Dynamics of Multi-strain Age-structured Model for Malaria Transmission

by

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Abstract

The thesis is based on the use of mathematical modeling and analysis to gain insight into the transmission dynamics of malaria in a community. A new deterministic model for assessing the role of age-structure on the disease dynamics is designed. The model undergoes backward bifurcation, a dynamic phenomenon characterized by the co-existence of a stable disease-free and an endemic equilibrium of the model when the associated reproduction number is less than unity. It is shown that adding age-structure to the basic model for malaria transmission does not alter its essential qualitative dynamics. The study is extended to incorporate the use of anti-malaria drugs. Numerical simulations of the extended model suggest that for the case when treatment does not cause drug resistance (and the reproduction number of each of the two strains exceed unity), the model undergoes competitive exclusion. The impact of various effectiveness levels of the treatment strategy is assessed.

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Dedication

To my parents, who shine into my life like the sun.

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Glossary

Abbreviation	Meaning
DFE	Disease-free equilibrium
EEP	Endemic equilibrium point
GAS	Globally-asymptotically stable
LAS	Locally-asymptotically stable
ODE	Ordinary differential equation

Chapter 1

Introduction

Malaria is a major vector-borne disease that continues to inflict enormous public health burden in many parts of the world [61]. The disease, which is endemic in over 100 countries (representing nearly 40% of the world's population; mostly in the tropical and sub-tropical regions of the world [6]), accounts for about 300 million cases and over one million fatalities annually (with children under the age of five suffering the most mortality burden) [61]. In addition to the public health burden it incurs, malaria also inflicts enormous socio-economic burden in malaria-endemic nations. For example, the annual economic burden of malaria in Africa alone was estimated to be around US $8 billion [6]. A global map of malaria, showing the geographic spread of the disease, is depicted in Figure 1.1.

The study of malaria transmission dynamics is further motivated by the increased mobility of people, increased distribution of mosquitoes due to climate change, the ongoing global effort to eradicate malaria [62], and malaria spread in new geographical regions (due to immigration and global travel).

The incubation period of malaria is between from 7 to 30 days [12], and the common symptoms of the disease malaria include: chills, fever, sweating, headache, malaise, fatigue, muscular pains, occasional nausea, vomiting and diarrhea [46, 69].

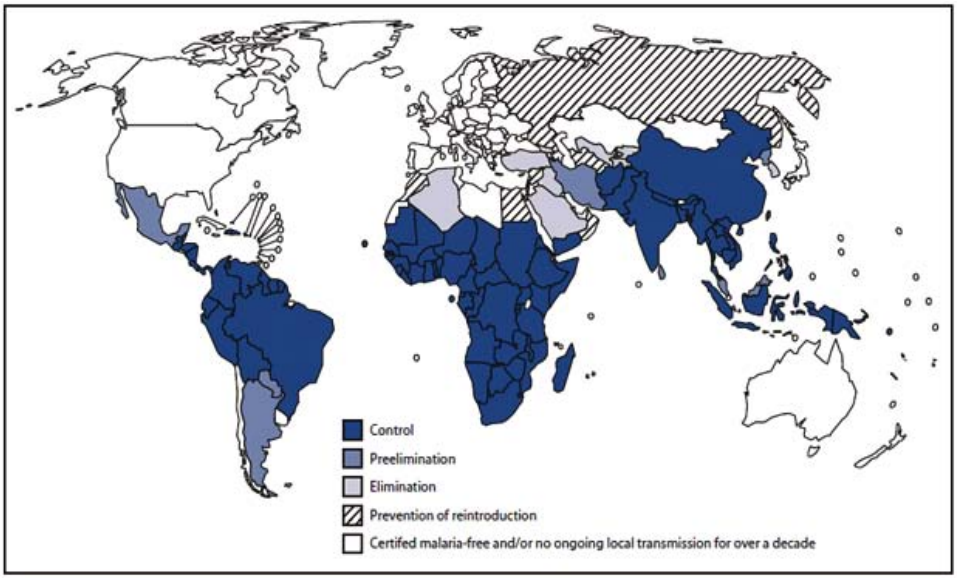

Figure 1.1: Malaria global map (source://www.cdc.gov).

There is currently no effective and safe vaccine for use against malaria in humans (although concerted global efforts are underway to develop such a vaccine [5, 18, 19, 27, 35, 42, 43, 44, 47, 53, 54, 59, 63, 66]). Consequently, malaria control is based on the use of preventive measures (such as mosquito-reduction strategies and personal protection against mosquito bite) and the use of anti-malaria drugs (see, for instance, [23, 25, 50, 51, 69, 72]). The use of anti-malarial drugs is, however, known to pose the problem of the emergence and transmission of drug-resistant malaria strain [4, 6, 36, 46].

Numerous mathematical models have been designed and used to gain insight into malaria transmission dynamics in a community, dating back to the classical malaria models of Ross [52] and Macdonald [40]. Although these classical models have, over the decades, been extended to incorporate various aspects related to malaria transmission dynamics and control, such as repeated exposure [45], the use of preventive and therapeutic strategies [72], effect of climate change [39] etc., not much work has been done in modeling the effect of age-structure on malaria spread and control. This is particularly important considering the fact that malaria mortality is age-

dependent (with, as stated above, children under the age of five bearing the most burden [69]).

1.1 Reproduction Number and Bifurcation

Disease transmission models, typically obtained by splitting the total population into mutually-exclusive compartments based on infection status, have contributed greatly to providing insight into the dynamics of infectious diseases, dating back to the pioneering works of Bernoulli, Ross, Kermack and McKendrick and others (see, for instance, [2, 3, 32] and some of the references therein). The dynamics of such models is often characterized by the reproduction number ($\mathcal{R}_0$), a threshold quantity which measures the average number of new cases generated by a typical infected individual in a completely-susceptible population [2, 16, 32].

Typically, when $\mathcal{R}_0$ is less than unity, a small influx of infected individuals will not generate large outbreaks, and the disease dies out in time (in this case, the corresponding disease-free equilibrium (DFE) of the model is asymptotically-stable). On the other hand, the disease will persist in the population if $\mathcal{R}_0$ exceeds unity, where, typically, an asymptotically-stable endemic equilibrium point (EEP) exists [2, 32, 65]. This phenomenon, where the DFE and an EEP of a model exchange their stability at $\mathcal{R}_0 = 1$, is known as *forward bifurcation* [28, 32, 57, 71]. Bifurcation represents a change in the qualitative behaviour of the model as a related parameter or quantity (typically $\mathcal{R}_0$) varies. A schematic description of forward bifurcation is given in Figure 1.2.

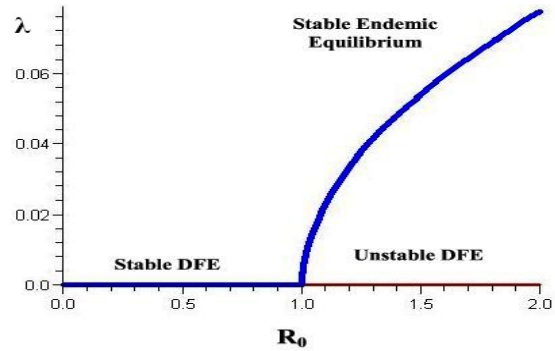

Figure 1.2: Forward bifurcation diagram, showing the infection rate (λ) as a function of the reproduction number ($\mathcal{R}_0$).

In general, for models that exhibit forward bifurcation, the requirement $\mathcal{R}_0 < 1$ is necessary and sufficient for effective community-wide disease control or elimination. However, some modelling studies show that although $\mathcal{R}_0 < 1$ is necessary for effective disease control or elimination, the condition may not be sufficient. This is owing to a dynamic phenomenon known as *backward bifurcation* [10, 21, 28, 29, 30, 71, 26, 57, 55, 45], where two stable attractors (the DFE and a stable EEP) co-exist when $\mathcal{R}_0 < 1$ (see Figure 1.3). The public health implication of backward bifurcation is that disease control or elimination (when $\mathcal{R}_0 < 1$) is dependent on the initial sizes of the sub-populations of the model. Thus, the presence of backward bifurcation in the transmission dynamics of a disease in a population makes its effective community-wide control difficult.

