Mathematical models and analysis for the transmission dynamics of malaria

by

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Declaration

I, the undersigned declare that the dissertation, which I hereby submit for the degree Magister Scientiae at the University of Pretoria, is my own work and has not previously been submitted by me for a degree at this or any other tertiary institution.

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Dedication

This work is dedicated to my late grand parents.

Title Mathematical models and analysis for the transmission dynamics of malaria

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Abstract

Malaria is one of the most widespread and complex parasitic diseases in the world. According to the World Health Organization's records for the year 2013, there were 207 million malaria cases with 627,000 deaths in 2012 globally. Although its control and prevention has been pursued for a long time, however, because the parasite developed resistance to many of the standard treatments, it is becoming more difficult for researchers to stay ahead of the disease. In this dissertation, two deterministic models for the transmission dynamics of malaria are presented. First we comprehensively studied the dynamical interaction of sporozoites with humans, production of merozoites, and the invasion of red blood cells during erythrocytic stage of malaria infection. Then we construct a model, which takes the form of an autonomous deterministic system of non-linear differential equations with standard incidence, consisting of seven mutually-exclusive compartments representing the human and vector dynamics. The model is then extended to incorporate additional compartment of vaccinated individuals. Rigorous analysis of the two models

(with and without vaccine) shows that, both the non-vaccinated and vaccinated models have a locally asymptotically stable disease-free equilibrium (DFE) whenever their respective threshold parameters, known as the basic reproduction number and the vaccinated reproduction number are respectively less than unity, and the DFE is unstable when they are greater than unity. In addition, the models exhibit the phenomenon of backward bifurcation, where the stable disease-free equilibrium coexists with a stable endemic equilibrium when the associated reproduction numbers are less than unity. Furthermore, it was shown that, the backward bifurcation phenomenon can be removed by substituting the associated standard incidence function with the mass action incidence, this is achieved using Lyapunov functions in conjunction with LaSalle invariance principle. We further presented numerical simulations using parameter values for both low and high malaria incidence regions.

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Chapter 1

Introduction to Malaria

1.1 Introduction

This chapter is devoted to the study of some of the fundamental concepts of malaria.

1.2 Malaria

Malaria is a complex parasitic disease, it is mostly confined to tropical and subtropical regions of Africa and Asia because of rainfall, warm temperatures, stagnant waters, and poor sanitation that pave way for the provision of conducive environment for mosquito breeding [3, 52, 69]. Although there were tremendous progresses in the fight against malaria, according to the World Health Organization's records for the year 2013, there were 207 million malaria cases worldwide with 627,000 deaths in 2012 [73].

Malaria infection is characterized by high fever, chills, sweating, fatigue, headache, and nausea which if left untreated can cause acute anemia, organ failure or brain damage among other problems. It can be treated and cured but because the par-

asite has developed resistance to many of the standard treatments, it is becoming more difficult for researchers to stay ahead of the disease [24, 29, 72].

Malaria is common and life-threatening public health problem in many tropical and subtropical areas of the world. It is currently endemic in over hundred countries. Each year, approximately three hundred million people fall ill with malaria and one million deaths are recorded. It is transmitted by female Anopheles mosquitoes which bite mainly between sunset and sunrise [5, 71].

1.2.1 Causes of Malaria

Human malaria is caused by five different species of the parasite belonging to genus Plasmodium: Plasmodium falciparum (the most deadly), Plasmodium vivax, Plasmodium knowlesi, Plasmodium malariae, and Plasmodium ovale, the last two are fairly uncommon. Many animals can get malaria but human malaria does not spread to animals, except for Plasmodium knowlesi, animal malaria does not spread to humans [47]. A person gets malaria when bitten by a female mosquito who is looking for a blood meal and is infected with the malaria parasite [24]. The parasites enter the blood stream and travel to the liver where they multiply, when they re-emerge into the blood, symptoms appear. By the time a patient shows symptoms, the parasites have reproduced very rapidly, clogging blood vessels and rupturing blood cells. Malaria cannot be casually transmitted directly from one person to another, instead, a mosquito bites an infected person and then passes the infection on to the next human it bites [27, 29].

1.2.2 Symptoms of Malaria

The amount of time between the mosquito bite and the appearance of symptoms varies depending on the strain of parasite involved. The incubation period is usually

between 8 to 12 days for falciparum malaria, but it can be as long as a month for the other types. Symptoms from some strains of P. vivax may not appear until 8 to 10 months after the mosquito bite occurred. The primary symptom of all types of malaria is the "malaria ague" (chills and fever), in most cases, the fever has three stages, beginning with uncontrollable shivering for an hour or two, followed by a rapid spike in temperature (as high as 41^0C) which lasts three to six hours, and suddenly the patient begins to sweat profusely which will bring down the fever. Other symptoms may include fatigue, severe headache or nausea and vomiting, as the sweating subsides, the patient typically feels exhausted and falls asleep. In many cases, this cycle of chills, fever and sweating occurs every other day or every third day and may last for between a week and a month. Those with the chronic form of malaria may have a relapse as long as 50 years after the initial infection [27, 29].

1.2.3 Treatment

Falciparum malaria is a medical emergency that should be treated in the hospital. The type of drugs, method of administration and length of the treatment depend on where the malaria was contracted and how sick the patient is. Except for falciparum, the treatment for malaria is usually Chloroquine (Aralen) taken by mouth for three days, strains of falciparum suspected to be resistant to chloroquine are usually treated with a combination of quinine and tetracycline. In countries where quinine resistance is developing, other treatments may include Clindamycin (Cleocin), Mefloquin (Lariam) or Sulfadoxone/Pyrimethamine (Fansidar). Those who are very ill may need intensive care and intravenous (IV) malaria treatment for the first three days. Chloroquine is an early antimalarial drug first used in the 1940s, but it lost its effectiveness against Plasmodium falciparum, the deadliest of the malaria parasites, however, it is still used in many African countries because

of its affordability [27, 29].

1.2.4 Control

Malaria control requires an integrated approach, comprising of prevention (basically vector control) and treatment with effective antimalarial drug [73]. The increase in drug resistance to the antimalarial drugs has intensified the need for a malaria vaccine, a new candidate for malaria vaccine with the potential to neutralise all strains of the most deadly species of malaria parasite has been developed and the Phase III efficacy trials in Burkina-Faso, Gabon, Ghana, Kenya, Malawi, Mozambique and Tanzania have shown that it offers protection of about 18 months, it was particularly observed that it nearly reduced to half the total number of malaria cases in young children (aged 5-17 months at first vaccination) and to around a quarter of the malaria cases in infants (aged 6-12 weeks at first vaccination) [29, 61].

Mathematical modeling plays some vital and important roles in quantifying the effects of disease control strategies and helps in determining which strategies are more effective in the control or even eradication process.

1.2.5 Prognosis and prevention

If treated in the early stages, malaria can be cured. Those who live in areas where malaria is endemic can however, contract the disease repeatedly and may not fully recover between bouts of acute infection. The complex life cycle of the parasite makes it difficult to develop a vaccine for it. A parasite has much more genetic material than a virus or bacterium, for that reason, it has been difficult to develop a successful vaccine. Malaria is an especially difficult disease to prevent by vaccination because the parasite goes through several separate stages [29].

The World Health Organization (WHO) has been trying to eliminate malaria for the past 30 years by controlling mosquitoes, their efforts were successful as long as the pesticides dichlorodiphenyltrichloroethane (DDT) kills mosquitoes and antimalarial drugs cure those who were infected. However, the problem has returned a hundredfold, especially in Africa, because the parasite is now extremely resistant to the insecticides designed to kill it, governments are now trying to teach people to take antimalarial drugs as a preventive medicine and avoid getting bitten by mosquitoes [27, 71].

Chapter 2

Mathematical and Epidemiological Preliminaries

2.1 Mathematical Preliminaries

This section provides the basic mathematical theories and methodologies required, in the analysis and understanding of the results presented in subsequent chapters. Throughout this section, for any $n \in \mathbb{N}$, we denote by $\mathbb{R}^n$ the Euclidean space of dimension n.

2.1.1 Equilibria of linear and non-linear autonomous systems

Consider the system of differential equation below,

$$\dot{x} = f(x,t) \quad x(0) = x_0. \tag{2.1}$$

Here $f : U \times \mathbb{R}_+ \to \mathbb{R}^n$ with $x \in U \subset \mathbb{R}^n$, $t \in \mathbb{R}_+$, $n \in \mathbb{N}$, and U open in $\mathbb{R}^n$. The over dot in (2.1) represents the derivative with respect to time ($\frac{d}{dt}$) and (2.1) is referred to as a vector field on $\mathbb{R}^n$ or ordinary differential equation.

Vector fields which explicitly depend on time are called non-autonomous, while vector fields that are independent of time are called autonomous, we will be restricted to the autonomous type in this work, hence, for $x \in U \subset \mathbb{R}^n$,

$$\dot{x} = f(x), \quad x(0) = X \in \mathbb{R}^n. \tag{2.2}$$

Definition 2.1.1. By a solution of (2.2), we mean a continuously differentiable function $x : I(X) \to \mathbb{R}^n$ such that $x(t)$ satisfies (2.2) [66].

Definition 2.1.2. System (2.2) defines a dynamical system in a subset $E \subset \mathbb{R}^n$ if, for every $X \in E$, there exist a unique solution of (2.2) defined for all $t \in \mathbb{R}_+$ [66].

Definition 2.1.3. Let U be an open subset of $\mathbb{R}^n$. A function $f : U \to \mathbb{R}^n$ is Lipschitz if for all $x, y \in U$, there is a K called Lipschitz constant such that

$$||f(x) - f(y)|| \leq K||x - y||.$$

Here $||.||$ stands for the Euclidean norm in $\mathbb{R}^n$. If f is Lipschitz on every bounded subset of $\mathbb{R}^n$, then f is said to be globally Lipschitz [51].

Theorem 2.1.1. Let $f : \mathbb{R}^n \to \mathbb{R}^n$ be globally Lipschitz on $\mathbb{R}^n$. Then there exist a unique solution $x(t)$ to (2.2) $\forall\ t \in \mathbb{R}_+$. Therefore (2.2) defines a dynamical system in $\mathbb{R}^n$ [66].

Definition 2.1.4. An equilibrium (fixed) point of (2.2) is a point $\bar{x} \in \mathbb{R}$ such that $f(\bar{x}) = 0$.

Clearly, the constant function $x(t) \equiv \bar{x}$ is a solution of (2.2) and by uniqueness of solutions, no other solution curve can pass through $\bar{x}$.
If U is the state space of some biological systems described by (2.2), then $\bar{x}$ is an equilibrium state if when the system starts at $\bar{x}$ it will always be at $\bar{x}$ [70].

Theorem 2.1.2. Consider (2.1) where $f(x,t) \in C^r, r \geq 1$, on some open set $U \subseteq \mathbb{R}^n \times \mathbb{R}_+$, and let $(x_0, t_0) \in U$. Then there exist a local solution to the equation through the point x_0 at $t = t_0$ denoted by $x(t, t_0, x_0)$ with $x(t_0, t_0, x_0) = x_0$ for $\mid t - t_0 \mid$ sufficiently small. This solution is unique in the sense that any other solution through x_0 at $t = t_0$ must be the same as $x(t, t_0, x_0)$ on their common interval of existence. Moreover $x(t, t_0, x_0)$ is a C^r function of t, t_0 and x_0 [70].

Theorem 2.1.3. Let $C \subset U \subseteq \mathbb{R}^n \times \mathbb{R}_+$ be a compact set containing (x_0, t_0). The solution $x(t, t_0, x_0)$ can be uniquely extended forward in t up to the boundary of C [44, 70].

Theorem 2.1.4. Gronwall Lemma Let $x(t)$ satisfy

$$\frac{dx}{dt} \leq px + q, \quad x(0) = x_0,$$

for p, q constants. Then for $t \geq 0$

$$x(t) \leq e^{pt}x_0 + \frac{q}{p}(e^{pt} - 1), \quad p \neq 0$$

and

$$x(t) \leq x_0 + qt, \quad p = 0 \quad [66].$$

2.1.2 Stability of solutions

Intuitively speaking, we say that an equilibrium point $\bar{x}(t)$ of the differential equation (2.2) is locally stable if all solutions starting near $\bar{x}(t)$ (meaning that the initial condition is in the neighborhood of $\bar{x}(t_0)$) at a given time remains near $\bar{x}(t)$ for all later times. It is locally asymptotically stable if it is locally stable and furthermore, all solutions starting near $\bar{x}(t)$ tend to $\bar{x}(t)$ as $t \longrightarrow \infty$. These concepts are formally defined as:

Definition 2.1.5. Let $\bar{x} \in \mathbb{R}^n$ be an equilibrium point of a dynamical system on E defined by (2.2). Then $\bar{x}$ is said to be:

1. stable if for any $\epsilon > 0$, there exist $\delta = \delta(\epsilon) > 0$ such that if $||\bar{x}(0) - y(0)|| < \delta$, then, $||\bar{x}(t) - y(t)|| < \epsilon$ for all $t \geq 0$,

2. locally attractive if $||\bar{x}(t) - y(t)|| \to 0$ as $t \to \infty$ for all $||\bar{x} - y(0)||$ sufficiently small,

3. locally asymptotically stable if $\bar{x}$ is stable and locally attractive. For an asymptotically stable equilibrium point $\bar{x}$ of (2.2), the set of all initial data $x(0)$ such that
$$\lim_{t \to \infty} \Phi(t)x(0) = \bar{x}$$
is said to be the basin of attraction of $\bar{x}$,

4. globally attractive if (2) holds for any $x(0) \in E$, i.e. the basin of attraction of $\bar{x}$ is E,

5. globally asymptotically stable if (1) and (4) hold,

6. unstable if (1) fails

2.1.3 Hartman-Grobman theorem

Definition 2.1.6. The Jacobian matrix of f at the equilibrium $\bar{x}$, denoted by $Df(\bar{x})$, is the matrix

$$\begin{pmatrix} \frac{\partial f_1}{\partial x_1}(\bar{x}) & . & . & . & \frac{\partial f_1}{\partial x_n}(\bar{x}) \\ . & . & & & . \\ . & & . & & . \\ . & & & . & . \\ \frac{\partial f_n}{\partial x_1}(\bar{x}) & . & . & . & \frac{\partial f_n}{\partial x_n}(\bar{x}) \end{pmatrix},$$

of partial derivatives of f evaluated at $\bar{x}$ [51].

It is not generally easy to investigate the stability and asymptotic stability of an equilibrium solution of (2.2) using Definition 2.1.5 and 2.1.6. The easiest way is by considering the linearized form of (2.2) given by

$$\dot{U} = JU \tag{2.3}$$

near $\bar{x}(t)$ where J is the Jacobian of the function f at $\bar{x}$. It is assumed that f is differentiable.

Definition 2.1.7. Let $x = \bar{x}$ be an equilibrium solution of (2.2), $\bar{x}$ is called a hyperbolic equilibrium point if none of the eigenvalues of $Df(\bar{x})$ have zero real part [70]. An equilibrium point that is not hyperbolic is called non hyperbolic.

Let X and Y be two topological spaces.

Definition 2.1.8. A function $f : X \to Y$ is a homeomorphism if it is continuous, bijective with a continuous inverse [51].

Definition 2.1.9. A function $h : X \to Y$ is a C^1 diffeomorphism if it is invertible and both h and it's inverse h^{-1} are C^1 maps [51].

Consider two functions $f : \mathbb{R}^n \to \mathbb{R}^n$ and $g : \mathbb{R}^m \to \mathbb{R}^m$.

Definition 2.1.10. f and g are said to be conjugate if there exist a homeomorphism $h : \mathbb{R}^n \to \mathbb{R}^m$ such that, the composition $goh = hof$ (sometimes written as $g(h(x)) = h(f(x))), x \in \mathbb{R}^n$ [51].

Definition 2.1.11. A $C^r(r \geq 1)$ function $\phi : U \times \mathbb{R}_+ \to \mathbb{R}^n$, $U \subset \mathbb{R}^n$ is called a flow for (2.2) if it satisfies the following properties

- $\phi(x_0, 0) = x_0$
- $\phi(x_0, s + t) = \phi(\phi(x_0, s), t)$

Definition 2.1.12. The set of all points in a flow $\phi(t; x_o)$ for (2.2) is called the orbit or trajectory of $f(x)$ with initial condition x_0, we write the orbit $\phi(x_0)$. When we consider $t \geq 0$, we say that, $\phi(t; x_o)$ is a forward orbit or forward trajectory.

Proposition 2.1.5. If f and g are C^k conjugate, then the orbits of f maps to the orbits of g under h, as f, g and h were defined in Definition 2.1.12.

Proposition 2.1.6. If f and g are C^k conjugate, $k \geq 1$, and x_0 is a fixed point of f, then the eigenvalues of $Df(x_0)$ are equal to the eigenvalues of $Dg(h(x_0))$.

Theorem 2.1.7. (Hartman and Grobman) Assume that $f : \mathbb{R}^n \to \mathbb{R}^n$ is of class C^1 and consider a hyperbolic equilibrium point $\bar{x}$ of the dynamical system defined by (2.2). Then there exist $\delta > 0$, a neighborhood $\mathcal{N} \subset \mathbb{R}^n$ of the origin and a homeomorphism h defined from the ball $B = \{x \in R^n : ||x - \bar{x}|| < \delta\}$ onto $\mathcal{N}$ such that

$$u(t) = h(x(t)) \text{ solves (2.3) if and only if } x(t) \text{ solves (2.2).}$$

The direct application of the Hartman-Grobman theorem is that an orbit structure near a hyperbolic equilibrium solution is qualitatively the same as the orbit

structure given by the associated linearized (around the zero equilibrium) dynamical system.

Theorem 2.1.8. Suppose all of the eigenvalues of $Df(\bar{x})$ have negative real parts. Then the equilibrium solution $x = \bar{x}$ of the non linear vector field (2.2) is asymptotically stable [70].

2.1.4 Bifurcation Theory

Mathematical models of phenomena in applied sciences like medicine, biology, physics or engineering typically lead to equations depending on one or more parameters, which are allowed to vary over specified set (the parameter space).

Definition 2.1.13. Bifurcation can be defined as a qualitative change in dynamics of $\dot{x} = f(x, \mu)$ occurring upon a small change in the parameter (μ).

Bifurcation occurs at parameter values where the qualitative nature of the flow, such as the number of stationary points or periodic orbits change. If the stationary point $(\bar{x})$ is hyperbolic, a small perturbation of the system will not change the stability characteristics of the stationary point, hyperbolic stationary points are structurally stable, so local bifurcations occur at points in parameter space where a stationary point is non hyperbolic [64].

Definition 2.1.14. Consider a one-parameter family of one-dimensional vector field $\dot{x} = f(x, \mu)$, an equilibrium solution given by $(\bar{x}, \mu) = (0, 0)$ is said to undergo bifurcation at $\mu = 0$ if the flow for x near zero is not qualitatively the same as the flow near $x = 0$ at $\mu = 0$ [44].

There are several types of bifurcations but we are interested in only two in this dissertation, they are: forward and backward bifurcations, their definitions follow in the next section.

2.1.5 Lyapunov functions and LaSalle's invariance principle

Definition 2.1.5 and 2.1.6 are local, that is they describe the behavior of the system near an equilibrium point.

Definition 2.1.15. A function $V : \mathbb{R}^n \longrightarrow \mathbb{R}$ is said to be positive definite if,

- $V(x) > 0$, for all $x \neq 0$,
- $V(x) = 0$, if and only if $x = 0$,
- $V(x) \longrightarrow \infty$ as $x \longrightarrow \infty$.

The function V is locally positive definite if there exists $U \subset \mathbb{R}^n$ containing a fixed point $x = \bar{x}$ such that

- $V(\bar{x}) = 0$,
- $V(x) > 0$ for all $x \in U \backslash \{\bar{x}\}$.

Definition 2.1.16. Assume that (2.2) defines a dynamical system on an open subset $U \subset \mathbb{R}^n$ and $\bar{x}$ is an equilibrium point. A function $V \in C^1(U, \mathbb{R})$ is called a Lyapunov function of the system (2.2) for $\bar{x}$ on a neighborhood $B \subset U$ of $\bar{x}$ if

$$\dot{V}(x) := \lim_{h \to 0} \frac{V(x + hf(x)) - V(x)}{h} = \bigtriangledown V(x).f(x) \leq 0, \quad \forall x \in B, \tag{2.4}$$

where $\dot{V}(x)$ is the directional derivative of V in the direction of f. If in addition, $V(\bar{x}) = 0$ and $V(x) > 0$ $\forall x \in U \backslash \{\bar{x}\}$, then V is said to be a positive definite Lyapunov function at $\bar{x}$.

Theorem 2.1.9. Let V be a positive definite Lyapunov function of the dynamical system (2.2) on a neighbourhood U of an equilibrium point $\bar{x}$. Then $\bar{x}$ is stable. If, in addition, $\dot{V}(x) < 0$ $\forall x \in U \backslash \{\bar{x}\}$, then $\bar{x}$ is asymptotically stable, and $\bar{x}$ is unstable if $\dot{V}(x) > 0$, $\forall x \in U \backslash \{\bar{x}\}$.

2.1.6 Limit sets and invariance principle

Since general epidemiology models deal with population of humans or animals, it is important to consider non negative populations, thus, epidemiological models should be considered in (feasible) regions where such property of non-negativity is preserved.

Definition 2.1.17. Let $x(t)$ be a solution of (2.2). A point p is said to be a positive limit of $x(t)$, if there exists a sequence $\{t_n\}$ with $t_n \longrightarrow \infty$ as $n \longrightarrow \infty$, such that $x(t_n) \longrightarrow p$ as $n \longrightarrow \infty$. The set of all positive limit points of $x(t)$ is called the positive limit set of $x(t)$.

Definition 2.1.18. Let ϕ be the flow of (2.1). A point $x_0 \in \mathbb{R}^n$ is called ω-limit point of $x \in \mathbb{R}^n$, denoted by $\omega(x)$, if there exists a sequence $\{t_n\}, t_n \longrightarrow \infty$ such that,

$$\phi(t_n, x) \longrightarrow x_0.$$

Similarly, a point $x_0 \in \mathbb{R}^n$ is called α-limit point of $x \in \mathbb{R}^n$, denoted by $\alpha(x)$, if there exists a sequence $\{t_n\}, t_n \longrightarrow -\infty$ such that,

$$\phi(t_n, x) \longrightarrow x_0.$$

The set of all ω-limit points of a flow is called the ω-limit set, while the set of all α-limit points of a flow is called the α-limit set [70].

Definition 2.1.19. A set M is said to be an invariant set with respect to the autonomous ordinary differential equation (2.2) if,

$$x(0) \in M \Rightarrow x(t) \in M, \forall t \in \mathbb{R}.$$

That is, if any trajectory starts in M, it will stay in M for all time [64].

If we restrict $t \geq 0$ in the above definition, then M is said to be positively invariant set. In other words, solutions in a positively invariant set remain there for all positive time.

Theorem 2.1.10. (LaSalle's invariance principle)
Let $\bar{x}$ be an equilibrium point of (2.2) defined on $\Omega \subset \mathbb{R}^n$. Let V be a positive definite Liapunov function for $\bar{x}$ on the set Ω. Furthermore let $\Omega_a = \{x \in \bar{\Omega} : \dot{V}(x) = 0\}$ and if

$$S = \{\text{the union of all trajectories that start and remain in } \Omega_a \text{ for all } t > 0\},$$

that is, S is the largest positively invariant subset of Ω_a such that $S \subset \Omega$, then $\bar{x}$ is globally asymptotically stable on Ω if and only if it is globally asymptotically stable on S [70].

2.1.7 Methods for local stability of equilibria

Here we will study two standard methods for analyzing the local stability of equilibria of disease transmission models.

2.1.8 Linearization

Determining the stability of an equilibrium (fixed) point $\bar{x}(t)$ requires the understanding of the nature of solutions near it. Let,

$$x = \bar{x}(t) + \epsilon. \tag{2.5}$$

If we substitute (2.5) in the general autonomous system (2.2) where f is at least twice differentiable and apply Taylor's expansion at $\bar{x}$ we get,

$$\dot{x} = \dot{\bar{x}} + \dot{\epsilon} = f(\bar{x}(t)) + Df(\bar{x}(t))\epsilon + O(|\epsilon|^2),$$

where $|.|$ is the Euclidean norm on $\mathbb{R}^n$. Hence,

$$\dot{\epsilon} = Df(\bar{x}(t))\epsilon + O(|\epsilon|^2). \tag{2.6}$$

Equation (2.6) describes the evolution of orbits near $\bar{x}$ [64, 37]. The behavior of the solutions arbitrarily close to $\bar{x}$ is obtained by studying the associated linear system,

$$\dot{\epsilon} = Df(\bar{x}(t))\epsilon. \tag{2.7}$$

However, if $\bar{x}(t)$ is an equilibrium solution, i.e $f(\bar{x}) = 0$, then $Df(\bar{x})$ is a matrix with constant entries, and the solution of (2.7) through the point $\epsilon_0 \in \mathbb{R}^n$ at $t = 0$ is given by,

$$\epsilon(t) = \exp(Df(\bar{x}(t)))\epsilon_0. \tag{2.8}$$

Theorem 2.1.11. Suppose all of the eigenvalues of $Df(\bar{x})$ have negative real parts, then, the equilibrium solution $x = \bar{x}$ of the non-linear system (2.2) is asymptotically stable [10, 37].

