μ_h	0.00004 per day	$(0, 0.001)$	§2.4
μ_m	0.065 per day	$(0.001, 0.1)$	[20]
β_h	0.02 per day	$(0.001, 0.2)$	[20]
β_m	0.192 per day	$(0.005, 0.4)$	[20]
γ_h	0.10 per day	$(0.06, 0.2)$	[68]
γ_m	0.09 per day	$(0.02, 0.4)$	[20]
α_h	0.0035 per day	$(0.001, 0.02)$	[68]
ρ_h	0.0005 per day	$(0, 0.01)$	[20]
δ_h	0.0006 per day	$(0, 0.001)$	§2.4
A	$0 - \infty$	$(0, \infty)$	§2.4
c	$0 - \infty$	$(0, \infty)$	§2.4

From Equation (2.6), $\mathcal{R}_0$ is a constant derived from disease-specific parameters whereas from Equation (2.7), $\mathcal{R}_c$ depends on the control parameters A and c. It is clear that $\mathcal{R}_c$ decreases with increasing A, but the reductions in $\mathcal{R}_c$ are negligible if A is negligible compared with λ_h. Taking the limit as $A \to \infty$ gives $\mathcal{R}_c = 0$. For disease eradication based on artificial feeders, A should be increased to be comparable to λ_h for all endemic equilibria to vanish. This effect is illustrated in Figure 2.1.

By Equation (2.7), $\mathcal{R}_c$ increases linearly with c. The number of positive real roots admitted by (2.14) is 0 or 2 or 1, depending on A and c. For disease eradication based on mosquito bias, c should be reduced to near zero for all endemic equilibria to vanish. This effect is illustrated in Figure 2.1.

The dependence of $\mathcal{R}_c$ on the control parameters has an effect on the number of endemic equilibria. A and c have a combined effect on the number of endemic equilibria. Figure 2.1 is used to illustrate Conjecture 2.3.4 which states that there are subcritical endemic equilibria at small values of c, given A. For disease eradication based on the value of $\mathcal{R}_c$, c should satisfy $c < c^*$ depending on A, which gives region **0** of Figure 2.1.

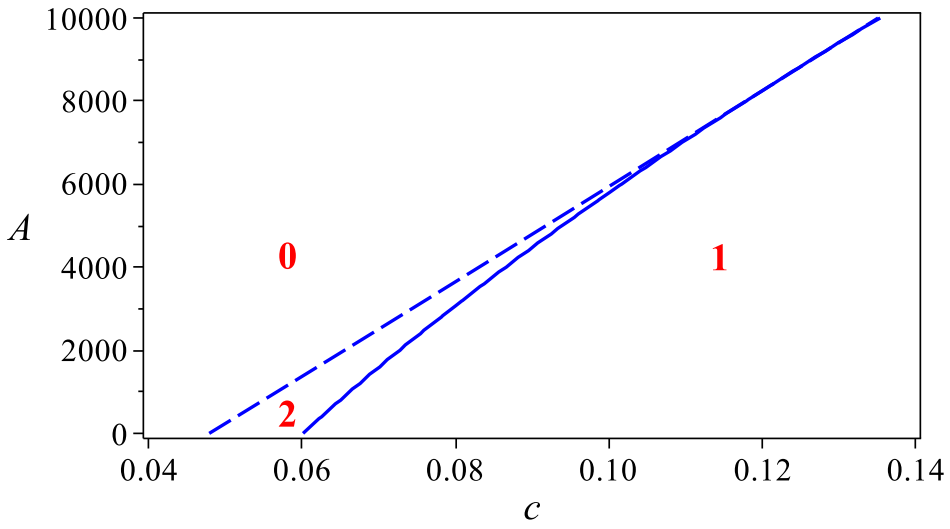

Figure 2.1: Bifurcations in the c-A plane. The solid curve is $\mathcal{R}_c = 1$, which gives $c = c^1$, whereas the dashed curve is $q_1^2 = 4q_2q_0$, giving $c = c^*$. In addition to the disease-free equilibrium, given A, the number of endemic equilibria can be 0 for $c < c^*$; 2 for $c^* < c < c^1$; or 1 for $c \geq c^1$.

Recall from Equation (2.1) that A is the number of feeders scaled by the relative attraction of mosquitoes to feeders. Hence, increasing A means increasing the number of feeders or increasing the attractiveness of the feeders relative to humans.

Bifurcation analysis suggests that there exists a backward bifurcation giving rise to two endemic equilibria depending on A, c or δ_h. Using c as the bifurcation parameter, the analysis shows that the direction of bifurcation can be backward or forward, depending on A and δ_h. This is illustrated in Figure 2.2 with the curve of A_{min} from Equation (2.16). $A > A_{min}$ gives $a_B < 0$, hence the bifurcation becomes forward.

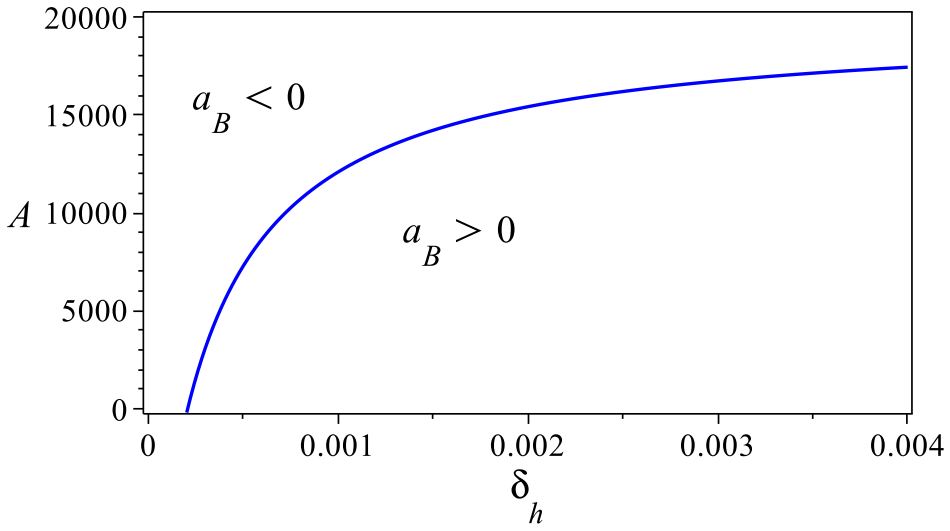

Figure 2.2: Effect of A on subcritical bifurcation. The curve $a_B = 0$ gives A_{min}. Given δ_h, the bifurcation is backward if $a_B > 0$, which applies to $A < A_{min}$, and $A > A_{min}$ gives $a_B < 0$ and hence a forward bifurcation.

Conjecture 2.3.4 states that, given c^* and c^1, a backward bifurcation exists for $c^* < c^1$. The analysis shows that a large value of δ_h/μ_h facilitates a backward bifurcation with $a_B > 0$. The properties of g_1 and g_2 show that there is exactly one endemic equilibrium for $c \geq \xi_1$. The sign change in a_B as A increases implies that c^* and c^1 are two different values. Thus, the curve $a_B = 0$ should match the intersection of c^* and c^1. The curve of Figure 2.2 is the locus of the fold bifurcation of Figure 2.1 following the intersection of the dashed (c^*) and solid (c^1) curves in the figure. With $c^* = c^1$, there are no endemic equilibria for $c < c^1$ and there is exactly one endemic equilibrium for $c > c^1$. This gives support to Conjecture 2.3.4. Moreover, the monotonicity of a_B with A implies that Figure 2.1 is generic, which gives further support to the conjecture. Since $A = 0$ gives $a_B > 0$ for large δ_h/μ_h, two endemic equilibria I_h^* exist for $c^* \leq c < c^1$ or region **2** of Figure 2.3.

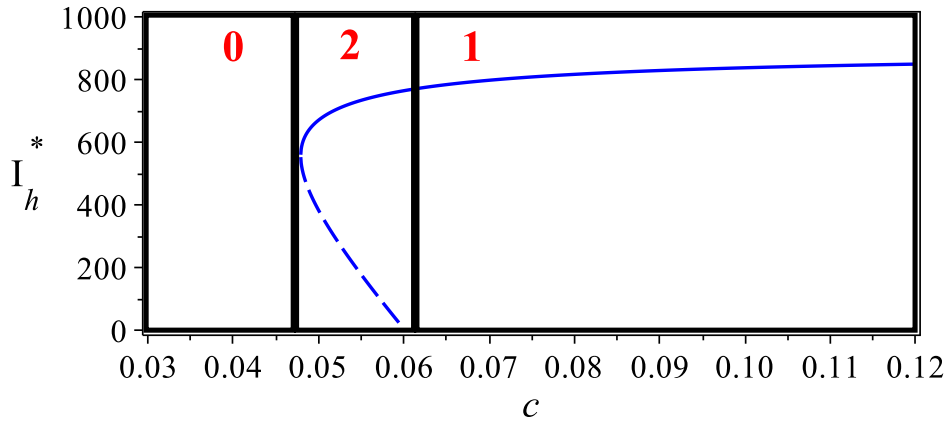

Figure 2.3: Effect of c on I_h^* with A negligible. $a_B > 0$ for δ_h/μ_h large and A negligible. Two endemic equilibria exist for $c^* \leq c < c^1$ inside region **2**.

As a consequence of Conjecture 2.3.4, if $c^* < c^1$, then there is a backward bifurcation at c^1 with large δ_h/μ_h and there are two endemic equilibria as well as a bistability for $c^* \leq c < c^1$ (region **2** of Figure 2.3). In Figure 2.4, the curve with $\delta_h = 0.0006$ illustrates that the backward bifurcation is pronounced with large δ_h/μ_h. In contrast, for δ_h/μ_h small, c^* does not exist, hence there is no region of bistability for c. As illustrated in Figure 2.2, the backward bifurcation disappears as $\delta_h \to 0$. This is the reason why Figure 2.4 gives a forward bifurcation with $\delta_h = 0$.

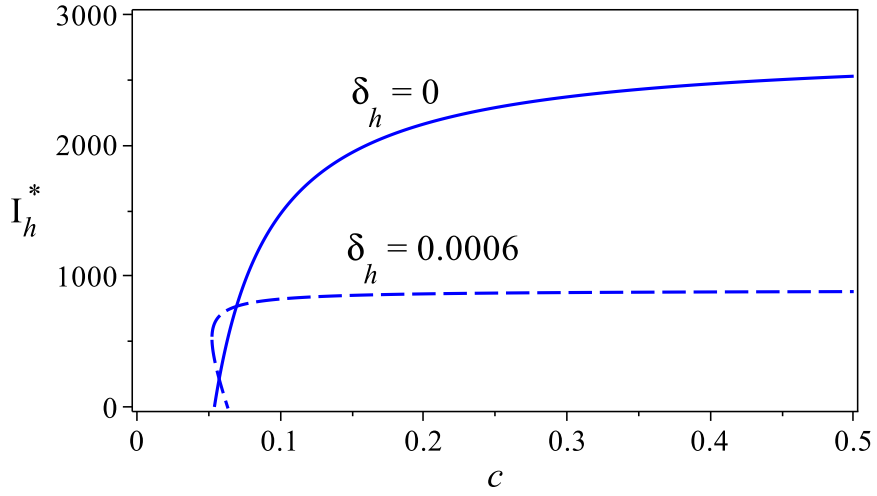

Figure 2.4: Effect of c on I_h^* with δ_h negligible. Setting $A = 500$ gives A/λ_h small. With A small, there is a backward bifurcation for δ_h/μ_h large ($\delta_h = 0.0006$) and a forward bifurcation for δ_h/μ_h negligible ($\delta_h = 0$).

By Theorem 2.3.2, the disease-free equilibrium is stable for $\mathcal{R}_c < 1$ and unstable for $\mathcal{R}_c > 1$. Figure 2.5 illustrates the result that the disease-free equilibrium is stable for $\mathcal{R}_c < 1$, that is, for $c < c^1$. Conjecture 2.3.5 implies

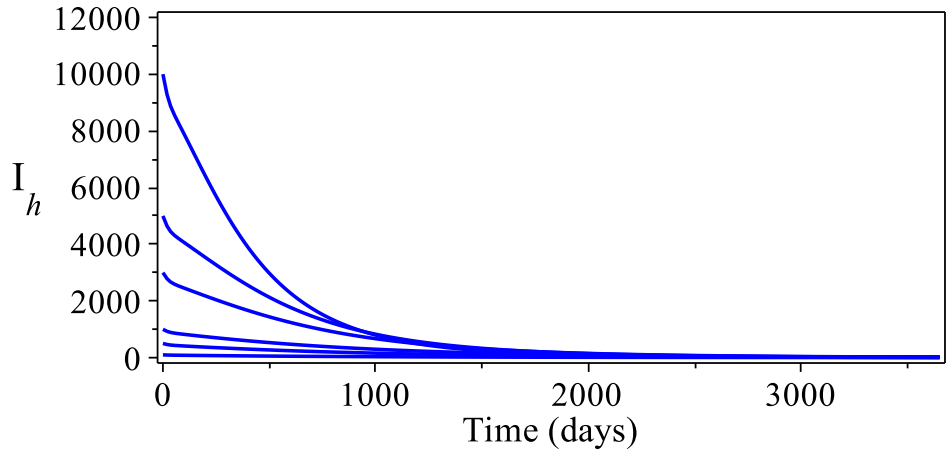

Figure 2.5: Stability of the disease-free equilibrium with $A = 10000$ and $c = 0.1$. $\mathcal{R}_c < 1$, and the disease dies out regardless of the initial values.

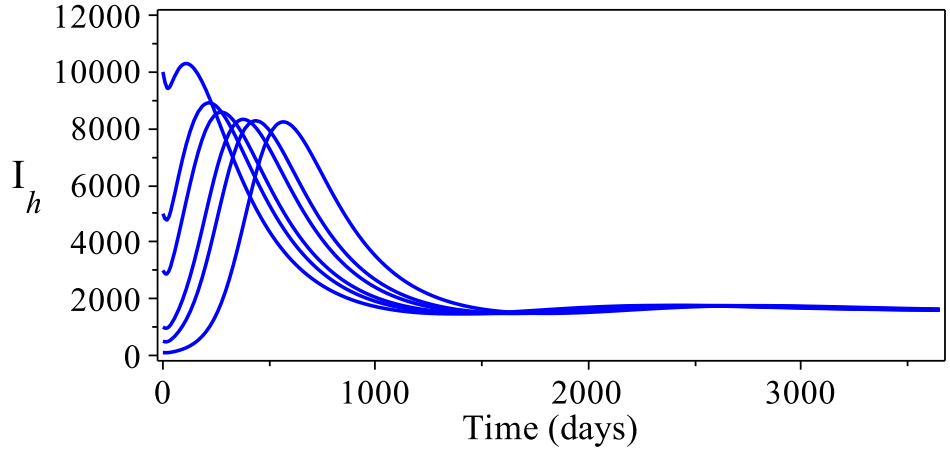

Figure 2.6: Stability of the endemic equilibrium with $A = 10000$ and $c = 0.8$. $\mathcal{R}_c > 1$, and the disease prevails regardless of the initial values.

that the endemic equilibrium is stable for $c > c^1$. Figure 2.6 illustrates this with parameter values satisfying $\mathcal{R}_c > 1$. Although this may need to be

explored further, Figure 2.5 and Figure 2.6 illustrate the properties of the equilibria in favour of Conjecture 2.3.5. Thus, it can be concluded that the disease-free equilibrium is globally stable in region **0** of Figure 2.1, whereas the endemic equilibrium is globally stable in region **1** of Figure 2.1.

2.6 Concluding remarks

The artificial-feeder model allows a critical analysis of disease-control options. The objective was to examine the effect of artificial feeders and mosquito bias on disease transmission and spread. c large and δ_h/μ_h large give a backward bifurcation, whereas A/λ_h large facilitates a forward bifurcation. c small and A/λ_h large give $\mathcal{R}_c$ small. Thus, the direction of bifurcation can be switched from backward to forward by increasing A/λ_h or by decreasing c and δ_h/μ_h, and disease spread can be stopped by increasing A/λ_h or by decreasing c.

Disease spread can be stopped by increasing A. Increasing A implies increasing artificial feeders relative to humans and increasing the attractiveness of the feeders relative to uninfected humans. Potter [83] and Tauxe et al. [101] suggest that mosquito attraction can be manipulated using attractants. In the artificial-feeder model, the attractiveness of the feeders can be boosted using attractants. Thus, disease spread can be stopped by increasing the number and attractiveness of artificial feeders relative to humans.