1.2 Thesis Outline

The aim of this thesis is to qualitative assess the role of age-structure and drug treatment on the transmission dynamics and control of malaria in a population. The thesis is organized as follows. Chapter 1 covers the introductory epidemiological aspects of malaria transmission dynamics. The basic mathematical concepts relevant to the thesis are reviewed in Chapter 2. A new age-structured model for malaria

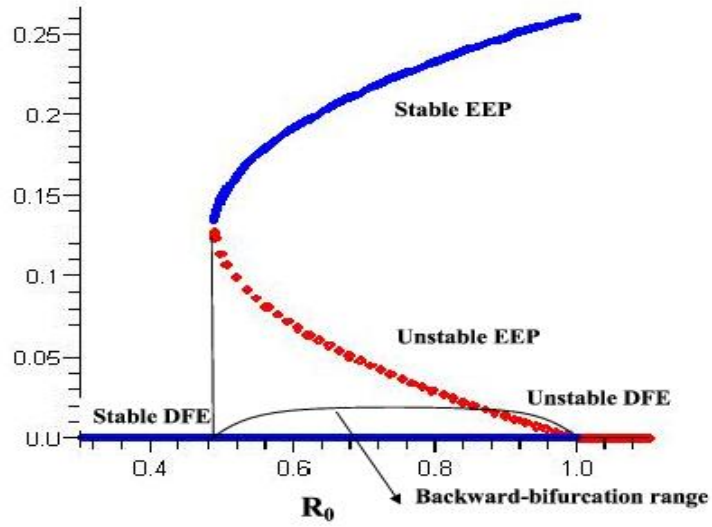

Figure 1.3: Backward bifurcation diagram, showing the co-existence of a stable DFE and two branches of endemic equilibria (a stable and an unstable branch) .

transmission dynamics is designed and rigorously analysed in Chapter 3. The model is extended, in Chapter 4, to incorporate anti-malaria drug treatment. The resulting two-strain age-structured model is also rigorously analysed. Some of the specific questions to be addressed in the thesis include:

(a) What are the main qualitative features of an age-structured malaria model in a population? The aim here is to determine conditions for the existence and asymptotic stability of the associated equilibria, as well as to characterize the types of bifurcation the model may undergo;

(b) What is the qualitative impact of the use of anti-malaria drugs on malaria transmission dynamics? In particular, does the resulting two-strain malaria model exhibit the phenomena of competitive exclusive and/or strain co-existence? If yes, under what conditions do these phenomena occur?

(c) What is the community-wide impact of some of the standard non-pharmaceutical interventions (i.e., anti-malaria control strategies based on using mosquito-

reduction strategies and personal protection against mosquito bite) for combating malaria spread in the community?

(d) What is the impact of various effectiveness levels of the treatment strategy in combating the spread of malaria in the community?

Chapter 2

Mathematical Preliminaries

This chapter introduces some of the basic mathematical definitions, theories and methodologies relevant used in the thesis.

2.1 Equilibria of Autonomous Systems of Ordinary Differential Equations (ODEs)

It should be mentioned that the thesis only considers *autonomous* systems of ODEs, given by (where a dot represents differentiation with respect to time)

$$\dot{x} = f(x), \quad x \in \mathbb{R}^n. \tag{2.1}$$

That is, *non-autonomous* ODE systems of the form,

$$\dot{x} = f(x,t), \quad x \in \mathbb{R}^n, \quad \text{and} \quad t \in \mathbb{R}, \tag{2.2}$$

where $f(x,t) \in C^r$ (with $r \geq 1$) depend on the independent variable t, are not considered in the thesis.

Definition 2.1. *A point $\bar{x} \in \mathbb{R}^n$ is called an equilibrium point of the autonomous*

system (2.1) if $f(\bar{x}) = 0$.

Theorem 2.1. (Fundamental Existence- Uniqueness Theorem [48]). *Let* E *be an open subset of* $\mathbb{R}^n$ *containing* x_0 *and assume that* $f \in C^1(E)$. *Then, there exists an* $a > 0$ *such that the initial value problem:*

$$\dot{x} = f(x), \quad x(0) = x_0,$$

has a unique solution $x(t)$ *on the interval* $[-a, a]$.

Definition 2.2. *The Jacobian matrix of* f *at the equilibrium* $\bar{x}$, *denoted by* $Df(\bar{x})$, *is the matrix,*

$$J(\bar{x}) = \begin{pmatrix} \frac{\partial f_1}{\partial x_1}(\bar{x}) & \cdots & \frac{\partial f_1}{\partial x_n}(\bar{x}) \\ \vdots & \vdots & \vdots \\ \frac{\partial f_n}{\partial x_1}(\bar{x}) & \cdots & \frac{\partial f_n}{\partial x_n}(\bar{x}) \end{pmatrix},$$

of partial derivatives of f *evaluated at* $\bar{x}$.

Definition 2.3. *The linear system* $\dot{x} = Ax$, *with the matrix* $A = Df(\bar{x})$, *is called the linearization of the system (2.1) at* $\bar{x}$.

Definition 2.4. *An equilibrium point* $\bar{x}$ *is called a hyperbolic equilibrium point of the autonomous system (2.1) if none of the eigenvalues of* $Df(\bar{x})$ *has zero real part.*

Definition 2.5. *An equilibrium point that is not hyperbolic is called non-hyperbolic.*

2.2 Hartman-Grobman Theorem

Let,

$$\begin{aligned} \dot{x} &= f(x), \quad x \in \mathbb{R}^n, \\ \dot{y} &= g(y), \quad y \in \mathbb{R}^n, \end{aligned} \tag{2.3}$$

be two C^r $(r \geq 1)$ vector fields on $\mathbb{R}^n$.

Definition 2.6. [68]. *The dynamics generated by the vector fields f and g of (2.3) are said to be locally C^k conjugate $(k \leq r)$ if there exists a C^k diffeomorphisim h which takes the orbits of the flow generated by f, $\phi(t, x)$, to the orbits of the flow generated by g, $\psi(t, y)$, preserving orientation and parameterization by time.*

Theorem 2.2. (Hartman-Grobman Theorem [68]). *Consider a $C^r(r \geq 1)$ vector field*

$$\dot{x} = f(x), \quad x \in \mathbb{R}^n, \tag{2.4}$$

with domain of f to be a large open subset of $\mathbb{R}^n$. Suppose also that (2.4) has a equilibrium solutions which are hyperbolic. Consider the associated linear vector field

$$\dot{\xi} = Df(\bar{x})\xi, \quad \xi \in \mathbb{R}^n. \tag{2.5}$$

Then the flow generated by (2.4) is C^0 conjugate to the flow generated by the linearized system (2.5) in a neighborhood of the equilibrium point $x = \bar{x}$.

It should be noted that the Hartman-Grobman Theorem guarantees a homeomorphism between the flow of the non-linear ODE system and that of its linearization. In general, near a hyperbolic equilibrium point $\bar{x}$, the non-linear system $\dot{x} = f(x)$ has the same qualitative structure as the linear system $\dot{x} = Ax$ with $A = Df(\bar{x})$.

2.3 Stability Theory

Definition 2.7. [68]. *The equilibrium $\bar{x}$ is said to be stable if given $\epsilon > 0$, there exists a $\delta = \delta(\epsilon) > 0$ such that, for any solution $y(t)$ of (2.1) satisfying $|\bar{x} - y(t_0)| < \delta$, $|\bar{x} - y(t)| < \epsilon$ for $t > t_0, t_0 \in \mathbb{R}$.*

Definition 2.8. [68]. *The equilibrium $\bar{x}$ is said to be asymptotically-stable if it is*

stable and there exists a constant $c > 0$ such that, for any solution $y(t)$ of (2.1) satisfying $|\bar{x} - y(t_0)| < c$, then $\lim_{t\to\infty} |\bar{x} - y(t)| = 0$.

Definition 2.9. *An equilibrium solution which is not stable is said to be unstable.*

Theorem 2.3. [68]. *Suppose all the eigenvalues of $Df(\bar{x})$ have negative real parts. Then the equilibrium solution $x = \bar{x}$ of the system (2.1) is locally asymptotically stable, and unstable if at least one of the eigenvalues has positive real part.*

2.4 Center Manifold Theory

Center Manifold theory is (essentially) a theory for reducing the dimensionality of a given non-linear system near an equilibrium point. Consider the non-linear dynamical system (2.1). Let,

$$\dot{x} = Ax, \tag{2.6}$$

be the corresponding linearized system (with $A = Df(\bar{x})$) near a hyperbolic equilibrium point $\bar{x}$.

Definition 2.10. *The stable, unstable, and center subspaces of the linear system (2.6) are defined by (where $A \in M_{nn}(\mathbb{R})$)*

$$\begin{aligned} E^s &= span\left\{u_j, v_j; a_j < 0\right\}, \\ E^u &= span\left\{u_j, v_j; a_j > 0\right\}, \\ E^c &= span\left\{u_j, v_j; a_j = 0\right\}, \end{aligned}$$

where $w_j = u_j \pm iv_j$ are eigenvectors corresponding to the eigenvalues $\lambda_j = a_j \pm ib_j$.