2.2 Epidemiological preliminaries

This section discusses some of the basic principles and methods associated with modeling in epidemiology. Epidemic models are used to describe rapid outbreaks that occur in less than one year, while endemic models are used for studying diseases over a longer periods, during which there is renewal of susceptibles by birth or recovery from partial immunity [43].

2.2.1 Incidence function

In this subsection, we give short descriptions of some of the most commonly used incidence functions, we refer to [43, 68] for more details on various incidence functions in mathematical epidemiology.

Consider a community where the total population is denoted by N, the susceptibles by S while the infectives by I. Disease incidence is defined as the infection rate of susceptible individuals through their contact with infectives [28]. Incidence in disease models is generally characterized by an incidence function (a function that describes the mixing pattern within the community). Infections are transmitted through contact. The number of times an infective individual comes into contact with other members per unit time is defined as the contact rate, it often depends on the total number N of individuals in the population, and it is denoted by a function $C(N)$. If the individuals contacted by an infected individual are susceptible, then they may be infected, assuming that the probability of infection by every contact is β_0, then the product $\beta_0 C(N)$ is called the effective contact rate, it shows the ability of an infected individual infecting others (depending on the environment, the toxicity of the virus or bacterium, etc). Since apart from the susceptibles, the individuals in other compartments of the population can not be infected when they make contact with the infectives, and the fraction of the susceptibles in the total

population is $\frac{S(t)}{N(t)}$, therefore, the mean adequate contact rate of an infective to the susceptible individuals is $\beta_0 C(N)\frac{S(t)}{N(t)}$, which is called the infective rate. Further, the total number of new infected individuals resulting per unit time at time t is $\beta_0 C(N)\frac{S(t)}{N(t)}I(t)$, which is called the incidence of the disease.

When $C(N) = kN$, that is the contact rate is proportional to the size of the total population, the incidence is $\beta_0 kS(t)I(t) = \beta S(t)I(t)$ (where $\beta_0 k = \beta$ is defined as the transmission coefficient) is called the bilinear incidence or simple mass-action incidence [68].

When $C(N) = k$, that is the contact rate is a constant, the incidence becomes $\beta_0 k\frac{S(t)}{N(t)}I(t) = \beta\frac{s(t)}{N(t)}I(t)$ (where $\beta_0 k = \beta$), this type of incidence function is termed as the standard incidence [68].

Conventionally, it is assumed that new cases are generated through homogeneous mixing, yielding either the mass action incidence term (independent of the total population as described above) or the standard incidence term (dependent on the total population), this assumption may be inaccurate, particularly under certain circumstances, examples where the incidence does not depend linearly on the number of currently infected individuals include, situations where a larger density of infected individuals decrease their per capita infectivity (saturation effect) and situations where multiple exposure to an infected individuals are required for transmission to occur (threshold effect) [11].

Other forms of contact rates were also proposed, such as those with saturation as introduced by Dietz in 1982 [68] and Heesterbeek and Metz in 1993 [10], with contacts respectively given by

$$C(N) = \frac{\alpha N}{1+\omega N}, \quad \text{and,} \quad C(N) = \frac{\alpha N}{1+bN+\sqrt{1+2bN}}$$

satisfying

$$C(0) = 0, \quad C'(N) \geq 0, \quad \left(\frac{C(N)}{N}\right)' \leq 0 \quad \lim_{N\to\infty} C(N) = C_0 \quad [68].$$

Moreover, other incidences for special cases such as $\beta S^p I^q$, $\frac{\beta S^p I^q}{N}$ were also introduced [68].

2.2.2 Reproduction number

One of the fundamental results in mathematical epidemiology is that, mathematical epidemic models, including those that have high degree of heterogeneity exhibit a threshold behavior. In epidemiological terms, this can be stated as follows: There is a difference in epidemic behavior when the average number of secondary infections caused by an average infective individual during his or her period of infectiousness, called the basic reproduction number, is less than one and when this quantity exceeds one [23]. The basic reproduction number R_0 is defined as the number of secondary infections caused by a single infectious individual introduced into a wholly susceptible population over the course of the infection of this single infectious individual [10]. The famous threshold criterion states that:

The disease can invade the population if $R_0 > 1$, whereas it cannot invade the population if $R_0 < 1$ [26, 28].

The course of the disease outbreak could be rapid enough that there are no significant demographic effects in the population, or there is flow of individuals into the population who may become infected, in either case, the disease will die out if the basic reproduction number is less than one, and if it is greater than one, there will be an epidemic. Mathematically, if $R_0 < 1$, the disease-free equilibrium is approached by solutions of the model describing the situation. If $R_0 > 1$, the disease-free equilibrium is unstable and solutions flow away from it. There is also

an endemic equilibrium, with a positive number of infective individuals, therefore, the disease remains in the population [23]. However, the situation may be more complicated with more than one stable equilibrium when the basic reproduction number is less than one.

2.2.3 Next generation method

Although the linearization is the standard method that is applied in the analysis of the stability of equilibria in general, the next generation method, which is also a linearization method is used to establish the local asymptotic stability of the disease-free equilibrium (DFE). The method was first introduced by Diekmann and Hesterbeek [26] and refined for epidemiological models by van den Driessche and Watmough [28], we shall follow the description in [10].

Consider a heterogeneous population whose individuals are distinguishable by their disease status and can be grouped into n homogeneous compartments. The idea is based on computing a matrix whose (i, j) element represents the number of secondary infections in compartment i caused by an individual in compartment j. We refer to disease compartment as the compartment where individuals are infected. We should note that, we will consider the disease compartment in a broader way compared to the clinical method hence it includes stages of infection like exposed stages in which infected individuals are not necessarily infective.
Suppose there are n disease compartments and m non disease compartments, and let $x \in \mathbb{R}^n$ and $y \in \mathbb{R}^m$ be the sub populations in each of these compartments. Further, we denote by $\mathfrak{F}_i$ the rate at which secondary infections increase the $i-th$ disease compartment and by $\mathcal{V}_i$ the rate at which disease progression, death, and recovery decrease the $i-th$ compartment. The compartmental model can then

be written in the form

$$\begin{aligned} x_i^{'} &= \mathfrak{F}_i(x,y) - \mathcal{V}_i(x,y), \quad i = 1,2,...n, \\ y_j^{'} &= \mathrm{g}_j(x,y), \quad j = 1,2,...,m. \end{aligned} \tag{2.9}$$

Note that the decomposition of the dynamics into $\mathfrak{F}$ and $\mathcal{V}$ and the designation of compartments as infected or uninfected may not be unique; different decompositions correspond to different epidemiological interpretations of the model.

The derivation of the basic reproduction number is based on the linearization of the ODE model about a disease-free equilibrium. For an epidemic model with a line of equilibria, it is customary to use the equilibrium with all members of the population susceptible. We assume:

- $\mathfrak{F}_i(0,y) = 0$ and $\mathcal{V}_i(0,y) = 0$ for all $y = 0$ and $i = 1,...,n$.
- The disease-free system $y^{'} = \mathrm{g}(0,y)$ has a unique equilibrium that is asymptotically stable, that is, all solutions with initial conditions of the form $(0,y)$ approach a point $(0,y_0)$ as $t \to \infty$. We refer to this point as the disease-free equilibrium.

The first assumption says that all new infections are secondary infections arising from infected hosts; there is no immigration of individuals into the disease compartments. It ensures that the disease-free set, which consists of all points of the form $(0,y)$, is invariant. That is, any solution with no infected individuals at some point in time will be free of infection for all time. The second assumption ensures that the disease-free equilibrium is also an equilibrium of the full system. The uniqueness of the disease-free equilibrium in the second assumption is required for models with demographics. Although it is not satisfied in epidemic models, the specification of a particular disease-free equilibrium with all members of the population susceptible is sufficient to validate the results.

Next, we assume:

- $\mathfrak{F}_i(x, y) \geq 0$ for all nonnegative x and y and $i = 1, ..., n$.
- $\mathcal{V}_i(x, y) \leq 0$ whenever $x_i = 0, i = 1, ..., n$.
- $\sum_{i=1}^{n} \mathcal{V}_i(x, y) \geq 0$ for all nonnegative x and y.

The reasons for these assumptions are that the function $\mathfrak{F}$ represents new infections and cannot be negative, each component $\mathcal{V}_i$ represents a net outflow from compartment i and must be negative (inflow only) whenever the compartment is empty, and the sum $\sum_{i=1}^{n} \mathcal{V}_i(x, y)$ represents the total outflow from all infected compartments. Terms in the model leading to increases in $\sum_{i=1}^{n} x_i$ are assumed to represent secondary infections and therefore belong to $\mathfrak{F}$.

Suppose that a single infected person is introduced into a population originally in the absence of disease. The initial ability of the disease to spread through the population is determined by an examination of the linearization of (2.9) about the disease-free equilibrium $(0, y_0)$. It is easy to see that the assumption $\mathfrak{F}_i(0, y) = 0, \mathcal{V}_i(0, y) = 0$ implies

$$\frac{\partial \mathfrak{F}_i}{\partial y_j}(0, y_0) = \frac{\partial \mathcal{V}_i}{\partial y_j}(0, y_0) = 0$$

for every pair (i, j). This implies that the linearized equations for the disease compartments x are decoupled from the remaining equations and can be written as

$$x^{'} = (F - V)x, \tag{2.10}$$

where F and V are the $n \times n$ matrices with entries

$$F = \frac{\partial \mathfrak{F}_i}{\partial x_j} \quad \text{and} \quad V = \frac{\partial \mathcal{V}_i}{\partial x_j}.$$

Because of the assumption that the disease-free system $y^{'} = \mathrm{g}(0, y)$ has a unique asymptotically stable equilibrium, the linear stability of the system (2.9) is completely determined by the linear stability of the matrix $(F - V)$ in (2.10).

The number of secondary infections produced by a single infected individual can be expressed as the product of the expected duration of the infectious period and the rate at which secondary infections occur [10].

Definition 2.2.1. The Matrix $K = FV^{-1}$ is referred to as the next generation matrix for the system (2.9) at the disease-free equilibrium [10].

The (i, j) entry of K is the expected number of secondary infections in compartment i produced by individuals initially in compartment j, assuming, of course, that the environment experienced by the individual remains homogeneous for the duration of its infection [10].

Lemma 2.2.1. The basic reproduction number $R_0 = \rho(FV^{-1})$ and the disease-free equilibrium is asymptotically-stable if $R_0 < 1$ and unstable if $R_0 > 1$ [10].

2.2.4 Backward Bifurcations

Bifurcation analysis is the mathematical study of changes in the solutions of the system of differential equations when changing the parameters. These qualitative changes in the dynamics of the system are called bifurcations. The parameter values where they occur are called bifurcation points. By analyzing the existence of behavior of the model in such points, one can derive much about the systems properties. It is well known in disease transmission modeling that a disease can be eradicated when the basic reproduction number $R_0 < 1$.

However, when a backward bifurcation occurs, stable endemic equilibria may also exist for $R_0 < 1$, this means that the condition that $R_0 < 1$ is only a necessity but not sufficient to guarantee the elimination of the disease, indeed,

the quantity R_0 must be reduced further to avoid endemic states and guarantee eradication. The scenario is qualitatively described as follows: in the neighborhood of 1, for $R_0 < 1$, a stable disease-free equilibrium coexists with stable endemic equilibrium. The endemic equilibrium disappears by saddle-node bifurcation when R_0 is decreased below a critical value $R_c < 1$ [14, 39].

Definition 2.2.2. A forward bifurcation occurs when R_0 crosses unity from below; a small positive asymptotically-stable equilibrium appears and the disease-free equilibrium losses its stability. Backward bifurcation happens when R_0 is less than unity; a small positive unstable equilibrium appears while the disease-free equilibrium and a larger positive endemic equilibrium are locally-asymptotically stable [16].

Chapter 3

Basic malaria model and analysis

3.1 Introduction

Malaria infection starts with a bite and injection of sporozoites by an infectious mosquito, the sporozoites are taken to the liver cells where they asexually reproduce uninucleate merozoites, they flow into and invade the red blood cells which result to the disease. Some merozoites evolve to male and female gametocytes that circulate the peripherals of the blood until they are taken by a female mosquito [22, 30].

The gametocytes taken by mosquito develop into male and female gametes, they fertilize and form zygotes within the lumen of the mosquitos gut, the zygotes penetrate the guts wall and form oocytes, multiplication occurs within the oocytes which results in the formation of sporozoites that move to the salivary glands [24, 30]. Figure 3.1 summarizes the process.

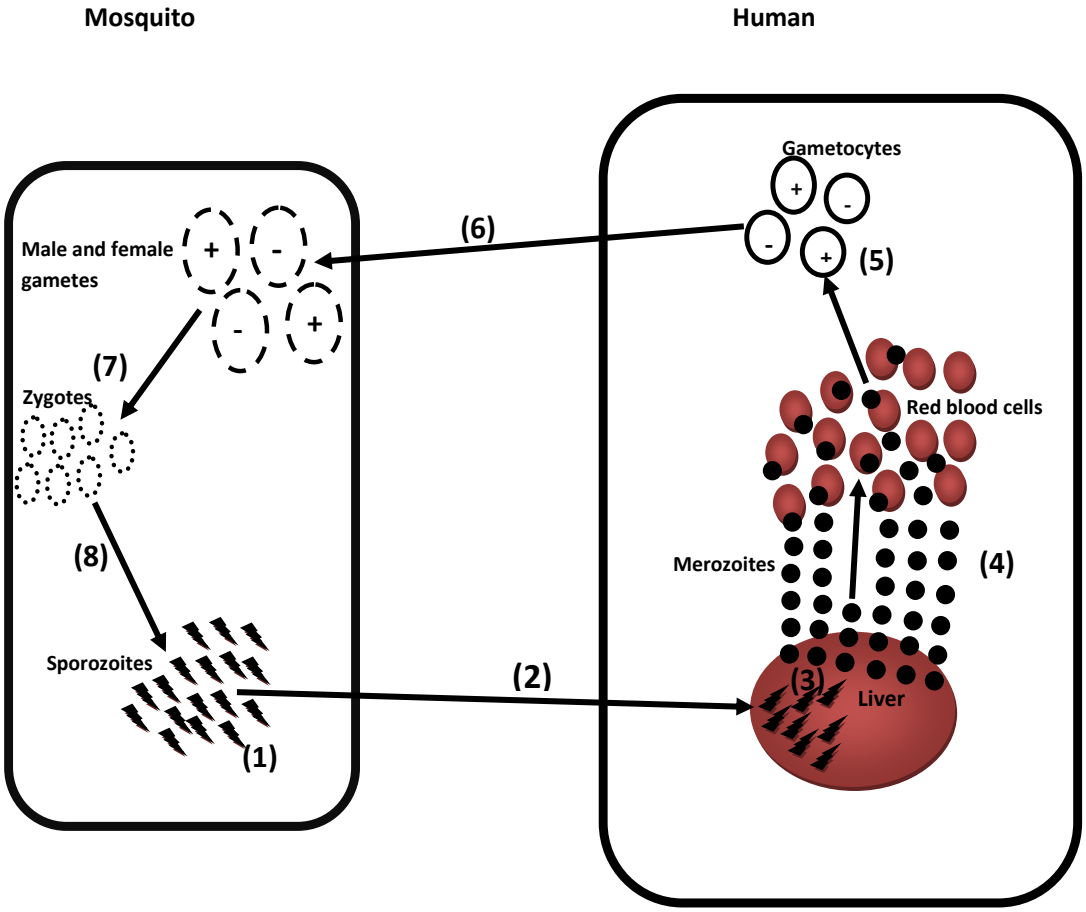

Figure 3.1: Life cycle of Plasmodium:- (1) Sporozoites in salivary glands of an infected mosquito, (2) Sporozoites transported to liver cells, (3) Invasion of liver cells and production of merozoites, (4) Flow and invasion of red blood cells by the merozoites, (5) Merozoites that developed into male and female gametocytes and circulate the peripherals of blood, (6) Taking up of gametocytes by a susceptible mosquito which mature to male and female gametes, (7) Fertilized zygotes which produce sporozoites, (8) Movement of sporozoites to salivary glands of a mosquito.

Modeling the transmission dynamics of malaria can be dated back to 1911 when Sir Ronald Ross, the 1902 Nobel prize winner in physiology constructed and analysed a mathematical model that captures the transmission dynamics of malaria in the second edition of his book, The Prevention of Malaria in 1911 [13, 60]. Kermack and McKendrick collaborated and worked on different epidemic models including Ross's work on malaria [13].

Since then, there has been surge in the development of new models which attempt to capture as much as possible, essential dynamical features in the transmission dynamics of malaria, some of which include: J.C. Aron [7], N. Chitnis et al. [20, 21], J.C. Koella [48], S. Mandal [50], Ngwa and Shu [53], F.T. Oduro et al. [55]. In this dissertation, following some recent facts on malaria pathogenesis [22, 24, 30, 54], we attempted to improve on the afore mentioned work, for instance by incorporating additional compartment for the vaccinated individuals and allowing for malaria transmission by the exposed individuals.

3.2 Model formulation

The model considered in this study consists of seven non intersecting compartments describing the dynamics of the disease, the first four of the compartments represent the human population while the remaining three represent the mosquito population.

The state vector for the model is given by $(S_H,\ E_H,\ I_H,\ R_H,\ S_V,\ E_V,\ I_V)$, where the various state variables respectively represent the populations of susceptible humans, exposed humans, infected humans, recovered humans, susceptible mosquitoes, exposed mosquitoes and infected mosquitoes. The total human population, denoted by N_H is given by $N_H = S_H + E_H + I_H + R_H$, while the total mosquito population, also denoted by N_V is given by $N_V = S_V + E_V + I_V$.

At any time t, the susceptible humans have either never had malaria or they have recovered from it without having partial immunity at that time, hence they are prone to infection, they can get the disease after receiving sufficient amount of bites capable of transmission either from an infected or exposed mosquito. Human infectivity increases with the increase in the amount of gametocytes in a typical blood meal [30], so that the class of humans at an early stage of infection (do not typically show physical sign of infection but they are clinically infectious) are considered exposed, they can probably transmit the disease to a susceptible mosquito, though with a reduced probability compared with infected humans, for that reason we introduce a parameter η_H $(0 < \eta_H < 1)$ to cater for the reduction in the transmissibility. Infected humans are at the stage where the amount of gametocytes in the blood compelled physical signs of the disease, high fever, vomiting, etc., they are assumed to transmit the disease to mosquitoes whenever they bite them, the disease is at its peak, because they have shown signs of infectivity, they may undergo treatment.

Infectious gametocytes could be found in the blood for many days after a malaria patient has been treated with the artemisinin-based combination therapy and likely doing better, nonetheless, the artemisinin-based combination therapy is the recommended and most widely used, this happens because it primarily targets the asexual stage of malaria parasite [8, 46, 57, 67], with this fact, recovered humans may still be infectious and some of them may have partial immunity, we similarly use the parameter η_R $(0 < \eta_R < 1)$ to cater for the reduction in the transmissibility of the recovered humans in comparison to the infected humans, on receiving bites, fraction of individuals in the recovered class progress to the exposed class, while the gametocytes completely dies out or their immunity wanes without getting reinfection to move to the susceptible class.

The susceptible vectors consist of mosquitoes that have never had malaria but they

can get infection either from an exposed, infected or recovered humans, afterwards, they move to the exposed class, a class where they can infect a susceptible human, although with a reduction in transmissibility in comparison with the infected mosquitoes, we again introduce a parameter η_V $(0 < \eta_V < 1)$ to account for the reduction, the increase in the amount of the parasite to a stage when each bite is capable of disease transmission transfers the vector from the exposed to the infected class, once a mosquito is infected, it lives with the infection to the end of its life.

3.2.1 Incidence function

Here, we formulated the functional form of the standard incidence function used in the transmission dynamics of malaria. Similar to those in [9, 34, 35], the formulation was based on the fact that anopheles mosquitoes bite humans only, so that in any community, the average number of bites by anopheles mosquitoes is equal to the average number of bites received by humans. Furthermore, we assumed that, each bite by an infectious (exposed or infected) mosquito has an equal probability of transmitting the disease to a susceptible human in the population, or susceptible mosquito acquiring infection from infectious (exposed, infected or recovered) human. The force of infection of the humans (the rate at which new infections occur in human population) is therefore given by:

$$\lambda_H = \frac{C_{VH}}{N_V}(\eta_V E_V + I_V), \tag{3.1}$$

while, the force of infection of the mosquito (the rate at which new infections occur in the mosquito population) is also given by:

$$\lambda_V = \frac{C_{HV}}{N_H}(\eta_H E_H + I_H + \eta_R R_H). \tag{3.2}$$

As previously discussed, the parameters $0 < \eta_V, \eta_H, \eta_R < 1$ account for the reduction in the transmissibility of an exposed mosquito relative to an infected mosquito, exposed and recovered humans relative to an infected humans, respectively. C_{HV} represents the effective contact rate of mosquitoes (contact capable of leading to infection from human to mosquito), it is the product of the transmission probability from humans to mosquitoes (P_{HV}) and the average biting rate of susceptible mosquitoes (b_s), that is,

$$C_{HV} = P_{HV} b_s.$$

Similarly, C_{VH} represents the effective contact rate of humans (contact capable of leading to infection from mosquito to human) defined as the product of the transmission probability from mosquitoes to humans (P_{VH}) and the average biting rate of infectious (infected or exposed) mosquitoes (b_i), such that,

$$C_{VH} = P_{VH} b_i.$$

The fact that anopheles mosquitoes feed on human blood [54, 74], together with the assumption that both humans and mosquitoes live in the same community, the conservation of the total number of bites in the population implies that, the total number of bites by the mosquito population should be equal to the total number of bites received by humans, and since each mosquito bite has equal probability of disease transmission we have,

$$C_{HV} N_V = C_{VH}(N_H, N_V) N_H. \tag{3.3}$$

Assuming that, in any population with homogeneous mixing of humans and mosquitoes, $C_{HV} \neq 0$, therefore we have,

$$N_V = \frac{C_{VH}(N_H, N_V)N_H}{C_{HV}}, \tag{3.4}$$

which implies that,

$$\lambda_H = \frac{C_{HV}}{N_H}(\eta_V E_V + I_V). \tag{3.5}$$

3.2.2 Model equation

The susceptible human population is generated either by birth or immigration at a constant rate Π_H, or from recovered humans at the rate $(1-\pi)\xi_H$, where $0 \leq \pi < 1$ with $\pi = 0$ representing the case when all recovered humans are immune from mosquito bites and hence, either their partial immunity wanes out or they totally recover without partial immunity and move to the susceptible class, the population decreases due to infection at the rate λ_H, or as a result of natural death at the rate μ_H, thus, the rate at which the susceptible human population changing is given by:

$$\frac{dS_H}{dt} = \Pi_H + (1-\pi)\xi_H R_H - S_H(\lambda_H + \mu_H).$$

The population of the exposed humans is generated either through the infection of susceptible humans at the rate λ_H, and by reinfection of recovered humans at the rate $\pi\xi_H$, it decreases due to disease progression at the rate τ_H, and natural death at the rate μ_H, such that:

$$\frac{dE_H}{dt} = S_H\lambda_H + \pi\xi_H R_H - E_H(\tau_H + \mu_H).$$

Infected human population is generated from the exposed class at the rate τ_H, and decreases as a result of the disease induced death at the rate δ_H, due to natural death at μ_H, or progression to the recovered class at the rate θ_H, so that:

$$\frac{dI_H}{dt} = E_H\tau_H - I_H(\theta_H + \delta_H + \mu_H).$$

The population of recovered individuals is generated by the recovery of infected humans at the rate θ_H. It decreases due to progression to susceptible and exposed humans (because of immunity wanning and reinfection respectively), and due to natural death, so that:

$$\frac{dR_H}{dt} = I_H\theta_H - R_H(\xi_H + \mu_H).$$

In a similar way, the population of the mosquitoes changes, except for the fact that once a mosquito is infected, it lives with the infection until it dies [24].
The following system of non-linear ordinary differential equations represents the dynamics of the model.

$$\begin{aligned}
\frac{dS_H}{dt} &= \Pi_H + (1-\pi)\xi_H R_H - S_H(\lambda_H + \mu_H),\\
\frac{dE_H}{dt} &= S_H\lambda_H + \pi\xi_H R_H - E_H(\tau_H + \mu_H),\\
\frac{dI_H}{dt} &= E_H\tau_H - I_H(\theta_H + \delta_H + \mu_H),\\
\frac{dR_H}{dt} &= I_H\theta_H - \xi_H R_H - \mu_H R_H,\\
\frac{dS_V}{dt} &= \Pi_V - \lambda_V S_V - \mu_V S_V,\\
\frac{dE_V}{dt} &= S_V\lambda_V - \tau_V E_V - \mu_V E_V,\\
\frac{dI_V}{dt} &= E_V\tau_V - \delta_V I_V - \mu_V I_V,
\end{aligned} \tag{3.6}$$

The restriction on the initial population arises from the fact that, the variables describe the dynamics of human and mosquito populations, therefore, for the model to be biologically meaningful, all the initial conditions and parameters must be non-negative. Thus $S_H(0) > 0$, $E_H(0) \geq 0$, $I_H(0) \geq 0$, $R_H(0) \geq 0$, $S_V(0) > 0$, $E_V(0) \geq 0$, $I_V(0) \geq 0$.