Disease spread can be stopped by decreasing c. From the bifurcation analysis, disease eradication is not guaranteed even when mosquito bias c

is very small. Decreasing c implies decreasing the relative attractiveness of infectious humans. There are subcritical endemic equilibria at a relatively low attractiveness of infectious humans. Thus, the disease persists in the populations for some values of c for which the control reproduction number is less than unity. Our analysis shows that the endemic equilibria vanish by increasing A/λ_h and by further decreasing c to near zero, which guarantees disease eradication and global stability of the disease-free equilibrium.

There are no analytic global-stability results for the endemic equilibria. Global stability of the endemic equilibrium has not been analyzed previously for SEIRS models with mosquito bias. For SIS models, Buonomo and Vargas-De-Leon [14] use the geometric method due to Li and Muldowney [57] and show that the endemic equilibrium is globally stable if $\mathcal{R}_0 > 1$. Analysis is available for single-population models (Korobeinikov [51]) and vector-borne models without mosquito bias ([54], [113] and [114]) where it is concluded that the endemic equilibrium is globally stable if $\mathcal{R}_0 > 1$. The models are SEIR, SEI, SI or SIR. For [51, 54, 113], Lyapunov functions are used. System (2.2) is SEIRS with mosquito bias. The analysis of the endemic equilibria will be improved in future work to better understand the dynamics of the disease with the proposed controls.

Chapter 3

A mosquito-bias model with protective odorants for hosts in the infectious stage

3.1 Introduction

Mosquito bias increases the speed of disease spread among humans. The bias is expressed by the increased preference of infectious humans relative to uninfected individuals (as discussed in Chapter 2). Mosquito bias can be influenced by increasing or reducing mosquito attraction to hosts. From Chapter 2, reducing attractiveness of infected humans to mosquitoes reduces the disease control reproduction number. Thus, reducing the attractiveness of infected humans in the infectious stage can slow or stop disease spread.

The attractiveness of hosts to vectors can be masked using protective odorants or repellents to prevent infectious bites. In the artificial-feeder model, the protective odorant is applied immediately at the onset of the infectious period of infected humans. In this study we consider the case where protective odorants are acquired by recruitment at the rate which can be increased or decreased to improve the outcomes of disease control.

Repellents provide partial protection from bites, and the rate at which the repellent is acquired may influence the effect of the repellent on disease spread. We develop and analyze a mosquito-bias model to examine how the recruitment rate for infected humans to use odorants affects disease spread. The dependence of disease spread on the effectiveness of the odorant is also discussed. Mosquito bias is modelled following the approach of Chapter 2.

3.2 The mosquito-bias model

3.2.1 Model formulation

The human population is divided into compartments S_h, E_h, I_u, I_p and R_h, where S_h is the number of susceptible humans, E_h is the number of latently infected humans (noninfectious), I_u is the number of unprotected-infectious humans, I_p is the number of protected-infectious humans, and R_h is the number of recovered humans. Let $N_h(t)$ be the total human population at time t; thus $N_h(t) = S_h(t) + E_h(t) + I_u(t) + I_p(t) + R_h(t)$.

Humans are recruited to the susceptible class through birth at the rate

$\mu_h\lambda_h$ assumed to be balanced by deaths, where μ_h is the per capita natural death rate and λ_h is the constant human population in the absence of the disease. People may become infected through contacts with infectious mosquitoes. It is assumed that only infectious mosquitoes can transmit infection to susceptible humans through bites. Infected humans go through a latent period, during which they do not transmit infection, and they progress to the infectious stage at the rate γ_h. Infectious individuals are recruited at the rate ν_p (odorant-acquisition rate) to use protective odorants and recover at the rate α_h with temporary immunity to the disease or suffer disease-related death at the rate δ_h. Recovered humans lose their immunity and return to the susceptible class at the rate ρ_h.

Let N_m be the total vector-mosquito population with three compartments where S_m is the number of susceptible mosquitoes, E_m is the number of latently infected mosquitoes (not infectious), and I_m is the number of infectious mosquitoes. Thus, at time t, $N_m(t) = S_m(t) + E_m(t) + I_m(t)$.

Mosquitoes are assumed susceptible at birth. As with humans, mosquitoes are born at the rate $\mu_m\lambda_m$ balanced by deaths, where μ_m is the per capita death rate and λ_m is the constant mosquito population in the absence of the disease. It is probable that the parasite enters the mosquito through biting an infectious human and we assume that only infectious humans can transmit the infection to susceptible mosquitoes. Mosquitoes progress to the infectious stage at the rate γ_m and remain infectious for life. Mosquitoes leave the population through natural death.

Let β be the average biting rate of a mosquito. Following Chapter 2, let c_i, $i = 1, 2, 3$ be the probability of a mosquito biting a noninfectious host, a protected infectious host or an unprotected infectious host, respectively, given an encounter with such a host. It is assumed that every mosquito makes (on average) β bites per day, regardless of the sequence in which they encounter hosts. In this case, the distribution of bites depends on the probabilities c_i.

The daily number of potentially infectious bites from mosquitoes is βI_m. Let p_1 be the probability a bite by an infectious mosquito on a susceptible host leads to infection of the host. Thus

$$\frac{c_1 p_1 \beta S_h I_m}{c_1(S_h + E_h + R_h) + c_2 I_p + c_3 I_u}$$

is the incidence of new human infections. Similarly, let p_2 be the probability a bite by a susceptible mosquito on an infectious host leads to infection of the mosquito. Thus the incidence of new mosquito infections is

$$\frac{p_2 \beta S_m (c_2 I_p + c_3 I_u)}{c_1(S_h + E_h + R_h) + c_2 I_p + c_3 I_u}.$$

$c_3 > c_2$ if the odorant repels mosquitoes and $c_3 = c_2$ in the absence of the protective odorant. Unlike in Chapter 2 where the protective odorant is acquired by all infected humans at the onset of the infectious period, we focus on the case where some infected humans do not acquire the repellent and hence attract mosquitoes more than repellent-users do.

With the above description, the mosquito-bias model consists of the

following system of differential equations.

$$
\begin{aligned}
S_h' &= \mu_h(\lambda_h - S_h) - \frac{\beta_h S_h I_m}{S_h + E_h + cI_p + \varepsilon I_u + R_h} + \rho_h R_h, \\
S_m' &= \mu_m(\lambda_m - S_m) - \frac{\beta_m S_m (cI_p + \varepsilon I_u)}{S_h + E_h + cI_p + \varepsilon I_u + R_h}, \\
E_h' &= \frac{\beta_h S_h I_m}{S_h + E_h + cI_p + \varepsilon I_u + R_h} - (\gamma_h + \mu_h) E_h, \\
E_m' &= \frac{\beta_m S_m (cI_p + \varepsilon I_u)}{S_h + E_h + cI_p + \varepsilon I_u + R_h} - (\gamma_m + \mu_m) E_m, \\
I_u' &= \gamma_h E_h - (\alpha_h + \mu_h + \delta_h) I_u - \nu_p I_u, \\
I_p' &= \nu_p I_u - (\alpha_h + \mu_h + \delta_h) I_p, \\
I_m' &= \gamma_m E_m - \mu_m I_m, \\
R_h' &= \alpha_h (I_p + I_u) - (\rho_h + \mu_h) R_h,
\end{aligned}
$$

where

$$
\beta_h = p_1 \beta; \quad \beta_m = p_2 \beta; \quad c = \frac{c_2}{c_1}; \quad \text{and} \quad \varepsilon = \frac{c_3}{c_1} \tag{3.1}
$$

to simplify the incidence terms. ε represents the natural mosquito-preference of infectious humans over noninfectious individuals, thus $\varepsilon > 1$. c is the controlled relative attractiveness of infectious humans who use the repellent. In the absence of the protective repellent, $c = \varepsilon$

The above system can easily be written in a rescaled form. We scale the number of individuals in each class by the constant species population. This enables us to study proportions of the populations with respect to the

constant population size in the absence of the disease. The proportions are

$$\bar{S}_h = \frac{S_h}{\lambda_h}, \quad \bar{E}_h = \frac{E_h}{\lambda_h}, \quad \bar{I}_u = \frac{I_u}{\lambda_h}, \quad \bar{I}_p = \frac{I_p}{\lambda_h}, \quad \text{and} \quad \bar{R}_h = \frac{R_h}{\lambda_h},$$

for the host population; and

$$\bar{S}_m = \frac{S_m}{\lambda_m}, \quad \bar{E}_m = \frac{E_m}{\lambda_m}, \quad \text{and} \quad \bar{I}_m = \frac{I_h}{\lambda_m},$$

for the vector population. We drop the bars to simplify notation. Thus, the rescaled system consists of the following equations.

$$\begin{aligned}
S_h' &= \mu_h(1 - S_h) - \frac{m_0\beta_h S_h I_m}{S_h + E_h + cI_p + \varepsilon I_u + R_h} + \rho_h R_h, \\
S_m' &= \mu_m(1 - S_m) - \frac{\beta_m S_m(cI_p + \varepsilon I_u)}{S_h + E_h + cI_p + \varepsilon I_u + R_h}, \\
E_h' &= \frac{m_0\beta_h S_h I_m}{S_h + E_h + cI_p + \varepsilon I_u + R_h} - (\gamma_h + \mu_h)E_h, \\
E_m' &= \frac{\beta_m S_m(cI_p + \varepsilon I_u)}{S_h + E_h + cI_p + \varepsilon I_u + R_h} - (\gamma_m + \mu_m)E_m, \\
I_u' &= \gamma_h E_h - (\alpha_h + \mu_h + \delta_h)I_u - \nu_p I_u, \\
I_p' &= \nu_p I_u - (\alpha_h + \mu_h + \delta_h)I_p, \\
I_m' &= \gamma_m E_m - \mu_m I_m, \\
R_h' &= \alpha_h(I_p + I_u) - (\rho_h + \mu_h)R_h,
\end{aligned} \tag{3.2}$$

where $m_0 = \dfrac{\lambda_m}{\lambda_h}$, which is the ratio of the total vector population to the total host population in the absence of the disease. Thus, m_0 is the approximate

number of female mosquitoes per person in the absence of the disease.

The malaria model (3.2) is based on the assumptions A1-A5 of the artificial-feeder model discussed in Chapter 2.

Using vector notation, let $X = (S_h, S_m, E_h, E_m, I_u, I_p, I_m, R_h)$ denote a solution of System (3.2) and $X_0 = (S_{h0}, S_{m0}, E_{h0}, E_{m0}, I_{u0}, I_{p0}, I_{m0}, R_{h0})$ be the nonnegative initial data, where $X_0 = X(0)$.

The parameters for the mosquito-bias model are outlined in Table 3.1. All parameters are positive. c and ν_p are the control parameters.

Table 3.1: Parameters for the mosquito-bias model

Parameter	**Description**
μ_h	Natural death rate of humans.
μ_m	Natural death rate of female mosquitoes.
β_h	Mosquito biting rate leading to infection of the human host.
β_m	Mosquito biting rate leading to infection of the mosquito.
γ_h	Rate at which a human becomes infectious after infection.
γ_m	Rate at which a mosquito becomes infectious after infection.
α_h	Rate at which a human recovers from infection.
ρ_h	Rate at which a recovered human loses partial immunity.
δ_h	Malaria-induced death rate of infectious humans.
m_0	Ratio of total mosquito population to human population.
ε	Natural relative attractiveness of infectious humans.
c	Controlled relative attractiveness of infectious humans.
ν_p	Recruitment rate for infectious humans to use odorants.

3.2.2 Well-posedness

Following similar approaches of Chapter 2, the right hand side of (3.2) is differentiable on $\mathbb{R}^8$, which implies that a unique solution X exists for every initial condition. The following theorems guarantee that System (3.2) is mathematically and epidemiologically well-posed with a solution which is always positive and bounded given nonnegative initial data.

Theorem 3.2.1. *For Model* (3.2)*, the disease-free plane is invariant. All solutions starting with* $E_h = E_m = I_u = I_p = I_m = 0$ *remain in the disease-free plane for all time* $t > 0$ *with* $S_h > 0$*,* $S_m > 0$*, and* $R_h \geq 0$*.*

Theorem 3.2.2 (Positivity of solutions)**.** *Model* (3.2) *is mathematically and epidemiologically well-posed with a unique solution. Given nonnegative initial data* X_0*, the solution* X *is positive for all time* $t \geq 0$*.*

Theorem 3.2.3 (Boundedness of solutions)**.** *Model* (3.2) *is mathematically and epidemiologically well-posed. The solution* X *is bounded given nonnegative initial data* X_0*.*

Corollary 3.2.4 (Domain of attraction)**.** *For Model* (3.2) *with nonnegative initial data* X_0*, there exists a domain attracting all solutions* $X \in \mathbb{R}^8_+$*.*

Following a similar approach of Chapter 2, it can be shown that there exists a domain of attraction such that for any trajectory that starts in the domain, the solution X is always contained in the interior and boundary of the domain. Let the domain of attraction be denoted by D. Since the

components of X are positive and bounded, we write

$$D = \left\{ \begin{array}{l|c} X \quad \in \mathbb{R}^8_+ & \begin{array}{c} S_h > 0, S_m > 0, E_h \geq 0, E_m \geq 0, \\ I_u \geq 0, I_p \geq 0, I_m \geq 0, R_h \geq 0 \\ S_h + E_h + I_u + I_p + R_h \leq 1 \\ S_m + E_m + I_m = 1 \end{array} \end{array} \right\}.$$

3.3 Equilibria and their stability

3.3.1 Disease-free equilibrium

As seen in Chapter 2, a constant solution to a system of equations is referred to as an equilibrium solution. The Equilibrium solutions of System (3.2) satisfy the following equations.

$$\mu_h(1 - S_h) - \frac{m_0\beta_h S_h I_m}{S_h + E_h + \varepsilon I_u + cI_p + R_h} + \rho_h R_h = 0, \tag{3.3a}$$

$$\mu_m(1 - S_m) - \frac{\beta_m S_m(\varepsilon I_u + cI_p)}{S_h + E_h + \varepsilon I_u + cI_p + R_h} = 0, \tag{3.3b}$$

$$\frac{m_0\beta_h S_h I_m}{S_h + E_h + \varepsilon I_u + cI_p + R_h} - (\gamma_h + \mu_h)E_h = 0, \tag{3.3c}$$

$$\frac{\beta_m S_m(\varepsilon I_u + cI_p)}{S_h + E_h + \varepsilon I_u + cI_p + R_h} - (\gamma_m + \mu_m)E_m = 0, \tag{3.3d}$$

$$\gamma_h E_h - (\alpha_h + \mu_h + \delta_h)I_u - \nu_p I_u = 0, \tag{3.3e}$$

$$\nu_p I_u - (\alpha_h + \mu_h + \delta_h)I_p = 0, \tag{3.3f}$$

$$\gamma_m E_m - \mu_m I_m = 0, \tag{3.3g}$$

$$\alpha_h(I_u + I_p) - (\rho_h + \mu_h)R_h = 0. \tag{3.3h}$$

For a disease-free equilibrium, there is no disease and hence all components corresponding to infected individuals are empty.

Theorem 3.3.1 (Boundary equilibria)**.** *System* (3.2) *has a unique disease-free equilibrium and no other equilibria on the boundary of* D*.*

This theorem is similar to Theorem 2.3.1. The domain D is positively invariant and the equilibrium in the boundary is the only equilibrium of (3.2) without the disease. By Theorem 3.2.2 and Equations (3.3), it is straight forward that if any of $E_h, E_m, I_u, I_p, I_m, R_h$, is positive, then all components of X are positive and the equilibrium is strictly positive. Let X^0 denote the disease-free equilibrium solution. It follows that

$$X^0 = (1, 1, 0, 0, 0, 0, 0, 0).$$

Local stability analysis of X^0 follows similar analyses in Chapter 2. Let $\mathcal{R}_c$ denote the control reproduction number for System (3.2). Further, let

$$\omega_h = \alpha_h + \mu_h + \delta_h. \tag{3.4}$$

ω_h is the rate at which infected humans leave the infectious stage.

Definition 3.3.1. *For the malaria model* (3.2)*, the control reproduction number* $\mathcal{R}_c$ *is defined as*

$$\mathcal{R}_c = \frac{m_0\beta_h\beta_m\gamma_h\gamma_m(\omega_h\varepsilon + \nu_p c)}{(\gamma_h + \mu_h)(\omega_h + \nu_p)(\gamma_m + \mu_m)\omega_h\mu_m}. \tag{3.5}$$

$\mathcal{R}_c$ is the expected number of new infected hosts as a result of introducing one infected host in a completely susceptible population in the presence of disease control methods.

Theorem 3.3.2. *For System* (3.2)*, the disease-free equilibrium is locally asymptotically stable if* $\mathcal{R}_c < 1$ *and unstable if* $\mathcal{R}_c > 1$.