Remark 2.1. *For a hyperbolic flow of a linear system, $\mathbb{R}^n = E^s \oplus E^c$. These subspaces become manifolds for nonlinear ODEs.*

Theorem 2.4. (Stable Manifold Theory [48]). *Let $f \in C^1(E)$ where E is an open subset of $\mathbb{R}^n$ containing the origin, and let ϕ_t be the flow of non-linear system (2.1). Suppose that $f(0) = 0$ and $D(0)$ has k eigenvalues with negative real parts, and $q = n - k$ eigenvalues with positive real parts. Then, there exists a k-dimensional differentiable manifold S tangent to the stable subspace E^s of the linear system (2.6) at 0 such that for all $t \geq 0, \phi_t(S) \subset S$ and for all $x_0 \in S$*

$$\lim_{t\to\infty} \phi_t(x_0) = 0,$$

and there exists a q-dimensional differentiable manifold U tangent to the unstable subspace E^u of the linear system (2.6) at 0 such that for all $t \geq 0, \phi_t(U) \subset U$ and for all $x_0 \in U$

$$\lim_{t\to-\infty} \phi_t(x_0) = 0.$$

Definition 2.11. [48]. *Let ϕ_t be the flow of non-linear system (2.1). The global stable and unstable manifolds of (2.6) at 0, defined, respectively, by*

$$W^s(0) = \bigcup_{t\leq 0} \phi_t(S),$$

and

$$W^u(0) = \bigcup_{t\geq 0} \phi_t(U),$$

are also, respectively, referred to as the global stable and unstable manifolds of the origin.

Theorem 2.5. [48]. *Let $f \in C^r(E)$ where E is an open subset of $\mathbb{R}^n$ containing the origin and $r \geq 1$. Suppose that $f(0) = 0$ and that $Df(0)$ has k eigenvalues with negative real parts, j eigenvalues with positive real parts, and $m = n - k - j$ eigenvalues with zero real parts. Then, there exists an $m-$ dimensional center manifold $W^c(0)$ of class C^r tangent to center subspace E^c of (2.6) which is invariant*

under the flow ϕ_t of (2.1).

Lemma 2.1. [48]. *The local center manifold of the system (2.1) at 0,*

$$W^c_{loc}(0) = \{(x, y) \in \mathbb{R}^m \times \mathbb{R}^k \mid y = h(x) \quad \text{for} \quad |x| < \delta\}, \tag{2.7}$$

for some $\delta > 0$, where $h \in C^r(N_\delta(0))$, $h(0) = 0$ and $Dh(0) = O$ since $W^c(0)$ is tangent to the center subspace

$$E^c = \{(x, y) \in \mathbb{R}^m \times \mathbb{R}^k \mid y = 0\},$$

at the origin.

Theorem 2.6. (Center Manifold Theory [48]). *Let $f \in C^r(E)$ where E is an open subset of $\mathbb{R}^n$ containing the origin and $r \geq 1$. Suppose that $f(0) = 0$ and that $Df(0)$ has m eigenvalues with zero real parts and k eigenvalues with negative real parts, where $m + k = n$. The system (2.1) then can be written in diagonal form*

$$\begin{aligned} \dot{x} &= Cx + F(x, y), \\ \dot{y} &= Py + G(x, y), \end{aligned}$$

where $(x, y) \in \mathbb{R}^m \times \mathbb{R}^k$, C is a square matrix with m eigenvalues having zero real parts, P is a square matrix with k eigenvalues with negative real parts, and $F(0) = G(0) = 0$, $DF(0) = DG(0) = O$; furthermore, there exists a $\delta > 0$ and a function $h \in C^r(N_\delta(0))$ that defines the local center manifold (2.7) and satisfies

$$Dh(x)[Cx + F(x, h(x))] - Ph(x) - G(x, h(x)) = 0$$

for $|x| < \delta$; and the flow on the center manifold $W^c(0)$ is defined by the system of

differential equations

$$\dot{x} = Cx + F(x, h(x))$$

for all $x \in \mathbb{R}^m$ *with* $|x| < \delta$.

Theorems 2.5 and 2.6 can be used to determine the flow near non-hyperbolic equilibrium points [9, 48].

2.5 Bifurcation Theory

In general, real-life systems arising, for instance, in the natural and engineering sciences typically involve parameters which appear in their governing system of equations. As these parameters are varied, changes may occur in the qualitative structures of the solutions of the system of equations for certain parameter values. These changes are called bifurcations [34]. The parameter values where bifurcations occur are called bifurcation values (or bifurcation points). A formal definition of bifurcation at a point is given below.

Definition 2.12. [68]. *Let*

$$\dot{x} = f(x, \mu), x \in \mathbb{R}^n, \mu \in \mathbb{R}, \tag{2.8}$$

be a one-parameter family of one-dimensional ODEs. An equilibrium solution of (2.8) given by $(x, \mu) = (0, 0)$ *is said to undergo bifurcation at* $\mu = 0$ *if the flow for* μ *near zero and* x *near zero is not qualitatively the same as the flow near* $x = 0$ *at* $\mu = 0$.

There are numerous types of bifurcations, including saddle-node, transcritical, pitchfork, Hopf, and backward bifurcation [29, 31, 32, 48, 57]. The following theorem is used to establish the existence of the backward bifurcation phenomenon for the models in Chapters 3 and 4.

Theorem 2.7. [11, 20, 65]. *Consider the following general system of ordinary differential equations with a parameter ϕ*

$$\frac{dx}{dt} = f(x,\phi), f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}^n \quad \textit{and} \quad f \in \mathbb{C}^2\left(\mathbb{R}^n \times \mathbb{R}\right), \tag{2.9}$$

where 0 is an equilibrium point of the system (that is, $f(0,\phi) \equiv 0$ for all ϕ) and assume

A.1) $A = D_x f(0,0) = \left(\frac{\partial f_i}{\partial x_j}(0,0)\right)$ is the linearization matrix of the system (2.9) around the equilibrium 0 with ϕ evaluated at 0. Zero is a simple eigenvalue of A and other eigenvalues of A have negative real parts;

A.2) Matrix A has a right eigenvector w and a left eigenvector v (each corresponding to the zero eigenvalue).

Let f_k be the k-th component of f and

$$\begin{aligned} a &= \sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0), \\ b &= \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0). \end{aligned}$$

Then the local dynamics of the system around the equilibrium point 0 is totally determined by the signs of a and b. Particularly, if $a > 0$ and $b > 0$, then a backward bifurcation occurs at $\phi = 0$.

2.6 Lyapunov Function Theory

Definition 2.13. [48]. *A point $x_0 \in \mathbb{R}^n$ is called an $\omega-$limit point of $x \in \mathbb{R}^n$, denoted by $\omega(x)$, if there exists a sequence $\{t_i\}$ such that*

$$\phi(t_i, x) \to x_0 \quad \text{as} \quad t_i \to \infty.$$

Definition 2.14. [48]. *A point $x_0 \in \mathbb{R}^n$ is called an $\alpha-$limit point of $x \in \mathbb{R}^n$, denoted by $\alpha(x)$, if there exists a sequence $\{t_i\}$ such that*

$$\phi(t_i, x) \to x_0 \quad \text{as} \quad t_i \to -\infty.$$

Definition 2.15. [48]. *The set of all $\omega-$limit points of a flow is called the $\omega-$limit set. Similarly, The set of all $\alpha-$limit points of a flow is called the $\alpha-$limit set.*

Definition 2.16. [68]. *Let $S \subset \mathbb{R}^n$ be a set. Then, S is said to be invariant under the flow generated by $\dot{x} = f(x)$ if for any $x_0 \in S$ we have $\phi(t, x_0) \in S$ for all $t \in \mathbb{R}$.*

Lemma 2.2. [68]. *A set $S \subset \mathbb{R}^n$ is positively-invariant if for every $x_0 \in S$, $\phi(t, x_0) \in S$, $\forall t \geq 0$.*

Definition 2.17. [68]. *A function $V : \mathbb{R}^n \to \mathbb{R}$ is said to be positive-definite if:*

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

Definition 2.18. [68] *Consider the system (2.1). Let, $\bar{x}$ be an equilibrium solution of (2.1) and let $V : U \to \mathbb{R}$ be a C^1 function defined on some neighbourhood U of $\bar{x}$ such that*

i) V is positive-definite,

ii) $\dot{V}(x) \leq 0$ in $U \setminus \{\bar{x}\}$.

Corollary 2.1. [68]. *Any function, V, that satisfies Conditions (i) and (ii) above is called a Lyapunov function.*

Theorem 2.8. (LaSalle's Invariance Principle [31]). *Consider the system (2.1). Let,*

$$S = \{x \in \bar{U} : \dot{V}(x) = 0\} \tag{2.10}$$

and M be the largest positive invariant set of (2.1) in S. If V is a Lyapunov function on U and $\gamma^+(x_0)$ is a bounded orbit of (2.1) which lies in S, then the $\omega-$limit set of $\gamma^+(x_0)$ belongs to M; that is, $x(t, x_0) \to M$ as $t \to \infty$.

Corollary 2.2. *If $V(x) \to \infty$ as $|x| \to \infty$ and $\dot{V} \leq 0$ on $\mathbb{R}^n$, then every solution of (2.1) is bounded and approaches the largest invariant set M of (2.1) in the set where $\dot{V} = 0$. In particular, if $M = \{0\}$, then the solution $x = 0$ is globally-asymptotically stable (GAS).*

2.7 Comparison Theorem

Consider the autonomous system

$$\dot{x} = f(x), x \in \mathbb{R}^n, \tag{2.11}$$

where f is continuously-differentiable on an open subset $\mathcal{D} \subset \mathbb{R}^n$. Let $\phi_t(x)$ denote the solution of the system (2.11) with initial value x.