The model represented by (3.6) extends numerous malaria transmission models in the literature, such as those in [20, 21, 50, 53, 55] by:

- Allowing for malaria transmission by the exposed humans and vectors.
- Allowing the movement of a fraction of recovered individuals to the exposed class.
- Introducing modification parameters in the transmission of the recovered and exposed individuals.
- Analysing malaria model with mass action incidence function.
- Incorporating additional compartment for the vaccinated individuals.

None of these extensions were considered in any of [20, 21, 50, 53, 55]. The model is represented by the flow chart in Figure 3.2 and Table 3.1 gives the description of the parameters used in the model for the human and mosquito populations:

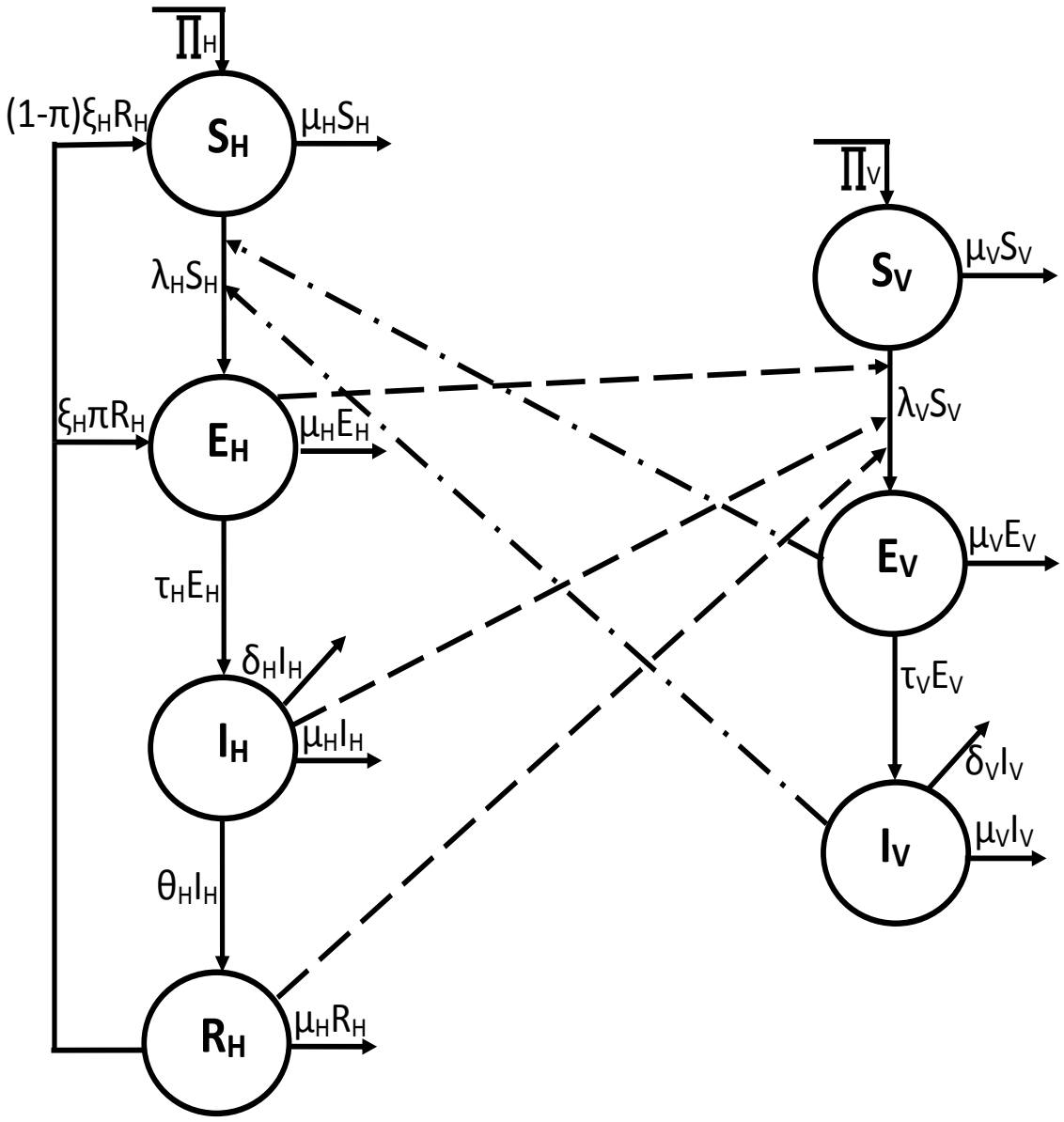

Figure 3.2: Model flow chart

Table 3.1: Parameters descriptions in both human and mosquito populations

Parameter	Interpretation	Dimension
Π_H	Recruitment rate of humans	Humans$\times$day^{-1}
λ_H	Transmission rate of humans	Day $^{-1}$
μ_H	Natural death rate of humans	Humans$\times$day^{-1}
τ_H	Progression rate from exposed to infected humans	Day^{-1}
δ_H	Disease induced death rate of humans	Day^{-1}
θ_H	Progression rate from infected to recovered humans	Day^{-1}
ξ_H	Progression rate from recovered to exposed humans	Day^{-1}
π	Modification parameters in humans population	
η_H	Reduction in infectiousness of exposed humans	
η_R	Reduction in infectiousness of recovered humans	
Π_V	Recruitment rate of mosquitoes	Mosquitoes$\times$day^{-1}
λ_V	Transmission rate of mosquitoes	Day $^{-1}$
μ_V	Natural death rate of mosquitoes	Mosquitoes$\times$day^{-1}
τ_V	Progression rate from exposed to infected mosquitoes	Day^{-1}
δ_V	Disease induced death rate of mosquitoes	Day^{-1}
η_V	Modification parameter in mosquito population	
σ_H	Vaccination rate of susceptible humans	Day^{-1}
ρ	Vaccination rate of newly recruited people	Day^{-1}
φ_H	Vaccine waning rate	
ϵ	Vaccine efficacy	

3.3 Basic properties of the model

Here we explore some of the basic dynamical properties of system (3.6).

3.3.1 Existence, positivity and boundedness of solutions

For the model represented by (3.6), with non-negative initial populations to be biologically meaningful and consistent, then, at any time t, all the state variables must remain non-negative and bounded.

Theorem 3.3.1. The solution $\big(S_H(t), E_H(t), I_H(t), R_H(t), S_V(t), E_V(t), I_V(t)\big)$ of the system (3.6) with non-negative initial condition exist for all $t \geq 0$ and is unique. Furthermore, it is positive and bounded for all $t \geq 0$.

Proof. It easy to see that each of the right hand side of (3.6) and its partial derivative with respect to the variables exist and continuous, by the existence and uniqueness theorem, the solution to the initial value problem (3.6) exist and it is unique locally [51, 70].

Observe that the system represented by (3.6) is monotone with positive initial condition and a local unique solution, therefore by applying proposition B.7 of [63] we can conclude that the solution is non-negative for all $t \geq 0$.

Furthermore, adding the first four and last three equations of system (3.6) we have:

$$\frac{dN_H}{dt} = \Pi_H - N_H\mu_H - \delta_H I_H, \tag{3.7}$$

and,

$$\frac{dN_V}{dt} = \Pi_V - N_V\mu_V - \delta_v I_V. \tag{3.8}$$

which implies,

$$\frac{dN_H}{dt} \leq \Pi_H - \mu_H N_H, \quad \text{and,} \quad \frac{dN_V}{dt} \leq \Pi_V - \mu_V N_V,$$

therefore, applying Gronwall lemma we have,

$$N_H(t) \leq N_H(0)e^{-t\mu_H} + \frac{\Pi_H}{\mu_H}(1 - e^{-t\mu_H}), \tag{3.9}$$

and,

$$N_V(t) \leq N_V(0)e^{-t\mu_V} + \frac{\Pi_V}{\mu_V}(1 - e^{-t\mu_V}). \tag{3.10}$$

which are bounded. □

Theorem 3.3.2. The model (3.6) is a dynamical system in the biologically-feasible region given by

$$\Omega = \left\{(S_H, E_H, I_H, R_H, S_V, E_V, I_V) \in \mathbb{R}^7_+ : N_H \leq \frac{\Pi_H}{\mu_H}, N_V \leq \frac{\Pi_V}{\mu_V}\right\},$$

Proof. It is clear from (3.9) and (3.10) that $N_H(t) \leq \frac{\Pi_H}{\mu_H}$ if $N_H(0) \leq \frac{\Pi_H}{\mu_H}$, and $N_V(t) \leq \frac{\Pi_V}{\mu_V}$ if $N_V(0) \leq \frac{\Pi_V}{\mu_V}$. Consequently, all solutions of the model with initial conditions in Ω remains in Ω for all $t > 0$ (the ω-limits set of the system are contained in Ω). Therefore the system represented by (3.6) is a dynamical system in Ω [66].

The implication of the theorem is that, model (3.6) is well-posed epidemiologically and mathematically in Ω [43], hence, it is sufficient to study qualitatively the dynamics of (3.6) in Ω.

3.4 Existence and stability of equilibria

Well constructed epidemic models support at least two equilibria, the disease-free equilibrium and the endemic equilibrium [17], though they may not explicitly be determined, but their existence can be shown. The existence and stability of the equilibria of system (3.6) are explored as follows.

3.4.1 Disease-free equilibrium (DFE)

In the absence of the disease (i.e. $\lambda_H = \lambda_V = 0 \Rightarrow, E_H = I_H = R_H = E_V = I_V = 0$), we obtain an equilibrium point known as the disease-free equilibrium (DFE) by setting the right hand side of (3.6) to be equal to zero, such that,

$$\begin{aligned} \Pi_H - S_H\mu_H = 0 \Rightarrow S_H = \frac{\Pi_H}{\mu_H}, \quad E_H = 0, \quad I_H = 0, \quad R_H = 0, \\ \Pi_V - S_V\mu_V = 0 \Rightarrow S_V = \frac{\Pi_V}{\mu_V}, \quad E_V = 0, \quad I_V = 0, \end{aligned} \tag{3.11}$$

and therefore, from (3.11) the DFE is given by,

$$P_0 = (S_H^*, E_H^*, I_H^*, R_H^*, S_V^*, E_V^*, I_V^*) = \left(\frac{\Pi_H}{\mu_H}, 0, 0, 0, \frac{\Pi_V}{\mu_V}, 0, 0\right). \tag{3.12}$$

The local stability of P_0 can be established using the next generation operator method on the system (3.6) [28]. For P_0, the vector of appearance of new infections and that of the transfers out of and into the compartments are respectively given by:

$$\mathfrak{F} = \begin{pmatrix} S_H\frac{C_{HV}}{N_H}(\eta_V E_V + I_V) \\ 0 \\ 0 \\ S_V\frac{C_{HV}}{N_H}(\eta_H E_H + I_H + \eta_R R_H) \\ 0 \end{pmatrix}, \quad \mathcal{V} = \begin{pmatrix} E_H K_1 - \pi\xi_H R_H \\ I_H K_2 - E_H\tau_H \\ R_H K_3 - I_H\theta_H \\ E_V K_4 \\ I_V K_5 - E_V\tau_V \end{pmatrix},$$

where,

$K_1 = \mu_H + \tau_H, \quad K_2 = \mu_H + \delta_H + \theta_H, \quad K_3 = \mu_H + \xi_H, \quad K_4 = \mu_V + \tau_V$ and,

$K_5 = \mu_V + \delta_V$.

The matrix of the partial derivatives of $\mathcal{F}$ and $\mathcal{V}$ with respect to the variables at the disease-free equilibrium P_0, represented by F and V are respectively given by:

$$F = \begin{pmatrix} 0 & 0 & 0 & C_{HV}\eta_V & C_{HV} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ \frac{C_{HV}S_V^*\eta_H}{N_H^*} & \frac{C_{HV}S_V^*}{N_H^*} & \frac{C_{HV}S_V^*\eta_R}{N_H^*} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

$$V = \begin{pmatrix} K_1 & 0 & -\xi_H\pi & 0 & 0 \\ -\tau_H & K_2 & 0 & 0 & 0 \\ 0 & -\theta_H & K_3 & 0 & 0 \\ 0 & 0 & 0 & K_4 & 0 \\ 0 & 0 & 0 & -\tau_V & K_5 \end{pmatrix},$$

Following [28, 41], the basic reproduction number of the system (3.6), which is the spectral radius of the next generation matrix (FV^{-1}) denoted by R_0 is given by,

$$R_0 = \rho(FV^{-1}) = \sqrt{\frac{C_{HV}^2 \Pi_V \mu_H (\eta_V K_5 + \tau_V)(K_2 K_3 \eta_H + K_3 \tau_H + \theta_H \tau_H \eta_R)}{\mu_V \Pi_H K_4 K_5 (K_1 K_2 K_3 - \theta_H \tau_H \xi_H \pi)}}.$$

Evaluating part of the denominator in R_0 we have,

$$K_1 K_2 K_3 - \theta_H \tau_H \xi_H \pi = (\mu_H + \tau_H)(\mu_H + \delta_H + \theta_H)(\mu_H + \xi_H) - \theta_H \tau_H \xi_H \pi,$$

$$= \mu_H K_3 \big(K_2 + \tau_H\big) + \tau_H \xi_H \big(\mu_H + \delta_H\big) + \tau_H \xi_H \theta_H \big(1 - \pi\big) > 0.$$

Observe that, if $\pi = 0$, then R_0 reduces to

$$R_0 = \rho(FV^{-1}) = \sqrt{\frac{C_{HV}^2 \Pi_V \mu_H (\eta_V K_5 + \tau_V)(K_2 K_3 \eta_H + K_3 \tau_H + \theta_H \tau_H \eta_R)}{\mu_V \Pi_H K_1 K_2 K_3 K_4 K_5}},$$

Thus, we claim the following result (Theorem 2 of [28]):

Lemma 3.4.1. The disease-free equilibrium (P_0) of the model (3.6) represented by (3.12) is locally asymptotically stable (LAS) if $R_0 < 1$, and unstable if $R_0 > 1$.

The basic reproduction number (R_0) of the disease, is the expected number of secondary cases produced, in a completely susceptible population, by a typical infective individual [26, 28].

On average, if $R_0 < 1$, an infected individual produces less than one new infection over the course of it's infectious period, and the disease dies out with time. On the contrary, if $R_0 > 1$, then, each infected individual produces on average, more than one new infection, and the disease can invade the population [4, 28].

The direct consequence of Lemma 3.4.1 is that, when the basic reproduction number is less than one, introducing a small number of infected mosquitoes into a community means there will be no disease outbreak, which means the disease eventually dies out, however we will later see that, the disease may still persist even when $R_0 < 1$.

3.4.2 Interpretation of R_0

The basic reproduction number is interpreted as follows: Through an effective contact with either an exposed human(E_H), an infected human(I_H), or a recovered human(R_H), susceptible mosquito can acquire infection. The number of infection by an exposed human (near the DFE) is given by the product of the infection rate of exposed human $\left(C_{HV}\ \eta_H\ \frac{\mu_H}{\Pi_H}\right)$, the average duration spent in the exposed class $\left(\frac{1}{K_1}\right)$, and the probability that an individual survives the infection through exposed, infected, and recovered class $\frac{K_1K_2K_3}{\left(K_1K_2K_3-\tau_H\theta_H\xi_H\pi\right)}$.
The number of infections generated by an infected human (near the DFE) is given by the product of its infection rate $\left(C_{HV}\ \frac{\mu_H}{\Pi_H}\right)$, the probability that an individual survives exposed class and move to the infected class $\frac{\tau_H}{K_1}$, the average duration spent in that class $\frac{1}{K_2}$, and the probability that an individual survives the infection through exposed, infected, and recovered class $\frac{K_1K_2K_3}{\left(K_1K_2K_3-\tau_H\theta_H\xi_H\pi\right)}$.
The number of infections caused by a recovered human near DFE is given by the product of its infection rate $\left(C_{HV}\ \eta_R\ \frac{\mu_H}{\Pi_H}\right)$, the probability that an individual survives exposed class and move to the infected class $\frac{\theta_H}{K_2}$, the probability that an individual survives the infected class and move to recovered class, the average duration spent in recovered class $\frac{1}{K_3}$, and the probability that an individual survives the infection through exposed, infected, and recovered class $\frac{K_1K_2K_3}{\left(K_1K_2K_3-\tau_H\theta_H\xi_H\pi\right)}$.
Therefore, the total average number of new vector infections (near the DFE) is the total average number of new vector infections caused by exposed, infected, and recovered humans, which is given by:

$$\frac{C_{HV}S_V^*\mu_H}{\Pi_H\left(K_1K_2K_3-\tau_H\theta_H\xi_H\pi\right)}\Big[K_2K_3\eta_H+K_3\tau_H+\theta_H\tau_H\eta_R\Big].$$

At DFE, $S_V^* = \frac{\Pi_V}{\mu_V}$ so that the above equation can be simplified to,

$$\frac{C_{HV}\Pi_V\mu_H}{\Pi_H\mu_V\left(K_1K_2K_3 - \tau_H\theta_H\xi_H\pi\right)}\left[\eta_H K_2K_3 + \tau_H K_3 + \eta_R\theta_H K_1\right]. \tag{3.13}$$

Similarly, susceptible humans acquire infection after receiving effective number of bites from either exposed or infected mosquito. Therefore, the number of human infections generated by an exposed and infected mosquitoes are respectively given by,

$$\frac{C_{HV}\mu_H\eta_V}{\Pi_H K_4}S_H^* \quad \text{and} \quad \frac{C_{HV}\mu_H\tau_V}{\Pi_H K_4K_5}S_H^*. \tag{3.14}$$

So that the average number of new human infections can be obtained by taking the sum of (3.14) which we obtained,

$$\left(\frac{C_{HV}\mu_H\eta_V}{\Pi_H K_4} + \frac{C_{HV}\mu_H\tau_V}{\Pi_H K_4K_5}\right)S_H^* = C_{HV}\left(\frac{K_5\eta V + \tau_V}{K_4K_5}\right), \text{ since } S_H^* = \frac{\Pi_H}{\mu_H} \text{ at DFE.} \tag{3.15}$$

The square root of the product of (3.13) and (3.15) gives the basic reproduction number.

3.4.3 Endemic equilibrium and backward bifurcation

The endemic equilibrium occurs when at least one of the infected components of (3.6) is non-zero, let P_1 be any arbitrary endemic equilibrium, it can be obtained by setting the right hand side of (3.6) to be zero, considering the first four equations

of (3.6) (human components) we have,

$$\Pi_H + (1-\pi)\xi_H R_H^{**} - S_H^{**}(\lambda_H + \mu_H) = 0 \Rightarrow S_H^{**} = \frac{\Pi_H + (1-\pi)\xi_H R_H}{(\lambda_H + \mu_H)},$$

$$S_H^{**}\lambda_H + \pi\xi_H R_H^{**} - E_H^{**}(\tau_H + \mu_H) = 0 \Rightarrow E_H^{**} = \frac{\lambda_H S_H^{**} + \pi\xi_H R_H^{**}}{(\tau_H + \mu_H)},$$

$$E_H^{**}\tau_H - I_H^{**}(\theta_H + \delta_H + \mu_H) = 0 \Rightarrow I_H^{**} = \frac{\tau_H E_H^{**}}{(\theta_H + \delta_H + \mu_H)}$$

$$I_H^{**}\theta_H - R_H^{**}(\xi_H + \mu_H) = 0 \Rightarrow R_H^{**} = \frac{\theta_H I_H^{**}}{(\xi_H + \mu_H)} = \frac{\tau_H\theta_H E_H^{**}}{(\theta_H + \delta_H + \mu_H)(\xi_H + \mu_H)} \therefore$$

$$R_H^{**} = \frac{\Big[\lambda_H\Pi_H + \lambda_H(1-\pi)\xi_H R_H^{**} + (\lambda_H + \mu_H)\pi\xi_H R_H^{**}\Big]\tau_H\theta_H}{(\tau_H + \mu_H)(\theta_H + \delta_H + \mu_H)(\xi_H + \mu_H)(\lambda_H + \mu_H)} \Rightarrow$$

$$R_H^{**} = \frac{\lambda_H\Pi_H\tau_H\theta_H}{(\tau_H + \mu_H)(\theta_H + \delta_H + \mu_H)(\xi_H + \mu_H)(\lambda_H + \mu_H) - \theta_H\tau_H\xi_H(\lambda_H + \pi\mu_H)}$$

and substituting the value of R_H^{**} in S_H^{**}, the value of S_H^{**}, R_H^{**} in E_H^{**} and E_H^{**} in I_H^{**} we obtained,

$$S_H^{**} = \frac{\Pi_H\big[(\tau_H + \mu_H)(\theta_H + \delta_H + \mu_H)(\xi_H + \mu_H) - \theta_H\tau_H\xi_H\pi\big]}{(\tau_H + \mu_H)(\theta_H + \delta_H + \mu_H)(\xi_H + \mu_H)\big(\lambda_H^{**} + \mu_H\big) - \theta_H\tau_H\xi_H\big(\lambda_H^{**} + \mu_H\pi\big)},$$

$$E_H^{**} = \frac{\lambda_H^{**}\Pi_H(\theta_H + \delta_H + \mu_H)(\xi_H + \mu_H)}{(\tau_H + \mu_H)(\theta_H + \delta_H + \mu_H)(\xi_H + \mu_H)\big(\lambda_H^{**} + \mu_H\big) - \theta_H\tau_H\xi_H\big(\lambda_H^{**} + \mu_H\pi\big)},$$

$$I_H^{**} = \frac{\lambda_H^{**}\Pi_H\tau_H(\xi_H + \mu_H)}{(\tau_H + \mu_H)(\theta_H + \delta_H + \mu_H)(\xi_H + \mu_H)\big(\lambda_H^{**} + \mu_H\big) - \theta_H\tau_H\xi_H\big(\lambda_H^{**} + \mu_H\pi\big)},$$

$$R_H^{**} = \frac{\lambda_H^{**}\Pi_H\tau_H\theta_H}{(\tau_H + \mu_H)(\theta_H + \delta_H + \mu_H)(\xi_H + \mu_H)\big(\lambda_H^{**} + \mu_H\big) - \theta_H\tau_H\xi_H\big(\lambda_H^{**} + \mu_H\pi\big)}.$$

Furthermore, equating the right hand side of the last three equations of (3.6) (the vector components) to zero gives,

$$\Pi_V - S_V^{**}(\lambda_V + \mu_V) = 0 \Rightarrow S_V^{**} = \frac{\Pi_V}{(\mu_V + \lambda_V^{**})},$$

$$S_V^{**}\lambda_V - E_V^{**}(\tau_V + \mu_V) = 0 \Rightarrow E_V^{**} = \frac{\lambda_V^{**} S_V^{**}}{\tau_V + \mu_V} = \frac{\lambda_V^{**}\Pi_V}{(\mu_V + \lambda_V^{**})(\tau_V + \mu_V)},$$

$$E_V^{**}\tau_V - I_V^{**}(\delta_V + \mu_V) = 0 \Rightarrow I_V^{**} = \frac{\tau_V E_V^{**}}{\delta_V + \mu_V} = \frac{\tau_V \lambda_V^{**}\Pi_V}{(\mu_V + \lambda_V^{**})(\tau_V + \mu_V)(\delta_V + \mu_V)}.$$

Therefore the endemic equilibrium point $P_1 = \left(S_H^{**}, E_H^{**}, I_H^{**}, R_H^{**}, S_V^{**}, E_V^{**}, I_V^{**}\right)$ has coordinates given by,

$$\begin{aligned}
S_H^{**} &= \frac{\Pi_H\left(K_1K_2K_3 - \theta_H\tau_H\xi_H\pi\right)}{K_1K_2K_3\left(\lambda_H^{**} + \mu_H\right) - \theta_H\tau_H\xi_H\left(\lambda_H^{**} + \mu_H\pi\right)},\\
E_H^{**} &= \frac{\lambda_H^{**}\Pi_H K_2K_3}{K_1K_2K_3\left(\lambda_H^{**} + \mu_H\right) - \theta_H\tau_H\xi_H\left(\lambda_H^{**} + \mu_H\pi\right)},\\
I_H^{**} &= \frac{\lambda_H^{**}\Pi_H\tau_H K_3}{K_1K_2K_3\left(\lambda_H^{**} + \mu_H\right) - \theta_H\tau_H\xi_H\left(\lambda_H^{**} + \mu_H\pi\right)},\\
R_H^{**} &= \frac{\lambda_H^{**}\Pi_H\tau_H\theta_H}{K_1K_2K_3\left(\lambda_H^{**} + \mu_H\right) - \theta_H\tau_H\xi_H\left(\lambda_H^{**} + \mu_H\pi\right)},\\
S_V^{**} &= \frac{\Pi_V}{\mu_V + \lambda_V^{**}} \quad E_V^{**} = \frac{\lambda_V^{**}\Pi_V}{(\mu_V + \lambda_V^{**})K_4}, \quad I_V^{**} = \frac{\tau_V\lambda_V^{**}\Pi_V}{(\mu_V + \lambda_V^{**})K_4K_5},
\end{aligned} \tag{3.16}$$