Proof. Let $J(X^0)$ denote the Jacobian matrix at X^0. The Jacobian matrix has the block structure

$$J(X^0) = \begin{bmatrix} J_{11} & J_{12} & J_{13} \\ 0 & F - V & 0 \\ 0 & J_{32} & -(\rho_h + \mu_h) \end{bmatrix},$$

with

$$J_{11} = \begin{bmatrix} -\mu_h & 0 \\ 0 & -\mu_m \end{bmatrix}, \quad J_{12} = \begin{bmatrix} 0 & 0 & 0 & 0 & -m_0\beta_h \\ 0 & 0 & -\varepsilon\beta_m & -c\beta_m & 0 \end{bmatrix},$$

$$J_{13} = \begin{bmatrix} \rho_h \\ 0 \end{bmatrix}, \quad J_{32} = \begin{bmatrix} 0 \\ 0 \\ \alpha_h \\ \alpha_h \\ 0 \end{bmatrix}^T, \quad F = \begin{bmatrix} 0 & 0 & 0 & 0 & m_0\beta_h \\ 0 & 0 & \varepsilon\beta_m & c\beta_m & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

and

$$V = \begin{bmatrix} \gamma_h + \mu_h & 0 & 0 & 0 & 0 \\ 0 & \gamma_m + \mu_m & 0 & 0 & 0 \\ -\gamma_h & 0 & \omega_h + \nu_p & 0 & 0 \\ 0 & 0 & -\nu_p & \omega_h & 0 \\ 0 & -\gamma_m & 0 & 0 & \mu_m \end{bmatrix},$$

where $\omega_h = \alpha_h + \mu_h + \delta_h$ from Equation (3.4). X^0 is locally asymptotically stable if all eigenvalues of $J(X^0)$ have negative real parts (Theorem 1.4.4). From the structure of $J(X^0)$, all eigenvalues of $[F-V]$ must have negative real parts. By the decomposition method of van den Driessche and Watmough [106], all eigenvalues of $[F-V]$ have negative real parts iff $\rho(FV^{-1}) < 1$. We set $\mathcal{R}_c = (\rho(FV^{-1}))^2$, which yields Equation (3.5). The conclusion of the proof follows from Theorem 1.4.5. □

$\mathcal{R}_c$ is referred to as the control reproduction number for System (3.2). The corresponding basic reproduction number $\mathcal{R}_0$ accounts for disease spread without protection, that is for $\nu_p = 0$ and $c = \varepsilon$. It follows that

$$\mathcal{R}_0 = \frac{\varepsilon m_0 \beta_h \beta_m \gamma_h \gamma_m}{(\gamma_h + \mu_h)(\gamma_m + \mu_m)\omega_h \mu_m}. \tag{3.6}$$

Equations (3.5) and (3.6) give

$$\mathcal{R}_c = \mathcal{R}_0 \left(\frac{\omega_h + \frac{c}{\varepsilon}\nu_p}{\omega_h + \nu_p} \right). \tag{3.7}$$

For the malaria model (3.2), $\mathcal{R}_0$ is the expected number of new infected hosts as a result of introducing one infected host in a completely susceptible population in the absence of the protection.

From Equation (3.7), $\mathcal{R}_c$ increases linearly with c, whereas the effect of ν_p depends on the ratio c/ε. Increasing ν_p decreases $\mathcal{R}_c$ if $c < \varepsilon$. If $\mathcal{R}_c < 1$, then each infected human produces, on average, less than one new infected human over the course of their infectious period in the presence of the protection, and the infection cannot grow. Conversely, if $\mathcal{R}_c > 1$, then each infected human produces, on average, more than one new infected human in the presence of the protection and the disease can invade the population.

3.3.2 Endemic equilibria

For System (3.2), any equilibrium solution in the interior of D is referred to as an endemic equilibrium. Let $X^* = (S_h^*, S_m^*, E_h^*, E_m^*, I_u^*, I_p^*, I_m^*, R_h^*)$ denote the endemic equilibrium solution of System (3.2) satisfying Equations (3.3). Solving Equations (3.3) in terms of I_u^* and I_m^* gives

$$\begin{cases} S_h^* = 1 - \eta_p I_u^*, & E_h^* = \dfrac{(\omega_h + \nu_p) I_u^*}{\gamma_h}, & I_p^* = \dfrac{\nu_p I_u^*}{\omega_h}, \\ R_h^* = \dfrac{\alpha_h(\omega_h + \nu_p) I_u^*}{\omega_h(\rho_h + \mu_h)}, & S_m^* = 1 - \dfrac{(\gamma_m + \mu_m) I_m^*}{\gamma_m}, & E_m^* = \dfrac{\mu_m I_m^*}{\gamma_m}, \end{cases} \tag{3.8}$$

where

$$\eta_p = \frac{(\omega_h + \nu_p)[\gamma_h(\rho_h + \mu_h)(\mu_h + \delta_h) + \gamma_h \alpha_h \mu_h + (\rho_h + \mu_h)\omega_h \mu_h]}{(\rho_h + \mu_h)\gamma_h \omega_h \mu_h}. \tag{3.9}$$

We continue to solve for I_u^* and I_m^* and obtain the simultaneous equations

$$\begin{aligned} g_1 &= \frac{I_m^*}{I_u^*} = \frac{(\gamma_h+\mu_h)(\omega_h+\nu_p)(\omega_h-\nu_p(\xi_2^*-c)I_u^*)}{m_0\beta_h\gamma_h\omega_h(1-\eta_p I_u^*)}, \\ g_2 &= \frac{I_m^*}{I_u^*} = \frac{\beta_m\gamma_m(\omega_h\varepsilon+\nu_p c)}{(\gamma_m+\mu_m)(\mu_m\omega_h-\nu_p(\mu_m+\beta_m)(\xi_1^*-c)I_u^*)}, \end{aligned}$$

where

$$\xi_1^* = \frac{\mu_m}{\mu_m+\beta_m}\left(1+\frac{\delta_h}{\mu_h}\right)\left(1+\frac{\omega_h}{\nu_p}\right)-\frac{\omega_h}{\nu_p}\varepsilon,$$

and

$$\xi_2^* = \left(1+\frac{\delta_h}{\mu_h}\right)\left(1+\frac{\omega_h}{\nu_p}\right)-\frac{\omega_h}{\nu_p}\varepsilon.$$

The functions g_1 and g_2 are obtained following the approach of Chapter 2. Equating g_1 and g_2 leads to the quadratic equation

$$q_2 I_u^{*2} + q_1 I_u^* + \mu_m\omega_h^2(1-\mathcal{R}_c) = 0, \tag{3.10}$$

where

$$\begin{aligned} q_2 &= \nu_p^2(\mu_m+\beta_m)(\xi_1^*-c)(\xi_2^*-c), \\ q_1 &= \omega_h^2\mu_m\eta_p\mathcal{R}_c - \omega_h\nu_p[(\mu_m+\beta_m)(\xi_1^*-c)+\mu_m(\xi_2^*-c)]. \end{aligned}$$

The positive solutions of (3.10) correspond to the endemic equilibria of (3.2) if they are in the interior of D. By Equations (3.8), the solutions satisfy $0 \le I_u^* < 1/\eta_p$. The number of positive solutions depends on the signs of q_2, q_1 and $1-\mathcal{R}_c$. ξ_1^* and ξ_2^* are two critical values of c giving $q_2 = 0$ and exactly

one solution. To examine the existence of endemic equilibria for c from 0 to ∞, we use a similar approach of Chapter 2. Notice that g_1 and g_2 give rectangular hyperbolas whose properties change as c passes ξ_1^* and ξ_2^*. The hyperbolas intersect only once in the positive quadrant with $0 \leq I_u^* < 1/\eta_p$ if $c \geq \xi_1^*$. Since $\xi_2^* > \xi_1^*$, a deduction can be made leading to a conjecture on the existence of two endemic equilibria. In fact, if $0 \leq c < \xi_1^*$, then System (3.2) has two or no endemic equilibria or exactly one endemic equilibrium. If $\xi_1^* \leq c < \infty$, then the system has no endemic equilibria or exactly one endemic equilibrium. Let c^* be the positive solution of the equation

$$q_1^2 - 4q_2\mu_m\omega_h^2(1 - \mathcal{R}_c) = 0.$$

Given $-q_1/q_2 > 0$, Equation (3.10) has two positive real roots for c satisfying

$$q_1^2 - 4q_2\mu_m\omega_h^2(1 - \mathcal{R}_c) > 0.$$

Since q_1, q_2 and $\mathcal{R}_c$ increase with c, the inequality holds for $c > c^*$ if $\mathcal{R}_c < 1$, and if $\mathcal{R}_c = 1$, then Equation (3.10) has exactly one root and the inequality holds for a relatively higher value of c. It is now clear that for $\mathcal{R}_c < 1$, there are two positive roots for $c > c^*$ or one root for $c >> c^*$.

Definition 3.3.2. *Let c^1 be a value of c satisfying $\mathcal{R}_c = 1$. For System* (3.2)*,*

$$c^1 = \frac{\varepsilon}{\mathcal{R}_0}\left(1 - (\mathcal{R}_0 - 1)\frac{\omega_h}{\nu_p}\right). \tag{3.11}$$

Since $\mathcal{R}_c < 1 \Leftrightarrow c < c^1$ and $\mathcal{R}_c > 1 \Leftrightarrow c > c^1$, we conjecture using c^1.

Conjecture 3.3.3. *Let c^1 be a value of c satisfying $\mathcal{R}_c = 1$. For System (3.2), there exists a subcritical value $c^* \leq c^1$ such that,*

(i) if $0 \leq c < c^*$, then the system has no endemic equilibria;

(ii) if $c^* < c < c^1$, then the system has two endemic equilibria; and

(iii) if $c^1 \leq c < \infty$, then the system has exactly one endemic equilibrium.

In the special case if $c^* = c^1$, then there are no endemic equilibria for $c < c^1$ and there is exactly one endemic equilibrium for $c \geq c^1$.

The disease-free equilibrium is unstable if $\mathcal{R}_c > 1$. Conjecture 3.3.3 implies that the malaria model (3.2) has exactly one endemic equilibrium and an unstable disease-free equilibrium if $\mathcal{R}_c > 1$. There are no analytic global-stability results for the endemic equilibria of System (3.2). The control parameters c and ν_p and ratio c/ε are still under investigation.

3.4 Results and discussion

Given below are the results of the model together with supporting figures. All numerical simulations are done using parameter values in Table 3.2. A discussion of the values and range can be found in Section 2.4.

Equation (3.7) shows that $\mathcal{R}_c$ increases linearly with c. Since protection is a repellent, improved protection is modelled by decreasing c. Reducing the

Table 3.2: Parameter values used for simulations

Parameter	**Value**	**Range**	**Source**
μ_h	0.00004 per day	$(0, 0.001)$	§2.4
μ_m	0.065 per day	$(0.001, 0.1)$	[20]
β_h	0.02 per day	$(0.001, 0.2)$	[20]
β_m	0.192 per day	$(0.005, 0.4)$	[20]
γ_h	0.10 per day	$(0.06, 0.2)$	[68]
γ_m	0.09 per day	$(0.02, 0.4)$	[20]
α_h	0.0035 per day	$(0.001, 0.02)$	[68]
ρ_h	0.0005 per day	$(0, 0.01)$	[20]
δ_h	0.0006 per day	$(0, 0.001)$	§2.4
m_0	2.0 mosquitoes per person	$(0, 10)$	§2.4
ε	1.5	$(1.0, 2.0)$	
c	$0 - \varepsilon$	$(0, \varepsilon)$	§2.4
ν_p	$0 - \infty$ per day	$(0, \infty)$	

relative attractiveness of infectious humans who use the repellent decreases the disease control reproduction number. The ratio c/ε is the preference for protected humans over unprotected individuals, given both are infectious. For a mosquito repellent $c/\varepsilon < 1$, hence $c < \varepsilon$. $\mathcal{R}_c$ increases linearly with c from $\mathcal{R}_0 \dfrac{\omega_h}{\omega_h + \nu_p}$ to $\mathcal{R}_0$ as c increases from 0 to ε.

Further, Equation (3.7) shows that $\mathcal{R}_c$ increases or reduces nonlinearly with ν_p, depending on c. $\mathcal{R}_c = \mathcal{R}_0$ when $\nu_p = 0$, and $\mathcal{R}_c = \mathcal{R}_0 \dfrac{c}{\varepsilon}$ as $\nu_p \to \infty$. Thus $\mathcal{R}_c$ is decreasing (hyperbolically) with ν_p if $c < \varepsilon$. If $c > \varepsilon$, then $\mathcal{R}_c$ increases with ν_p. The combined effect is that $\mathcal{R}_c \to 0$ if $\nu_p \to \infty$ and $c \to 0$. The dependence of $\mathcal{R}_c$ on the control parameters is illustrated in Figure 3.1. With $\varepsilon = 1.5$, $\mathcal{R}_c$ decreases with increasing ν_p for $c < 1.5$.

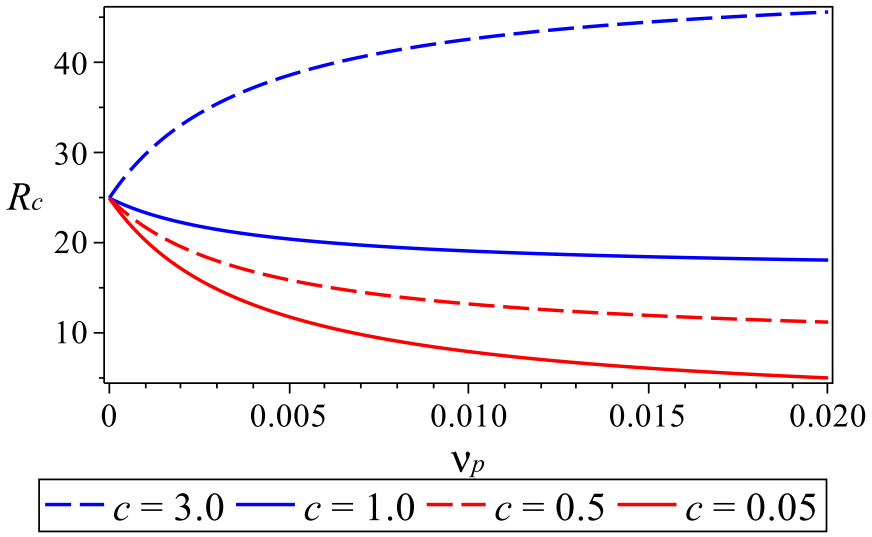

Figure 3.1: Effect of odorant acquisition on $\mathcal{R}_c$. Increasing ν_p reduces $\mathcal{R}_c$ if $c < \varepsilon$, whereas $\mathcal{R}_c$ increases with increasing ν_p if $c > \varepsilon$. Notice that $\varepsilon = 1.5$ and the curve $c = 3$ increases with increasing ν_p.

Form the quadratic equation (3.10), the malaria model (3.2) has exactly one endemic equilibrium for $\mathcal{R}_c > 1$ and two or no endemic equilibria if $\mathcal{R}_c < 1$. Conjecture 3.3.3 claims that there are no equilibria if $c < c^*$; there are two equilibria if $c^* \leq c < c^1$; and there is exactly one endemic equilibrium if $c \geq c^1$. The conjecture can be supported using a bifurcation diagram in the c-ν_p plane. Figure 3.2 is a bifurcation diagram obtained from two curves giving c^* and c^1. The figure illustrates three regions with the number of endemic equilibria for Model (3.2) in each region. The number of endemic equilibria depends on the controls c and ν_p.

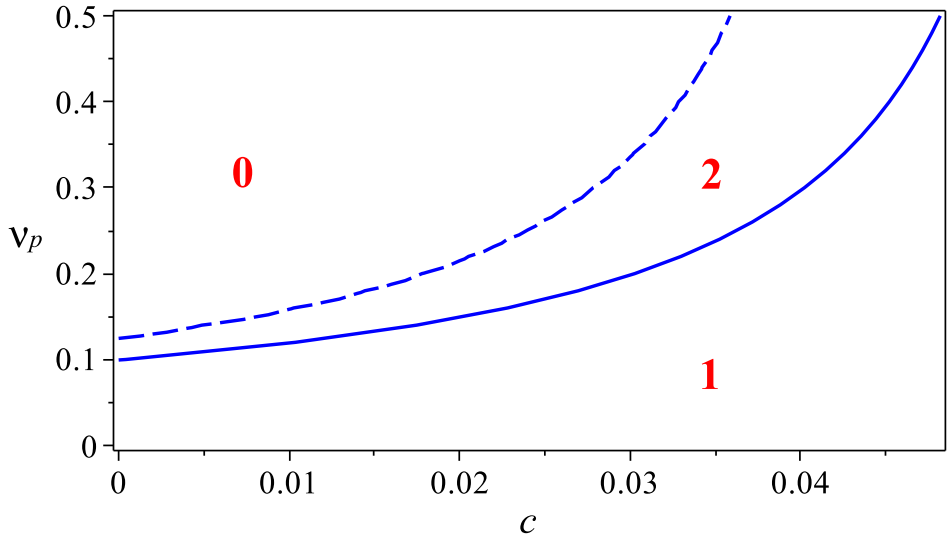

Figure 3.2: Bifurcations in the c-ν_p plane. The solid curve is $\mathcal{R}_c = 1$, which gives c^1, whereas the dashed curve is $q_1^2 = 4q_2\mu_m\omega_h^2(1-\mathcal{R}_c)$, which gives c^*. In addition to the disease-free equilibrium, the number of endemic equilibria is 0 or 2 for $\mathcal{R}_c < 1$ and 1 for $\mathcal{R}_c > 1$, depending on c and ν_p.