Definition 2.19. [58]. *f is said to be Type $\mathcal{K}$ in $\mathcal{D}$ if for each i, $f_i(a) < f_i(b)$ for any two points in $\mathcal{D}$ satisfying $a \leq b$ and $a_i = b_i$.*

The Type $\mathcal{K}$ Condition can be identified from the sign structure of the associated Jacobian matrix of the system (2.11), as described above.

Definition 2.20. [58]. *$\mathcal{D}$ is P-convex if $tx + (1-t)y \in \mathcal{D}$ for all $t \in [0, 1]$ whenever $x, y \in \mathcal{D}$ and $x < y$.*

It is clear that if $\mathcal{D}$ is a convex set, then it is also p-convex. Furthermore, if $\mathcal{D}$ is a p-convex subset of $\mathbb{R}^n$ and

$$\frac{\partial f_i}{\partial x_j} \geq 0, \quad i \neq j, \quad x \in \mathcal{D},$$

then f is of Type $\mathcal{K}$ in $\mathcal{D}$.

Another approach for establishing the global asymptotic stability of equilibria of dynamical system is by using the comparison theorem [58]. This entails comparing the solution of the non-linear system.

$$\dot{x} = f(t, x), \tag{2.12}$$

with the solution of the differential inequality system

$$\dot{z} \leq f(t, z), \tag{2.13}$$

or,

$$\dot{y} \geq f(t, y), \tag{2.14}$$

on an interval. This method requires that the solution of the system (2.12) is unique, and that f is of Type $\mathcal{K}$.

Theorem 2.9. (Comparison Theorem [58]). *Let f be continuous on $\mathbb{R} \times \mathcal{D}$ and of Type $\mathcal{K}$. Let $x(t)$ be a solution of* (2.12) *defined on $[a, b]$. If $z(t)$ is a continuous function on $[a, b]$ satisfying (2.13) on (a, b) with $z(a) \leq x(a)$, then $z(t) \leq x(t)$ for all t in $[a, b]$. If $y(t)$ is continuous on $[a, b]$ satisfying* (2.14) *on (a, b) with $y(a) \geq x(a)$, then $y(t) \geq x(t)$, for all t in $[a, b]$.*

2.8 Next Generation Operator Method

The next generation operator method [15, 65] is popularly used in the mathematical biology literature to compute the reproduction number ($\mathcal{R}_0$) of disease transmission models (and, subsequently, to establish the local asymptotic stability of the associated DFE). The formulation given in [65] is briefly described below. Suppose

the given disease transmission model, with non-negative initial conditions, can be written in terms of the following autonomous system:

$$\dot{x}_i = f(x) = F_i(x) - V_i(x), \quad i = 1, ..., n, \tag{2.15}$$

where $V_i = V_i^- - V_i^+$ and the functions satisfy the following axioms bellow. First of all, $\{X_s = x \geq 0 | x_i = 0, i = 1, ..., m\}$ is defined as the disease-free states (non-infected state variables) of the model, where $x = (x_1, ..., x_n)^t$, $x_i \geq 0$ represents the number of individuals in each compartment of the model.

(A1) If $x \geq 0$, then F_i, V_i^+, $V_i^- \geq 0$ for $i = 1, ..., m$.

(A2) If $x_i = 0$, then $V_i^- = 0$. In particular, if $x \in X_s$ then $V_i^- = 0$ for $i = 1, ..., m$.

(A3) $F_i = 0$ if $i > m$.

(A4) If $x \in X_s$, then $F_i(x) = 0$ and $V_i^+(x) = 0$ for $i = 1, ..., m$.

(A5) If $F(x)$ is set to zero, then all eigenvalues of $D(f(x_0))$ have negative real parts.

In the formulation above, $F_i(x)$ represents the rate of appearance of new infections in compartment i, $V_i^+(x)$ represents the rate of transfer of individuals into compartment i. It is assumed that these functions are at least twice continuously-differentiable in each variable [65].

Definition 2.21. *(M-Matrix). An $n \times n$ matrix A is an M-matrix if and only if every of off-diagonal entries of A is non-positive and the diagonal entries are all positive.*

Lemma 2.3. (van den Driessche and Watmough [65]). *If $\bar{x}$ is a DFE of (2.15) and $f_i(x)$ satisfy $(A1) - (A5)$, then the derivative $DF(\bar{x})$ and $DV(\bar{x})$ are petitioned as*

$$DF(\bar{x}) = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix}, DV(\bar{x}) = \begin{pmatrix} V & 0 \\ J_3 & J_4 \end{pmatrix},$$

where F and V are the $m \times m$ matrices defined by,

$$F = \left[\frac{\partial F_i}{\partial x_j}(\bar{x})\right] \quad \textit{and} \quad V = \left[\frac{\partial V_i}{\partial x_j}(\bar{x})\right] \quad \textit{with} \quad 1 \leq i, j \leq m.$$

Furthermore, F is non-negative, V is non-singular M-matrix and J_3 and J_4 are matrices associated with the transition terms of the model, and all eigenvalues of J_4 have positive real parts.

Theorem 2.10. (van den Driessche and Watmough [65]). *Consider the disease transmission model given by (2.15) with f(x) satisfying axioms (A1)-(A5). If $\bar{x}$ is a DFE of the model, then $\bar{x}$ is LAS if $\mathcal{R}_0 = \rho(FV^{-1}) < 1$ (where ρ is the spectral radius), but unstable if $\mathcal{R}_0 > 1$.*

Chapter 3

Age-Structured Model

3.1 Introduction

Malaria, caused by the protozoan plasmodium parasite, is transmitted to humans by female anopheles mosquitoes (after taking a blood meal from the human host). Although malaria has been endemic in many parts of the world (notably the tropical and subtropical region of Africa, Asia and South America) for hundreds of years, the disease continues to inflict major public health burden in affected areas [69]. For instance, it accounted for 216 million cases and 655,000 million deaths in 2010 [69, 70]. Furthermore, malaria inflicts significant mortality among children under the age of five [14]. As stated in Chapter 1, in the absence of a safe and effective anti-malaria vaccine, malaria control is focussed on using preventive measures (such as mosquito-reduction strategies and personal protection against mosquito bite) and the use of anti-malaria drugs (see, for instance, [23, 25, 50, 51, 69, 72]). The aim of this chapter is to design, and rigorously analyse, a new age-structured ODE model for the transmission dynamics of malaria in a community. The model to be designed represents an extension of other age-structured ODE models in the literature, particularly those in [1, 49].

3.2 Model Formulation

The new (single-strain) age-structured malaria model is designed by splitting the total human population at time t, denoted by $N_H(t)$, into the mutually-exclusive sub-populations of susceptible juveniles ($S_{HJ}(t)$), susceptible adults ($S_{HA}(t)$), latently-infected (asymptomatic) juveniles ($E_{HJ}(t)$), latently-infected (asymptomatic) adults ($E_{HA}(t)$), symptomatic juveniles ($I_{HJ}(t)$), symptomatic adults ($I_{HA}(t)$), recovered juveniles ($R_{HJ}(t)$) and recovered adults ($R_{HA}(t)$), so that

$$N_H(t) = S_{HJ}(t) + S_{HA}(t) + E_{HJ}(t) + E_{HA}(t) + I_{HJ}(t) + I_{HE}(t) + R_{HJ}(t) + R_{HA}(t).$$

It should be emphasized that individuals in the latently-infected (E_{HJ} and E_{HA}) classes are infected (i.e, they are in the early stage of infection, but show no clinical symptoms of the disease).