$K_1 = \tau_H + \mu_H$, $K_2 = \theta_H + \delta_H + \mu_H$, $K_3 = \xi_H + \mu_H$, $K_4 = \tau_V + \mu_V$, $K_5 = \delta_V + \mu_V$.
The forces of infections are given by:

$$\lambda_H^{**} = \frac{C_{HV}(\eta_V E_V^{**} + I_V^{**})}{N_H^{**}}, \tag{3.17}$$

and

$$\lambda_V^{**} = \frac{C_{HV}(\eta_H E_H^{**} + I_H^{**} + \eta_R R_H^{**})}{N_H^{**}}, \tag{3.18}$$

with,

$$N_H^{**} = S_H^{**} + E_H^{**} + I_H^{**} + R_H^{**}.$$

Substituting the values of E_H^{**}, I_H^{**}, R_H^{**}, E_V^{**}, I_V^{**} from (3.16) in (3.17) and (3.18) gives:

$$\lambda_H^{**}\lambda_V^{**}K_4K_5N_H + \lambda_H^{**}\mu_V K_4K_5N_H - C_{HV}\Pi_V\lambda_V^{**}\left(\eta_V K_5 + \tau_V\right) = 0, \tag{3.19}$$

with

$$\lambda_V^{**} = \frac{C_{HV}\lambda_H^{**}\Pi_H\left(\eta_H K_2K_3 + \tau_H K_3 + \eta_R\theta_H\tau_H\right)}{N_H\left[K_1K_2K_3\left(\lambda_H^{**} + \mu_H\right) - \theta_H\tau_H\xi_H\left(\lambda_H^{**} + \mu_H\pi\right)\right]}, \tag{3.20}$$

and

$$N_H^{**} = \frac{\Pi_H\left\{\left(K_1K_2K_3 - \tau_H\theta_H\xi_H g\right) + \lambda_H^{**}\left(K_2K_3 + \tau_H K_3 + \tau_H\theta_H\right)\right\}}{\left[K_1K_2K_3\left(\lambda_H^{**} + \mu_H\right) - \theta_H\tau_H\xi_H\left(\lambda_H^{**} + \mu_H\pi\right)\right]}. \tag{3.21}$$

Therefore, substituting (3.20) and (3.21) in (3.19), it can be shown that λ_H^{**} satisfies the following polynomial:

$$\lambda_H^{**}\left[a(\lambda_H^{**})^2 + b\lambda_H^{**} + c\right] = 0, \tag{3.22}$$

where,

$$a = \left(K_2K_3 + \tau_H K_3 + \theta_H\tau_H\right)\left(\Pi_H\right)^2 K_4K_5\Big[C_{HV}\eta_H K_2K_3 + C_{HV}\tau_H K_3 + C_{HV}\eta_R\tau_H$$
$$\theta_H + \mu_V K_2K_3 + \mu_V\tau_H K_3 + \mu_V\tau_H\theta_H\Big],$$

$$b = (\Pi_H)^2 K_4 K_5 (K_1 K_2 K_3 - \tau_H \theta_H \xi_H \pi) \Big[C_{HV} (\eta_H K_2 K_3 + \tau_H K_3 + \eta_R \tau_H \theta_H) + 2\mu_V (K_2 K_3 + \tau_H K_3 + \tau_H \theta_H) \Big] - \Big[C_{HV}^2 \Pi_V \Pi_H (\eta_V K_5 + \tau_V)(K_1 K_2 K_3 - \tau_H \theta_H \xi_H) (\eta_H K_2 K_3 + \tau_H K_3 + \eta_R \tau_H \theta_H) \Big] \text{ and,}$$

$$c = K_4 K_5 \mu_V (K_1 K_2 K_3 - \tau_H \theta_H \xi_H \pi)^2 (\Pi_H)^2 \Big[1 - R_0^2 \Big].$$

Notice that, $\lambda_H^{**} = 0$ corresponds to the DFE. Further, the coefficient a in the polynomial is always positive, while b can either be positive or negative, and the positivity or otherwise of c depends on whether R_0 is less than or greater than unity. Suppose $\lambda_H^{**} \neq 0$, then the positive endemic equilibrium of the model can be obtained by solving for the non-negative roots of λ_H^{**} in equation (3.22) and substituting the result in (3.16). The values of λ_H^{**} depends on the nature of the discriminant. The next theorem summarizes the different possibilities:

Theorem 3.4.2. The malaria model represented by (3.6) has;
(i) a unique endemic equilibrium if $c < 0$;
(ii) a unique endemic equilibrium if $b < 0$ and either of $c = 0$ or $b^2 - 4ac = 0$;
(iii) two endemic equilibria if $c > 0, b < 0$ and $b^2 - 4ac > 0$, else;
(iv) no endemic equilibrium.

Proof. If $c < 0$ $(R_0 > 1)$, the model has a unique positive endemic equilibrium, which corresponds to Case (i). Furthermore, the model has a unique positive endemic equilibrium $\left(\lambda^{**} = \frac{-b}{a}\right)$ when $c = 0$ $(R_0 = 1)$ and $b < 0$, otherwise there is no positive endemic equilibrium, hence Case (ii).
If $c > 0$ $(R_0 < 1)$, then $b^2 - 4ac = 0$ corresponds to Case (ii), else if $b^2 - 4ac > 0$, $c > 0$ and $b < 0$, we have two positive roots of λ_H^{**}, stable and unstable, this indicates the possibility of backward bifurcation, that is, the phenomenon where a stable endemic equilibrium co-exists with a stable disease-free equilibrium when

the associated reproduction number is less than unity ($R_0 < 1$) [12, 16, 39] and no endemic equilibrium otherwise. □

Assume that $b < 0$, $a > 0$, $b^2 - 4ac > 0$, and c depending on R_0, $\lambda_H^{**} = \frac{-b \pm \sqrt{b^2-4ac}}{2a} \geq 0$, then the function $f(\lambda_H^{**}) = a\big((\lambda_H^{**} + \frac{b}{2a})^2 - \frac{(b^2-4ac)}{4a^2}\big)$ has global minimum $\lambda_H^{**} = \frac{-b}{2a} > 0$, which is attained when $b^2 - 4ac = 0$, that it is the critical value of $R_0 = R_c$ given by

$$R_c = \sqrt{1 - \frac{b^2}{4a\big(\Pi_H\big)^2\big(K_1K_2K_3 - \tau_H\theta_H\xi_H\pi\big)^2K_4K_5\mu_V}}.$$

Using the numerical values in Table 3.2 which were chosen for simulation purposes and may be epidemiologically unrealistic, the simulation of the existence of backward bifurcation for model (3.6) is depicted in Figure 3.3. below,

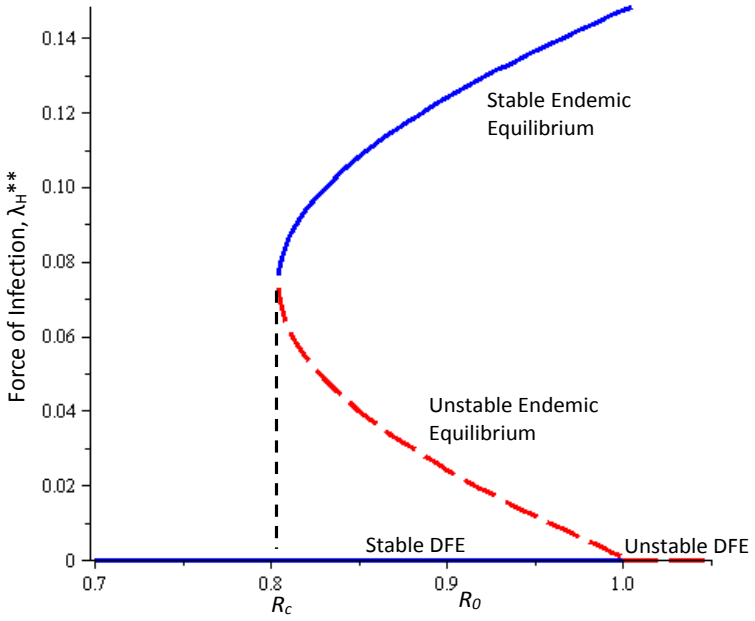

Figure 3.3: Backward Bifurcation diagram

Table 3.2: Parameters values used in illustrating the backward bifurcation

Parameter	Value	Parameter	Value
C_{HV}	0.9028	Π_H	20
δ_H	0.9994	Π_V	30
δ_V	0.047167	μ_V	0.017
τ_H	0.455	μ_H	0.024599
θ_H	0.07	τ_V	0.25
π	0.5	η_V	0.209
ξ_H	0.99	η_H	0.9902
η_R	0.6		

Computation from values in Table 3.2 shows that $R_0 = 0.9309204015 < 1$ and $R_c = 0.8044563559 < 1$ satisfying $R_c < R_0 < 1$. Similarly $a = 0.5052161735$, $b = -0.0740325169$ and $c = 0.001025254966$. Numerically, Figure 3.3 shows that model (3.6) undergoes backward bifurcation when Case (iii) of Theorem 3.4.2 holds and $R_c < R_0 < 1$. The consequence of the phenomenon is that locally asymptotically stable DFE co-exists with a locally asymptotically stable EE though $R_0 < 1$, epidemiologically, the basic requirement for the reproduction number to be less than unity becomes only a necessity, but not sufficient enough to guarantee the elimination of the disease (hence, the presence of this phenomenon in the transmission dynamics of a disease makes its control more difficult) [14, 39].

3.5 Numerical simulations

In [21], the authors determined the values of important parameters in areas of high and low malaria incidences. Data from [21] in Table 3.3 was used for simulation.

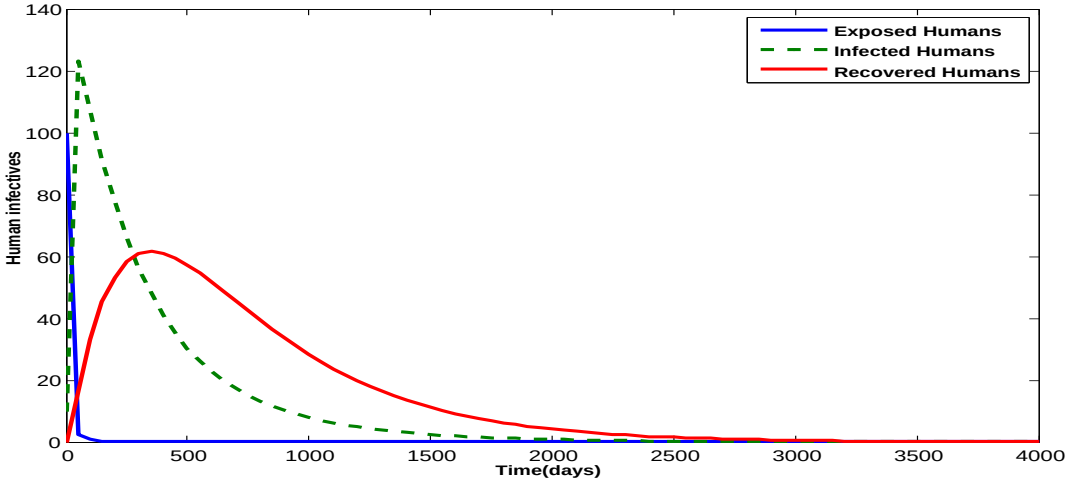

Figure 3.4: Simulation of model (3.6) for the exposed, infected and recovered humans converge to the DFE when $R_0 = 0.1923$ in areas of low malaria incidence using parameter values in Table 3.3 with $S_H(0) = 5000, E_H(0) = 100, I_H(0) = 10, R_H(0) = 0, S_V(0) = 500, E_V(0) = 20$, and $I_V(0) = 10$.

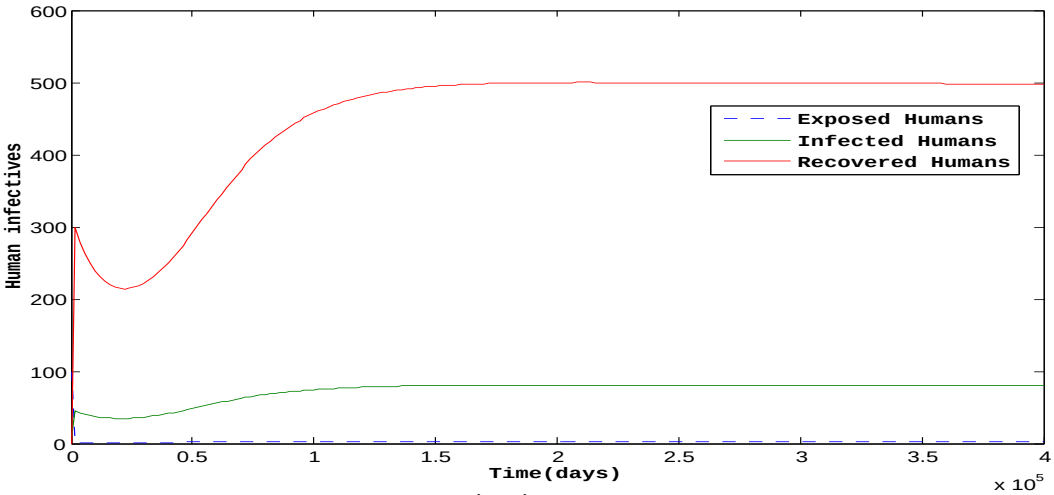

Figure 3.5: Simulation of model (3.6) for the exposed, infected and recovered humans converge to a non-zero solution(EE) when $R_0 = 2.4073$ in areas of high malaria incidence using parameter values in Table 3.3 with $S_H(0) = 5000, E_H(0) = 100, I_H(0) = 10, R_H(0) = 0, S_V(0) = 500, E_V(0) = 20$, and $I_V(0) = 10$.

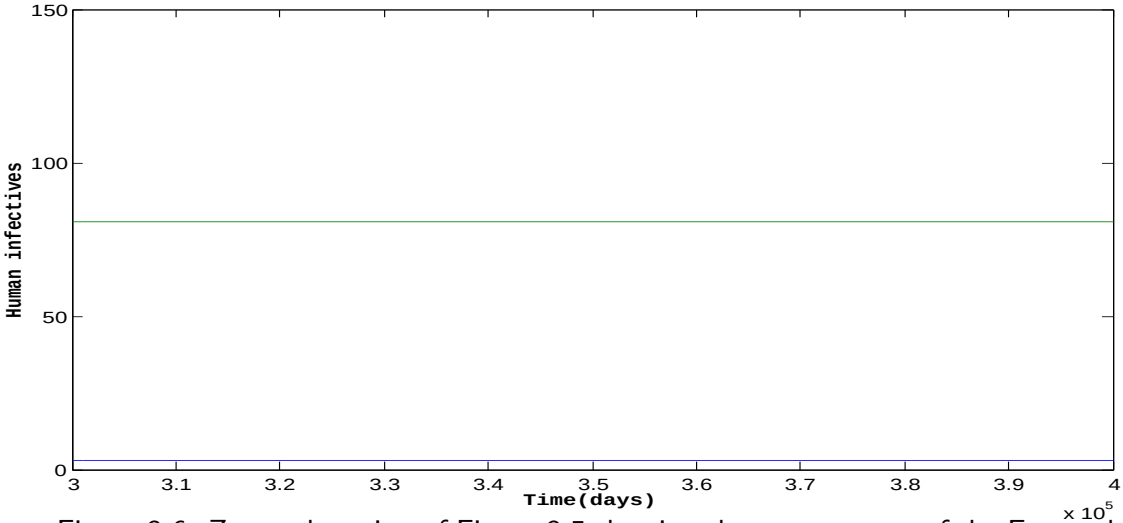

Figure 3.6: Zoomed section of Figure 3.5 showing the convergence of the Exposed class to a non-zero solution.

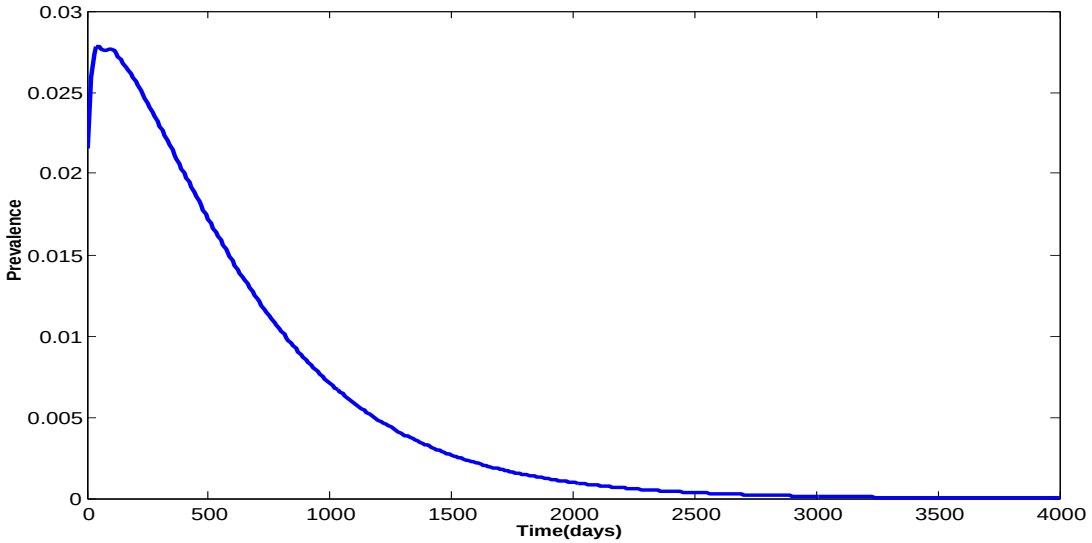

Figure 3.7: Simulation of the model (3.6) showing disease prevalence in areas of low malaria infection using parameter values in Table 3.3 with $S_H(0) = 5000, E_H(0) = 100, I_H(0) = 10, R_H(0) = 0, S_V(0) = 500, E_V(0) = 20, I_V(0) = 10$ so that $R_0 = 0.1923$.

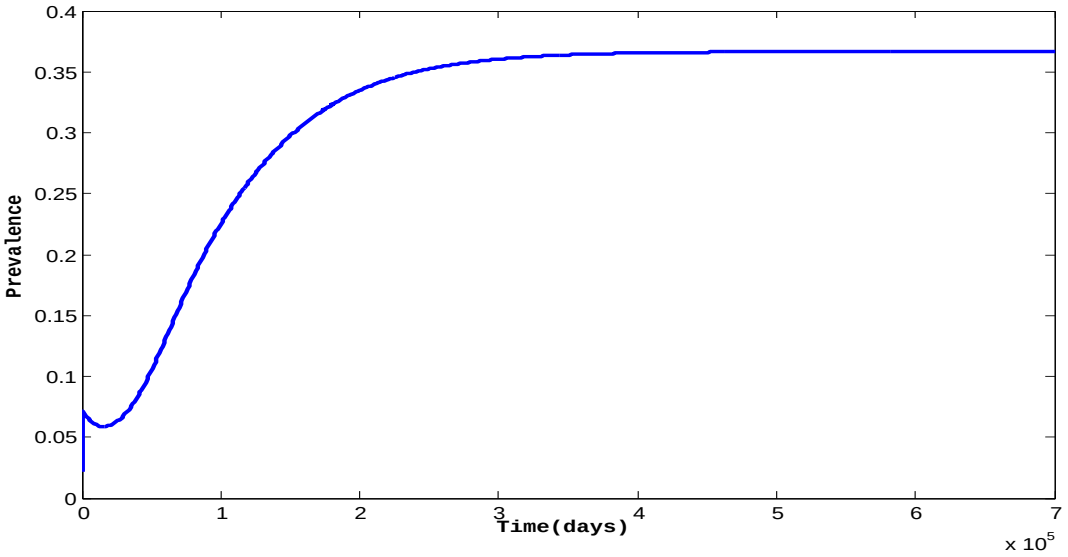

Figure 3.8: Simulation of the model (3.6) showing disease prevalence in areas of high malaria infection using parameter values in Table 3.3 with $S_H(0) = 5000, E_H(0) = 100, I_H(0) = 10, R_H(0) = 0, S_V(0) = 500, E_V(0) = 20, I_V(0) = 10$ so that $R_0 = 2.4073$.

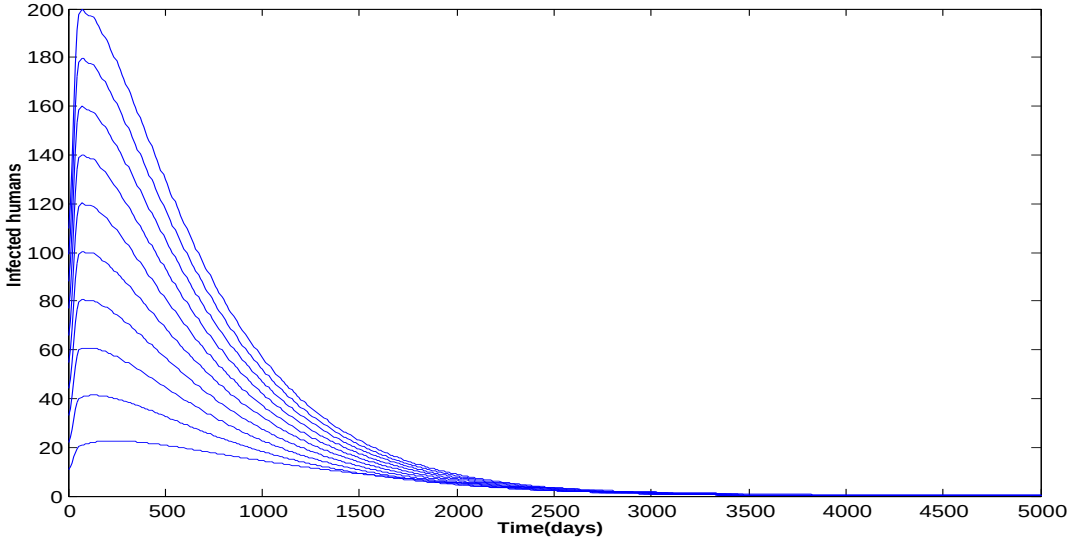

Figure 3.9: Simulation of the model (3.6) showing the total infectives (Exposed + Infected + Recovered) with different initial conditions converging to the DFE in areas of low malaria infection using parameter values in Table 3.3 with $S_H(0) = 5000, E_H(0) = 100, I_H(0) = 10, R_H(0) = 0, S_V(0) = 500, E_V(0) = 20$, and $I_V(0) = 10$ so that $R_0 = 0.1923$.

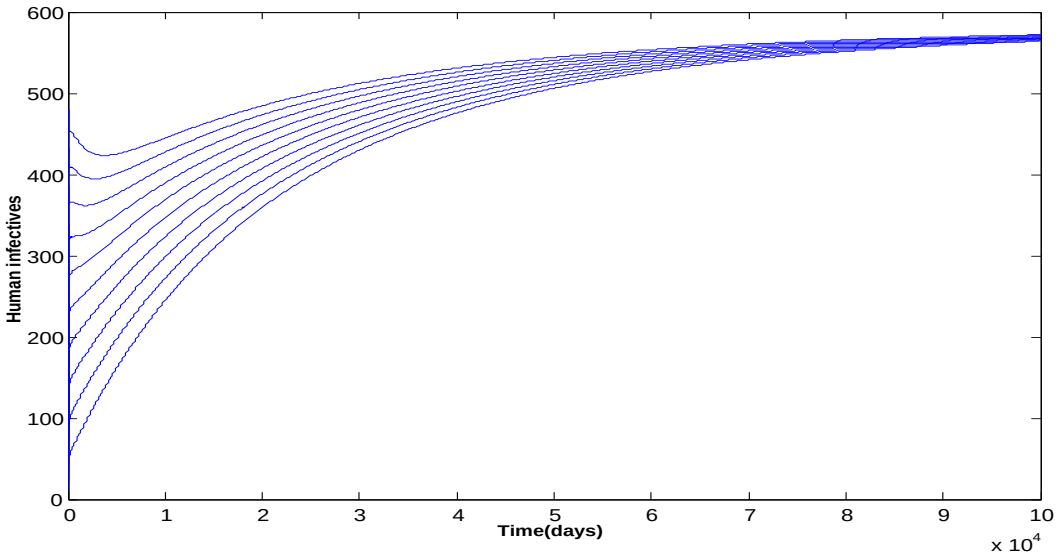

Figure 3.10: Simulation of the model (3.6) showing the total infectives (Exposed + Infected + Recovered) with different initial conditions converging to the EE in areas of high malaria infection using parameter values in Table 3.3 with $S_H(0) = 5000, E_H(0) = 100, I_H(0) = 10, R_H(0) = 0, S_V(0) = 500, E_V(0) = 20,$ and $I_V(0) = 10$ so that $R_0 = 2.4073$.