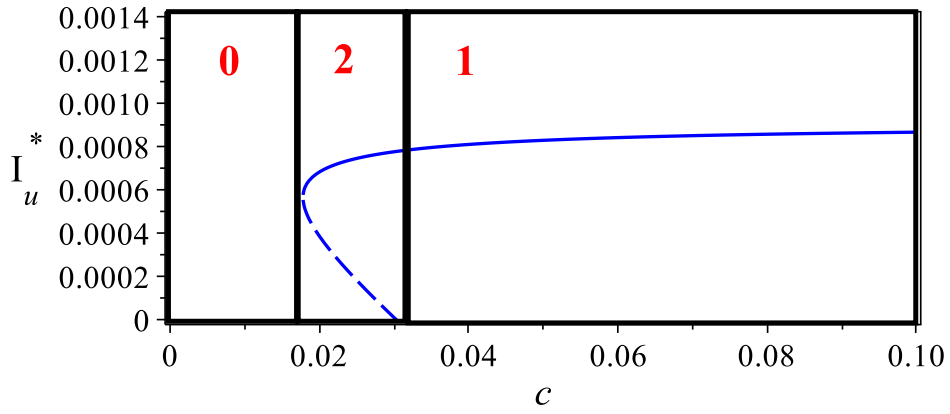

Figure 3.3: Effect of c on I_u^*. We use $\nu_p = 0.2$. As c increases, the number of endemic equilibria changes according to regions **0**, **2** and **1**.

Figure 3.3 illustrates that the endemic-equilibrium values change as c increases. The number of endemic equilibria changes according to the three regions **0**, **2** and **1** illustrated in Figure 3.2 and Figure 3.3.

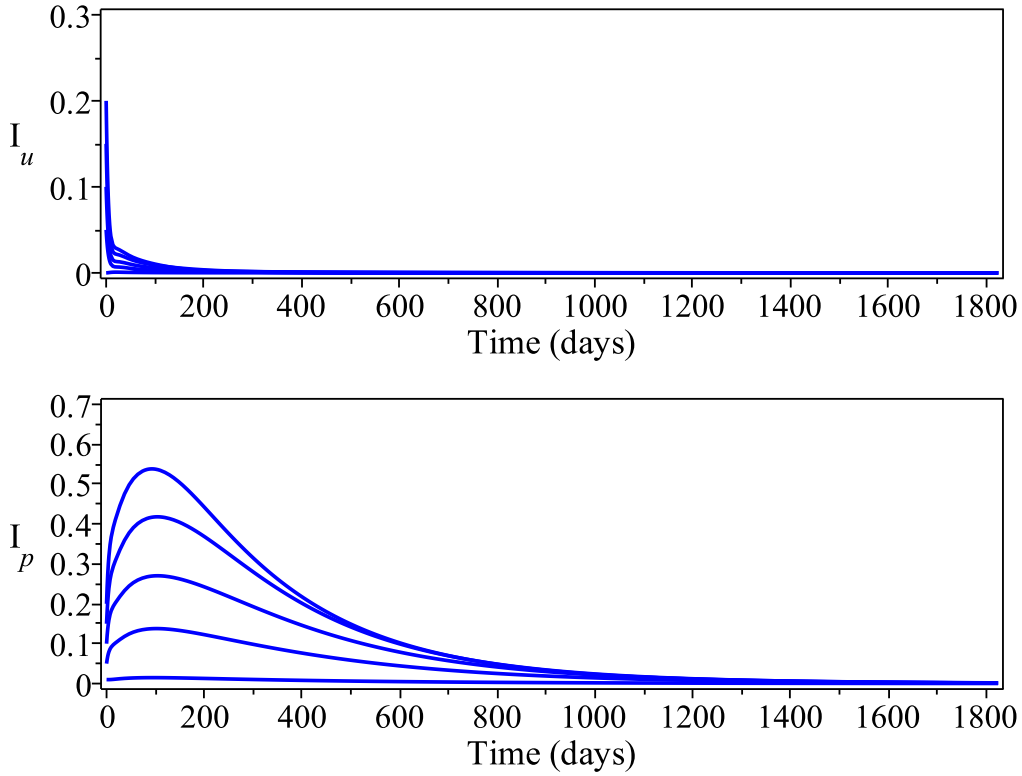

Figure 3.4: Stability of the disease-free equilibrium with parameter values in Table 3.2, where $c = 0.01$ and $\nu_p = 0.2$. This gives $\mathcal{R}_c < 1$, and the disease dies out regardless of large initial values.

Stability analysis of the equilibria shows that the disease-free equilibrium is locally stable if $\mathcal{R}_c < 1$ and unstable if $\mathcal{R}_c > 1$. A bistability exists for $c^* \leq c < c^1$, arising from the existence of a stable endemic equilibrium in the presence of a stable disease-free equilibrium. The stability properties of the

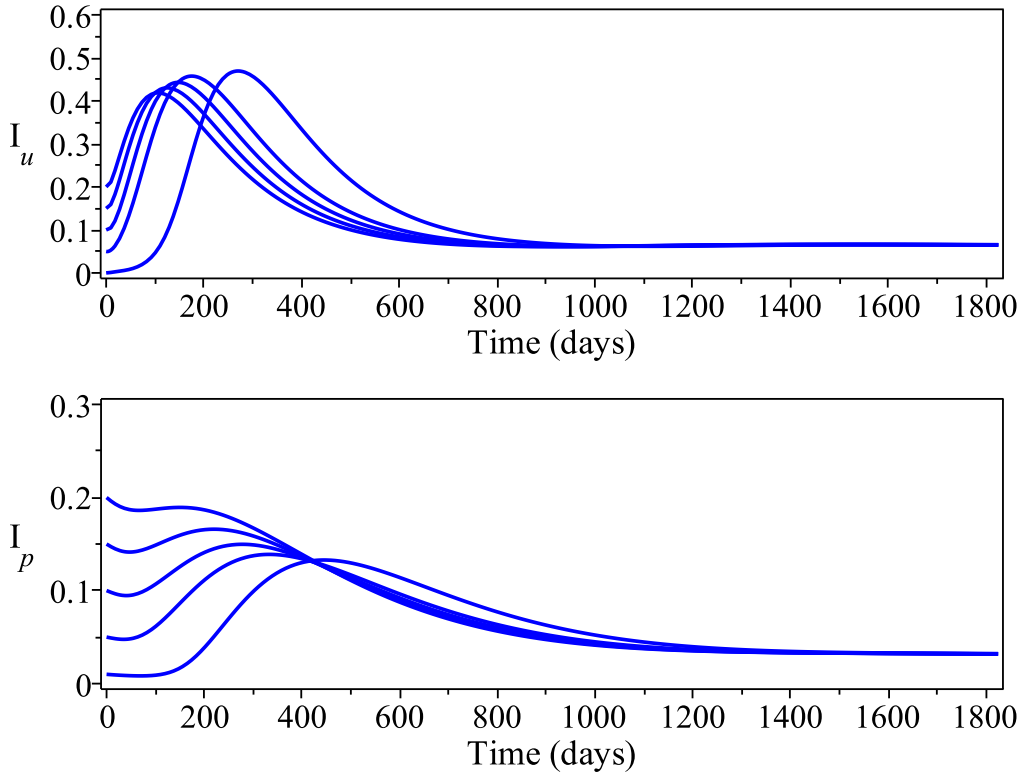

Figure 3.5: Stability of the endemic equilibrium with parameter values in Table 3.2, where $c = 0.01$ and $\nu_p = 0.002$. This gives $\mathcal{R}_c > 1$, and the disease persists regardless of small initial values.

equilibria are illustrated in the figures 3.4 and 3.5. From the figures, it can be guessed that the disease-free equilibrium is globally stable if $c < c^*$, that is, in region **0** of Figure 3.3. It remains to be shown if the endemic equilibrium is stable for $c \geq c^1$, that is, in region **1** of Figure 3.3. As mentioned in Chapter 2, global stability of endemic equilibria has not been studied previously for SEIRS models with dynamics involving mosquito bias.

3.5 Summary and conclusion

This study is focussed on the formulation and analysis of the mosquito-bias model to examine the effect of a repellent for infectious humans on disease transmission and spread. The effectiveness of a protective repellent depends on the relative attractiveness of infectious humans who use the repellent. The model is a modification of the artificial-feeder model of Chapter 2, with the infectious humans progressing to the class of repellent users to prevent bites, and without artificial feeders.

The disease control reproduction number was derived together with the corresponding basic reproduction number to examine the effect of the controls on disease spread. The control reproduction number is a function of the relative attractiveness of infectious humans who use repellents and the rate at which the repellent is obtained after the onset of the infectious stage. This number increases linearly with the relative attractiveness of repellent users, and changes nonlinearly with the repellent-acquisition rate.

For effective disease control based on odorant usage, the rate at which the odorant is acquired by infected humans should be inversely proportional to the relative attractiveness of odorant users. In other words, to reduce disease spread, the repellent-acquisition rate should be directly proportional to the effectiveness of the repellent. If there is increased attractiveness of odorant users relative to non-users, then increasing the odorant-acquisition rate for infected humans increases disease spread. Conversely, if the relative

attractiveness of odorant users is decreased, then increasing the odorant-acquisition rate for infected humans decreases disease spread. There are subcritical endemic equilibria for a relatively low attractiveness of infected repellent users, and no endemic equilibria if the relative attractiveness of infected repellent users is decreased beyond the subcritical value c^*, and if the odorant-acquisition rate is maximized in the infectious stage. Thus, disease elimination requires decreasing the relative attractiveness of infected repellent users and increasing the repellent-acquisition rate at the same time.

Chapter 4

A bed-net model for Malaria control with artificial feeders and protective odorants

4.1 Introduction

Humans are plagued by vector-borne diseases. Every year there are more than one billion cases and over one million deaths from vector-borne diseases such as malaria, dengue, yellow fever, Chagas disease, Japanese encephalitis, African trypanosomiasis, schistosomiasis, leishmaniasis and onchocerciasis, globally [112]. The diseases are preventable through informed protective measures, but the need for more effective disease control approaches has come as a result of global challenges such as insecticide and drug resistance,

genetic variations in pathogens, and demographic changes [37].

The prevention and control of vector-borne diseases requires reducing vector-human contacts. Many vectors are bloodsucking insects, which ingest disease-producing pathogens during a blood meal from an infected host and later inject it into a new host during a subsequent blood meal. Mosquitoes are the most common disease vectors. Mosquitoes transmit malaria, dengue, Rift Valley fever, yellow fever, Chikungunya, lymphatic filariasis, Japanese encephalitis, and West Nile fever through bites [94, 95, 77, 109, 112]. Female mosquitoes require a blood meal to initiate and develop eggs [23, 109].

From Chapter 1, mosquito-human contacts can be reduced by using bed nets, protective odorants or repellents and artificial feeders. The use of bed nets, also known as mosquito nets, has been dated to prehistoric times. Further, the artificial-feeder model (Chapter 2) suggests that disease control can be boosted with mosquito feeders. Simplified devices can be used to artificially blood-feed mosquitoes. Artificial feeders can be treated with attractants to increase their relative attractiveness to mosquitoes. Thus, we investigate disease-control dynamics with a combination of bed nets and artificial feeders.

Bed nets are usually treated with insecticides to divert or kill mosquitoes and prevent mosquito-human contacts. Lengeler [56] studied the effectiveness of insecticide-treated bed nets and concluded that bed-net usage reduced malaria cases by 50%. Agusto et al. [2] and Buonomo [15] model bed nets by a mosquito-human contact rate that is a linearly decreasing function of

bed-net usage. With bed nets, the contact rate is maximized if there are no users, or minimized if all hosts are users. The models [2, 15] ignore bites during the day, and so assume that bed nets are 100% effective. In reality, bed nets are not 100% effective. They are only used by a fraction of the population for a fraction of each day.

We develop a mathematical model of malaria control to study disease dynamics in a region where mosquito feeders, untreated bed nets and protective odorants are used. The human population is divided into two main classes. The first class is made up of bed-net users, and the second class is for bed-net non-users. Protective odorants can be used by bed-net users and this increases the relative attractiveness of bed-net non-users to mosquitoes. Conversely, if the odorants are used by bed-net non-users, then the relative attractiveness of bed-net users increases and mosquitoes are more biased towards bed-net users. Thus, mosquito bias is modelled by a dependence of the relative biting rates on bed-net usage. The resulting bed-net model is analyzed to examine the effectiveness of an integrated disease-control approach where mosquito nets, protective odorants and mosquito feeders are used. We derive a disease control reproduction number to measure transmission intensity in the presence of the proposed control methods. The model is used to examine the effect of increasing or decreasing the relative attractiveness of bed-net users (to mosquitoes) on disease spread. It is shown that the dynamics are completely determined by the disease control reproduction number.

4.2 The bed-net model

4.2.1 Model formulation

Let $N_1 + N_2$ be the total host population where N_1 is the number of bed-net users and N_2 is the number of bed-net non-users. Either protective odorants are used by all bed-net users or the odorants are used by all bed-net non-users. Further decompose the host population into S_i, E_i, I_i, and R_i, where S_i is the number of susceptible humans; E_i is the number of latently infected humans (noninfectious); I_i is the number of infectious humans; and R_i is the number of recovered humans, given that $i = 1$ denotes bed-net users and $i = 2$ denotes bed-net non-users. Thus, at time t,

$$N_1(t) = S_1(t) + E_1(t) + I_1(t) + R_1(t),$$
$$N_2(t) = S_2(t) + E_2(t) + I_2(t) + R_2(t).$$

People are recruited to the susceptible class through birth at a constant rate $\mu_h\lambda_h$ assumed to be balanced by death, where μ_h is the per capita natural death rate, and λ_h is the constant human population in the absence of the disease. A proportion ϕ accounts for the people recruited to the susceptible population of bed-net users, whereas $1 - \phi$ accounts for the people recruited to the susceptible class of bed-net non-users. Susceptible individuals may become infected through contacts with infectious mosquitoes. It is assumed that only infectious mosquitoes can transmit infection to susceptible humans

through bites. Infected individuals go through a latent period, during which they do not transmit infection. They progress from the latent stage to the infectious stage at the rate γ_h. Infectious individuals recover at the rate α_h with temporary immunity to the disease. Recovered humans lose their immunity and return to the susceptible class at the rate ρ_h. Although there is evidence of disease-related deaths, the death rate is negligible compared to all the other disease-specific parameters, and we assume this can be ignored to simplify analysis. Thus humans leave the population only by natural death.

Let N_m be the number of female mosquitoes of which S_m are susceptible, E_m are latently infected (non-infectious) and I_m are infectious. At time t,

$$N_m(t) = S_m(t) + E_m(t) + I_m(t).$$

Mosquitoes enter the susceptible class through birth at a constant rate $\mu_m\lambda_m$ assumed to be balanced by deaths, where μ_m is the per capita natural death rate, and λ_m is the constant mosquito population in the absence of the disease. It is probable that the parasite enters the mosquito through biting an infectious human. It is assumed that only infectious humans can transmit infection to susceptible mosquitoes through bites. Infected mosquitoes go through a latent period, during which they do not transmit infection. They progress from the latent stage to the infectious stage at the rate γ_m, and remain infectious for life. Mosquitoes leave the population only through natural death.