The total mosquito population at time t, denoted by $N_V(t)$, is sub-divided into the mutually-exclusive compartments of susceptible ($S_V(t)$) and infected ($I_V(t)$) mosquitoes, so that

$$N_V(t) = S_V(t) + I_V(t).$$

The population of susceptible juveniles is generated by the birth (or immigration) of juveniles (at a rate Π_J). Although vertical transmission of malaria can occur (see [22] and some of the references there in), it is assumed that all children are born susceptible (i.e., it is assumed, in this thesis that vertical transmission does not occur). This population is increased by loss of infection-acquired immunity by recovered juveniles (at a *per capita* rate ψ_{HJ}). It is decreased by infection, following effective contacts with infected mosquitoes, at a rate λ_{HJ}, given by

$$\lambda_{HJ} = \frac{b_1(N_V, N_H)\beta_{HJ} I_V}{N_V}. \tag{3.1}$$

In (3.1), $b_1(N_V, N_H)$ is the *per capita* biting rate of mosquitoes on susceptible humans (juveniles and adults) *per* unit time, and β_{HJ} is the probability of infection of susceptible juveniles *per* bite by an infected mosquito. It is further decreased by maturation to adulthood (at a rate ξ; this rate is assumed, for mathematical convenience, to be same for all the epidemiological classes for humans) and natural death (at a rate μ_H; it is assumed that natural death occurs in all human epidemiological classes at this rate). Thus,

$$\frac{dS_{HJ}}{dt} = \Pi_J + \psi_J R_{HJ} - \lambda_{HJ} S_{HJ} - (\xi + \mu_H) S_{HJ}. \tag{3.2}$$

The population of susceptible adults is generated by the maturation of susceptible juveniles (at the rate ξ) and by the loss of infection-acquired immunity by recovered adults (at a rate ψ_A). It is decreased by infection at a rate λ_{HA}, given by

$$\lambda_{HA} = \frac{b_1(N_V, N_H)\beta_{HA} I_V}{N_V}, \tag{3.3}$$

where β_{HA} is the probability of infection of susceptible adults *per* bite by an infected mosquito. This population is further decreased by natural death. Hence,

$$\frac{dS_{HA}}{dt} = \xi S_{HJ} + \psi_A R_{HA} - \lambda_{HA} S_{HA} - \mu_H S_{HA}. \tag{3.4}$$

The population of latently-infected juveniles is generated, following the infection of

susceptible juveniles (at the rate $b_1(N_V, N_H)\beta_{HJ}$). It is decreased by the development of clinical symptoms of malaria (at a rate σ_{HJ}), maturation to adulthood (at the rate ξ) and natural death, so that

$$\frac{dE_{HJ}}{dt} = \frac{b_1(N_V, N_H)\beta_{HJ}I_V}{N_V}S_{HJ} - (\sigma_{HJ} + \xi + \mu_H)E_{HJ}. \tag{3.5}$$

Similarly, the population of latently-infected adults is generated by the maturation of latently-infected juveniles (at the rate ξ) and by the infection of susceptible adults (at the rate $b_1(N_V, N_H)\beta_{HA}$). It is diminished by the development of malaria symptoms (at a rate σ_{HA}) and natural death. Hence,

$$\frac{dE_{HA}}{dt} = \xi E_{HJ} + \frac{b_1(N_V, N_H)\beta_{HA}I_V}{N_V}S_{HA} - (\sigma_{HA} + \mu_H)E_{HA}. \tag{3.6}$$

The population of symptomatic juveniles is generated when latently-infected juveniles develop clinical symptoms of malaria (at the rate σ_{HJ}). It is decreased by maturation (at the rate ξ), recovery (at a rate γ_J), natural death and disease-induced death (at a rate δ_{HJ}). Hence,

$$\frac{dI_{HJ}}{dt} = \sigma_{HJ}E_{HJ} - (\xi + \gamma_J + \mu_H + \delta_{HJ})I_{HJ}. \tag{3.7}$$

Similarly, the population of symptomatic adults is generated at the rates ξ and σ_{HA}, and reduced by recovery (at a rate γ_A), natural death and disease-induced death (at a rate δ_{HA}), so that,

$$\frac{dI_{HA}}{dt} = \sigma_{HA}E_{HA} + \xi I_{HJ} - (\gamma_A + \mu_H + \delta_{HA})I_{HA}. \tag{3.8}$$

The population of recovered juveniles is generated at the rate γ_J, and decreased by the loss of infection-acquired immunity (at the rate ψ_J), maturation (at the rate ξ) and natural death. Thus,

$$\frac{dR_{HJ}}{dt} = \gamma_J I_{HJ} - (\psi_J + \xi + \mu_H)R_{HJ}. \tag{3.9}$$

The population of recovered adults is increased by the recovery of symptomatic adults (at the rate γ_A) and the maturation of recovered juveniles (at the rate ξ). It is decreased by the loss of infection-acquired immunity (at the rate ψ_A) and natural death. Thus,

$$\frac{dR_{HA}}{dt} = \gamma_A I_{HA} + \xi R_{HJ} - (\psi_A + \mu_H)R_{HA}. \tag{3.10}$$

The population of susceptible mosquitoes is generated by the birth of adult mosquitoes (at a *per capita* rate Π_V). It is reduced by infection, following effective contacts with infected humans, at a rate λ_V, where

$$\lambda_V = \frac{b_2(N_V, N_H)\beta_V[\eta(E_{HJ} + E_{HA}) + I_{HJ} + I_{HA}]}{N_H}. \tag{3.11}$$

In (3.11), $b_2(N_V, N_H)$ is *per capita* biting rate of susceptible mosquitoes on infected humans, β_V is the probability of infection of a susceptible mosquito *per* bite on an infected human) at a rate and $0 \leq \eta < 1$ is a modification parameter accounting for

the assumption that latently-infected humans are less infectious than symptomatic humans. This population is further decreased by natural death (at a rate μ_V). Hence,

$$\frac{dS_V}{dt} = \Pi_V - \lambda_V S_V - \mu_V S_V. \tag{3.12}$$

The population of infected mosquitoes is generated by the infection of susceptible mosquitoes (at the rate $b_2(N_V, N_H)\beta_V$) and decreased by natural death (at the rate μ_V). Thus,

$$\frac{dI_V}{dt} = \lambda_V S_V - \mu_V I_V. \tag{3.13}$$

It is assumed that mosquitoes do not suffer additional disease-induced death [49].

An important requirement for a mosquito-borne disease model, such as the model given by equations $\{(3.1), ..., (3.13)\}$, is that the total number of bites made by mosquitoes must balance the total number of bites received by the human hosts (see, for instance, [8, 24, 26, 45]). This constraint is implemented as follows. First of all, mosquitoes bite both susceptible and infected humans. Hence, it is assumed that the average number of mosquito bites received by humans depends on the total sizes of the populations of mosquitoes and humans in the community. Furthermore, it is assumed that the human hosts are always sufficient in abundance so that it is reasonable to consider the biting rate $b_2(N_V, N_H) = b_2$, a constant. Thus, in order for the total number of bites made by mosquitoes to balance the total number of bites received by the human hosts, the following conservation law must hold:

$$b_2 N_V = b_1(N_V, N_H) N_H, \tag{3.14}$$

so that,

$$N_V = \frac{b_1(N_V, N_H)N_H}{b_2}. \tag{3.15}$$

It follows, based on the above derivations and assumptions, and using (3.1), (3.3) and (3.11) with (3.15) in $\{(3.2), (3.4), (3.5), (3.6)\}$, that the new, single-strain, age-structured model for the transmission dynamics of malaria in a community is given by the following deterministic system of non-linear differential equations (a flow diagram of the model is depicted in Figure 3.1, and the state variables and parameters of the model are described in Tables 3.1 and 3.2, respectively):

$$\begin{aligned}
\frac{dS_{HJ}}{dt} &= \Pi_J + \psi_J R_{HJ} - \frac{b_2\beta_{HJ}I_V}{N_H}S_{HJ} - (\xi + \mu_H)S_{HJ},\\
\frac{dS_{HA}}{dt} &= \xi S_{HJ} + \psi_A R_{HA} - \frac{b_2\beta_{HA}I_V}{N_H}S_{HA} - \mu_H S_{HA},\\
\frac{dE_{HJ}}{dt} &= \frac{b_2\beta_{HJ}I_V}{N_H}S_{HJ} - (\sigma_{HJ} + \xi + \mu_H)E_{HJ},\\
\frac{dE_{HA}}{dt} &= \xi E_{HJ} + \frac{b_2\beta_{HA}I_V}{N_H}S_{HA} - (\sigma_{HA} + \mu_H)E_{HA},\\
\frac{dI_{HJ}}{dt} &= \sigma_{HJ}E_{HJ} - (\xi + \gamma_J + \mu_H + \delta_{HJ})I_{HJ},\\
\frac{dI_{HA}}{dt} &= \sigma_{HA}E_{HA} + \xi I_{HJ} - (\gamma_A + \mu_H + \delta_{HA})I_{HA},\\
\frac{dR_{HJ}}{dt} &= \gamma_J I_{HJ} - (\psi_J + \xi + \mu_H)R_{HJ},\\
\frac{dR_{HA}}{dt} &= \gamma_A I_{HA} + \xi R_{HJ} - (\psi_A + \mu_H)R_{HA},\\
\frac{dS_V}{dt} &= \Pi_V - \frac{b_2\beta_V[\eta(E_{HJ} + E_{HA}) + I_{HJ} + I_{HA}]}{N_H}S_V - \mu_V S_V,\\
\frac{dI_V}{dt} &= \frac{b_2\beta_V[\eta(E_{HJ} + E_{HA}) + I_{HJ} + I_{HA}]}{N_H}S_V - \mu_V I_V.
\end{aligned} \tag{3.16}$$

The model (3.16) is an extension of many of the malaria transmission models published in the literature (such as those in [13, 17, 23, 39, 40, 45, 52]), by adding

age-structure. Furthermore, it extends the age-structured (ODE) malaria model in [49] by including:

(i) separate compartments for susceptible juveniles and susceptible adults (the two compartments are lumped together in [49]);

(ii) the dynamics of (and transmission by) latently-infected individuals (E_{HJ} and E_{HA}; with $\eta \neq 0$);

(iii) loss of infection-acquired immunity by recovered individuals ($\psi_J \neq 0$ and $\psi_A \neq 0$);

(iv) disease-induced death ($\delta_{HJ} \neq 0$ and $\delta_{HA} \neq 0$).