From the above simulation, Figure 3.4 shows that when $R_0 = 0.1923 < 1$, solution of (E_H, I_H, R_H) approaches zero, while from Figure 3.5 and Figure 3.6, the solution (E_H, I_H, R_H) does not approaches zero when $R_0 = 2.4073 > 1$, this is in line with Lemma 3.4.1. Similarly, Figure 3.7 ($R_0 = 0.1923$) and Figure 3.8 ($R_0 = 2.4073$) respectively show the disease prevalence dies and persists with time. In Figure 3.9, for different initial conditions, infectives approach zero solution (DFE) while Figure 3.10 shows the convergence to non-zero solution (EE) of infectives when the basic reproduction number is less than and greater than one respectively, thus, the Lemma 3.4.1.

Table 3.3: High and low incidence Parameters values used in numerical simulations

Parameter	High	Low	Dimension
Π_H	0.03311	0.041055	Human$\times$day^{-1}
μ_H	0.0000163	0.000009	Human$\times$day^{-1}
τ_H	0.1	0.1	Day^{-1}
β_{HV}	0.48	0.24	Day^{-1}
κ_H	19	4.3	Day^{-1}
δ_H	0.00009	0.000018	Day^{-1}
θ_H	0.0035	0.0035	Day^{-1}
ξ_H	0.00055	0.0027	Day^{-1}
π	0.7	0.1	-
η_H	0.2	0.05	-
η_R	0.3	0.01	-
Π_V	0.13	0.13	Mosquito$\times$day^{-1}
μ_V	0.03302	0.03304	Mosquito$\times$day^{-1}
τ_V	0.091	0.083	Day^{-1}
δ_V	0.0005	0.0005	Day^{-1}
κ_V	0.5	0.33	Day^{-1}
η_V	0.01	0.01	-.

3.6 Analysis of the mass action model

One of the causes of the backward bifurcation as highlighted by [39], is the use of standard incidence function, it can be removed by substituting it with the associated mass action incidence function. The mass action incidence is obtained when the effective contact rate per infectious human (exposed, infected or recovered), or per infectious mosquito (exposed or infected), is proportional to the total population [43, 68], that is when the total population is assumed to be constant, such assumption could be made in cases where a disease occurs within a short period of time, the case of Dengue in some countries is an example. In the case of the mass action incidence, the forces of infection for human and vector are respectively given by,

$$\lambda_H^m = C_{HV}(\eta_V E_V + I_V), \tag{3.23}$$

and,

$$\lambda_V^m = C_{HV}(\eta_H E_H + I_H + \eta_R R_H). \tag{3.24}$$

It can be shown that the disease-free equilibrium of the model with mass action incidence is the same as (3.12), consequently, at the DFE, the vector of appearance of new infections and that of the transfers out of and into the compartments are respectively given by:

$$\mathcal{F} = \begin{pmatrix} S_H C_{HV}(\eta_V E_V + I_V) \\ 0 \\ 0 \\ S_V C_{HV}(\eta_H E_H + I_H + \eta_R R_H) \\ 0 \end{pmatrix}, \quad \mathcal{V} = \begin{pmatrix} E_H K_1 - \pi \xi_H R_H \\ I_H K_2 - E_H \tau_H \\ R_H K_3 - I_H \theta_H \\ E_V K_4 \\ I_V K_5 - E_V \tau_V \end{pmatrix}$$

so that, the associated next generation matrices for the mass action incidence are given by:

$$F_m = \begin{pmatrix} 0 & 0 & 0 & C_{HV}\eta_V S_H^* & C_{HV} S_H^* \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ C_{HV} S_V^* \eta_H & C_{HV} S_V^* & C_{HV} S_V^* \eta_t & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

$$V_m = \begin{pmatrix} K_1 & 0 & -\pi\xi_H & 0 & 0 \\ -\tau_H & K_2 & 0 & 0 & 0 \\ 0 & -\theta_H & K_3 & 0 & 0 \\ 0 & 0 & 0 & K_4 & 0 \\ 0 & 0 & 0 & -\tau_V & K_5 \end{pmatrix}.$$

The basic reproduction number for the model with the mass action incidence formulation, denoted by $R_0^m = \rho(F_m V_m^{-1})$, is given by:

$$R_0^m = \sqrt{\frac{C_{HV}^2 \Pi_V \Pi_H (\eta_V K_5 + \tau_V)(K_2 K_3 \eta_H + K_3 \tau_H + \theta_H \tau_H \eta_R)}{\mu_V \mu_H K_4 K_5 (K_1 K_2 K_3 - \theta_H \tau_H \pi \xi_H)}} = R_0 \frac{\Pi_H}{\mu_H}.$$

Recall that, we have seen the positivity of $K_1 K_2 K_3 - \theta_H \tau_H \pi \xi_H$ in subsection 3.4.1. Next result follows from Theorem 2 of [28]:

Lemma 3.6.1. The disease-free equilibrium (P_0) of the mass action model (3.6) with the forces of infections given by (3.23) and (3.24) is locally asymptotically stable if $R_0^m < 1$, and unstable if $R_0^m > 1$.

Theorem 3.6.2. The mass action model (3.6) with the forces of infections given by (3.23) and (3.24) has no endemic equilibrium when $R_0^m < 1$ and has a unique endemic equilibrium when $R_0^m > 1$.

Proof. The endemic equilibrium occurs when at least one of the infected compartments is different from zero, it is the similar to the endemic equilibrium point obtained in subsection 3.4.3, let $J_1 = \left(S_H^{m*}, E_H^{m*}, I_H^{m*}, R_H^{m*}, S_V^{m*}, E_V^{m*}, I_V^{m*}\right)$ be

an endemic equilibrium, where:

$$
\begin{aligned}
S_H^{m*} &= \frac{\Pi_H\big(K_1K_2K_3 - \theta_H\tau_H\pi\xi_H\big)}{K_1K_2K_3\big(\lambda_H^{m*}+\mu_H\big) - \theta_H\tau_H\xi_H\big(\lambda_H^{m*}+\mu_H\pi\big)},\\
E_H^{m*} &= \frac{\lambda_H^{m*}\Pi_H K_2K_3}{K_1K_2K_3\big(\lambda_H^{m*}+\mu_H\big) - \theta_H\tau_H\xi_H\big(\lambda_H^{m*}+\mu_H\lambda\big)},\\
I_H^{m*} &= \frac{\lambda_H^{m*}\Pi_H\tau_H K_3}{K_1K_2K_3\big(\lambda_H^{m*}+\mu_H\big) - \theta_H\tau_H\xi_H\big(\lambda_H^{m*}+\mu_H\pi\big)},\\
R_H^{m*} &= \frac{\lambda_H^{m*}\Pi_H\tau_H\theta_H}{K_1K_2K_3\big(\lambda_H^{m*}+\mu_H\big) - \theta_H\tau_H\xi_H\big(\lambda_H^{m*}+\mu_H\pi\big)},\\
S_V^{m*} &= \frac{\Pi_V}{\mu_V+\lambda_V^{m*}}, \quad E_V^{m*} = \frac{\lambda_V^{m*}\Pi_V}{(\mu_V+\lambda_V^{m*})K_4}, \quad I_V^{m*} = \frac{\tau_V\lambda_V^{m*}\Pi_V}{(\mu_V+\lambda_V^{m*})K_4K_5},
\end{aligned}
\tag{3.25}
$$

with the forces of infections given by (3.23) and (3.24). Substituting (3.25) in (3.23) and (3.24), the forces of infections satisfy the following equations:

$$
\lambda_H^{m*}\lambda_V^{m*}K_4K_5 + \lambda_H^{m*}\mu_V K_4K_5 - C_{HV}\Pi_V\lambda_V^{m*}(\eta_V K_5+\tau_V) = 0, \tag{3.26}
$$

and,

$$
\lambda_V^{m*} = \frac{C_{HV}\lambda_H^{m*}\Pi_H\big(\eta_H K_2K_3 + \tau_H K_3 + \theta H\tau H\big)}{\big(K_1K_2K_3 - \theta_H\tau_H\xi_H\big)\lambda_H^{m*} + \big(K_1K_2K_3 - \theta_H\tau_H\pi\xi_H\big)\mu_H}. \tag{3.27}
$$

Substituting (3.26) in (3.27), it can be shown that the non-zero equilibria of the model satisfies the following polynomial equation:

$$
\begin{aligned}
&\lambda_H^{m*}K_4K_5\Bigg[\frac{C_{HV}\Pi_H\lambda_H^{m*}\big[K_2K_3\eta_H + \tau_H K_3 + \eta_R\tau_H\theta_H\big]}{\big(K_1K_2K_3 - \theta_H\tau_H\xi_H\big)\lambda_H^{m*} + \big(K_1K_2K_3 - \theta_H\tau_H\pi\xi_H\big)\mu_H} + \mu_V -\\
&\frac{C_{HV}^2\Pi_H\Pi_V\big(\eta_V K_5+\tau_V\big)\big(K_2K_3\eta_H + \tau_H K_3 + \eta_R\tau_H\theta_H\big)}{K_4K_5\big[\big(K_1K_2K_3 - \theta_H\tau_H\xi_H\big)\lambda_H^{m*} + \big(K_1K_2K_3 - \theta_H\tau_H\pi\xi_H\big)\mu_H\big]}\Bigg] = 0,
\end{aligned}
\tag{3.28}
$$

but from the basic reproduction number,

$$C_{HV}^2\Pi_H\Pi_V\big(\eta_V K_5+\tau_V\big)\big(K_2K_3\eta_H+\tau_H K_3+\eta_R\tau_H\theta_H\big)=R_0^2K_4K_5\mu_V\mu_H\big(K_1K_2K_3 - \tau_H\theta_H\pi\xi_H\big) \tag{3.29}$$

so that, substituting (3.29) in (3.28), and after simplification, λ_H^{m*} satisfies:

$$\frac{\lambda_H^{m*}K_4K_5}{\big[\big(K_1K_2K_3-\theta_H\tau_H\xi_H\pi\big)\lambda_H^{m*}+\big(K_1K_2K_3-\theta_H\tau_H\pi\xi_H\big)\mu_H\big]}\Big[a\lambda_H^{m*}+b\Big]=0$$

where,

$$a=C_{HV}\Pi_H\big(K_2K_3\eta_H+\tau_H K_3+\eta_R\tau_H\theta_H\big)+\mu_V\big(K_1K_2K_3-\theta_H\tau_H\xi_H\big)$$

and,

$$b=\mu_V\mu_H\big[K_1K_2K_3-\theta_H\tau_H\pi\xi_H\big]\Big[1-(R_0^m)^2\Big].$$

The case when $\lambda_H^{m*}=0$ corresponds to the DFE. Further, it is clear that, $a>0$ and $\lambda_H^{m*}=\frac{-b}{a}$, so that if $b<0$ $(R_0^m>1)$, then, $\lambda_H^{m*}=\frac{-b}{a}>0$. Thus, the mass action model (3.6) has a unique endemic equilibrium whenever $R_0^m>1$. □

3.6.1 Global stability of the DFE

To show the global stability of the DFE, we use similar approach as that of [62]. The following set

$$\Omega=\Big\{(S_H,E_H,I_H,R_H,S_V,E_V,I_V)\in\mathbb{R}^7: S_H+E_H+I_H+R_H\leq\frac{\Pi_H}{\mu_H},S_V+ E_V+I_V\leq\frac{\Pi_V}{\mu_V}\Big\}$$

was in Theorem 3.3.2 shown to be positively-invariant, hence we claim the following:

Theorem 3.6.3. The DFE P_0 of the mass action model represented by (3.6) with the forces of infection given by (3.23) and (3.24) is globally asymptotically stable (GAS) in Ω if $R_0^m \leq 1$.

Proof. Consider the following function,

$$V = H_1 E_H + H_2 I_H + H_3 R_H + H_4 E_V + H_5 I_V,$$

where,

$$\begin{aligned}
H_1 &= C_{HV}\Pi_V \mu_H R_0^m \big(\eta_V K_5 + \tau_V\big)\big(K_2 K_3 \eta_H + K_3 \tau_H + \eta_R \theta_H \tau_H\big),\\
H_2 &= C_{HV}\Pi_V \mu_H R_0^m \big(\eta_V K_5 + \tau_V\big)\big(\eta_H \theta_H \xi_H \pi + \eta_R \theta_H K_1 + K_1 K_3\big),\\
H_3 &= C_{HV}\Pi_V \mu_H R_0^m \big(\eta_V K_5 + \tau_V\big)\big(K_2 \eta_H \xi_H \pi + \tau_H \xi_H \pi + \eta_R K_1 K_2\big),\\
H_4 &= \big(R_0^m\big)^2 \mu_V \mu_H \big(\eta_V K_5 + \tau_V\big)\big(K_1 K_2 K_3 - \theta_H \tau_H \xi_H \pi\big),\\
H_5 &= \big(R_0^m\big)^2 \mu_V \mu_H K_4 \big(K_1 K_2 K_3 - \theta_H \tau_H \xi_H \pi\big).
\end{aligned} \tag{3.30}$$

The derivative $\dot{V}$ in the direction of the right-hand side of (3.6) is given by

$$\dot{V} = H_1 \dot{E_H} + H_2 \dot{I_H} + H_3 \dot{R_H} + H_4 \dot{E_V} + H_5 \dot{I_V},$$

and substituting the values of $\dot{E_H}$, $\dot{I_H}$, $\dot{R_H}$, $\dot{E_V}$, $\dot{I_V}$ from (3.6) and λ_H^m, λ_V^m from

(3.23) and (3.24) we have:

$$\dot{V} = H_1\Big[C_{HV}\big(E_V\eta_V + I_V\big)S_H + R_H\pi\xi_H - E_HK_1\Big] + H_2\Big[E_H\tau_H - I_HK_2\Big] + H_3\Big[I_H\theta_H - R_HK_3\Big] + H_4\Big[C_{HV}\big(E_H\eta_H + I_H + R_H\eta_R\big)S_V - E_VK_4\Big] + H_5\Big[E_V\tau_V - I_VK_5\Big].$$

which is simplified to:

$$\dot{V} = E_H\Big(- K_1H_1 + H_2\tau_H + H_4C_{HV}S_V\eta_H\Big) + I_H\Big(H_3\theta_H + H_4C_{HV}S_V - H_2K_2\Big) + R_H\Big(\xi_H\pi H_1 + H_4C_{HV}S_V\eta_R - H_3K_3\Big) + E_V\Big(H_1C_{HV}S_H\eta_R + H_5\tau_V - H_4K_4\Big) + I_V\Big(H_1C_{HV}S_H - H_5K_5\Big).$$

But at DFE $S_V \leq \frac{\Pi_V}{\mu_V}$, $S_H \leq \frac{\Pi_H}{\mu_H}$, so that substituting the inequality and the values of H_i in (3.30) in the above expression, after simplification we have:

$$\dot{V} \leq E_H\Big[C_{HV}\Pi_V\mu_H\eta_HR_0^m\big(K_1K_2K_3 - \theta_H\tau_H\pi\xi_H\big)\big(\eta_VK_5 + \tau_V\big)\big(R_0^m - 1\big)\Big] + I_H\Big[C_{HV}\Pi_V\mu_HR_0^m\big(K_1K_2K_3 - \theta_H\tau_H\pi\xi_H\big)\big(\eta_VK_5 + \tau_V\big)\big(R_0^m - 1\big)\Big] + R_H\Big[C_{HV}\Pi_V R_0^m\mu_H\eta_R\big(K_1K_2K_3 - \theta_H\tau_H\pi\xi_H\big)\big(\eta_VK_5 + \tau_V\big)\big(R_0^m - 1\big)\Big] + E_V\Big[\big(R_0^m\big)^2\mu_H\mu_VK_4K_5\eta_V\big(K_1K_2K_3 - \theta_H\tau_H\pi\xi_H\big)\big(R_0^m - 1\big)\Big] + I_V\Big[\big(R_0^m\big)^2\big(K_1K_2K_3 - \theta_H\tau_H\pi\xi_H\big)\mu_H\mu_VK_4\big(R_0^m - 1\big)\Big],$$

further simplification gives,

$$\dot{V} \leq \left(R_0^m - 1\right)\Bigg\{ E_H\Big[C_{HV}\Pi_V\mu_H\eta_H R_0^m\left(\eta_V K_5 + \tau_V\right)\left(K_1K_2K_3 - \theta_H\tau_H\xi_H\right)\Big] + I_H\Big[C_{HV}\Pi_V\mu_H R_0^m\left(\eta_V K_5 + \tau_V\right)\left(K_1K_2K_3 - \theta_H\tau_H\xi_H\right)\Big] + R_H\Big[C_{HV}\Pi_V R_0^m\mu_H \eta_R\left(\eta_V K_5 + \tau_V\right)\left(K_1K_2K_3 - \theta_H\tau_H\xi_H\right)\Big] + E_V\Big[\left(R_0^m\right)^2\mu_H\mu_V K_4K_5\eta_V\left(K_1K_2K_3 - \theta_H\tau_H\xi_H\right)\Big] + I_V\Big[\left(R_0^m\right)^2\mu_H\mu_V K_4\left(K_1K_2K_3 - \theta_H\tau_H\xi_H\right)\Big]\Bigg\}.$$

It should be recalled from subsection 3.4.1 that $K_1K_2K_3 - \theta_H\tau_H\xi_h\pi > 0$, so that $\dot{V} \leq 0$ if $R_0^m \leq 0$.

Let $\mathcal{M} \subset \Omega$ such that, $x \in \mathcal{M} \Rightarrow \dot{V}(x) = 0$ and $\mathcal{S}$ be a positively invariant subset of $\mathcal{M}$. If $R_0^m < 1$ and $\bar{X}(t) \in \mathcal{S}$ then $\dot{V}(\bar{X}) = 0 \Rightarrow \mathcal{S} = P_0$.

On the other hand, suppose $R_0^m = 1$ and $\bar{X}(t) \in \mathcal{S}$, then $\frac{dV(\bar{X}(t))}{dt} = 0$ which implies that

$$H_1\dot{E}_H + H_2\dot{I}_H + H_3\dot{R}_H + H_4\dot{E}_V + H_5\dot{I}_V = 0$$

which is equivalent to

$$H_1E_H + H_2I_H + H_3R_H + H_4E_V + H_5I_V = K \text{ for all } t, \text{ where } K \text{ is a constant}$$

but,

$$H_1, H_2, H_3, H_4, H_5 > 0 \text{ while } E_H \geq 0, I_H \geq 0, R_H \geq 0, E_V \geq 0, I_V \geq 0, \Rightarrow$$

$$E_H = C_1, I_H = C_2, R_H = C_3, E_V = C_4, I_V = C_5, C_1, C_2, C_3, C_4, C_5 \text{ constants,} \tag{3.31}$$

therefore from (3.31) we have

$$\frac{dE_H}{dt} = \frac{dI_H}{dt} = \frac{dR_H}{dt} = \frac{dE_V}{dt} = \frac{dI_V}{dt} = 0 \Rightarrow E_H = I_H = R_H = E_V = I_V = 0,$$

so that,

$$\frac{dN_H}{dt} = \Pi_H - \mu_H N_H \Rightarrow \frac{dS_H}{dt} = \Pi_H - \mu_H S_H,$$
$$\frac{dN_V}{dt} = \Pi_V - \mu_V N_V \Rightarrow \frac{dS_V}{dt} = \Pi_V - \mu_V S_V,$$

hence,

$$S_H \to \frac{\Pi_H}{\mu_H}, \quad S_V \to \frac{\Pi_V}{\mu_V} \text{ as } t \to \infty.$$

Claim:

$$\bar{X}(t) = \{\frac{\Pi_H}{\mu_H}, 0, 0, 0, \frac{\Pi_V}{\mu_V}, 0, 0\} = P_0 \text{ for all } t,$$

Otherwise then,

$$\bar{X}(t) \to \{\frac{\Pi_H}{\mu_H}, 0, 0, 0, \frac{\Pi_V}{\mu_V}, 0, 0\} = P_0 \text{ even when } R_0 > 1.$$

Therefore

$$\bar{X}(t) = P_0 \quad \forall \quad t.$$

Hence, V is a Lyapunov function on Ω, in addition, the largest invariant set in Ω such that $\dot{V}(x) = 0$ is the singleton set $\{P_0\}$. Therefore, it follows by LaSalle's invariance principle [40] that every solution of (3.6) with mass action incidence converges to P_0 as $t \longrightarrow \infty$ whenever $R_0^m \leq 1$. □

The result shows that, for the mass action incidence function, the disease can be eliminated from the community if the associated basic reproduction number R_0^m is less than unity, unlike when we used the standard incidence function, where it was established that, bringing the associated basic reproduction number R_0 below unity was only a necessarily condition but was not sufficient to guarantee the

elimination of malaria from a community. Data strongly suggest that, standard incidence formulation is more suited for modeling human diseases [4, 68], the above result shows that, the backward bifurcation is an important property of the transmission dynamics of malaria. It is worth mentioning that, similar approach was used by Garba et al. [34] for dengue model and west nile virus model [35], Gumel [39] in showing the causes of backward bifurcation and Sharomi et al. [62] for HIV model.

Chapter 4

Malaria model with vaccination

4.1 Introduction

Although vaccination is a common method for controlling diseases, there is yet no vaccine for malaria, recently, there were breakthrough in the development of malaria vaccine, the RTS,S/AS01 has been clinically effective, trials in Gabon, Kenya, Malawi etc., have shown that it is safe, immunogenic, tolerated by human system and produces some efficacy [2, 38, 58, 61]. Researches are ongoing to improve and maximize it's efficacy. In this chapter we investigate the impact of a malaria vaccine by adding to the model (3.6) a compartment consisting of people vaccinated with an imperfect malaria vaccine.