With the above details, our mathematical model consists of the following system of differential equations.

$$
\begin{aligned}
S_1' &= \mu_h\phi\lambda_h + \rho_h R_1 - \Gamma_1 S_1 - \mu_h S_1,\\
S_2' &= \mu_h(1-\phi)\lambda_h + \rho_h R_2 - \Gamma_2 S_2 - \mu_h S_2,\\
S_m' &= \mu_m\lambda_m - \Gamma_m S_m - \mu_m S_m,\\
E_1' &= \Gamma_1 S_1 - \gamma_h E_1 - \mu_h E_1,\\
E_2' &= \Gamma_2 S_2 - \gamma_h E_2 - \mu_h E_2,\\
E_m' &= \Gamma_m S_m - \gamma_m E_m - \mu_m E_m,\\
I_1' &= \gamma_h E_1 - \alpha_h I_1 - \mu_h I_1,\\
I_2' &= \gamma_h E_2 - \alpha_h I_2 - \mu_h I_2,\\
I_m' &= \gamma_m E_m - \mu_m I_m,\\
R_1' &= \alpha_h I_1 - \rho_h R_1 - \mu_h R_1,\\
R_2' &= \alpha_h I_2 - \rho_h R_2 - \mu_h R_2,
\end{aligned}
\tag{4.1}
$$

where $\Gamma_i S_i$, $i = 1, 2, m$, are the incidence terms and Γ_i are functions of state variables, to be discussed later.

From Chapter 2, Chapter 3 and previous studies (Buonomo and Vargas-De-Leon [14], Chamchod and Britton [19]), mosquito bias is modelled by the attractiveness of infectious humans to mosquitoes relative to that of uninfected individuals. A vector (female mosquito) approaches the vicinity of a human host, but this does not always lead to biting.

Let N_a be the number of artificial feeders. Let β be the average biting rate of a female mosquito. Let $c_i, i = 1, 2, 3$ be the probability of a mosquito biting a bed-net user, a bed-net non-user or an artificial feeder, respectively, given an encounter with such a host. Thus, the distribution of bites depends on the probabilities c_i ignoring the natural mosquito bias towards infectious individuals. Given an encounter rate θ (per day), a mosquito is likely to bite

$$\theta(c_1N_1 + c_2N_2 + c_3N_a)$$

hosts per day. Further, let b, $0 \leq b < 1$, be the fraction of each day for which a bed net is used. Thus $1 - b$ is the fraction of each day without bed-net protection, and $b = 0$ if the bed net is not used for the whole day.

The total daily number of potentially infectious bites from mosquitoes is βI_m. Let p_1 be the probability a bite by an infected mosquito on a susceptible human host leads to infection of the human. The incidence of new human infections among bed-net users is $\Gamma_1 S_1$, where

$$\Gamma_1 = \frac{c_1p_1(1-b)\beta I_m}{c_1N_1 + c_2N_2 + c_3N_a}$$

is the force of infection among bed-net users. Similarly, the incidence of new human infections among bed-net non-users is $\Gamma_2 S_2$, where

$$\Gamma_2 = \frac{c_2p_1\beta I_m}{c_1N_1 + c_2N_2 + c_3N_a}$$

is the force of infection among individuals who never use bed nets. The daily number of bites by susceptible mosquitoes is βS_m. Let p_2 be the probability a bite by a susceptible mosquito on an infected human host leads to infection of the mosquito. The incidence of new mosquito infections is $\Gamma_m S_m$, where

$$\Gamma_m = \frac{c_1 p_1 (1-b)\beta I_1 + c_2 p_2 \beta I_2}{c_1 N_1 + c_2 N_2 + c_3 N_a}$$

is the force of infection among susceptible mosquitoes.

4.2.2 Rescaled bed-net model

We introduce the following parameters to simplify the incidence terms.

$$\beta_h = p_1\beta; \quad \beta_m = p_2\beta; \quad \text{and} \quad c = \frac{c_2}{c_1}.$$

Following the technique of Chapter 3, we re-write System (4.1) in a rescaled form by scaling human and mosquito populations using λ_h and λ_m, respectively. Thus, we study proportions of the populations with respect to the constant population size in the absence of the disease. For $i = 1, 2$, let

$$\bar{S}_i = \frac{S_i}{\lambda_h}, \quad \bar{E}_i = \frac{E_i}{\lambda_h}, \quad \bar{I}_i = \frac{I_i}{\lambda_h}, \quad \text{and} \quad \bar{R}_i = \frac{R_i}{\lambda_h},$$

for the human population; and

$$\bar{S}_m = \frac{S_m}{\lambda_m}, \quad \bar{E}_m = \frac{E_m}{\lambda_m}, \quad \text{and} \quad \bar{I}_m = \frac{I_h}{\lambda_m},$$

for the mosquito population. Further, let

$$A = \frac{c_3}{c_1}\frac{N_a}{\lambda_h} \quad \text{and} \quad m_0 = \frac{\lambda_m}{\lambda_h}. \tag{4.2}$$

Keeping the same notation as in System (4.1) (for simplicity), the rescaled system consists of the following differential equations.

$$\begin{aligned}
S_1' &= \mu_h\phi + \rho_h R_1 - \Gamma_1 S_1 - \mu_h S_1,\\
S_2' &= \mu_h(1-\phi) + \rho_h R_2 - \Gamma_2 S_2 - \mu_h S_2,\\
S_m' &= \mu_m - \Gamma_m S_m - \mu_m S_m,\\
E_1' &= \Gamma_1 S_1 - \gamma_h E_1 - \mu_h E_1,\\
E_2' &= \Gamma_2 S_2 - \gamma_h E_2 - \mu_h E_2,\\
E_m' &= \Gamma_m S_m - \gamma_m E_m - \mu_m E_m,\\
I_1' &= \gamma_h E_1 - \alpha_h I_1 - \mu_h I_1,\\
I_2' &= \gamma_h E_2 - \alpha_h I_2 - \mu_h I_2,\\
I_m' &= \gamma_m E_m - \mu_m I_m,\\
R_1' &= \alpha_h I_1 - \rho_h R_1 - \mu_h R_1,\\
R_2' &= \alpha_h I_2 - \rho_h R_2 - \mu_h R_2,
\end{aligned} \tag{4.3}$$

where

$$\Gamma_1 = \frac{m_0(1-b)\beta_h I_m}{N_1 + cN_2 + A}, \quad \Gamma_2 = \frac{c\Gamma_1}{1-b}, \quad \Gamma_m = \frac{(1-b)\beta_m I_1 + c\beta_m I_2}{N_1 + cN_2 + A}. \tag{4.4}$$

Let $X = (S_1, S_2, S_m, E_1, E_2, E_m, I_1, I_2, I_m, R_1, R_2)$ denote a solution of the system to be studied with initial data $X_0 = X(0)$. We write $S_i(0) = S_{i0}$, $E_i(0) = E_{i0}$, $I_i(0) = I_{i0}$, $R_i(0) = R_{i0}$, and $N_i(0) = N_{i0}$, $i = 1, 2, m$.

The malaria model 4.3 is based on the following set of assumptions.

A1: There is a constant recruitment to the susceptible human population as a result of birth, which is balanced by natural deaths.

A2: There is a constant recruitment to the susceptible mosquito population as a result of birth, which is balanced by natural deaths.

A3: Transmission takes place only from infectious mosquitoes to susceptible humans and from infectious humans to susceptible mosquitoes.

A4: Infected mosquitoes do not live long enough to recover from infection.

A5: Recovered humans have full immunity to the disease for a few years after which the individuals become susceptible.

A6: Artificial feeders do not harbour or preserve disease parasites.

A7: Disease-related deaths are ignored to simplify analysis.

A8: Humans don't switch status with regards to bed-net usage.

Assumption A6 ensures that there is no possibility for the transfer and survival of the pathogen in the artificial feeder should an infectious mosquito feed from the feeder, otherwise this may lead to unintended effects.

Assumption A7 enables analysis with constant population. There are studies (such as [16, 20, 75, 78, 79], and Chapter 2) suggesting that the disease-induced death may facilitate a backward bifurcation. In that case, disease eradication may not be guaranteed even when the disease control reproduction number is less than unity.

Table 4.1: Parameters for the bed-net model

Parameter	**Description**
μ_h	Natural death rate of humans.
μ_m	Natural death rate of female mosquitoes.
β_h	Mosquito biting rate leading to infection of the human host.
β_m	Mosquito biting rate leading to infection of the mosquito.
γ_h	Rate at which a human becomes infectious after infection.
γ_m	Rate at which a mosquito becomes infectious after infection.
α_h	Rate at which a human recovers from infection.
ρ_h	Rate at which a recovered human loses partial immunity.
m_0	Ratio of total mosquito population to human population.
b	Effectiveness of bed nets (as a fraction of each day).
A	Ratio of adjusted number of feeders to number of humans.
c	Relative attractiveness of bed-net non-users to mosquitoes.
ϕ	Bed-net coverage or usage (a proportion for bed-net users).

The parameters for the model are outlined in Table 4.1. All parameters are positive. The parameter m_0 is the ratio of the total vector population to the total host population in the absence of the disease. A is the ratio of the adjusted number of artificial feeders to total human population when a mosquito is equally attracted to susceptible humans and artificial feeders. c represents the attractiveness of bed-net non-users (to mosquitoes) compared

to that of bed-net users. For System (4.3), c takes the following cases.

$c > 1$: A mosquito is more attracted to a bed-net non-user than to a bed-net user upon encounter, that is, the odorant is used by bed-net users.

$c = 1$: A mosquito is equally attracted to a bed-net user and a bed-net non-user upon encounter, that is, no odorant usage and mosquito bias.

$c < 1$: A mosquito is less attracted to a bed-net non-user than to a bed-net user upon encounter, that is, the odorant is used by bed-net non-users.

4.2.3 Well-posedness

By the basic theory of ordinary differential equations (Theorem 1.4.1), the right hand side of (4.3) is differentiable on $\mathbb{R}^{11}$, which implies that a unique solution X exists for every initial condition. Following the approaches of Chapter 2, it can be shown that System (4.3) has positive and bounded solutions. In fact, it is found that the positive cone $\mathbb{R}^{11}_{+}$ is forward-invariant and the unique solution X is positive for all $t \geq 0$.

Theorem 4.2.1. *For Model* (4.3)*, the disease-free plane is invariant. All solutions starting with* $E_i = E_m = I_i = I_m = 0$ *(for i=1,2) remain in the disease-free plane for all time* $t > 0$ *with* $S_i > 0$*,* $S_m > 0$*, and* $R_i \geq 0$*.*

Proof. With $E_i = E_m = I_i = I_m = 0$, $i = 1, 2$, it follows that $\Gamma_i = \Gamma_m = 0$. Hence System (4.3) gives $S_1' = \mu_h(\phi - S_1) + \rho_h R_1$, $S_2' = \mu_h(1 - \phi - S_2) + \rho_h R_2$, $S_m' = \mu_m(1 - S_m)$, $R_i' = -(\rho_h + \mu_h)R_i$, and $E_i' = E_m' = I_i' = I_m' = 0$. Solving

these yields $E_i = E_m = I_i = I_m = 0$, $S_1 = \phi - S_{10}e^{-\mu_h t} - R_{10}e^{-(\rho_h+\mu_h)t} > 0$, $S_2 = 1 - \phi - S_{20}e^{-\mu_h t} - R_{20}e^{-(\rho_h+\mu_h)t} > 0$, $S_m = 1 + (S_{m0} - \lambda_m)e^{-\mu_m t} > 0$, and $R_i = R_{i0}e^{-(\rho_h+\mu_h)t} \geq 0$. The solutions exist in the disease-free plane and form the disease-free set $\{S_1, S_2, S_m, R_1, R_2\}$. □

Theorem 4.2.2 (Positivity of solutions)**.** *Model* (4.3) *is mathematically and epidemiologically well-posed with a unique solution. Given nonnegative initial data X_0, the solution X is positive for all time $t \geq 0$.*

Proof. For System (4.3), suppose $X_0 > 0$ and that at least one component of X is negative at some time $t > 0$. By continuity and differentiability of X, there must be some time t_0 such that $X(t) > 0\ \forall t \in [0, t_0)$ and one or more components of $X(t_0)$ are zero with nonpositive derivatives. By the equation for S_1', if $S_1(t_0) = 0$ and $\mu_h\phi + \rho_h R_1(t_0) \leq 0$, then $R_1(t_0) < 0$ and R_1 must be zero somewhere on $(0, t_0)$. Hence $S_1(t_0) > 0$. Continuing with the approach used for the proof of Theorem 2.2.2 in Chapter 2, it is found that if $X(t) > 0$ on $[0, t_0)$ and any component of $X(t_0)$ is zero, then $E_i, E_m, I_i, I_m = 0$ at t_0 with $E_i', E_m', I_i', I_m' = 0$, $i = 1, 2$. From the invariance of the disease-free set (Theorem 4.2.1) and the uniqueness of solutions, having $E_i, E_m, I_i, I_m = 0$ at t_0 implies that $E_i, E_m, I_i, I_m = 0$, $S_i > 0$, $S_m > 0$ and $R_i \geq 0\ \forall t > 0$, contradicting the supposition that $X(t) > 0\ \forall t \in [0, t_0)$. □

Theorem 4.2.3 (Boundedness of solutions)**.** *Model* (4.3) *is mathematically and epidemiologically well-posed. The unique solution X is bounded given nonnegative initial data X_0.*

Proof. By the definitions of N_1, N_2 and N_m, and Equations (4.3), we obtain $N_1' = S_1' + E_1' + I_1' + R_1'$, $N_2' = S_2' + E_2' + I_2' + R_2'$ and $N_m' = S_m' + E_m' + I_m'$. We solve the derivatives to give

$$\begin{cases} N_1 = \phi + (N_{10} - \phi)e^{-\mu_h t}, \\ N_2 = 1 - \phi + (N_{20} - 1 - \phi)e^{-\mu_h t}, \\ N_m = 1 + (N_{m0} - 1)e^{-\mu_m t}, \end{cases} \tag{4.5}$$

$\forall t \geq 0$, where N_{10}, N_{20} and N_{m0} are initial values. By positivity, N_1, N_2 and N_m are bounded between 0 and the solutions of (4.5), hence so are all components of X (by positivity of each component). □

Corollary 4.2.4 (Domain of attraction)**.** *For Model* (4.3) *with nonnegative initial data X_0, there exists a domain attracting all solutions $X \in \mathbb{R}^{11}_+$.*

By theorems 4.2.2 and 4.2.3, define a domain D such that

$$D = \left\{ X \in \mathbb{R}^{11}_+ \;\middle|\; \begin{array}{c} S_1 > 0, S_2 > 0, S_m > 0, E_1 \geq 0, E_2 \geq 0, E_m \geq 0 \\ I_1 \geq 0, I_2 \geq 0, I_m \geq 0, R_1 \geq 0, R_2 \geq 0 \\ S_1 + E_1 + I_1 + R_1 = \phi \\ S_2 + E_2 + I_2 + R_2 = (1 - \phi) \\ S_m + E_m + I_m = 1 \end{array} \right\}.$$

It can be verified from (4.5) that for any initial data $X_0 \in D$, the solution X is always contained in the interior and boundary of D, and there are no orbits leaving D. Thus the domain D is invariant and attracting.

4.3 Equilibria and their stability

4.3.1 Disease-free equilibrium

A constant solution to a system of equations is referred to as an equilibrium solution. If in addition, $E_i = I_i = 0$, $i = 1, 2, m$, then X is referred to as a disease-free equilibrium. Otherwise, X is referred to as an endemic equilibrium. Below we show that System (4.3) has a unique disease-free equilibrium, and that any endemic equilibria are strictly positive.

An equilibrium solution of Equations (4.3) satisfies

$$\mu_h\phi + \rho_h R_1 - \Gamma_1 S_1 - \mu_h S_1 = 0, \tag{4.6a}$$

$$\mu_h(1-\phi) + \rho_h R_2 - \Gamma_2 S_2 - \mu_h S_2 = 0, \tag{4.6b}$$

$$\mu_m - \Gamma_m S_m - \mu_m S_m = 0, \tag{4.6c}$$

$$\Gamma_1 S_1 - (\gamma_h + \mu_h) E_1 = 0, \tag{4.6d}$$

$$\Gamma_2 S_2 - (\gamma_h + \mu_h) E_2 = 0, \tag{4.6e}$$

$$\Gamma_m S_m - (\gamma_m + \mu_m) E_m = 0, \tag{4.6f}$$

$$\gamma_h E_1 - (\alpha_h + \mu_h) I_1 = 0, \tag{4.6g}$$

$$\gamma_h E_2 - (\alpha_h + \mu_h) I_2 = 0, \tag{4.6h}$$

$$\gamma_m E_m - \mu_m I_m = 0, \tag{4.6i}$$

$$\alpha_h I_1 - (\rho_h + \mu_h) R_1 = 0, \tag{4.6j}$$

$$\alpha_h I_2 - (\rho_h + \mu_h) R_2 = 0. \tag{4.6k}$$

Theorem 4.3.1 (Boundary Equilibria)**.** *System* (4.3) *has a unique disease-free equilibrium and no other equilibria on the boundary of* D*.*

The above theorem can be proven by following a similar approach of Chapter 2 (see Theorem 2.3.1). For System (4.3), there exists exactly one disease-free equilibrium. In addition, any equilibrium that exists in the boundary of $D \subset \mathbb{R}^{11}_{+}$ does so with $E_i = E_m = I_i = I_m = R_i = 0$, where $i = 1, 2$, and the equilibrium is disease-free. Otherwise, the equilibrium is strictly positive and endemic. The domain D is positively invariant and the disease-free equilibrium in the boundary is the only equilibrium of (4.3) without the disease. By Theorem 4.2.2 and Equations (4.6), it is straight forward that if any of E_i, E_m, I_i, I_m, R_i, is positive, where $i = 1, 2$, then all components of X are positive and the equilibrium is strictly positive.