Furthermore, the model (3.16) extends the age-structured malaria model in [1] (which uses mass action incidence for the infection rate) by including:

(a) separate compartments for latently-infected juveniles and latently-infected adults;

(b) the dynamics of (and transmission by) latently-infected individuals (E_{HJ} and E_{HA}; with $\eta \neq 0$).

It should be mentioned that, unlike in [1, 49], detailed qualitative analysis of the model developed in this chapter will be provided (only local asymptotic stability results are given for the disease-free equilibria of the models in [1, 49]. Local asymptotic stability result is provided for the endemic equilibrium of the model in [49]).

3.2.1 Basic properties

The basic dynamical features of the model (3.16) will now be explored. Since the model monitors human and mosquito populations, all its associated parameters and state variables are non-negative for $t \geq 0$. For the model (3.16) to be epidemiologically meaningful, it is important to prove that all its state variables are non-negative

for all times. In other words, solutions of the model (3.16) with positive initial data will remain positive for all time $t > 0$.

Theorem 3.1. *Let the initial data be $S_{HJ}(0) > 0$, $S_{HA}(0) > 0$, $E_{HJ}(0) \geq 0$, $E_{HA}(0) \geq 0$, $I_{HJ}(0) \geq 0$, $I_{HA}(0) \geq 0$, $R_{HJ}(0) \geq 0$, $R_{HA}(0) \geq 0$, $S_V(0) > 0$ and $I_V(0) \geq 0$. Then the solutions $(S_{HJ}(t), S_{HA}(t), E_{HJ}(t), E_{HA}(t), I_{HJ}(t), I_{HA}(t), R_{HJ}(t), R_{HA}(t), S_V(t), I_V(t))$ of the model (3.16), with positive initial data, will remain positive for all time $t > 0$.*

The proof of Theorem 3.1 is given in Appendix A.

Lemma 3.1. *The closed set*

$$\mathcal{D} = \{(S_{HJ}, S_{HA}, E_{HJ}, E_{HA}, I_{HJ}, I_{HA}, R_{HJ}, R_{HA}, S_V, I_V) \in \mathbb{R}_+^{10} : N_H \leq \frac{\Pi_J}{\mu_H}, \\ N_V \leq \frac{\Pi_V}{\mu_V}\} \tag{3.17}$$

is positively-invariant and attracting for the model (3.16).

Proof. Adding the first eight equations, and the last two equations, of the model (3.16), gives, respectively,

$$\begin{aligned} \frac{dN_H}{dt} &= \Pi_J - \mu_H N_H - (\delta_{HJ} I_{HJ} + \delta_{HA} I_{HA}), \\ \frac{dN_V}{dt} &= \Pi_V - \mu_V N_V. \end{aligned} \tag{3.18}$$

Since $\frac{dN_H}{dt} \leq \Pi_J - \mu_H N_H$ and $\frac{dN_V}{dt} \leq \Pi_V - \mu_V N_V$, it follows that $\frac{dN_H}{dt} \leq 0$ and $\frac{dN_V}{dt} \leq 0$ if $N_H(t) \geq \frac{\Pi_J}{\mu_H}$ and $N_V(t) \geq \frac{\Pi_V}{\mu_V}$, respectively. Hence, it follows, using comparison theorem [37], that

$$N_H(t) \leq N_H(0)e^{-\mu_H(t)} + \frac{\Pi_J}{\mu_H}[1 - e^{-\mu_H(t)}],$$

and,

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

In particular, $N_H(t) \leq \frac{\Pi_J}{\mu_H}$ if $N_H(0) \leq \frac{\Pi_J}{\mu_H}$ and $N_V(t) \leq \frac{\Pi_V}{\mu_V}$ if $N_V(0) \leq \frac{\Pi_V}{\mu_V}$, respectively. Thus, the region $\mathcal{D}$ is positively-invariant for the model (3.16). Furthermore, if $N_H(0) > \frac{\Pi_J}{\mu_H}$ and $N_V(0) > \frac{\Pi_V}{\mu_V}$, then either the solution enters $\mathcal{D}$ in finite time or $N_H(t) \to \frac{\Pi_J}{\mu_H}$ and $N_V(t) \to \frac{\Pi_V}{\mu_V}$ as $t \to \infty$. Hence, the region $\mathcal{D}$ attracts all solutions in $\mathbb{R}^{10}_+$. □

Since the region $\mathcal{D}$ is positively-invariant, the usual existence, uniqueness, continuation results hold for the system (hence, it is sufficient to consider the dynamics of the flow generated by the system (3.16) in the region $\mathcal{D}$ [32]).

3.3 Stability of DFE

The DFE of the model (3.16), obtained by setting the right-hand sides of the equations in (3.16) to zero, is given by,

$$\mathcal{E}_0 = (S^*_{HJ}, S^*_{HA}, E^*_{HJ}, E^*_{HA}, I^*_{HJ}, I^*_{HA}, R^*_{HJ}, R^*_{HA}, S^*_V, I^*_V)$$

$$= \left(\frac{\Pi_J}{(\xi + \mu_H)}, \frac{\xi \Pi_J}{\mu_H(\xi + \mu_H)}, 0, 0, 0, 0, 0, 0, \frac{\Pi_V}{\mu_V}, 0\right).$$

The local asymptotic stability of the DFE $\mathcal{E}_0$ can be established using the next generation operator method (as described in Section 2.9). The non-negative matrix $\mathcal{F}$ (of new infection terms), and the matrix $\mathcal{V}$ (of the transition terms) associated with the model (3.16), are given, respectively, by:

$$\mathcal{F} = \begin{bmatrix} 0 & 0 & 0 & 0 & \frac{b_2\beta_{HJ}S^*_{HJ}}{N^*_H} \\ 0 & 0 & 0 & 0 & \frac{b_2\beta_{HA}S^*_{HA}}{N^*_H} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ \frac{\eta b_2\beta_V S^*_V}{N^*_H} & \frac{\eta b_2\beta_V S^*_V}{N^*_H} & \frac{b_2\beta_V S^*_V}{N^*_H} & \frac{b_2\beta_V S^*_V}{N^*_H} & 0 \end{bmatrix},$$

and,

$$\mathcal{V} = \begin{bmatrix} g_2 & 0 & 0 & 0 & 0 \\ -\xi & g_3 & 0 & 0 & 0 \\ -\sigma_{HJ} & 0 & g_4 & 0 & 0 \\ 0 & -\sigma_{HA} & -\xi & g_5 & 0 \\ 0 & 0 & 0 & 0 & \mu_V \end{bmatrix},$$

where $g_2 = \sigma_{HJ}+\xi+\mu_H$, $g_3 = \sigma_{HA}+\mu_H$, $g_4 = \xi+\gamma_J+\mu_H+\delta_{HJ}$, $g_5 = \gamma_A+\mu_H+\delta_{HA}$, and $N^*_H = \dfrac{\Pi_J}{\mu_H}$. It follows, from [65], that the *basic reproduction number* ($\mathcal{R}_0 = \rho(\mathcal{F}\mathcal{V}^{-1})$), of the model (3.16), is given by (where ρ is the spectral radius of the next generation matrix, $\mathcal{F}\mathcal{V}^{-1}$)

$$\mathcal{R}_0 = \sqrt{\frac{b_2^2\beta_V\Pi_V\mu_H\{\beta_{HJ}\mu_H[\eta g_4 g_5(g_3+\xi)+\sigma_{HJ}g_3(g_5+\xi)+\sigma_{HA}\xi g_4]+\beta_{HA}\xi g_2 g_4(\eta g_5+\sigma_{HA})\}}{\mu_V^2\Pi_J(\xi+\mu_H)\left(\prod_{i=2}^{5} g_i\right)}}. \tag{3.19}$$

The result below follows from Theorem 2.10.

Lemma 3.2. *The DFE, $\mathcal{E}_0$, of the model (3.16), is LAS if $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$.*

The epidemiological implication of Lemma 3.2 is that malaria can be eliminated from the community (when $\mathcal{R}_0 < 1$) if the initial sizes of the sub-populations of the

model (3.16) are in the basin of attraction of the DFE, $\mathcal{E}_0$. The threshold quantity, $\mathcal{R}_0$, represents the average number of secondary infections that one infected individual (or infected mosquito) can generate if introduced into a completely-susceptible population. It can be epidemiologically interpreted as follows.