4.2 Model formulation

The model (3.6) was further extended to include additional compartment of vaccinated individuals denoted by V_H, it is generated either by vaccinating some susceptible humans at the rate σ_H, or through vaccinating newly recruited members of the population at the rate $\Pi_H\rho$, with $\rho \in [0, 1]$. The recruitment rate of the

susceptibles will be reduced to $\Pi_H(1-\rho)$, the fact that the vaccine is not perfect implies that, vaccinated individuals may acquire infection at a reduced rate $\lambda_H(1-\epsilon)V_H$, where $0 < \epsilon < 1$ accounts for the efficacy of the vaccine. Similarly, the vaccine waning effect allows for the movement of individuals from the vaccinated class back to the susceptible class at the rate φ_H. Thus the following system of nonlinear equation represents the transmission dynamics of malaria in human (with vaccination) and mosquito populations;

$$\begin{aligned}
\frac{dS_H}{dt} &= \Pi_H(1-\rho) + (1-\pi)\xi_H R_H + \varphi_H V_H - (\lambda_H + \sigma_H + \mu_H)S_H,\\
\frac{dV_H}{dt} &= \Pi_H\rho + \sigma_H S_H - \big[\lambda_H(1-\epsilon) + \varphi_H + \mu_H\big]V_H,\\
\frac{dE_H}{dt} &= \lambda_H\left((1-\epsilon)V_H + S_H\right) + \xi_H\pi R_H - (\tau_H + \mu_H)E_H,\\
\frac{dI_H}{dt} &= \tau_H E_H - \theta_H I_H - \delta_H I_H - \mu_H I_H,\\
\frac{dR_H}{dt} &= \theta_H I_H - \xi_H R_H - \mu_H R_H,\\
\frac{dS_V}{dt} &= \Pi_V - \lambda_V S_V - \mu_V S_V,\\
\frac{dE_V}{dt} &= \lambda_V S_V - \tau_V E_V - \mu_V E_V,\\
\frac{dI_V}{dt} &= \tau_V E_V - \delta_V I_V - \mu_V I_V,
\end{aligned} \tag{4.1}$$

with the forces of infections given by (3.2) and (3.5), while the model (4.1) can be represented by the following flow chart,

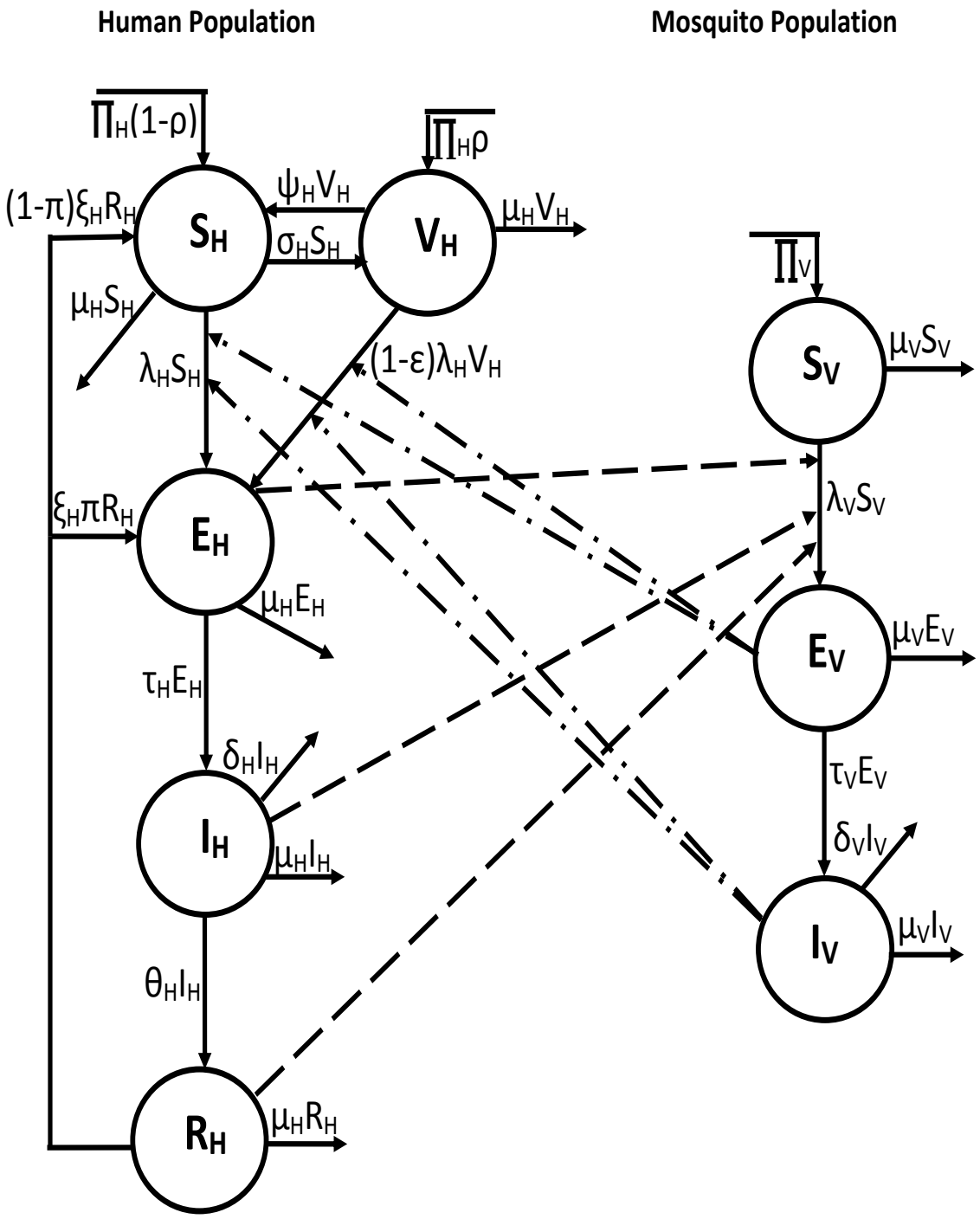

Figure 4.1: Flow chart of the Vaccinated Model (4.1)

4.3 Basic properties of the model

Here we explore the basic dynamical properties of model (4.1). All parameters of the model are assumed to be nonnegative. Furthermore, since the model monitors human and mosquito populations, it is assumed that all the state variables are nonnegative at time $t \geq 0$.

4.3.1 Existence, positivity and boundedness of solutions

Theorem 4.3.1. The solution $\big(S_H(t), V_H(t), E_H(t), R_H(t), S_V(t), E_V(t), I_V(t)\big)$ of the system (4.1) with non-negative initial condition exist for all $t \in \mathbb{R}_+$, and it is unique. Furthermore, the solution is positive and bounded.

Proof. The Theorem is proved using similar argument as in the proof of Theorem 3.3.1. □

Theorem 4.3.2. Consider the biologically-feasible region:

$$\Delta = \left\{(S_H, V_H, E_H, I_H, R_H, S_V, E_V, I_V) \in \mathbb{R}^8_+ : N_H \leq \frac{\Pi_H}{\mu_H}, N_V \leq \frac{\Pi_V}{\mu_V}\right\},$$

The model represented by (4.1) is a dynamical system on Δ.

Proof. The proof follows from the proof of Theorem 3.3.2. The dynamics of the vaccination model (4.1) will be studied in Δ defined above.

4.4 Stability analysis of the equilibria

In this section, as in the previous section, we will also analyse the stability of the disease-free and the endemic equilibria of the malaria model with vaccination represented by (4.1).

4.4.1 Existence and stability of the DFE

The DFE of the vaccination model (4.1) is obtained by equating the right-hand side of (4.1) to zero with the infected compartments $(E_H, I_H, R_H, E_V, I_V)$ also equal to zero, such that:

$$\begin{aligned}
&\Pi_H(1-\rho) + \varphi_H V_H - S_H(\sigma_H + \mu_H) = 0 \Rightarrow S_H = \frac{\Pi_H(1-\rho) + \psi_H V_H}{\sigma_H + \mu_H},\\
&\Pi_H\rho + \sigma_H S_H - V_H\big(\varphi_H + \mu_H\big) = 0 \Rightarrow V_H = \frac{\Pi_H\rho + \sigma_H S_H}{\psi_H + \mu_H},\\
&E_H = 0, \quad I_H = 0, \quad R_H = 0,\\
&\Pi_V - S_V(\lambda_V - \mu_V) = 0 \Rightarrow S_V = \frac{\Pi_V}{\lambda_V + \mu_V}, \quad E_V = 0, \quad I_V = 0,
\end{aligned} \tag{4.2}$$

solving for S_H and V_H from the first two equations of (4.2) we obtained

$$S_H = \frac{\Pi_H(\varphi_H + \mu_H - \rho\mu_H)}{\mu_H(\varphi_H + \sigma_H + \mu_H)}, \quad V_H = \frac{\Pi_H(\sigma_H + \rho\mu_H)}{\mu_H(\varphi_H + \sigma_H + \mu_H)}, \tag{4.3}$$

and hence, the DFE of (4.1) denoted by Z_0 is given by

$$Z_0 = (S_H^*, V_H^*, E_H^*, I_H^*, R_H^*, S_V^*, E_V^*, I_V^*) = (S_H^*, V_H^*, 0, 0, 0, S_V^*, 0, 0)\,, \tag{4.4}$$

with S_H^*, V_H^* as defined in (4.3) and S_V^* in (4.2).
The vectors of appearance of new infections and that of the transfers out of and into the compartments are respectively given by:

$$\mathcal{F} = \begin{pmatrix} \left[S_H + V_H(1-\epsilon)\right]\frac{C_{HV}}{N_H}(\eta_V E_V + I_V) \\ 0 \\ 0 \\ S_V\frac{C_{HV}}{N_H}(\eta_H E_H + I_H + \eta_R R_H) \\ 0 \end{pmatrix} \text{ and , } \quad \mathcal{V} = \begin{pmatrix} E_H K_1 - \pi\xi_H R_H \\ I_H K_2 - E_H\tau_H \\ R_H K_3 - I_H\theta_H \\ E_V K_4 \\ I_V K_5 - E_V\tau_V \end{pmatrix},$$

where,

$$K_1 = (\tau_H + \mu_H), \quad K_2 = (\theta_H + \delta_H + \mu_H), \quad K_3 = (\xi_H + \mu_H), \quad K_4 = (\mu_V + \tau_V)$$

and $K_5 = (\mu_V + \delta_V)$.

The next generation matrices of the model are given by:

$$F = \begin{pmatrix} 0 & 0 & 0 & \frac{C_{HV}((1-\epsilon)V_H^* + S_H^*)}{N_H^*} & \frac{C_{HV}((1-\epsilon)V_H^* + S_H^*)}{N_H^*} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ \frac{C_{HV}\eta_H S_V^*}{N_H^*} & \frac{C_{HV}S_H^*}{N_H^*} & \frac{C_{HV}\eta_R S_V^*}{N_H^*} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

$$V = \begin{pmatrix} K_1 & 0 & -\pi\xi_H & 0 & 0 \\ -\tau_H & K_2 & 0 & 0 & 0 \\ 0 & -\theta_H & K_3 & 0 & 0 \\ 0 & 0 & 0 & K_4 & 0 \\ 0 & 0 & 0 & -\tau_V & K_5 \end{pmatrix},$$

The vaccinated reproduction number of the model (4.1), which is the spectral radius of (FV^{-1}) [26, 28, 41, 42], denoted by R_{0v} is given by:

$$R_{0v} =$$

$$\sqrt{\frac{C_{HV}^2\Pi_V\mu_H(\eta_H K_2K_3 + \tau_H K_3 + \eta_R\theta_H\tau_H)(\eta_V K_5 + \tau_V)[\varphi_H + \mu_H(1-\epsilon\rho) + \sigma_H(1-\epsilon)]}{(K_1K_2K_3 - \tau_H\theta_H\xi_H\pi)(\varphi_H + \sigma_H + \mu_H)K_4K_5\Pi_H\mu_V}}$$

$$= R_0\sqrt{\frac{\varphi_H + \mu_H(1-\epsilon\rho) + \sigma_H(1-\epsilon)}{\varphi_H + \sigma_H + \mu_H}}.$$

Recall that $(K_1K_2K_3 - \theta_H\tau_H\xi_H\pi) > 0$ as shown in subsection 3.4.1. The following result from Theorem 2 of [28] follows:

Lemma 4.4.1. The DFE of the model with vaccination (4.1), Z_0, is LAS if $R_{0v} < 1$ and unstable if $R_{0v} > 1$.

R_{0v} represents the average number of new infections that one infected individual will generate in a population where fraction of susceptibles individuals are vaccinated.

4.4.2 Existence of the endemic equilibrium

The endemic equilibrium occurs when at least one of the infected compartments is not zero, it is obtained by equating the right hand side of (4.1) to zero. Equating the right hand side of (4.1) to zero and after simple evaluation we obtained

$$\begin{aligned}
S_H &= \frac{\Pi_H(1-\rho)+(1-\pi)\xi_H R_H+\varphi_H V_H}{\lambda_H+\sigma_H+\mu_H}, \quad V_H = \frac{\Pi_H\rho+\sigma_H S_H}{\lambda_H(1-\epsilon)+\varphi_H+\mu_H},\\
E_H &= \frac{\lambda_H\left((1-\epsilon)V_H+S_H\right)+\xi_H\pi R_H}{\tau_H+\mu_H}, \quad I_H = \frac{\tau_H E_H}{\theta_H+\delta_H+\mu_H},\\
R_H &= \frac{\theta_H I_H}{\xi_H+\mu_H}, \quad S_V = \frac{\Pi_V}{\lambda_V+\mu_V}, \quad E_V = \frac{\lambda_V S_V}{\tau_V+\mu_V}, \quad I_V = \frac{\tau_V E_V}{\delta_V+\mu_V},
\end{aligned} \tag{4.5}$$

after some simplifications, the endemic equilibrium of the vaccinated model (4.1) denoted by $J_1 = \left(S_H^{**}, V_H^{**}, E_H^{**}, I_H^{**}, R_H^{**}, S_V^{**}, E_V^{**}, I_V^{**}\right)$ has,

$$\begin{aligned}
S_H^{**} &= \frac{\Pi_H\left(M_1+M_2\right)}{M_3-M_4}, \quad V_H^{**} = \frac{\Pi_H\left[\rho\left(M_3-M_4\right)+\sigma_H\left(M_1+M_2\right)\right]}{M_5\left(M_3-M_4\right)},\\
E_H^{**} &= \frac{\lambda_H^{**}K_2K_3\left[\varphi_H+\mu(1-\epsilon\rho)+\sigma_H(1-\epsilon)\right]}{\left[K_1K_2K_3-\theta_H\tau_H\xi_H\pi\right]\left(\varphi_H+\sigma_H+\mu_H\right)},\\
I_H^{**} &= \frac{\lambda_H^{**}\tau_H K_3\left[\varphi_H+\mu(1-\epsilon\rho)+\sigma_H(1-\epsilon)\right]}{\left[K_1K_2K_3-\theta_H\tau_H\xi_H\pi\right]\left(\varphi_H+\sigma_H+\mu_H\right)},\\
R_H^{**} &= \frac{\lambda_H^{**}\tau_H\theta_H\left[\varphi_H+\mu(1-\epsilon\rho)+\sigma_H(1-\epsilon)\right]}{\left[K_1K_2K_3-\theta_H\tau_H\xi_H\pi\right]\left(\varphi_H+\sigma_H+\mu_H\right)},\\
S_V^{**} &= \frac{\Pi_V}{\mu_V+\lambda_V^{**}} \quad E_V^{**} = \frac{\lambda_V^{**}\Pi_V}{(\mu_V+\lambda_V^{**})K_4}, \quad I_V^{**} = \frac{\tau_V\lambda_V^{**}\Pi_V}{(\mu_V+\lambda_V^{**})K_4K_5},
\end{aligned} \tag{4.6}$$

where,

$$M_1 = \big[1-\rho\big]\big\{\big(K_1K_2K_3 - \theta_H\tau_H\xi_H\pi\big)\big(\lambda_H^{**}(1-\epsilon) + \psi_H + \mu_H\big)\big\},$$

$$M_2 = \rho\big\{\varphi_H\big[K_1K_2K_3 - \theta_H\tau_H\xi_H\pi\big] + [1-\epsilon](1-\pi)\xi_H\tau_H\theta_H\lambda_H^{**}\big\},$$

$$M_3 = \big(\lambda_H^{**}[1-\epsilon] + \psi_H + \mu_H\big)^2\big\{\big(K_1K_2K_3 - \theta_H\tau_H\xi_H\pi\big)\big[\lambda_H^{**} + \sigma_H + \mu_H\big] -$$

$$(1-\pi)\xi_H\theta_H\tau_H\lambda_H^{**}\big\},$$

$$M_4 = \sigma_H\big\{\varphi_H\big(K_1K_2K_3 - \theta_H\tau_H\xi_H\pi\big) + (1-\epsilon)(1-\pi)\big[\lambda_H^{**}\big(1-\epsilon\big) + \varphi_H + \mu_H\big]$$

$\xi_H\tau_H\theta_H\lambda_H^{**}\big\}$ and,

$$M_5 = \lambda_H^{**}(1-\epsilon) + \psi_H + \mu_H.$$

The endemic equilibrium can be explicitly obtained by solving for the positive values of λ_H^{**} and λ_V^{**} and substituting in (4.6) above.

4.4.3 Backward bifurcation analysis

Several factors could be responsible for a backward bifurcation in epidemiological models, some of which include: the use of an imperfect vaccine [12, 31, 39, 62], exogenous re-infection [1, 33], treatment [39], acquired immunity [59] etc.. The fact that, the model (3.6) possesses backward bifurcation is enough to investigate its existence or otherwise in model (4.1). However, the complex nature of the equilibrium points in (4.6) makes it difficult to apply the method used in subsection 3.4.2, its application will result to higher order polynomials, consequently, we opted on applying the Center Manifold theory [16, 28]. The Center Manifold theory can be used to describe not only the local stability of a non-hyperbolic equilibrium point but in settling the existence of another equilibrium point (bifurcated from a non hyperbolic equilibrium point). The theory follows:

Consider a general system of ODEs with a parameter ϕ:

$$\frac{dx}{dt} = f(x, \phi), f : \mathbb{R}^n \times \mathbb{R} \longrightarrow \mathbb{R}^n \text{ and } f \in \mathbb{C}^2(\mathbb{R}^n \times \mathbb{R}) \tag{4.7}$$

Without loss of generality, it is assumed that 0 is an equilibrium for system (4.7) for all values of the parameter ϕ, that is,

$$f(0, \phi) \equiv 0 \text{ for all } \phi \tag{4.8}$$

Theorem 4.4.2. (Castillo-Chavez and Song)[16].

A1: $A = D_x f(0,0) = \left(\frac{\partial f_i}{\partial x_i}(0,0)\right)$ is the linearization matrix of system (4.5) around the equilibrium 0 with ϕ evaluated at 0. Zero is a simple eigenvalue of A and all other eigenvalues of A have negative real parts;

A2: Matrix A has a nonnegative right eigenvector w and a left eigenvector v corresponding to the zero eigenvalue.

Let f_k be the kth component of f and,

$$a = \sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0) \tag{4.9}$$

$$b = \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0) \tag{4.10}$$

The local dynamics of (4.7) around 0 are totally determined by a and b.

i $a > 0, b > 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is locally asymptotically stable, and there exists a positive unstable equilibrium; when $0 < \phi \ll 1$, 0 is unstable and there exists a negative and locally asymptotically stable equilibrium;

ii $a < 0, b < 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable; when $0 < \phi \ll$

$1, \quad 0$ is locally asymptotically stable, and there exists a positive unstable equilibrium;

iii $a > 0, b < 0$. When $\phi < 0$ with $|\phi| \ll 1, \quad 0$ is unstable, and there exists a locally asymptotically stable negative equilibrium; when $0 < \phi \ll 1, \quad 0$ is stable, and a positive unstable equilibrium appears;

iv $a < 0, b > 0$. When ϕ changes from negative to positive, 0 changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable.

Remark 1 of [16] states that: The requirement that w is nonnegative in the theorem is not necessary. When some components in w are negative, we still can apply this theorem, but one has to compare w with the actual equilibrium because the general parametrization of the Center Manifold before the coordinate change is,

$$W^c = \left\{ x_0 + c(t)w + h(c, \phi) : v.h(c, \phi) = 0, |c| \leq c_0, c(0) = 0 \right\},$$

provided that x_0 is a nonnegative equilibrium of interest (usually x_0 is the disease-free equilibrium). Hence, $x_0 - \frac{2b\phi}{a} > 0$ requires that $w_j > 0$ whenever $x_0(j) = 0$. If $x_0(j) > 0$, then $w(j)$ need not be positive [16].

Corollary. When $a > 0$ and $b > 0$, then, the bifurcation at $\phi = 0$ is backward.

4.4.4 Existence of backward bifurcation

From (4.1), we let,

$$\left(S_H, V_H, E_H, I_H, R_H, S_V, E_V, I_V \right) = \left(x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8 \right),$$

and hence, the total human and mosquito populations are:

$$N_H = x_1 + x_2 + x_3 + x_4 + x_5 \quad \text{and} \quad N_V = x_6 + x_7 + x_8.$$

Using vector notation, we have,

$$x = \Big(x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8\Big)^T \quad \text{and} \quad \frac{dx}{dt} = \Big(f_1, f_2, f_3, f_4, f_5, f_6, f_7, f_8\Big),^T$$

where,

$$\begin{aligned}
\frac{dx_1}{dt} &= f_1 = \Pi_H(1-\rho) + \varphi_H x_2 + (1-\pi)\xi_H x_5 - \frac{C_{HV}(\eta_V x_7 + x_8)}{x_1 + x_2 + x_3 + x_4 + x_5} x_1 - x_1 K_1, \\
\frac{dx_2}{dt} &= f_2 = \Pi_H \rho + \sigma_H x_1 - \frac{C_{HV}(\eta_V x_7 + x_8)}{x_1 + x_2 + x_3 + x_4 + x_5} x_2(1-\epsilon) - x_2 K_2, \\
\frac{dx_3}{dt} &= f_3 = \frac{C_{HV}(\eta_V x_7 + x_8)}{x_1 + x_2 + x_3 + x_4 + x_5} \left((1-\epsilon)x_2 + x_1\right) + \pi \xi_H x_5 - x_3 K_3, \\
\frac{dx_4}{dt} &= f_4 = \tau_H x_3 - x_4 K_4, \\
\frac{dx_5}{dt} &= f_5 = \theta_H x_4 - x_5 K_5, \\
\frac{dx_6}{dt} &= f_6 = \Pi_V - \frac{C_{HV}(\eta_H x_3 + x_4 + \eta_R x_5)}{x_1 + x_2 + x_3 + x_4 + x_5} x_6 - x_6 \mu_V, \\
\frac{dx_7}{dt} &= f_7 = \frac{C_{HV}(\eta_H x_3 + x_4 + \eta_R x_5)}{x_1 + x_2 + x_3 + x_4 + x_5} x_6 - x_7 K_6, \\
\frac{dx_8}{dt} &= f_8 = \tau_V x_7 - x_8 K_7.
\end{aligned} \tag{4.11}$$

with,

$$K_1 = \sigma_H + \mu_H, \quad K_2 = \varphi_H + \mu_H, \quad K_3 = \tau_H + \mu_H, \quad K_4 = \theta_H + \delta_H + \mu_H,$$

$$K_5 = \xi_H + \mu_H, \quad K_6 = \mu_V + \tau_V \quad \text{and} \quad K_7 = \mu_V + \delta_V.$$

It is not convenient using R_0 directly as the bifurcation parameter [28], notwithstanding, we can conveniently choose a different parameter. Let C_{HV} be our bifurcation parameter, so that when $R_{0v} = 1$, we have:

$$C^*_{HV} = \sqrt{\frac{(K_1K_2K_3 - \tau_H\theta_H\xi_H\pi)K_4K_5\Pi^2_H\mu_V}{\Pi_V\mu^2_H(\eta_HK_2K_3 + \tau_HK_3 + \eta_H\theta_H\tau_H)(\eta_VK_5 + \tau_V)[S^*_H + V^*_H(1-\epsilon)]}}$$

The Jacobian of (4.1), evaluated at the disease-free equilibrium with $C_{HV} = C^*_{HV}$, is given by

$$J^* = \begin{pmatrix} -K_1 & \varphi_H & 0 & 0 & (1-\pi)\xi_H & 0 & d_{17} & d_{18} \\ \sigma_H & -K_2 & 0 & 0 & 0 & 0 & d_{27} & d_{28} \\ 0 & 0 & -K_3 & 0 & \pi\xi_H & 0 & d_{37} & d_{38} \\ 0 & 0 & \tau_H & -K_4 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \theta_H & -K_5 & 0 & 0 & 0 \\ 0 & 0 & d_{63} & d_{64} & d_{65} & -\mu_V & 0 & 0 \\ 0 & 0 & d_{73} & d_{74} & d_{75} & 0 & -K_6 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \tau_V & -K_7 \end{pmatrix},$$

where,

$$d_{17} = \frac{-C^*_{HV}\eta_V S^*_H}{S^*_H + V^*_H}, \quad d_{18} = \frac{-C^*_{HV} S^*_H}{S^*_H + V^*_H}, \quad d_{27} = \frac{-C^*_{HV}\eta_V(1-\epsilon)S^*_H}{S^*_H + V^*_H},$$
$$d_{28} = \frac{-C^*_{HV}(1-\epsilon)S^*_H}{S^*_H + V^*_H}, \quad d_{37} = \frac{C^*_{HV}\eta_V\left[(1-\epsilon)V^*_H + S^*_H\right]}{S^*_H + V^*_H},$$
$$d_{38} = \frac{C^*_{HV}\left[(1-\epsilon)V^*_H + S^*_H\right]}{S^*_H + V^*_H}, \quad d_{63} = \frac{-C^*_{HV}\eta_H S^*_V}{S^*_H + V^*_H}, \quad d_{64} = \frac{-C^*_{HV} S^*_V}{S^*_H + V^*_H},$$
$$d_{65} = \frac{-C^*_{HV}\eta_R S^*_V}{S^*_H + V^*_H}, \quad d_{73} = \frac{C^*_{HV}\eta_H S^*_V}{S^*_H + V^*_H}, \quad d_{74} = \frac{C^*_{HV} S^*_V}{S^*_H + V^*_H}, \quad d_{75} = \frac{C^*_{HV}\eta_R S^*_V}{S^*_H + V^*_H}.$$

According to [15, 70], the jacobian matrix of the system (4.1) has simple zero eigenvalues with all other eigenvalues having negative real parts. It can be shown that, the associated left eigenvector denoted by V_i are given by:

$$V_1 = 0, \quad V_2 = 0, \quad V_3 > 0 \text{ (psoitive constatnt)}$$
$$V_4 = \frac{V_3\left[\theta_H\left(\pi\xi_H K_6 K_7 + K_7 d_{75} d_{37} + \tau_V d_{75} d_{38}\right) + K_5 d_{74}\left(K_7 d_{37} + \tau_v d_{38}\right)\right]}{K_4 K_5 K_6 K_7},$$
$$V_5 = \frac{V_3\left[K_6 K_7 \pi\xi_H + d_{75}\left(K_7 d_{37} + \tau_V d_{38}\right)\right]}{K_5 K_6 K_7}, \quad V_6 = 0$$
$$V_7 = \frac{V_3\left(K_7 d_{37} + \tau_V d_{38}\right)}{K_6 K_7}, \quad V_8 = \frac{V_3 d_{38}}{K_7},$$

and the associated right eigenvector W_j are given by:

$$W_1 = \frac{W_2\varphi_H + W_5(1-\pi)\xi_H + W_7 d_{17} + W_8 d_{18}}{K_1},$$

$$W_2 = \frac{W_1\sigma_H + W_7 d_{27} + W_8 d_{28}}{K_2},$$

$$W_3 \geq 0 \text{ (positive constant)}, \quad W_4 = W_3\frac{\tau_H}{K_4}, \quad W_5 = W_3\frac{\theta_H\tau_H}{K_4K_5}$$

$$W_6 = \frac{W_3\Big(K_4K_5d_{63} + K_5\tau_H d_{64} + \theta_H\tau_H d_{65}\Big)}{K_4K_5\mu_V},$$

$$W_7 = \frac{W_3\Big(K_4K_5d_{73} + K_5\tau_H d_{74} + \theta_H\tau_H d_{75}\Big)}{K_4K_5K_6},$$

$$W_8 = \frac{W_3\Big(K_4K_5\tau_V d_{73} + K_5\tau_H\tau_V d_{74} + \theta_H\tau_H\tau_V d_{75}\Big)}{K_4K_5K_6K_7},$$

with the positive constants V_3 and W_3 chosen in such a way that,

$$V_3{\cdot}W_3 = \frac{K_4^2K_5^2K_6^2K_7^2}{K_4^2K_5^2K_6^2K_7^2 + M_1K_5K_6K_7 + M_2K_4K_6K_7 + M_3K_4K_5K_7 + M_4K_4K_5K_6}$$

in which case, it can be shown that $V{\cdot}W = 1$ with,

$$M_1 = \theta_H\tau_H\big(\pi\xi_H K_6K_7 + K_7d_{75}d_{37} + \tau_V d_{75}d_{38}\big) + K_5\tau_H d_{74}\big(K_7d_{37} + \tau_v d_{38}\big)$$

$$M_2 = \theta_H\tau_H\Big[K_6K_7\pi\xi_H + d_{75}\big(K_7d_{37} + \tau_V d_{38}\big)\Big]$$

$$M_3 = \Big[K_7d_{37} + \tau_V d_{38}\Big]\Big(K_4K_5d_{73} + K_5\tau_H d_{74} + \theta_H\tau_H d_{75}\Big) \text{ and,}$$

$$M_4 = d_{38}\Big(K_4K_5\tau_V d_{73} + K_5\tau_H\tau_V d_{74} + \theta_H\tau_H\tau_V d_{75}\Big).$$

Observe that, $V_i \geq 0$ for all $i \in \{1, 2, 3, 4, 5, 6, 7, 8\}$, while W_1 and W_2 are arbitrary and $W_6 < 0$, the choice of V_i strictly greater than zero follows from condition A2 of Theorem 4.1 in [16] and Lemma 3 of [28].