Let X^0 denote the disease-free equilibrium. It follows that

$$X^0 = (\phi, (1-\phi), 1, 0, 0, 0, 0, 0, 0, 0, 0).$$

Next we investigate the stability of the disease-free equilibrium using the Jacobian matrix of the system, evaluated at X^0.

An equilibrium of Equations (4.3) is said to be (locally asymptotically) stable if solutions with initial conditions in a sufficiently small neighbourhood of the equilibrium asymptotically approach the equilibrium.

Epidemiologically, stability of the disease-free equilibrium implies that small introductions of infected individuals into a population do not lead to

an outbreak. Thus, stability of the disease-free equilibrium can be described using the disease control reproduction number.

Definition 4.3.1. *The control reproduction number for System* (4.3) *is*

$$\mathcal{R}_c = \frac{m_0\beta_h\beta_m\gamma_h\gamma_m[(1-b)^2\phi + c^2(1-\phi)]}{(\phi + c(1-\phi) + A)^2(\gamma_h + \mu_h)(\alpha_h + \mu_h)(\gamma_m + \mu_m)\mu_m}. \tag{4.7}$$

As seen in the previous chapters, $\mathcal{R}_c$ is the expected number of new infected humans as a result of introducing one infected human in a population at a disease-free equilibrium in the presence of disease control methods.

Theorem 4.3.2. *For System* (4.3)*, the disease-free equilibrium is locally asymptotically stable if* $\mathcal{R}_c < 1$ *and unstable if* $\mathcal{R}_c > 1$.

Proof. From Theorem 1.4.4, an equilibrium solution is locally asymptotically stable if all eigenvalues of the Jacobian matrix have negative real parts. The Jacobian matrix evaluated at X^0 has the block structure

$$J(X^0) = \begin{bmatrix} J_{11} & J_{12} & J_{13} \\ 0 & J_{22} & 0 \\ 0 & J_{32} & J_{33} \end{bmatrix},$$

with submatrices

$$J_{11} = \begin{bmatrix} -\mu_h & 0 & 0 \\ 0 & -\mu_h & 0 \\ 0 & 0 & -\mu_m \end{bmatrix}, \quad J_{13} = \begin{bmatrix} \rho_h & 0 \\ 0 & \rho_h \\ 0 & 0 \end{bmatrix},$$

$$J_{12} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & \dfrac{-m_0(1-b)\phi\beta_h}{\phi + c(1-\phi) + A} \\ 0 & 0 & 0 & 0 & 0 & \dfrac{-m_0 c(1-\phi)\beta_h}{\phi + c(1-\phi) + A} \\ 0 & 0 & 0 & \dfrac{-(1-b)\beta_m}{\phi + c(1-\phi) + A} & \dfrac{-c\beta_m}{\phi + c(1-\phi) + A} & 0 \end{bmatrix},$$

$$J_{32} = \begin{bmatrix} 0 & 0 & 0 & \alpha_h & 0 & 0 \\ 0 & 0 & 0 & 0 & \alpha_h & 0 \end{bmatrix}, \quad J_{33} = \begin{bmatrix} -\rho_h - \mu_h & 0 \\ 0 & -\rho_h - \mu_h \end{bmatrix}.$$

X^0 is stable if all eigenvalues of $J(X^0)$ have negative real parts. By the block structure of $J(X^0)$, its eigenvalues are those of J_{11}, J_{22} and J_{33}. Since, by inspection, the eigenvalues of J_{11} and J_{33} have negative real parts, X^0 is stable if all eigenvalues of J_{22} have negative real parts. By the decomposition method of van den Driessche and Watmough [106], the submatrix J_{22} has the structure $F - V$, and all eigenvalues of J_{22} have negative real parts if and only if $\rho(FV^{-1}) < 1$, where ρ denotes the spectral radius. It follows that $J_{22} = F - V$ where

$$F = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & \dfrac{m_0(1-b)\phi\beta_h}{\phi + c(1-\phi) + A} \\ 0 & 0 & 0 & 0 & 0 & \dfrac{m_0 c(1-\phi)\beta_h}{\phi + c(1-\phi) + A} \\ 0 & 0 & 0 & \dfrac{(1-b)\beta_m}{\phi + c(1-\phi) + A} & \dfrac{c\beta_m}{\phi + c(1-\phi) + A} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

and

$$V = \begin{bmatrix} \gamma_h + \mu_h & 0 & 0 & 0 & 0 & 0 \\ 0 & \gamma_h + \mu_h & 0 & 0 & 0 & 0 \\ 0 & 0 & \gamma_m + \mu_m & 0 & 0 & 0 \\ -\gamma_h & 0 & 0 & \alpha_h + \mu_h & 0 & 0 \\ 0 & -\gamma_h & 0 & 0 & \alpha_h + \mu_h & 0 \\ 0 & 0 & -\gamma_m & 0 & 0 & \mu_m \end{bmatrix}.$$

We compute $\rho(FV^{-1})$ and set $\mathcal{R}_c = (\rho(FV^{-1}))^2$. Stability follows from the fact that $\rho(FV^{-1}) < 1$ implies $(\rho(FV^{-1}))^2 < 1$. □

In the special case where $c = 1$ and $\phi, A = 0$, the control reproduction number $\mathcal{R}_c$ gives the basic reproduction number, denoted $\mathcal{R}_0$. Thus,

$$\mathcal{R}_0 = \frac{m_0 \beta_h \beta_m \gamma_h \gamma_m}{(\gamma_h + \mu_h)(\alpha_h + \mu_h)(\gamma_m + \mu_m)\mu_m}. \tag{4.8}$$

For System (4.3), $\mathcal{R}_0$ is the expected number of new infected humans as a result of introducing one infected human in a population at a disease-free equilibrium in the absence of disease control methods.

From (4.7) and (4.8), it is immediately apparent that

$$\mathcal{R}_c = \mathcal{R}_0 \frac{(1-b)^2\phi + c^2(1-\phi)}{(\phi + c(1-\phi) + A)^2}. \tag{4.9}$$

A, c and ϕ are the control parameters. Given c and ϕ, $\mathcal{R}_c$ is decreasing with

A, but $\mathcal{R}_c$ may either increase or decrease with c and ϕ, so they are not necessarily good control parameters. Later we use Elasticity analysis of $\mathcal{R}_c$ to examine the effectiveness of the controls.

If $\mathcal{R}_c < 1$, then on average an infected human produces less than one new human infection over the course of the infectious period in the presence of disease control methods, and malaria will not spread. Conversely, if $\mathcal{R}_c > 1$, then each infected human produces, on average, more than one new human infection in the presence of disease control methods and malaria can invade the population.

4.3.2 Endemic equilibria

Theorem 4.3.3 (Existence of endemic equilibria)**.** *For the malaria model* (4.3)*, there are no endemic equilibria if* $\mathcal{R}_c < 1$ *and there is exactly one endemic equilibrium if* $\mathcal{R}_c > 1$*.*

Proof. Let $X^* = (S_1^*, S_2^*, S_m^*, E_1^*, E_2^*, E_m^*, I_1^*, I_2^*, I_m^*, R_1^*, R_2^*)$ be an equilibrium solution of System (4.3). Thus X^* satisfies Equations (4.6). Since $N_1 = S_1 + E_1 + I_1 + R_1$ and $N_2 = S_2 + E_2 + I_2 + R_2$, Equations (4.6) give $N_1^* = \phi$ and $N_2^* = 1 - \phi$. Substituting for N_1 and N_2 in Equation (4.4) gives

$$\Gamma_1^* = \frac{m_0(1-b)\beta_h I_m^*}{\phi + c(1-\phi) + A} \quad \text{and} \quad \Gamma_m^* = \frac{\beta_m((1-b)I_1^* + cI_2^*)}{\phi + c(1-\phi) + A}, \tag{4.10}$$

with $\Gamma_2^* = c\Gamma_1^*/(1-b)$. Below we solve Equations (4.6) for the endemic equilibria. First solve for S_1^* in terms of Γ_1^*, S_2^* in terms of Γ_2^*, and S_m^* in

terms of Γ_m^*. It follows that

$$S_1^* = \frac{\mu_h \phi}{\omega_1 \Gamma_1^* + \mu_h}, \quad S_2^* = \frac{\mu_h (1-\phi)}{\omega_1 \Gamma_2^* + \mu_h}, \quad \text{and} \quad S_m^* = \frac{\mu_m}{\Gamma_m^* + \mu_m}, \tag{4.11}$$

where

$$\omega_1 = \frac{(\gamma_h + \mu_h)(\alpha_h + \mu_h)(\rho_h + \mu_h) - \gamma_h \alpha_h \rho_h}{(\gamma_h + \mu_h)(\alpha_h + \mu_h)(\rho_h + \mu_h)}.$$

$0 < \omega_1 < 1$ by inspection.

Express E_1^* in terms of Γ_1^* using the relationship with S_1^* from (4.6d) and (4.11). The process continues for the rest of the state variables yielding

$$\begin{aligned}
E_1^* &= \frac{\mu_h \phi \Gamma_1^*}{(\gamma_h + \mu_h)(\omega_1 \Gamma_1^* + \mu_h)}, \quad I_1^* = \frac{\omega_2 \phi \Gamma_1^*}{(\omega_1 \Gamma_1^* + \mu_h)}, \\
E_2^* &= \frac{\mu_h (1-\phi) \Gamma_2^*}{(\gamma_h + \mu_h)(\omega_1 \Gamma_2^* + \mu_h)}, \quad I_2^* = \frac{\omega_2 (1-\phi) \Gamma_2^*}{(\omega_1 \Gamma_2^* + \mu_h)}, \\
E_m^* &= \frac{\mu_m \Gamma_m^*}{(\gamma_m + \mu_m)(\Gamma_m^* + \mu_m)}, \quad I_m^* = \frac{\gamma_m \Gamma_m^*}{(\gamma_m + \mu_m)(\Gamma_m^* + \mu_m)}, \\
R_1^* &= \frac{\omega_2 \alpha_h \phi \Gamma_1^*}{(\rho_h + \mu_h)(\omega_1 \Gamma_1^* + \mu_h)}, \quad R_2^* = \frac{\omega_2 \alpha_h (1-\phi) \Gamma_2^*}{(\rho_h + \mu_h)(\omega_1 \Gamma_2^* + \mu_h)},
\end{aligned} \tag{4.12}$$

where

$$\omega_2 = \frac{\gamma_h \mu_h}{(\gamma_h + \mu_h)(\alpha_h + \mu_h)}. \tag{4.13}$$

In the next step, I_1^*, I_2^*, I_m^*, Γ_1^*, Γ_2^*, and Γ_m^* are used to obtain an equation involving only Γ_1^*. Substitute I_1^* and I_2^* (4.12) into Γ_m^* (4.4), and use the relation $\Gamma_2^* = c\Gamma_1^*/(1-b)$, to yield

$$\Gamma_m^* = \frac{\beta_m \Gamma_1^* \omega_2}{(\phi + c(1-\phi) + A)} \left(\frac{(1-b)\phi}{\omega_1 \Gamma_1^* + \mu_h} + \frac{c^2 (1-\phi)}{\omega_1 c \Gamma_1^* + (1-b)\mu_h} \right). \tag{4.14}$$

Using Γ_m^*, I_m^* and Γ_1^* gives a cubic equation $q_2\Gamma_1^{*3} + q_1\Gamma_1^{*2} + q_0\Gamma_1^* = 0$ with the coefficients

$$
\begin{aligned}
q_2 &= \frac{\omega_1\omega_2 c\beta_m((1-b)\phi + c(1-\phi))}{(\phi + c(1-\phi) + A)} + c\mu_m\omega_1^2, \\
q_1 &= \frac{\mu_h\omega_2 c\beta_m((1-b)^2\phi + c^2(1-\phi))}{(\phi + c(1-\phi) + A)} + \mu_m\mu_h\omega_1(1-b+c)(1-\psi_0\mathcal{R}_c), \\
q_0 &= \mu_m\mu_h^2(1-b)(1-\mathcal{R}_c),
\end{aligned}
$$

where

$$\psi_0 = \frac{c(1-b)^2\phi + c^2(1-b)(1-\phi)}{(1-b+c)((1-b)^2\phi + c^2(1-\phi))}.$$

By inspection, $0 < \psi_0 < 1$ and q_2 is always positive.

The cubic equation has a trivial solution, $\Gamma_1^* = 0$, which corresponds to the disease-free equilibrium. The non-trivial solutions satisfy

$$q_2\Gamma_1^{*2} + q_1\Gamma_1^* + q_0 = 0. \tag{4.15}$$

If $\mathcal{R}_c < 1$, then $q_1 > 0$ and $q_0 > 0$, and since $q_2 > 0$, Descartes' Rule of Signs (Theorem 1.4.3) suggests that equation (4.15) has no positive real roots. Conversely, if $\mathcal{R}_c > 1$, then $q_0 < 0$ and, by Theorem 1.4.3, the equation has exactly one positive real root regardless of the sign of q_1. □

Let Γ_{1a}^* and Γ_{1b}^* denote the roots of equation (4.15) given by

$$\Gamma_{1a}^* = \frac{-q_1 + \sqrt{q_1^2 - 4q_2q_0}}{2q_2} \quad \text{and} \quad \Gamma_{1b}^* = \frac{-q_1 - \sqrt{q_1^2 - 4q_2q_0}}{2q_2}.$$

Equation (4.15) has no positive real roots if $\mathcal{R}_c < 1$ and there is exactly one positive real root if $\mathcal{R}_c > 1$. In fact $\Gamma^*_{1a} > 0$ and $\Gamma^*_{1b} < 0$ if $\mathcal{R}_c > 1$. Compute Γ^*_1, Γ^*_2 and Γ^*_m for substitution into Equations (4.11) and (4.12). It follows that there is exactly one endemic equilibrium solution if $\mathcal{R}_c > 1$, and the equilibrium coexists with an unstable disease-free equilibrium.

Conjecture 4.3.4 (Global stability of the disease-free equilibrium)**.** *For System* (4.3)*, the disease-free equilibrium is globally asymptotically stable if* $\mathcal{R}_c < 1$ *and unstable if* $\mathcal{R}_c > 1$.

As discussed in Chapter 2, global-stability analysis of endemic equilibria for SEIRS models with vector bias requires further consideration. For the SIS vector-bias model of Buonomo and Vargas-De-Leon [14], it is shown that the endemic equilibrium is globally stable if $\mathcal{R}_0 > 1$. Some SEIR, SEI, SI or SIR models without mosquito bias ([54], [113], [114]) have a globally stable endemic equilibrium if $\mathcal{R}_0 > 1$. System (4.3) has no endemic equilibria for $\mathcal{R}_c < 1$, hence we conjecture that the disease-free equilibrium is globally stable in the absence of endemic equilibria (Conjecture 4.3.4). Later we use numerical simulations to illustrate the stability properties of the equilibria.

4.3.3 Elasticity analysis of R_c

Elasticity of a function is the ratio of the percentage change in the function's output with respect to the percentage change in its input, for infinitesimal changes from a point (Hanoch [39], Sydsaeter and Hammond [99]). In this

section, Elasticity analysis measures the ratio of the relative change in $\mathcal{R}_c$ to the relative change in each of the control parameters A, c and ϕ.