3.3.1 Interpretation of $\mathcal{R}_0$

Equation (3.19) can be re-written in the following convenient form:

$$\mathcal{R}_0 = \sqrt{\mathcal{R}_J + \mathcal{R}_A},$$

where,

$$\mathcal{R}_J = \frac{b_2\mu_H\beta_{HJ}}{\mu_V(\xi+\mu_H)}\left(\frac{b_2\beta_V\mu_H\eta\Pi_V}{\Pi_J\mu_V g_2} + \frac{b_2\beta_V\mu_H\sigma_{HJ}\Pi_V}{\Pi_J\mu_V g_2 g_4}\right), \tag{3.20}$$

and,

$$\mathcal{R}_A = \frac{b_2\beta_{HA}\xi}{\mu_V(\xi+\mu_H)}\left(\frac{b_2\beta_V\mu_H\eta\Pi_V}{\Pi_J\mu_V g_3} + \frac{b_2\beta_V\mu_H\sigma_{HA}\Pi_V}{\Pi_J\mu_V g_3 g_5}\right) + \frac{b_2\beta_{HJ}\mu_H}{\mu_V(\xi+\mu_H)}\left(\frac{b_2\beta_V\mu_H\eta\xi\Pi_V}{\Pi_J\mu_V g_2 g_3}\right.$$
$$\left. + \frac{b_2\beta_V\xi\sigma_{HA}\Pi_V}{\Pi_J\mu_V g_2 g_3 g_5} + \frac{b_2\beta_V\mu_H\sigma_{HJ}\xi\Pi_V}{\Pi_J\mu_V g_2 g_4 g_5}\right). \tag{3.21}$$

(a) **Terms in the expression for $\mathcal{R}_J$**

The threshold quantity $\mathcal{R}_J$, given by (3.20), is associated with disease transmission by infected juveniles as well as the infection of susceptible juveniles by infected mosquitoes. Susceptible mosquitoes acquire malaria infection from infected juveniles

in two ways, namely by latently-infected or symptomatically-infected juveniles.

The factor, $\dfrac{b_2\beta_{HJ}\mu_H}{\mu_V(\xi+\mu_H)}$, in the expression for $\mathcal{R}_J$, captures the infection of susceptible juveniles by infected mosquitoes. It is the product of the infection rate of susceptible juveniles by infected mosquitoes $\left(\dfrac{b_2\beta_{HJ}S^*_{HJ}}{N^*_H} = \dfrac{b_2\beta_{HJ}\mu_H}{\xi+\mu_H}\right)$ and the average duration in the infected mosquito (I_V) class $\left(\dfrac{1}{\mu_V}\right)$. The first term in the parenthesis of (3.20) represents the infection of susceptible mosquitoes by latently-infected juveniles. It is the product of infection rate of susceptible mosquitoes by latently-infected juveniles $\left(\dfrac{b_2\beta_V\eta S^*_V}{N^*_H} = \dfrac{b_2\beta_V\eta\mu_H\Pi_V}{\Pi_J\mu_V}\right)$ and the average duration in the latently-infected juveniles class $\left(\dfrac{1}{g_2}\right)$. The second term in the parenthesis of (3.20) accounts for the infection of susceptible mosquitoes by symptomatic juveniles. It is the product of the the infection rate of susceptible mosquitoes by symptomatic juveniles $\left(\dfrac{b_2\beta_V S^*_V}{N^*_H} = \dfrac{b_2\beta_V\mu_H\Pi_V}{\Pi_J\mu_V}\right)$, the probability that a latently-infected juvenile survives the E_{HJ} class and move to the I_{HJ} class $\left(\dfrac{\sigma_{HJ}}{g_2}\right)$ and the average duration in the I_{HJ} class $\left(\dfrac{1}{g_4}\right)$. The sum of the above two terms, multiplied by the factor $\dfrac{b_2\beta_{HJ}\mu_H}{\mu_V(\xi+\mu_H)}$, gives $\mathcal{R}_J$.

(b) **Terms in the expression for $\mathcal{R}_A$**

The threshold quantity $\mathcal{R}_A$, given by (3.21), is associated with disease transmission by infected adults (including by infected juveniles who mature into the corresponding infected adults class) as well as the acquisition of infection by susceptible adults (from infected mosquitoes). Susceptible adults acquire infection following effective contacts with infected mosquitoes. This is accounted for by the factor $\dfrac{b_2\beta_{HA}\xi}{\mu_V(\xi+\mu_H)}$ in the first parenthesis of (3.21), which represents the product of the infection rate of susceptible adults by infected mosquitoes $\left(\dfrac{b_2\beta_{HA}S^*_{HA}}{N^*_H} = \dfrac{b_2\beta_{HA}\xi}{\xi+\mu_H}\right)$ and the average

duration in the I_V class $\left(\frac{1}{\mu_V}\right)$.

The first term in the first parenthesis of (3.21) accounts for the infection of susceptible mosquitoes by infected adults (both latently-infected and symptomatically-infected adults). The number of new mosquito infections generated by latently-infected adults is given by the infection rate of susceptible mosquitoes by latently-infected adults $\left(\frac{b_2\beta_V\eta S_V^*}{N_H^*} = \frac{b_2\beta_V\eta\mu_H\Pi_V}{\Pi_J\mu_V}\right)$ and the average duration in the E_{HA} class $\left(\frac{1}{g_3}\right)$. Furthermore, latently-infected adults can infect susceptible mosquitoes after progressing to the symptomatic adults (I_{HA}) class. This infection route is represented by the second term in the first parenthesis of (3.21). It is given by the product of the infection rate of susceptible mosquitoes by symptomatic adults $\left(\frac{b_2\beta_V S_V^*}{N_H^*} = \frac{b_2\beta_V\Pi_V\mu_H}{\Pi_J\mu_V}\right)$, the probability that a latently-infected adult survives the E_{HA} class and move to the symptomatic adults (I_{HA}) class $\left(\frac{\sigma_{HA}}{g_3}\right)$ and the average duration in the symptomatic adults class $\left(\frac{1}{g_5}\right)$.

Susceptible mosquitoes can also be infected by infected juveniles after they mature to the corresponding infected adults class. This process is represented by the three terms in the second parenthesis of (3.21) and by the aforementioned factor, $\frac{b_2\beta_{HJ}\mu_H}{\mu_V(\xi+\mu_H)}$ (for the infection of susceptible juveniles by infected mosquitoes). The first term in the second parenthesis of (3.21) is the product of infection rate of susceptible mosquitoes by latently-infected adults $\left(\frac{b_2\beta_V\eta S_V^*}{N_H^*} = \frac{b_2\beta_V\eta\mu_H\Pi_V}{\Pi_J\mu_V}\right)$, the probability that a latently-infected juvenile matures to the latently-infected adults class $\left(\frac{\xi}{g_2}\right)$ and the duration in the latently-infected adults (E_{HA}) class $\left(\frac{1}{g_3}\right)$. The second term in the second parenthesis of (3.21) is the product of the infection rate of susceptible mosquitoes by symptomatic adults $\left(\frac{b_2\beta_V S_V^*}{N_H^*} = \frac{b_2\beta_V\mu_H\Pi_V}{\Pi_J\mu_V}\right)$, the probability that a latently-infected juvenile matures to the latently-infected adults class $\left(\frac{\xi}{g_2}\right)$, the probability that a latently-infected adult survives the E_{HA} class and move to the symptomatic adults class $\left(\frac{\sigma_{HA}}{g_4}\right)$ and the average duration in the

symptomatic adults class $\left(\frac{1}{g_5}\right)$. The third term in the second parentheses of (3.21) is the product of the infection rate of susceptible mosquitoes by symptomatic adults $\left(\frac{b_2\beta_V S_V^*}{N_H^*} = \frac{b_2\beta_V\mu_H\Pi_V}{\Pi_J\mu_V}\right)$, the probability that a latently-infected juvenile survives the E_{HJ} class and move to the symptomatic juveniles class $\left(\frac{\sigma_{HJ}}{g_2}\right)$, the probability that a symptomatic juvenile matures to the symptomatic adults class $\left(\frac{\xi}{g_4}\right)$, and the average duration in the symptomatic adults class $\left(\frac{1}{g_5}\right)$. The sum of the terms in the first and second parentheses of (3.21), multiplied by the respective factors described in (b), gives $\mathcal{R}_A$.

The geometric mean (accounting for the human-mosquito-human transmission cycle) of the sum of equations (3.20) and (3.21) gives $\mathcal{R}_0$.

3.3.2 Existence of backward bifurcation

As discussed in Chapter 1, models for disease transmission typically undergo a forward bifurcation at $\mathcal{R}_0 = 1$ (see, for instance, [28, 32, 57, 71]). However, certain disease transmission models are known to exhibit the phenomenon of backward bifurcation, a dynamic scenario where the DFE of the model co-exists with a stable endemic equilibrium of the model when the associated reproduction number of the model is less than unity. Backward bifurcation has been observed in numerous disease transmission models, such as those for (or with) behavioural responses to perceived risk [30], multi-groups [10], re-infection [11, 29, 55], vaccination [21, 28, 57, 71], and vector-borne diseases [26, 28, 45]. The epidemiological consequence of the backward bifurcation phenomenon in disease transmission models is that having the associated reproduction number of the model to be less than unity, while necessary, is no longer sufficient for effective disease control (or elimination). In a backward bifurcation situation, effective community-wide control of the disease (when $\mathcal{R}_0 < 1$) is dependent on the initial sizes of the sub-populations of the model. In other words, backward bi-

furcation makes effective disease control in the community difficult. It is instructive, therefore, to explore the possibility of backward bifurcation in the age-structured malaria model (3.16).