We observe that, the second partial derivatives of f_4, f_5 and f_8 with respect to any of the variables are zero, hence, to compute a and b, we only need to compute the second partial derivatives of f_3 and f_7 with respect to the variables and the bifurcation parameter.

Computation of a: By direct computation, at the disease-free equilibrium, for $i = 1, 2, 3, 4, 5, 6$ we have:

$$\frac{\partial^2 f_3}{\partial x_1 \partial x_i} = \frac{\partial^2 f_3}{\partial x_2 \partial x_i} = \frac{\partial^2 f_3}{\partial x_3 \partial x_i} = \frac{\partial^2 f_3}{\partial x_4 \partial x_i} = \frac{\partial^2 f_3}{\partial x_5 \partial x_i} = \frac{\partial^2 f_3}{\partial x_6 \partial x_i} = 0,$$

where as,

$$\frac{\partial^2 f_3}{\partial x_1 \partial x_7} = \frac{\partial^2 f_3}{\partial x_7 \partial x_1} = C_{HV}\eta_V \left\{ \frac{1}{S_H^* + V_H^*} - \frac{\left[S_H^* + V_H^*(1-\epsilon)\right]}{\left(S_H^* + V_H^*\right)^2} \right\},$$

$$\frac{\partial^2 f_3}{\partial x_1 \partial x_8} = \frac{\partial^2 f_3}{\partial x_8 \partial x_1} = C_{HV} \left\{ \frac{1}{S_H^* + V_H^*} - \frac{\left[S_H^* + V_H^*(1-\epsilon)\right]}{\left(S_H^* + V_H^*\right)^2} \right\},$$

$$\frac{\partial^2 f_3}{\partial x_2 \partial x_7} = \frac{\partial^2 f_3}{\partial x_7 \partial x_2} = C_{HV}\eta_V \left\{ \frac{1-\epsilon}{S_H^* + V_H^*} - \frac{\left[S_H^* + V_H^*(1-\epsilon)\right]}{\left(S_H^* + V_H^*\right)^2} \right\},$$

$$\frac{\partial^2 f_3}{\partial x_2 \partial x_8} = \frac{\partial^2 f_3}{\partial x_8 \partial x_2} = C_{HV} \left\{ \frac{1-\epsilon}{S_H^* + V_H^*} - \frac{\left[S_H^* + V_H^*(1-\epsilon)\right]}{\left(S_H^* + V_H^*\right)^2} \right\},$$

$$\frac{\partial^2 f_3}{\partial x_3 \partial x_7} = \frac{\partial^2 f_3}{\partial x_4 \partial x_7} = \frac{\partial^2 f_3}{\partial x_5 \partial x_7} = -C_{HV}\eta_V \left[\frac{S_H^* + (1-\epsilon)V_H^*}{\left(S_H^* + V_H^*\right)^2} \right],$$

$$\frac{\partial^2 f_3}{\partial x_7 \partial x_3} = \frac{\partial^2 f_3}{\partial x_7 \partial x_4} = \frac{\partial^2 f_3}{\partial x_7 \partial x_5} = -C_{HV}\eta_V \left[\frac{S_H^* + (1-\epsilon)V_H^*}{\left(S_H^* + V_H^*\right)^2} \right],$$

$$\frac{\partial^2 f_3}{\partial x_3 \partial x_8} = \frac{\partial^2 f_3}{\partial x_4 \partial x_8} = \frac{\partial^2 f_3}{\partial x_5 \partial x_8} = -C_{HV} \left[\frac{S_H^* + (1-\epsilon)V_H^*}{\left(S_H^* + V_H^*\right)^2} \right],$$

$$\frac{\partial^2 f_3}{\partial x_8 \partial x_3} = \frac{\partial^2 f_3}{\partial x_8 \partial x_4} = \frac{\partial^2 f_3}{\partial x_8 \partial x_5} = -C_{HV} \left[\frac{S_H^* + (1-\epsilon)V_H^*}{\left(S_H^* + V_H^*\right)^2} \right].$$

In a similar way,

$$\frac{\partial^2 f_7}{\partial x_1 \partial x_i} = \frac{\partial^2 f_7}{\partial x_2 \partial x_i} = 0, \quad \text{for} \quad i = 1, 2, 6, 7, 8$$
$$\frac{\partial^2 f_7}{\partial x_3 \partial x_7} = \frac{\partial^2 f_7}{\partial x_3 \partial x_8} = 0,$$
$$\frac{\partial^2 f_7}{\partial x_4 \partial x_7} = \frac{\partial^2 f_7}{\partial x_4 \partial x_8} = 0,$$
$$\frac{\partial^2 f_7}{\partial x_5 \partial x_7} = \frac{\partial^2 f_7}{\partial x_5 \partial x_8} = 0,$$
$$\frac{\partial^2 f_7}{\partial x_6 \partial x_1} = \frac{\partial^2 f_7}{\partial x_6 \partial x_2} = \frac{\partial^2 f_7}{\partial x_6 \partial x_6} = \frac{\partial^2 f_7}{\partial x_6 \partial x_7} = \frac{\partial^2 f_7}{\partial x_6 \partial x_8} = 0,$$
$$\frac{\partial^2 f_7}{\partial x_1 \partial x_i} = \frac{\partial^2 f_7}{\partial x_1 \partial x_i} = 0, \quad \text{for} \quad i = 1, 2, 3, 4, 5, 6, 7, 8,$$

while,

$$\frac{\partial^2 f_7}{\partial x_1 \partial x_3} = \frac{\partial^2 f_7}{\partial x_2 \partial x_3} = \frac{\partial^2 f_7}{\partial x_3 \partial x_1} = \frac{\partial^2 f_7}{\partial x_3 \partial x_2} = -\frac{C_{HV} S_V^* \eta_H}{\left(S_H^* + V_H^*\right)^2},$$
$$\frac{\partial^2 f_7}{\partial x_1 \partial x_4} = \frac{\partial^2 f_7}{\partial x_2 \partial x_4} = \frac{\partial^2 f_7}{\partial x_4 \partial x_1} = \frac{\partial^2 f_7}{\partial x_4 \partial x_2} = -\frac{C_{HV} S_V^*}{\left(S_H^* + V_H^*\right)^2},$$
$$\frac{\partial^2 f_7}{\partial x_1 \partial x_5} = \frac{\partial^2 f_7}{\partial x_2 \partial x_5} = \frac{\partial^2 f_7}{\partial x_5 \partial x_1} = \frac{\partial^2 f_7}{\partial x_5 \partial x_2} = -\frac{C_{HV} S_V^* \eta_R}{\left(S_H^* + V_H^*\right)^2},$$
$$\frac{\partial^2 f_7}{\partial x_3 \partial x_3} = -\frac{2 C_{HV} S_V^* \eta_H}{\left(S_H^* + V_H^*\right)^2}$$
$$\frac{\partial^2 f_7}{\partial x_3 \partial x_4} = \frac{\partial^2 f_7}{\partial x_4 \partial x_3} = -\frac{C_{HV} S_V^* \eta_H}{\left(S_H^* + V_H^*\right)^2} - \frac{C_{HV} S_V^*}{\left(S_H^* + V_H^*\right)^2}$$
$$\frac{\partial^2 f_7}{\partial x_3 \partial x_5} = \frac{\partial^2 f_7}{\partial x_5 \partial x_3} = -\frac{C_{HV} S_V^* \eta_H}{\left(S_H^* + V_H^*\right)^2} - \frac{C_{HV} S_V^* \eta_R}{\left(S_H^* + V_H^*\right)^2}$$
$$\frac{\partial^2 f_7}{\partial x_3 \partial x_6} = \frac{\partial^2 f_7}{\partial x_6 \partial x_3} = \frac{C_{HV} \eta_H}{\left(S_H^* + V_H^*\right)}$$

$$\frac{\partial^2 f_7}{\partial x_4 \partial x_4} = -\frac{2C_{HV}S_V^*}{\left(S_H^* + V_H^*\right)^2},$$
$$\frac{\partial^2 f_7}{\partial x_4 \partial x_5} = \frac{\partial^2 f_7}{\partial x_5 \partial x_4} = -\frac{C_{HV}S_V^*}{\left(S_H^* + V_H^*\right)^2} - \frac{C_{HV}S_V^*\eta_R}{\left(S_H^* + V_H^*\right)^2},$$
$$\frac{\partial^2 f_7}{\partial x_4 \partial x_6} = \frac{\partial^2 f_7}{\partial x_6 \partial x_4} = \frac{C_{HV}}{\left(S_H^* + V_H^*\right)},$$
$$\frac{\partial^2 f_7}{\partial x_5 \partial x_6} = \frac{\partial^2 f_7}{\partial x_6 \partial x_5} = \frac{C_{HV}\eta_R}{\left(S_H^* + V_H^*\right)},$$

therefore, after computation, the value of **a** is given by:

$$a = \sum_{k,i,j=1}^{n} V_k W_i W_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0) = \frac{-2C_{HV}}{\left(S_H^* + V_H^*\right)^2}\Bigg\{W_7 V_3 \eta_V \Big(W_3 + W_4 + W_5\Big)\Big[S_H^* + V_H^*\Big] + V_H^* W_8 V_3 \Big(W_3 + W_4 + W_5\Big)\Big[1-\epsilon\Big] + S_H^* V_3^* \Big(W_2 W_8 \epsilon + W_3 W_8 + W_4 W_8 + W_5 W_8 + W_2 W_7 \eta_V \epsilon\Big) + S_V^* V_7 \Big(W_1 + W_2 + W_3 + W_4 + W_5\Big)\Big[W_3\eta_H + W_4 + W_5\eta_R\Big] - W_6 V_7 \Big(W_3\eta_H + W_4 + W_5\eta_R\Big)\Big[V_H^* + S_H^*\Big] - V_H^* V_3 \epsilon \Big(W_1 W_7 \eta_V + W_3 W_7 \eta_V + W_4 W_7 \eta_V + W_5 W_7 \eta_V + W_1 W_8\Big)\Bigg\}$$

Computation of b: To compute b, we need the second order partial derivatives of f_3 and f_7 with respect to x_i and C_{HV} as the second variable, but, at the disease-free equilibrium,

$$\frac{\partial^2 f_3}{\partial x_i \partial C_{HV}} = 0 \quad \text{for} \quad i = 1,2,3,4,5,6 \quad \text{while,}$$
$$\frac{\partial^2 f_3}{\partial x_7 \partial C_{HV}} = \frac{\eta_V\left[S_H^* + V_H^*(1-\epsilon)\right]}{\left(S_H^* + V_H^*\right)} \quad \text{and,}$$
$$\frac{\partial^2 f_3}{\partial x_8 \partial C_{HV}} = \frac{S_H^* + V_H^*(1-\epsilon)}{\left(S_H^* + V_H^*\right)},$$

similarly, at the disease-free equilibrium,

$$\frac{\partial^2 f_7}{\partial x_i \partial C_{HV}} = 0 \quad \text{for} \quad i = 1, 2, 6, 7, 8 \quad \text{also,}$$
$$\frac{\partial^2 f_7}{\partial x_3 \partial C_{HV}} = \frac{S_V^* \eta_H}{\left(S_H^* + V_H^*\right)},$$
$$\frac{\partial^2 f_7}{\partial x_4 \partial C_{HV}} = \frac{S_V^*}{\left(S_H^* + V_H^*\right)} \quad \text{and,}$$
$$\frac{\partial^2 f_7}{\partial x_5 \partial C_{HV}} = \frac{S_V^* \eta_H}{\left(S_H^* + V_H^*\right)},$$

so that, the value of b is given by:

$$b = \sum_{k,i=1}^{n} V_k W_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0) = V_3 \frac{\left[S_H^* + V_H^*(1-\epsilon)\right]}{\left(S_H^* + V_H^*\right)} \left\{W_7 \eta_V + W_8\right\} + \frac{S_V^* V_7}{\left(S_H^* + V_H^*\right)}$$
$$\times \left[W_3 \eta_H + W_4 + W_5 \eta_R\right].$$

Theorem 4.4.3. The malaria model with vaccination (4.1) has backward bifurcation if a is positive.

Proof. Following Theorems in [16, 28], the direction of the bifurcation is forward when $a < 0$ and $b > 0$, while it is backward when $a > 0$ and $b > 0$ as well. From the expression of b above coupled with the fact that, W_3, W_4, W_5, W_7 and W_8 are all positive implies that $b > 0$, therefore, the direction of the bifurcation is governed by the sign of a, such that, if $a > 0$ then, it is backward, else it is forward. □

4.5 Numerical simulation

Using data in Table 3.3 with $\sigma_H = 0.4$ and $\sigma_H = 0.8$ for low and high malaria incidences respectively, $\epsilon = 0.8$, $\rho = 0.3$ and $\psi_H = 0.2$ we have the following;

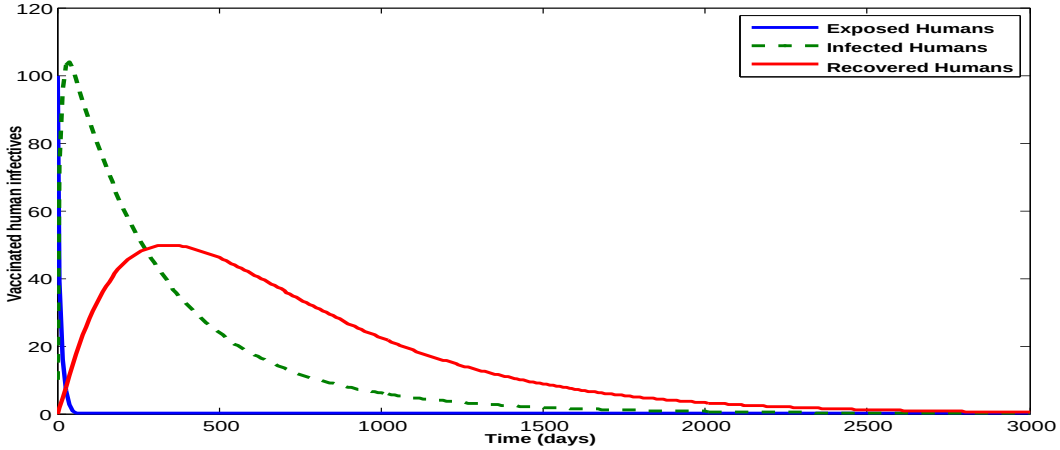

Figure 4.2: Simulation of the model (4.1) for the exposed, infected and recovered humans converge to the DFE when $R_{0v} = 0.0938$ in areas of low malaria incidence using parameter values in Table 3.3 with $S_H(0) = 5000, E_H(0) = 100, I_H(0) = 10, R_H(0) = 0, S_V(0) = 500, E_V(0) = 20, I_V(0) = 10$.

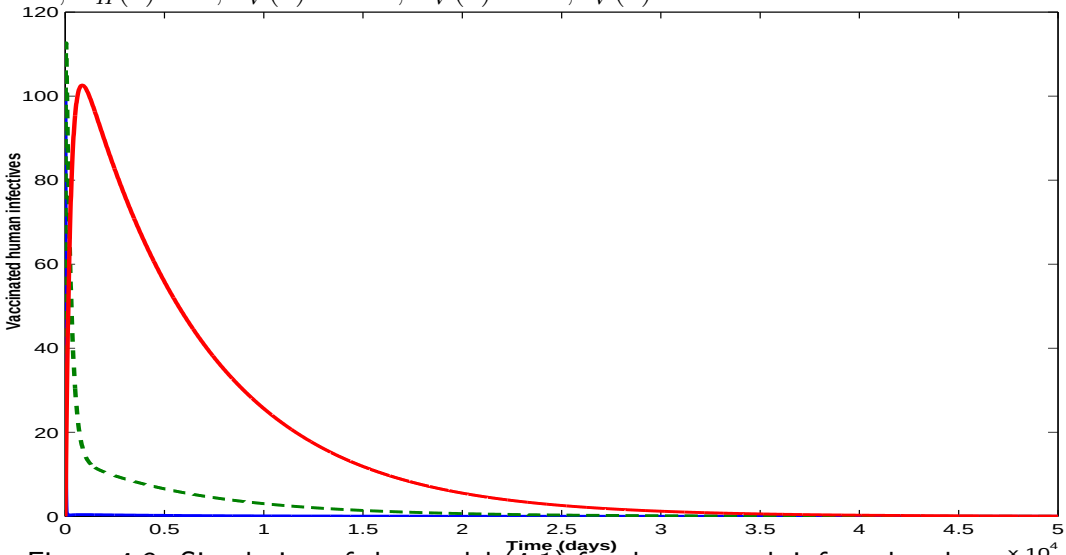

Figure 4.3: Simulation of the model (4.1) for the exposed, infected and recovered humans converge to the DFE when $R_{0v} = 0.9054$ in areas of high malaria incidence using parameter values in Table 3.3 with $S_H(0) = 5000, E_H(0) = 100, I_H(0) = 10, R_H(0) = 0, S_V(0) = 500, E_V(0) = 20, I_V(0) = 10$.

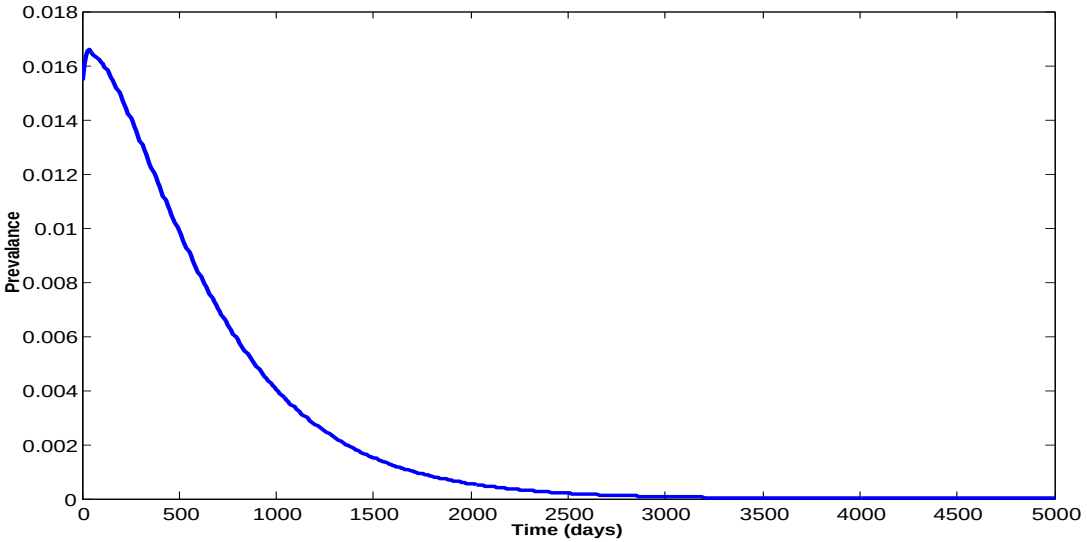

Figure 4.4: Simulation of the model (4.1) showing the disease prevalence in areas of low malaria infection using parameter values in Table 3.3 with $S_H(0) = 5000, E_H(0) = 100, I_H(0) = 10, R_H(0) = 0, S_V(0) = 500, E_V(0) = 20, I_V(0) = 10$ so that $R_{0v} = 0.0938$.

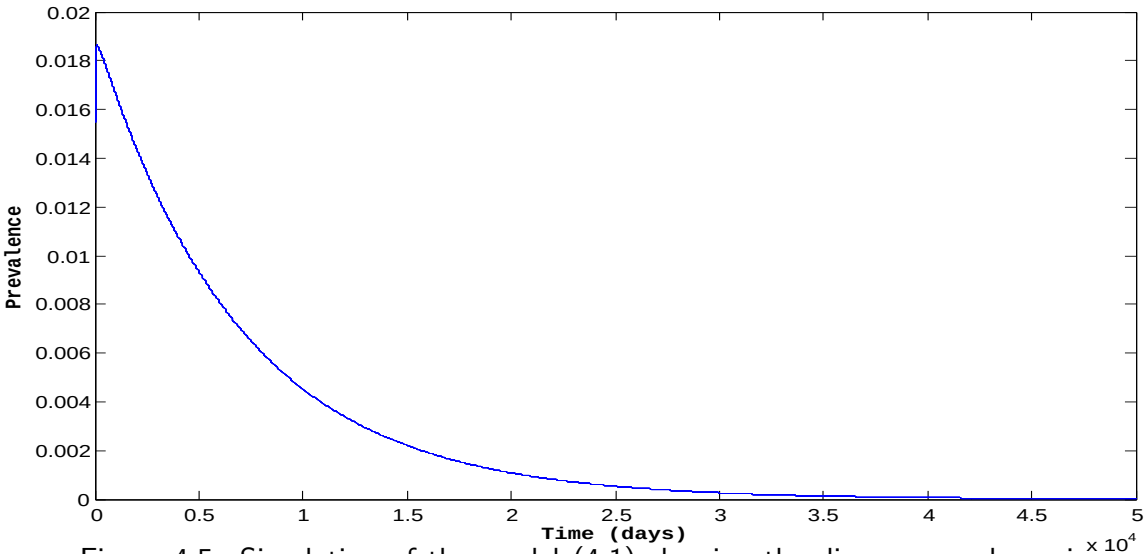

Figure 4.5: Simulation of the model (4.1) showing the disease prevalence in areas of high malaria infection using parameter values in Table 3.3 with $S_H(0) = 5000, E_H(0) = 100, I_H(0) = 10, R_H(0) = 0, S_V(0) = 500, E_V(0) = 20, I_V(0) = 10$ so that $R_{0v} = 0.9054$.