Definition 4.3.2 (Sydsaeter and Hammond [99]). *Suppose a function $\mathcal{R}_c$ is differentiable at x. If $\mathcal{R}_c(x) \neq 0$, the elasticity of $\mathcal{R}_c$ with respect to x is*

$$El_x\mathcal{R}_c(x) = \frac{x}{\mathcal{R}_c(x)}\mathcal{R}_c'(x).$$

From Equation (4.9), it is seen that $\mathcal{R}_c$ is continuous in its parameters. Below are the Elasticities of $\mathcal{R}_c$ with respect to the controls A, c and ϕ.

$$\begin{aligned}
El_A\mathcal{R}_c &= \frac{A}{\mathcal{R}_c}\frac{\partial\mathcal{R}_c}{\partial A} = \frac{-2A}{\phi + c(1-\phi) + A}, \\
El_c\mathcal{R}_c &= \frac{c}{\mathcal{R}_c}\frac{\partial\mathcal{R}_c}{\partial c} = \frac{2c(1-\phi)(c(A+\phi) - (1-b)^2\phi)}{(\phi + c(1-\phi) + A)((1-b)^2\phi + c^2(1-\phi))}, \\
El_\phi\mathcal{R}_c &= \frac{\phi}{\mathcal{R}_c}\frac{\partial\mathcal{R}_c}{\partial \phi} = \frac{\phi(((1-b)^2 - c^2)(c + A - (1-c)\phi) - 2(1-c)c^2)}{((1-b)^2\phi + c^2(1-\phi))(\phi + c(1-\phi) + A)}.
\end{aligned}$$

Since $\mathcal{R}_c$ is positive for positive parameters, the elasticities $El_A\mathcal{R}_c$, $El_c\mathcal{R}_c$ and $El_\phi\mathcal{R}_c$ define the percentage change as well as the slope of $\mathcal{R}_c$ with respect to A, c and ϕ, respectively, when other parameters are fixed.

$El_A\mathcal{R}_c = 0$ for $A = 0$, and $El_A\mathcal{R}_c < 0$ for all $A > 0$, which implies that $\mathcal{R}_c$ decreases with A. The elasticity with respect to A is monotone in A, ranging from 0 to -2 as A increases. For large A (relative to c), a percentage change in A leads to a 2% change in $\mathcal{R}_c$.

$El_c\mathcal{R}_c = 0$ for $c = 0$ or $\phi = 1$ or $c = c_{max}$, where

$$c_{max} = \frac{(1-b)^2\phi}{(A+\phi)} < 1.$$

Since the denominator of $El_c\mathcal{R}_c$ is positive, $El_c\mathcal{R}_c < 0$ for $c < c_{max}$ and $El_c\mathcal{R}_c > 0$ for $c > c_{max}$. This implies that $\mathcal{R}_c$ (versus c) has a local minimum at $c = c_{max}$. Thus c_{max} is an optimal target for c. c should be increased if it is below c_{max} and decreased if it is above c_{max}.

$El_\phi\mathcal{R}_c = 0$ if $\phi = 0$ or $\phi = \phi_{min}$ where

$$\phi_{min} = \frac{c+A}{1-c} - \frac{2c^2}{(1-b)^2 - c^2}.$$

$\mathcal{R}_c$ (versus ϕ) has a local maximum at ϕ_{min} if $(1-c)((1-b)^2 - c^2) > 0$ and a local minimum at ϕ_{min} if $(1-c)((1-b)^2 - c^2) < 0$. The latter holds if and only if $1 - b < c < 1$, which gives $\phi_{min} > 1$ and hence ϕ_{min} does not exist for $\phi \in [0, 1]$. As a result, the optimal value for ϕ is 1 if $1 - b < c < 1$ and ϕ should be increased to 1. Conversely, the optimal value is 0 or 1 if $(1-c)(1-b-c) > 0$ and ϕ should be decreased to 0 or increased to 1.

4.4 Discussion of results

Given below are the results of the bed-net model together with supporting figures. The figures are obtained using parameter values in Table 4.2. A discussion of the values and range can be found in Section 2.4.

Table 4.2: Parameter values used for simulations

Parameter	**Value**	**Range**	**Source**
μ_h	0.00004 per day	$(0, 0.001)$	§2.4
μ_m	0.065 per day	$(0.001, 0.1)$	[20]
β_h	0.02 per day	$(0.001, 0.2)$	[20]
β_m	0.192 per day	$(0.005, 0.4)$	[20]
γ_h	0.10 per day	$(0.06, 0.2)$	[68]
γ_m	0.09 per day	$(0.02, 0.4)$	[20]
α_h	0.0035 per day	$(0.001, 0.02)$	[68]
ρ_h	0.0005 per day	$(0, 0.01)$	[20]
m_0	2 mosquitoes per person	$(0, 10)$	§2.4
b	0.5	$(0, 1)$	
A	$0 - \infty$	$(0, \infty)$	§2.4
c	$0 - \infty$	$(0, \infty)$	§2.4
ϕ	$0 - 1$	$(0, 1)$	

The control reproduction number determines the dynamics of the disease in response to the control parameters A, c and ϕ. From Theorem 4.3.3, System (4.3) has no endemic equilibria if $\mathcal{R}_c < 1$, and the system has exactly one endemic equilibrium in addition to the disease-free equilibrium if $\mathcal{R}_c > 1$. Setting $\mathcal{R}_c = 1$ gives a threshold condition for the existence of the equilibria. Figure 4.1 illustrates the curve $\mathcal{R}_c = 1$ in the ϕ-A plane for $c = 2.0$, $c = 1.0$, and $c = 0.2$. Points in the region above the curve give $\mathcal{R}_c < 1$, which is when the system has only the disease-free equilibrium, and the disease cannot spread or invade the population.

From Equation 4.9, we write $\mathcal{R}_c = \mathcal{R}_c(A, c, \phi)$. Note that $\mathcal{R}_c(A, c, 1)$ is independent of c. This implies that at $\phi = 1$, $\mathcal{R}_c$ is purely determined by A

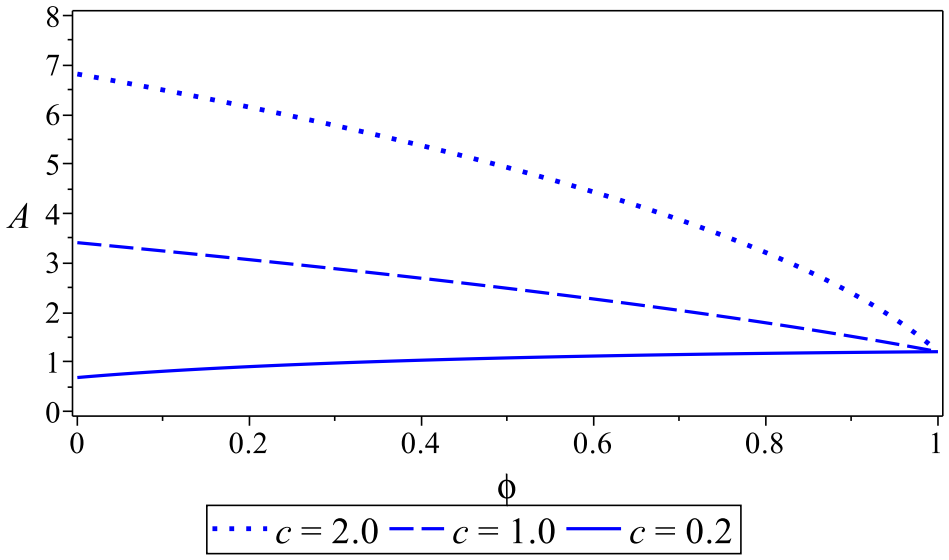

Figure 4.1: Bifurcation in the ϕ-A plane. Each level curve gives $\mathcal{R}_c = 1$ for a given c. For each curve, points in the region above the curve satisfy $\mathcal{R}_c < 1$, and points below each curve satisfy $\mathcal{R}_c > 1$.

for all c. $\mathcal{R}_c > 1$ for the region below the curve in Figure 4.1 and the disease can spread or invade the population. The endemic region (below the curve) can be reduced by decreasing c. Reducing c decreases the height of the curve at $\phi = 0$, hence $\mathcal{R}_c < 1$ can be obtained easily if A is large relative to c. Thus Figure 4.1 illustrates that eradication is easily done at a relatively low attractiveness of bed-net non-users.

Local-stability analysis suggest that the disease-free equilibrium is stable if $\mathcal{R}_c < 1$ and unstable if $\mathcal{R}_c > 1$ (Theorem 4.3.2). Theorem 4.3.3 guarantees that System (4.3) has an unstable disease-free equilibrium and exactly one

endemic equilibrium for $\mathcal{R}_c > 1$. The stability properties of the equilibria are illustrated in Figures 4.2, 4.3 and 4.4. In Figure 4.2, all solutions appear to converge to the disease-free set for $\mathcal{R}_c < 1$ regardless of large initial values. In Figure 4.3 and Figure 4.4, the solutions appear to converge to the endemic equilibrium for $\mathcal{R}_c > 1$ regardless of small initial values.

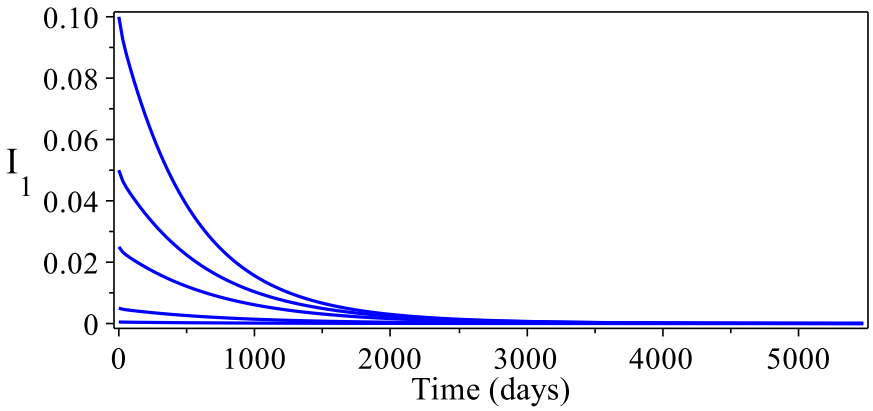

Figure 4.2: Stability of the disease-free equilibrium. $\mathcal{R}_c < 1$ with $A = 2$, $c = 0.5$ and $\phi = 0.5$. The solutions converge to the disease-free equilibrium regardless of large initial values.

By Elasticity $El_A\mathcal{R}_c$, $\mathcal{R}_c$ decreases with A. This means that increasing A can slow disease spread. Eradication is easily done if A is large relative to c. Recall from Equation (4.2) that A is the number of feeders scaled by the human population and the relative attraction of mosquitoes to feeders. Hence, increasing A means increasing the number or the attractiveness of the feeders relative to humans. Thus, disease spread can be stopped by increasing the number or attractiveness of artificial feeders relative to humans.

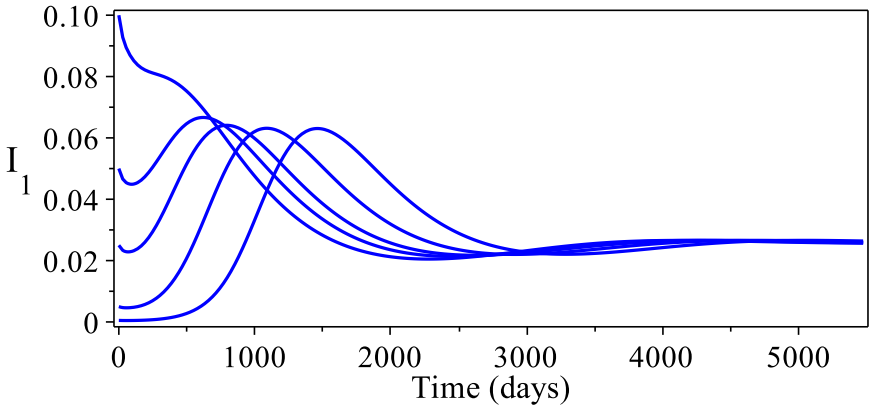

Figure 4.3: Malaria prevalence for bed-net users (I_1). $\mathcal{R}_c > 1$ with $A = 2$, $c = 2$ and $\phi = 0.5$. The endemic equilibrium appears to be stable regardless of small initial values.

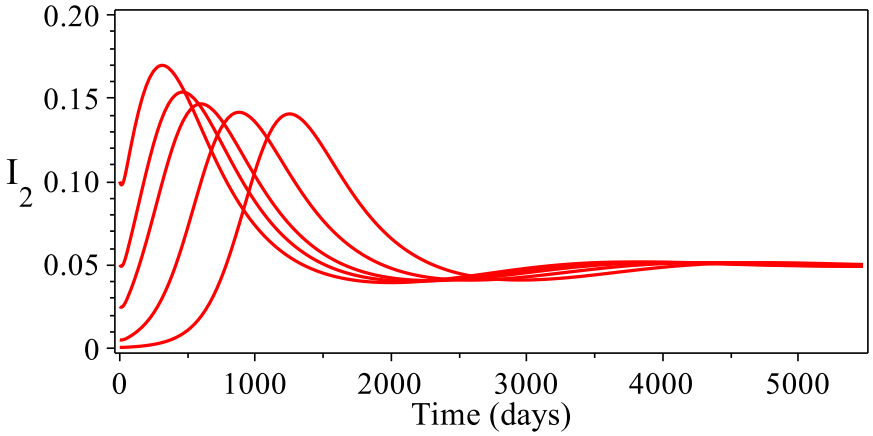

Figure 4.4: Malaria prevalence for bed-net non-users (I_2). $\mathcal{R}_c > 1$ with $A = 2$, $c = 2$ and $\phi = 0.5$. The endemic equilibrium appears to be stable regardless of small initial values.

By Elasticity $El_c\mathcal{R}_c$, $\mathcal{R}_c$ decreases with c for $c < c_{max}$ and increases with c for $c > c_{max}$. To slow or stop disease spread, the relative attractiveness of bed-net non-users should be increased if it is below c_{max} and decreased if it is above c_{max}. By inspection $c_{max} < 1$. Thus, the optimal value of c exists only for a relatively low attractiveness of bed-net non-users.

From $El_\phi\mathcal{R}_c$, $\mathcal{R}_c$ increases and decreases with ϕ for $0 < \phi < \phi_{min}$ and $\phi_{min} < \phi < 1$, respectively. The value of ϕ_{min} depends on A and c. By inspection, if A is small or negligible and c is large, then $\mathcal{R}_c$ is large but ϕ_{min} is small or negative. If A is small or negligible and c is small, then $\mathcal{R}_c$ is large and ϕ_{min} is large. ϕ_{min} large means that it is difficult to reduce $\mathcal{R}_c$ with bed nets alone, whereas ϕ_{min} small implies that it is easy to reduce $\mathcal{R}_c$ with bed nets alone. It follows that if mosquitoes are more attracted to bed-net non-users than to bed-net users (if the repellent is used by bed-net users), then increasing bed-net coverage decreases $\mathcal{R}_c$, but $\mathcal{R}_c$ is always large.

With bed nets alone, disease eradication is difficult. From Equation 4.9, if $A = 0$ and $c = 1$, then $\mathcal{R}_c(0, 1, \phi) = \mathcal{R}_0[(1-b)^2\phi+(1-\phi)]$. For the case with no bed-net usage, $\mathcal{R}_c(0, 1, 0) = \mathcal{R}_0$. For the case with full bed-net coverage, $\mathcal{R}_c(0, 1, 1) = \mathcal{R}_0(1-b)^2$. The disease cannot be eradicated with bed nets alone if $\mathcal{R}_0(1 - b)^2 > 1$, that is, if $\mathcal{R}_0 > 4$, assuming $b = 0.5$. Estimates for $\mathcal{R}_0$ are 16.63 and 24.94 from Chapter 2 and Chapter 3, respectively. For the bed-net model (4.6), $\mathcal{R}_0 = 19.44$, and eradication is possible if $19.44(1 - b)^2 < 1$. This holds if $\phi = 1$ and $b > 0.94$, that is, if all people use bed nets for more than 94% of the day, which may not be realistic.

Figure 4.5 illustrates the effect of ϕ on $\mathcal{R}_c$ for the given values of c with $A = 0$. It is seen that $\mathcal{R}_c$ is largely decreasing with ϕ as c decreases. Notice that A is negligible and $\mathcal{R}_c$ is large for all ϕ. At $\phi = 1$, $\mathcal{R}_c$ attains a value determined purely by A for all c. In Figure 4.6, the effect of ϕ on $\mathcal{R}_c$ is illustrated with $A = 0.1$. It is seen that $\mathcal{R}_c$ is largely decreasing with ϕ as c decreases. Notice that A is small ($A = 0.1$) and $\mathcal{R}_c$ is still large for all ϕ.

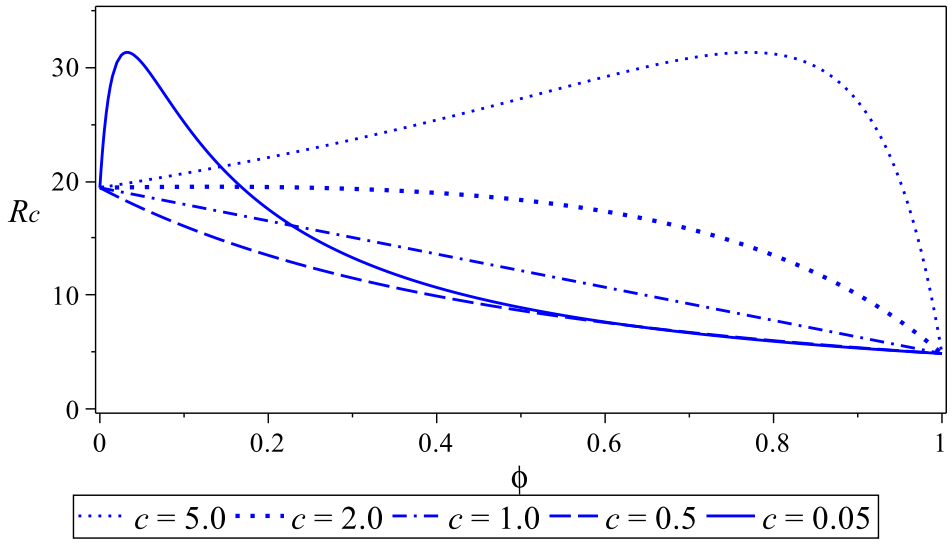

Figure 4.5: Effect of ϕ on $\mathcal{R}_c$ with A negligible. Let $A = 0$. At $\phi = 1$, $\mathcal{R}_c$ attains a value determined by A for all c.

If A is large and c is large, then $\mathcal{R}_c$ is large but ϕ_{min} is small or negative. If A is large and c is small, then $\mathcal{R}_c$ is small and ϕ_{min} is large. It follows that if mosquitoes are less attracted to bed-net non-users than to bed-net users (if the repellent is used by bed-net non-users), then increasing bed-net

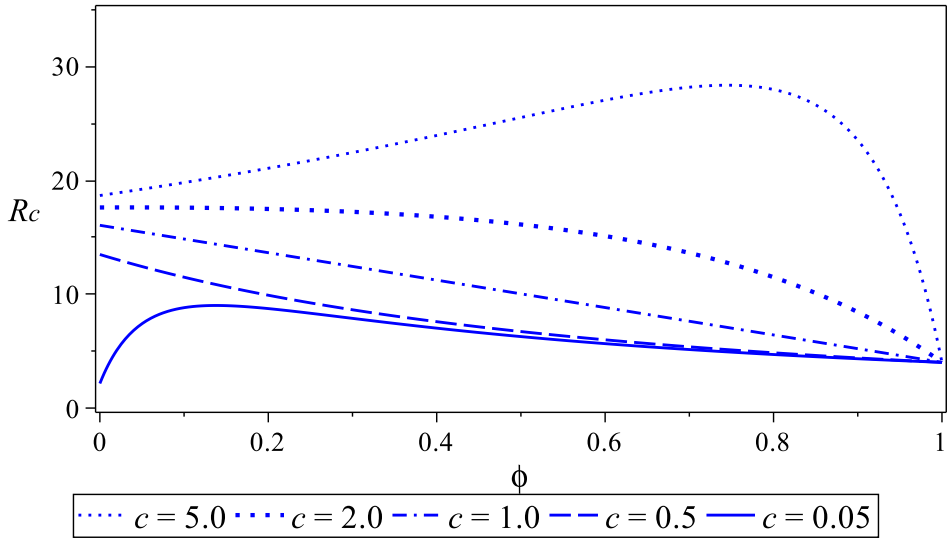

Figure 4.6: Effect of ϕ on $\mathcal{R}_c$ with A small. Let $A = 0.1$. At $\phi = 1$, all curves converge to a value determined by A. On average, increasing ϕ decreases $\mathcal{R}_c$.

coverage increases $\mathcal{R}_c$, but eradication is possible since $\mathcal{R}_c$ remains small. $\mathcal{R}_c$ can be decreased by increasing A or reducing c to zero, or increasing ϕ such that $\phi > \phi_{min}$, but the case of $c = 0$ is not realistic as it would mean that mosquitoes are not attracted to bed-net non-users at all. With artificial feeders, increasing A decreases $\mathcal{R}_c$ and eradication is possible with $\mathcal{R}_c$ small. Figure 4.7 illustrates that, given c and A, increasing ϕ decreases $\mathcal{R}_c$, except for $c < c_{max}$. The figure also illustrates that $\mathcal{R}_c$ is small for $A > 1$ and $c < 1$, hence disease eradication is possible even if $\mathcal{R}_c$ increases with ϕ.

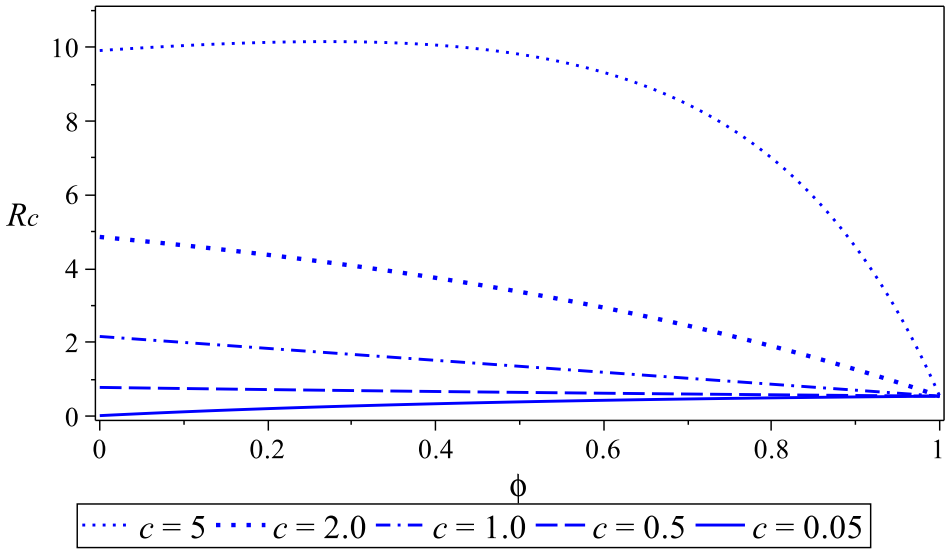

Figure 4.7: Effect of ϕ on $\mathcal{R}_c$ with A large. Let $A = 2$. The values of $\mathcal{R}_c$ have reduced compared to the values with A small or negligible. Increasing ϕ decreases $\mathcal{R}_c$, except for the curve with $c < c_{max}$.

4.5 Conclusion

The bed-net model allows a critical analysis of a multifaceted disease-control approach to examine the effect of bed nets, protective odorants and mosquito feeders on disease spread using the control reproduction number. Protective odorants are used by all bed-net users or all bed-net non-users. Elasticity analysis of $\mathcal{R}_c$ is used to examine how changes in the control parameters A, c and ϕ effect disease spread.

Our analysis shows that increasing artificial feeders decreases disease spread. Previously, Buonomo [15] suggested that increasing relative mosquito

attraction towards infected humans may negatively impact the response of malaria dynamics to bed-net usage. We have shown that such negative effects associated with increasing bed-net usage can be offset by increasing artificial feeders and encouraging bed-net non-users to use protective odorants.

For a relatively high mosquito attraction to non-users, increasing bed nets can worsen disease spread, except if a threshold proportion is reached. Agusto et al. [2] suggested that if 75% of the population were to use bed nets, malaria could be eliminated, but result ignores the exposure of bed-net users to mosquitoes. We have shown that 100% bed-net coverage does not guarantee disease eradication. The disease persists with bed nets alone. For a relatively low attractiveness of bed-net non-users, the negative effects of increasing bed-net coverage are limited by a reduced spread. To achieve this, bed-net non-users can use protective odorants. We conclude that disease spread can be stopped using a multifaceted approach where bed nets and artificial feeders are used, and the relative mosquito attraction towards bed-net non-users is reduced by encouraging the use of protective odorants.

Chapter 5

Results and Future work

5.1 Summary

Vector behaviour influences the speed of disease spread among humans. The biting behaviour of mosquitoes, expressed by nonrandom feeding, involves bias towards hosts with special characteristics as discussed in Chapter 1. Recent studies show that mosquitoes are more attracted to infected humans than to uninfected individuals [27, 45, 52, 93]. This suggests that mosquito bias can influence disease spread among populations. In order to eradicate vector-borne diseases, it is important to influence vector-host interactions. For mosquito-borne pathogens such as malaria, dengue, Rift Valley fever, yellow fever, Chikungunya, lymphatic filariasis, Japanese encephalitis, and West Nile fever, it is important to influence mosquito bias.

As discussed in Chapter 1, targeting mosquito bias requires a tactical

disease control approach with artificial feeders for mosquitoes, protective odorants and bed nets. A mosquito's detector of a host can be targeted using attractants (Potter [83] and Tauxe et al. [101]) or protective odorants. By this approach, attractants can be applied to artificial feeders such as glytubes (Costa-da-Silva et al. [25]) to increase mosquito attraction to the feeders. Further, several studies [2, 15, 22, 40, 111, 112] have suggested that people can acquire protection against mosquito bites through regular use of bed nets. To study the effectiveness of such a multifaceted control approach, three mathematical models are developed where people are the hosts and mosquitoes are the vectors.

For the artificial-feeder model (Chapter 2), mosquito bias is modelled by the relative attractiveness of infectious humans to mosquitoes, keeping in mind that this can be manipulated by disease [27, 45, 52, 93] or man [1, 69, 83, 101]. The model is used to study the effect of influencing mosquito bias on malaria transmission and spread in the presence of artificial feeders. Our analysis suggests that decreasing the attractiveness of infectious humans relative to uninfected individuals, facilitates disease eradication. Artificial feeders reduce disease spread. Malaria can be eradicated through the use of artificial feeders alone, but eradication is easily done if mosquitoes are more attracted to uninfected hosts than to infectious individuals.

Our second model is a modification of the artificial-feeder model without the artificial feeders, where there is an additional class of infectious humans who have not acquired a protective odorant to prevent bites. The resulting

mosquito-bias model is analyzed to examine how the odorant-acquisition rate for infectious hosts, affects disease spread. The effectiveness of the repellent depends on the relative attractiveness of the user. Our analysis suggests that, in order to stop disease spread using the odorant, the odorant-acquisition rate should be inversely proportional to the relative attractiveness of the odorant-user. Thus, disease spread can be stopped by minimizing the relative attractiveness of infectious humans while maximizing the rate at which infectious individuals acquire the protective repellent.

The bed-net model (Chapter 4) combines the use of artificial feeders with the use of untreated bed nets, where a proportion of the human population accounts for bed-net users. The model assumes the case where bed-net users or bed-net non-users can acquire protective odorants. Mosquito bias is modelled by a dependence of the relative biting rates on bed-net usage. The resulting bed-net model is used to study the effect of untreated bed nets, protective odorants and artificial feeders on disease transmission and spread. Our analysis suggests that increasing bed-net coverage increases disease transmission and spread if mosquitoes are more attracted to bed-net non-users than to bed-net users. The disease can be eliminated by increasing bed-net coverage and attractive mosquito feeders while reducing the relative attractiveness of bed-net non-users using protective odorants.

5.2 Results and Implications

We note from Chapter 1 that '**infectious**' hosts and vectors are carriers of transmissible gametocyte stages of malaria parasites, whereas uninfected individuals and carriers of non-transmissible stages are referred to as being '**noninfectious**'. We also note that the disease control reproduction number is a measure of transmission intensity in the presence of the controls. The results and epidemiological implications of the models studied in the previous sections include (and are not limited to) the following.

RE1: From Chapter 2, increasing A relative to λ_h switches the direction of bifurcation from backward to forward and decreases the disease control reproduction number $\mathcal{R}_c$. Malaria can be effectively controlled with artificial feeders by increasing the number and attractiveness of the feeders relative to humans.

RE2: From Chapters 2 and 3, decreasing c decreases $\mathcal{R}_c$ and vanishes all endemic equilibria. Malaria can be effectively controlled by decreasing the relative attractiveness of infectious individuals.

RE3: Chapters 2 and 3 show that mosquito bias complicates disease control. Decreasing c below c^1 gives two endemic equilibria, but no endemic equilibria exist for $c < c^*$, where $c^* \leq c^1$. Thus, disease spread can be stopped by minimizing the relative attractiveness of infectious humans and maximizing the odorant-acquisition rate at the same time.

RE4: Bed nets are beneficial in controlling mosquito-borne pathogens, but the method does better in the presence of artificial feeders. With bed nets alone, disease eradication is less likely because humans use bed nets for only a fraction of each day. Even with 100% bed-net coverage, the bed-net model in Chapter 4 suggests that disease eradication is not guaranteed for diseases with $\mathcal{R}_0 > 4$, unless bed nets are combined with other disease-control methods.

RE5: Bed-net users who also use protective repellents increase disease spread. For a relatively high mosquito attraction to non-users, increasing bed nets can worsen disease spread, except if a threshold proportion is reached. The disease persists with bed nets alone. The negative effects associated with increasing bed-net usage can be off-set by increasing mosquito feeders and reducing the attractiveness of bed-net non-users to facilitate disease eradication.

RE6: Following the above results, disease-control outcomes are influenced by the attractiveness of hosts to mosquitoes. Increasing the attractiveness of infected and unprotected humans increases the reproduction number and hence the speed of disease spread. Decreasing the attractiveness to zero can stop disease spread, but this may not be realistic. A tactical disease-control approach should aim at decreasing the attractiveness of infectious humans to mosquitoes by encouraging the use of protective odorants, artificial feeders, and optimizing bed-net coverage.

Our mathematical models are applicable to all mosquito-borne diseases. The proposed disease controls can be applied to all vector-borne pathogens. The multifaceted disease-control approach based on the proposed controls can be used to facilitate eradication. We conclude that the transmission and spread of mosquito-borne pathogens can be stopped by using artificial feeders that are attractive to mosquitoes, by increasing repellent-usage throughout the infectious stage, and by ensuring optimal bed-net coverage with protective odorants for all bed-net non-users.

5.3 Future work

The analysis of the three mathematical models can be improved in future to better understand disease dynamics in the presence of the proposed controls. The models follow the SEIRS framework with a large parameter space, which complicates some analyses.

SEIRS vector bias models have not been studied previously and there are no analytic global-stability results for the endemic equilibria. The results are available for SIS vector-bias models (Buonomo and Vargas-De-Leon [14]), and other models without mosquito bias [54, 55, 113, 114]. The authors use the geometric method for global-stability analysis due to Li and Muldowney [57] or the method of Lyapunov functions to show that the endemic equilibrium is globally stable in the domain of attraction if $\mathcal{R}_0 > 1$. For the SEIRS models developed in this study, global-stability analysis is cumbersome due

to the nonlinearities and a large control-parameter space. With supporting illustrations, the endemic equilibrium is conjectured to be globally stable for $\mathcal{R}_c > 1$. The analysis is left as part of future work.

The results of the artificial-feeder model and the mosquito-bias model suggest that increasing mosquito attraction towards infected humans increases disease spread. Previously, Kingsolver [48] suggested that models with random choice or consistent preference predict either a stable disease-free equilibrium or a stable endemic equilibrium, but increasing the consistent host preference makes it easier to obtain a stable endemic equilibrium relative to random choice models. Chapter 4 ignores mosquito bias towards infectious hosts. Increasing mosquito attraction of bed-net users facilitates disease eradication. It is not clear how the relative attractiveness of infectious hosts affects the stability of the equilibria.

In Chapter 4, the bed-net model assumes that there is no disease-induced death. This was a special case to simplify analysis of disease control options with a large model. From the models of Chapter 2 and 3, the disease-induced death facilitates the existence of subcritical endemic equilibria. The bed-net model can be revisited in future to find out the effect of the disease-induced death rate on the results of the model.

All in all, the models present challenging opportunities in mathematical modelling and disease control which can be explored in future to improve the effectiveness of disease control methods.

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Awards:

Intl. Differential Scholarship, University of New Brunswick, 2009-2013
Gov't Sponsorship on National Merit, Mbarara University, 2004-2007

Experience:

Research Assistant, Math & Stats, University of New Brunswick, 2009-2015
Tutor, Math Learning Centre, University of New Brunswick, 2012-2015
Teaching Assistant, Math & Stats, University of New Brunswick, 2012-2014
Graduate Teacher, Ntungamo High School, Uganda, 2007-2009

Related Accomplishments:

Monitoring & Evaluation of Malaria Programs, MEASURE Evaluation (2014)
Data Management for Clinical Research, Vanderbilt University MOOC (2014)
Bioinformatics: Introduction & Methods, Peking University MOOC (2014)
Data Analysis and Statistical Inference, Duke University MOOC (2014)