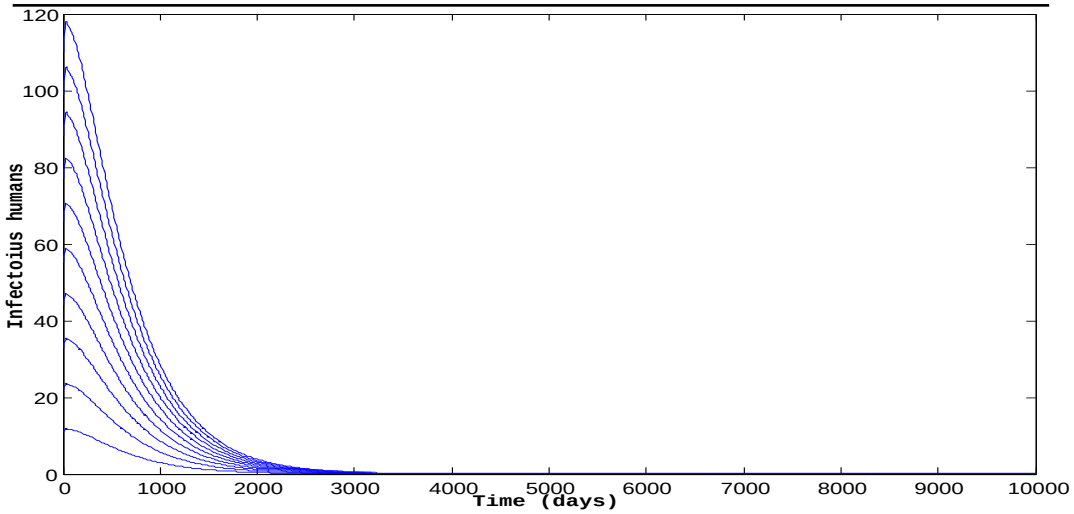

Figure 4.6: Simulation of the model (4.1) showing the total infectives (Exposed + Infected + Recovered) with different initial conditions converging to the DFE in areas of low malaria infection using parameter values in Table 3.3 with $S_H(0) = 5000, E_H(0) = 100, I_H(0) = 10, R_H(0) = 0, S_V(0) = 500, E_V(0) = 20$, and $I_V(0) = 10$ so that $R_{0v} = 0.0938$.

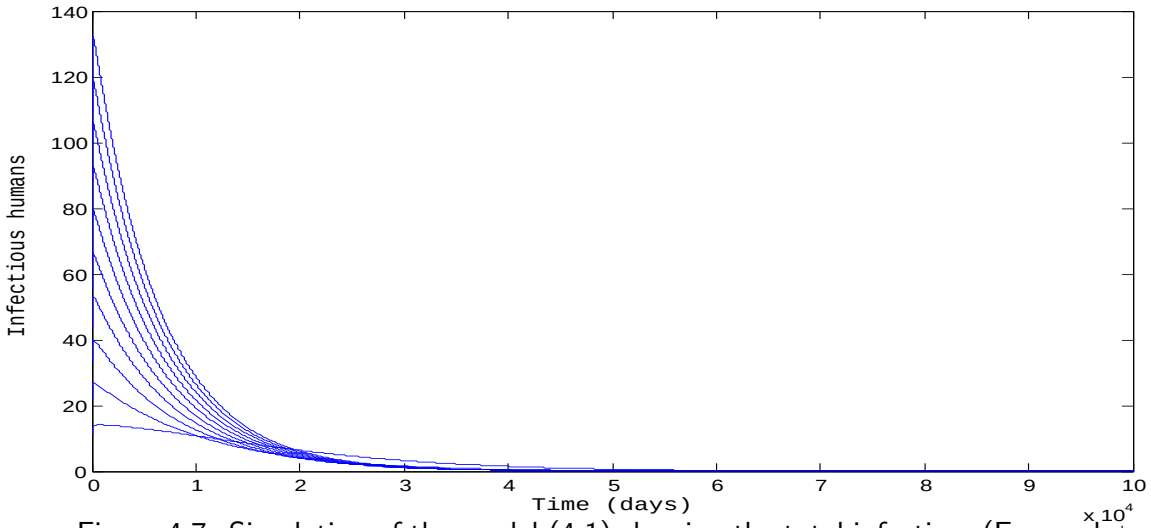

Figure 4.7: Simulation of the model (4.1) showing the total infectives (Exposed + Infected + Recovered) with different initial conditions converging to the DFE in areas of high malaria infection using parameter values in Table 3.3 with $S_H(0) = 5000, E_H(0) = 100, I_H(0) = 10, R_H(0) = 0, S_V(0) = 500, E_V(0) = 20$, and $I_V(0) = 10$ so that $R_0 = 0.9054$.

Using the parameter values in [21] together with the above assumed values for the vaccination parameters, the vaccinated reproduction number R_{0v} is less than the basic reproduction number, the simulation in Figure 4.2 shows that, the convergence to the DFE of the solution is faster with vaccination. In the model with vaccination, the solution converges to DFE even in areas of high malaria incidences as indicated in Figure 4.3, the prevalence dies in both high and low malaria incidence areas as in Figure 4.4 and Figure 4.5. The infectives also converge to the DFE in either cases, that shows numerically that, the use of an imperfect vaccine will have a positive impact in a society as in Figure 4.6 and Figure 4.7.

4.6 Vaccination model with the mass action incidence

Similar to model (3.6), we again replace the standard incidence function with the mass action incidence, in which case the backward bifurcation was found to be eliminated. Consider the system represented by (4.1) with the mass action incidence functions, the vectors of appearance of new infections and that of the transfers out of and into the compartments are respectively given by:

$$\mathcal{F} = \begin{pmatrix} [S_H + V_H(1-\epsilon)]C_{HV}(\eta_V E_V + I_V) \\ 0 \\ 0 \\ S_V C_{HV}(\eta_H E_H + I_H + \eta_R R_H) \\ 0 \end{pmatrix} \text{ and , } \quad \mathcal{V} = \begin{pmatrix} E_H K_1 - \pi \xi_H R_H \\ I_H K_2 - E_H \tau_H \\ R_H K_3 - I_H \theta_H \\ E_V K_4 \\ I_V K_5 - E_V \tau_V \end{pmatrix},$$

where,

$$K_1 = (\tau_H + \mu_H), \quad K_2 = (\theta_H + \delta_H + \mu_H), \quad K_3 = (\xi_H + \mu_H), \quad K_4 = (\mu_V + \tau_V),$$

and, $\quad K_5 = (\mu_V + \delta_V),$

so that the next generation matrices denoted by F and V are as follows:

$$F = \begin{pmatrix} 0 & 0 & 0 & C_{HV}((1-\epsilon)V_H^* + S_H^*) & C_{HV}((1-\epsilon)V_H^* + S_H^*) \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ C_{HV}\eta_H S_V^* & C_{HV} S_H^* & C_{HV}\eta_R S_V^* & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

and

$$V = \begin{pmatrix} K_1 & 0 & -\pi\xi_H & 0 & 0 \\ -\tau_H & K_2 & 0 & 0 & 0 \\ 0 & -\theta_H & K_3 & 0 & 0 \\ 0 & 0 & 0 & K_4 & 0 \\ 0 & 0 & 0 & -\tau_V & K_5 \end{pmatrix}.$$

The associated reproduction number of the vaccinated model (4.1) with the mass

action is therefore given by,

$$R_V^m = \sqrt{\frac{C_{HV}^2 \Pi_V (\eta_H K_2 K_3 + \tau_H K_3 + \eta_R \theta_H \tau_H)(\eta_V K_5 + \tau_V)\big[\varphi_H + \mu_H(1-\epsilon\rho) + \sigma_H(1-\epsilon)\big]}{\big(K_1 K_2 K_3 - \tau_H \theta_H \xi_H \pi\big)(\varphi_H + \sigma_H + \mu_H) K_4 K_5 \mu_V}}$$

$$= R_{0v}\sqrt{\frac{\Pi_H}{\mu_H}}. \tag{4.12}$$

Next lemma follows from Theorem 2 of [28]

Lemma 4.6.1. The DFE of the vaccinated model (4.1) with mass action is LAS if $R_V^m < 1$ and unstable if $R_V^m > 1$.

Theorem 4.6.2. The vaccination model (4.1) with mass action incidence function has no endemic equilibrium when $R_V^m \leq 1$ and has a unique endemic equilibrium otherwise.

Proof. The endemic equilibrium of model (4.1) denoted by J_1 is obtained similar

to (4.6) and given by:

$$S_H^{m*} = \frac{\Pi_H\Big(M_1 + M_2\Big)}{M_3 - M_4}, \quad V_H^{m*} = \frac{\Pi_H\Big[\rho\big(M_3 - M_4\big) + \sigma_H\big(M_1 + M_2\big)\Big]}{M_5\big(M_3 - M_4\big)},$$

$$E_H^{m*} = \frac{\lambda_H^{m*} K_2 K_3\Big[\varphi_H + \mu(1-\epsilon\rho) + \sigma_H(1-\epsilon)\Big]}{\big[K_1K_2K_3 - \theta_H\tau_H\xi_H\pi\big]\big(\varphi_H + \sigma_H + \mu_H\big)},$$

$$I_H^{m*} = \frac{\lambda_H^{m*} \tau_H K_3\Big[\varphi_H + \mu(1-\epsilon\rho) + \sigma_H(1-\epsilon)\Big]}{\big[K_1K_2K_3 - \theta_H\tau_H\xi_H\pi\big]\big(\varphi_H + \sigma_H + \mu_H\big)},$$

$$R_H^{m*} = \frac{\lambda_H^{m*} \tau_H\theta_H\Big[\varphi_H + \mu(1-\epsilon\rho) + \sigma_H(1-\epsilon)\Big]}{\big[K_1K_2K_3 - \theta_H\tau_H\xi_H\pi\big]\big(\varphi_H + \sigma_H + \mu_H\big)},$$

$$S_V^{m*} = \frac{\Pi_V}{\mu_V + \lambda_V^{m*}}, \quad E_V^{m*} = \frac{\lambda_V^{m*}\Pi_V}{(\mu_V + \lambda_V^{m*})K_4}, \quad I_V^{m*} = \frac{\tau_V\lambda_V^{m*}\Pi_V}{(\mu_V + \lambda_V^{m*})K_4K_5}, \tag{4.13}$$

with,

$$M_1 = \big[1-\rho\big]\Big[\big(K_1K_2K_3 - \theta_H\tau_H\xi_H\pi\big)\big(\lambda_H^{m*}(1-\epsilon) + \psi_H + \mu_H\big)\Big],$$

$$M_2 = \rho\Big[\varphi_H\big(K_1K_2K_3 - \theta_H\tau_H\xi_H\pi\big) + (1-\epsilon)(1-\pi)\xi_H\tau_H\theta_H\lambda_H^{m*}\Big],$$

$$M_3 = \big(\lambda_H^{m*}(1-\epsilon) + \psi_H + \mu_H\big)^2\Big[\big(K_1K_2K_3 - \theta_H\tau_H\xi_H\pi\big)\big(\lambda_H^{m*} + \sigma_H + \mu_H\big)$$

$$- (1-\pi)\xi_H\theta_H\tau_H\lambda_H^{m*}\Big],$$

$$M_4 = \sigma_H\Big[\varphi_H\big(K_1K_2K_3 - \theta_H\tau_H\xi_H\pi\big) + (1-\epsilon)(1-\pi)\big[\lambda_H^{m*}\big(1-\epsilon\big) + \varphi_H + \mu_H\big],$$

$$\xi_H\tau_H\theta_H\lambda_H^{m*}\Big] \text{ and,}$$

$$M_5 = \lambda_H^{m*}(1-\epsilon) + \psi_H + \mu_H$$

and the forces of infections given by (3.23) and (3.24), so that substituting E_V^{m*} and I_V^{m*} from (4.13) in (3.23) we obtained,

$$\lambda_H^{m*}\lambda_V^{m*}K_4K_5 + \lambda_H^{m*}\mu_V K_4K_5 - \lambda_V^{m*}C_{HV}\Pi_V(\eta_V K_5 + \tau_V) = 0, \tag{4.14}$$

similarly, substituting from (4.13), the values of E_H^{m*}, I_H^{m*} and R_H^{m*} in (3.24) we have,

$$\lambda_V^{m*} = \frac{\lambda_H^{m*}C_{HV}\left[V_H(1-\epsilon) + S_H\right]\left[\eta_H K_4K_5 + \tau_H K_5 + \eta_R\theta_H\tau_H\right]}{K_3K_4K_5 - \theta_H\tau_H\xi_H\pi}, \tag{4.15}$$

now, substituting λ_V^{m*} from (4.15) in (4.14) and after simplifications we have,

$$\lambda_H^{m*}\left\{\lambda_H^{m*}(R_0^M)^2 + \Pi_V\mu_V\left[\eta_V K_5 + \tau_V\right]\left[1 - (R_0^m)^2\right]\right\} = 0. \tag{4.16}$$

The case when $\lambda_H^m = 0$ corresponds to the DFE, else, if $\lambda_H^m \neq 0$ we have,

$$\lambda_H^{m*} = -\frac{\Pi_V\mu_V\left[\eta_V K_5 + \tau_V\right]\left[1 - (R_0^m)^2\right]}{(R_0^m)^2}. \tag{4.17}$$

From (4.17), it is clear that when $0 < R_0^m < 1$, then $\lambda_H^{m*} < 0$ which is biologically meaningless, therefore, when $R_0^m < 1$, no endemic equilibrium exist. On the other hand, if $R_0^m > 1$, then λ_H^{m*} is a unique positive constant, so that, substituting its value in (4.13) gives a unique endemic equilibrium, which completes the proof. □

4.6.1 Global stability of the DFE

Just like in subsection 3.5.2, the dynamic of the mass action model (4.1), with (3.23) and (3.24) will be considered in the positively invariant region Δ.

Theorem 4.6.3. The DFE of the of the vaccinated model (4.1) with the mass action incidence functions (3.23) and (3.24) is globally asymptotically stable (GAS)

in Δ if $R_0^m \leq 1$.

Proof. Consider the function defined by:

$$F = F_1 E_H + F_2 I_H + F_3 R_H + F_4 E_V + F_5 I_V,$$

where the constants are given by:

$$\begin{aligned}
F_1 &= C_{HV}\Pi_V\big(\eta_V K_5 + \tau_V\big)\big(K_2K_3\eta_H + K_3\tau_H + \eta_R\theta_H\tau_H\big),\\
F_2 &= C_{HV}\Pi_V\big(\eta_V K_5 + \tau_V\big)\big(\eta_H\theta_H\xi_H\pi + \eta_R K_1\theta_H + K_1K_3\big),\\
F_3 &= C_{HV}\Pi_V\big(\eta_V K_5 + \tau_V\big)\big(\eta_H\xi_H\pi K_2 + \xi_H\pi\tau_H + \eta_R K_1K_2\big),\\
F_4 &= R_0^m\mu_V\big(\eta_V K_5 + \tau_V\big)\big(K_1K_2K_3 - \theta_H\tau_H\xi_H\pi\big),\\
F_5 &= R_0^m\mu_V K_4\big(K_1K_2K_3 - \theta_H\tau_H\xi_H\pi\big),
\end{aligned}$$

therefore $\dot{F}$ in the direction of the right-hand side of (4.1) gives,

$$\dot{F} = F_1\dot{E_H} + F_2\dot{I_H} + F_3\dot{R_H} + F_4\dot{E_V} + F_5\dot{I_V} \tag{4.18}$$

and substituting $\dot{E_H}, \dot{I_H}, \dot{R_H}, \dot{E_V}, \dot{I_V}$ from (4.1), (3.23) and (3.24) in (4.18) together with the fact that at DFE $S_V^* \leq \frac{\Pi_V}{\mu_V}$ we obtained,

$$\begin{aligned}
\dot{F} \leq\ & E_H\Big[C_{HV}\Pi_V\eta_H\big(K_1K_2K_3 - \theta_H\tau_H\xi_H\pi\big)\big(\eta_V K_5 + \tau_V\big)\big(R_0^m - 1\big)\Big] + I_H\Big[\\
& C_{HV}\Pi_V\big(K_1K_2K_3 - \theta_H\tau_H\xi_H\pi\big)\big(\eta_V K_5 + \tau_V\big)\big(R_0^m - 1\big)\Big] + R_H\Big[C_{HV}\Pi_V\eta_R\\
& \big(K_1K_2K_3 - \theta_H\tau_H\xi_H\pi\big)\big(\eta_V K_5 + \tau_V\big)\big(R_0^m - 1\big)\Big] + E_V\Big[R_0^m\big(R_0^m - 1\big)K_4K_5\\
& \eta_V\mu_V\big(K_1K_2K_3 - \theta_H\tau_H\xi_H\pi\big)\Big] + I_V\Big[R_0^m K_4\mu_V\big(K_1K_2K_3 - \theta_H\tau_H\xi_H\pi\big)\big(R_0^m - 1\big)\Big],
\end{aligned}$$

therefore the above expression is simplified to,

$$\dot{F} \leq \left(R_0^m - 1\right)\Bigg\{E_H\Big[C_{HV}\Pi_V\eta_H(\eta_V K_5 + \tau_V)(K_1K_2K_3 - \theta_H\tau_H\xi_H\pi)\Big] + I_H\Big[$$
$$C_{HV}\Pi_V(\eta_V K_5 + \tau_V)\big(K_1K_2K_3 - \theta_H\tau_H\xi_H\pi\big)\Big] + R_H\Big[C_{HV}\Pi_V\eta_R\big(\eta_V K_5 + \tau_V\big)$$
$$\big(K_1K_2K_3 - \theta_H\tau_H\xi_H\pi\big)\Big] + E_V\Big[R_0^m\mu_V K_4K_5\eta_V\big(K_1K_2K_3 - \theta_H\tau_H\xi_H\pi\big)\Big]$$
$$+ I_V\Big[R_0^m K_4\mu_V\big(K_1K_2K_3 - \theta_H\tau_H\xi_H\pi\big)\Big]\Bigg\}.$$

The proof is completed using similar approach as in Theorem 3.6. □

4.7 Analysis of Vaccine impact

The main aim of vaccination programmes is to reduce the prevalence of an infectious disease and ultimately to eradicate it. Having seen that the two malaria models with the mass action incidence function posses the property that whenever the basic reproduction number is less than one, the disease-free equilibrium is globally asymptotically stable, we investigate the impact of the widespread use of an imperfect malaria vaccine in a community with the mass action incidence function and also analysed a threshold vaccine number.

4.7.1 Vaccine impact and critical coverage

Observe that the vaccinated reproduction number of the vaccinated model (4.1) is a function of both the basic reproduction number of the system (3.6) and the fraction of the vaccinated individuals, in fact, $R_v^m = R_0^m$ when $V_H = 0$, furthermore, at DFE, $S_H^* + V_H^* = N_H^*$ so that the fraction of the vaccinated

individuals $\rho = \frac{V_H^*}{N_H^*} < 1$, that is

$$R_v^m = R_0^m \sqrt{\frac{S_H^* + V_H^* - V_H^* \epsilon}{N_H^*}} = R_0^m \sqrt{\frac{S_H^* + V_H^*}{N_H^*} - \frac{V_H^* \epsilon}{N_H^*}} = R_0^m \sqrt{1 - \rho\epsilon}.$$

Therefore to qualitatively determine the vaccine impact, we find the partial derivative of the vaccinated reproduction number of model (4.1) with respect to the fraction of individuals that were vaccinated $(\rho = \frac{V_H^*}{N_H^*})$. Differentiating we obtain

$$\frac{\partial R_v^m}{\partial \rho} = -\frac{R_0^m \epsilon}{2\sqrt{1 - \rho\epsilon}}. \tag{4.19}$$

Since $0 < \epsilon < 1$ and $0 \leq \rho < 1$ then (4.19) is always negative, hence R_v^m is a decreasing function of $\rho = \frac{V_H^*}{N^*}$, therefore we conclude that an imperfect vaccine for malaria will have positive impact in any community whenever $0 < \rho = \frac{V_H^*}{N_H^*} < 1$ and $\epsilon > 0$, that is, so long as the vaccine is effective, vaccinating any fraction of the susceptible population at the DFE reduces the rate of infection in comparison to when vaccination is absent.

To compute the critical proportion needed to be vaccinated for the control of the disease, we need the vaccinated reproduction number to be less than one, that is equivalent to $\rho > \frac{1}{\epsilon}\left(1 - \frac{1}{(R_0^m)^2}\right)$, so that, the critical proportion needed to be vaccinated for the control of the disease will be $\rho_c = \frac{1}{\epsilon}\left(1 - \frac{1}{(R_0^m)^2}\right)$.

Theorem 4.7.1. The DFE (Z_0) of the model with vaccination (4.1) is GAS if $\rho > \rho_c$ and unstable if $\rho < \rho_c$.

Proof. Simplifying R_v^m we have,

$$R_v^m = R_0^m \sqrt{\frac{S_H + V_H - V_H \epsilon}{N_H}} = R_0^m \sqrt{1 - \rho\epsilon}, \tag{4.20}$$

since at DFE $S_H = S_H^*$, $V_H = V_H^*$ and $N_H = N_H^*$, also $S_H^* + V_H^* = N_H^*$, $\rho = \frac{V_H^*}{N_H^*}$.

From (4.20) it implies that,

$$R_v^m < 1 \quad \Leftrightarrow \quad R_0^m\sqrt{1-\rho\epsilon} < 1 \quad \Leftrightarrow \rho > \frac{1}{\epsilon}\left(1-\frac{1}{(R_0^m)^2}\right) = \rho_c.$$

By Theorem 4.6.3, the DFE is GAS whenever $R_v^m < 1$ which implies that $\rho > \rho_c$. From Lemma 4.6.1 the DFE is unstable when $R_v^m > 1$ which implies $\rho < \rho_c$. □

The theorem can be interpreted as follows; if the fraction of the vaccinated individuals at the steady state exceeds the threshold level ρ_c, then the DFE is globally asymptotically stable and unstable otherwise.

For disease to persist, we assume that $R_0^m > 1$, also, the requirement for disease eradication ($\rho > \rho_c$) is equivalent to

$$\frac{1}{\epsilon}\left(1-\frac{(R_v^m)^2}{(R_0^m)^2}\right) > \frac{1}{\epsilon}\left(1-\frac{1}{(R_0^m)^2}\right)$$

which is the same as,

$$(R_0^m)^2 - (R_v^m)^2 = (R_0^m)^2 - (R_0^m)^2[1-\epsilon\rho] = (R_0^m)^2\epsilon\rho > (R_0^m)^2 - 1 > 0$$

but then $(R_0^m)^2 - (R_v^m)^2$ is

$$\frac{C_{HV}^2\Pi_V\mu_H(\eta_V K_5+\tau_V)(K_2K_3\eta_H + K_3\tau_H + \theta_H\tau_H\eta_R)[\sigma_H+\rho\mu_H]\epsilon}{\mu_V\Pi_H K_4K_5[\varphi_H+\sigma_H+\mu_H](K_1K_2K_3 - \theta_H\tau_H\xi_H\pi)} > 0$$

this also shows that the vaccine will always have positive impact so long as the difference between the basic reproduction number and the vaccinated reproduction number is positive.

4.7.2 Vaccine efficacy and coverage

From the vaccinated reproduction number, we can clearly see that $\rho = \frac{1}{\epsilon}\left(1 - \frac{(R_0^m)^2}{(R_0^m)^2}\right)$, so that $\epsilon \to 0$ then ρ grows larger, that is more people will need to be vaccinated, while $\epsilon \to 1$ implies ρ reduces, therefore, increasing the vaccine efficacy will reduce the number of people that need to be vaccinated for the disease control. In essence, the vaccination coverage depends on the efficacy of the vaccine. Applying similar method with [31], we can determine the vaccine impact when the entire population were vaccinated, that is $V_H^* = N_H^*$ and $S_H^* = 0$, such that,

$$R_a^m = \sqrt{\frac{C_{HV}^2 \Pi_V \mu_H^2 (\eta_H K_2 K_3 + \tau_H K_3 + \eta_H \theta_H \tau_H)(\eta_V K_5 + \tau_V)(1-\epsilon)}{\left(K_1 K_2 K_3 - \tau_H \theta_H \xi_H \pi\right) K_4 K_5 \Pi_H^2 \mu_V}}, \quad (4.21)$$

we can therefore express R_a^m as follows,

$$(R_a^m)^2 = (R_0^m)^2(1-\epsilon) = (R_0^m)^2 - (R_0^m)^2 + (R_a^m)^2 = (R_0^m)^2\left[1 - \left(1 - \frac{(R_a^m)^2}{(R_0^m)^2}\right)\right] \quad (4.22)$$

the vaccine impact can be defined via $\digamma$, where,

$$\digamma = \left(1 - \frac{(R_a^m)^2}{(R_0^m)^2}\right), \quad (4.23)$$

Consequently, we claim the following

Theorem 4.7.2. The use of imperfect malaria vaccine in a community will

(i) Reduce infection if $\digamma > 0$;

(ii) Increase infection if $\digamma < 0$;

(iii) Have no impact on infection rate if $\digamma = 0$.

Proof. From (4.22) and (4.23), we have,

$$\frac{(R_a^m)^2}{(R_0^m)^2} = 1 - \digamma\,. \tag{4.24}$$

Obviously $R_a^m < R_0^m$ implies reduction in infection and $R_a^m > R_0^m$ means increase in infection due to vaccinating the entire population, similarly $R_a^m = R_0^m$ means vaccinating the entire population has no impact on the severity of infection. But from (4.24), $\digamma = \frac{R_0^m - R_a^m}{R_0^m}$ so that $\digamma > 0 \Rightarrow R_a^m < R_0^m$, $\digamma < 0 \Rightarrow R_a^m > R_0^m$ and $\digamma = 0 \Rightarrow R_a^m = R_0^m$.

It is also clear from (4.12) and (4.21) that,

$$\frac{(R_a^m)^2}{(R_0^m)^2} = 0 < (1 - \epsilon) < 1,$$

which implies that $R_0^m > R_a^m$, thus, the vaccine will always have positive impact.

□

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