Theorem 3.2. *The model* (3.16) *undergoes backward bifurcation at* $\mathcal{R}_0 = 1$ *whenever the Inequality (B-3), given in Appendix B, holds.*

The proof of Theorem 3.2, based on using Centre Manifold theory [9, 11, 20, 65], is given in Appendix B. Figure 3.2 depicts the backward bifurcation property of the age-structured model (3.16). The possible causes of the backward bifurcation phenomenon of the model (3.16) are investigated below.

Non-existence of backward bifurcation

Consider the model (3.16) with the associated disease-induced mortality rates, δ_{HJ} and δ_{HA}, set to zero, so that,

$$\frac{dN_H(t)}{dt} = \Pi_J - \mu_H N_H(t),$$

hence, $N_H(t) \to \frac{\Pi_J}{\mu_H}$ as $t \to \infty$. It can be shown, by substituting $N_H^* = \frac{\Pi_J}{\mu_H}$ into the model (3.16), that the associated bifurcation coefficient, a, given by equation (B-2) in Appendix B, reduces to

$$a = \frac{2b_2\mu_H}{\Pi_J}\{w_{10}(\beta_{HJ}v_3w_1 + \beta_{HA}v_4w_2) + v_{10}w_9[\beta_V\eta(w_3 + w_4) + \beta_V(w_5 + w_6)]\}, \tag{3.22}$$

where w_1, w_2, w_9, v_3, v_4 and v_{10} are eigenvectors of the linearized system of the model (3.16), and are defined in Appendix B. Since the eigenvectors w_1, w_2 and w_9 are negative (see Appendix B), it follows from (3.22) that the associated backward bifurcation coefficient, a, is negative. Hence, it can be concluded from Theorem

4.1 of [11] that the single-strain model (3.16) will not undergo backward bifurcation in the absence of malaria-induced mortality in humans. Thus, these analyses show that the malaria-induced mortality in humans causes the backward bifurcation phenomenon of the age-structured model (3.16). To further confirm the absence of the backward bifurcation phenomenon, the DFE of the model (3.16) is shown to be globally-asymptotically stable, for this special case, in Section 3.3.3.

3.3.3 Global asymptotic stability of the DFE: special case:

Consider the special case of the model (3.16) in the absence of disease-induced mortality (i.e., $\delta_{HJ} = \delta_{HA} = 0$, so that $N_H^* = \frac{\Pi_J}{\mu_H}$). Furthermore, the loss of infection-acquired immunity parameters, ψ_J and ψ_A, are set to zero for computational convenience.

Define the region:

$$\begin{aligned}\mathcal{D}_1 =& \{(S_{HJ}, S_{HA}, E_{HJ}, E_{HA}, I_{HJ}, I_{HA}, R_{HJ}, R_{HA}, S_V, I_V) \in \mathcal{D} : \\ & S_{HJ} \leq S_{HJ}^*, S_{HA} \leq S_{HA}^*, S_V \leq S_V^*\}.\end{aligned} \tag{3.23}$$

Lemma 3.3. *The region $\mathcal{D}_1$ is positively-invariant for the model (3.16) with $\delta_{HJ} = \delta_{HA} = \psi_J = \psi_A = 0$.*

Proof. It follows from the first equation of the model (3.16), with $\psi_J = \psi_A = 0$, that

$$\begin{aligned}\frac{dS_{HJ}}{dt} &= \Pi_J - \frac{b_2\beta_{HJ}I_V}{N_H}S_{HJ} - (\xi + \mu_H)S_{HJ}, \\ &\leq \Pi_J - \xi S_{HJ} - \mu_H S_{HJ} = (\xi + \mu_H)\frac{\Pi_J}{\xi + \mu_H} - (\xi + \mu_H)S_{HJ}, \\ &= (\xi + \mu_H)(S_{HJ}^* - S_{HJ}).\end{aligned} \tag{3.24}$$

Thus, $S_{HJ}(t) \leq S_{HJ}(0)e^{-(\xi+\mu_H)t} + \frac{\Pi_J}{\xi+\mu_H}(1 - e^{-(\xi+\mu_H)t})$. Furthermore, if $N(0) \leq \frac{\Pi_J}{\mu_H}$

and $S_{HJ}(0) \leq S^*_{HJ}$ for all $t \geq 0$, then $S_{HJ}(t) \leq S^*_{HJ}$ for all $t \geq 0$. Similarly, it follows from the second equation of the model (3.16), with $\psi_J = \psi_A = 0$, that

$$\begin{aligned}
\frac{dS_{HA}}{dt} &= \xi S_{HJ} - \frac{b_2\beta_{HA}I_V}{N_H}S_{HA} - \mu_H S_{HA}, \\
&\leq \xi S_{HJ} - \mu_H S_{HA}, \\
&= \xi\left(\frac{\Pi_J}{\mu_H} - S_{HA} - E_{HJ} - E_{HA} - I_{HJ} - I_{HA} - R_{HJ} - R_{HA}\right) - \mu_H S_{HA}, \\
&\leq \xi\frac{\Pi_J}{\mu_H} - \xi S_{HA} - \mu_H S_{HA}, \\
&\leq (\xi + \mu_H)\frac{\xi\Pi_J}{\mu_H(\xi + \mu_H)} - (\xi + \mu_H)S_{HA} = (\xi + \mu_H)(S^*_{HA} - S_{HA}).
\end{aligned} \tag{3.25}$$

Hence, $S_{HA}(t) \leq S_{HA}(0)e^{-(\xi+\mu_H)t} + \frac{\xi\Pi_J}{\mu_H(\xi+\mu_H)}(1 - e^{-(\xi+\mu_H)t})$. Thus, if $N(0) \leq \frac{\Pi_J}{\mu_H}$ and $S_{HA}(0) \leq S^*_{HA}$ for all $t \geq 0$, then $S_{HA}(t) \leq S^*_{HA}$ for all $t \geq 0$. Finally, it follows from the ninth equation of the model (3.16), with $\psi_J = \psi_A = 0$, that

$$\begin{aligned}
\frac{dS_V}{dt} &= \Pi_V - \frac{b_2\beta_V[\eta(E_{HJ} + E_{HA}) + I_{HJ} + I_{HA}]}{N_H}S_V - \mu_V S_V, \\
&\leq \Pi_V - \mu_V S_V = \mu_V\frac{\Pi_V}{\mu_V} - \mu_V S_V = \mu_V(S^*_V - S_V),
\end{aligned} \tag{3.26}$$

so that, $S_V(t) \leq S_V(0)e^{-\mu_V t} + \frac{\Pi_V}{\mu_V}(1 - e^{-\mu_V t})$. Similarly, if $N(0) \leq \frac{\Pi_V}{\mu_H}$ and $S_V(0) \leq S^*_V$ for all $t \geq 0$, then $S_V(t) \leq S^*_V$ for all $t \geq 0$. Thus, the region, $\mathcal{D}_1$, is positively-invariant for the model (3.16) with $\delta_{HJ} = \delta_{HA} = \psi_J = \psi_A = 0$. □

Theorem 3.3. *The DFE, $\mathcal{E}_0$, of the model (3.16), with $\delta_{HJ} = \delta_{HA} = \psi_J = \psi_A = 0$, is GAS in $\mathcal{D}_1$ whenever $\mathcal{R}_1 = \mathcal{R}_0 \mid_{\delta_{HJ}=\delta_{HA}=0} < 1$.*

The proof of Theorem 3.3, based on using Lyapunov function theory, is given in Appendix C. It should be recalled that the loss of infection-acquired immunity parameters, ψ_A and ψ_J, do not feature in the expression for $\mathcal{R}_0$ (hence, they do not affect $\mathcal{R}_1$). Figure 3.3 depicts the solution profiles of the model (3.16) for the case when $\mathcal{R}_1 < 1$ (showing convergence to the DFE, in line with Theorem 3.3).

Extensive numerical simulations of the age-structured model (3.16), in the absence of the requirement for the absence of the loss of infection-acquired immunity of recovered humans (i.e., with $\psi_J \neq 0$ and $\psi_A \neq 0$), show convergence of the initial solutions to the DFE ($\mathcal{E}_0$) whenever $\mathcal{R}_1 < 1$. Thus, these simulations suggest that the requirement for the loss of infection-acquired immunity of recovered humans ($\psi_J = \psi_A = 0$) is not necessary for the GAS property of the DFE ($\mathcal{E}_0$) of the model (3.16) for the case when $\mathcal{R}_1 < 1$. This suggests the following conjecture.

Conjecture 3.1. *The DFE, $\mathcal{E}_0$, of the model (3.16) with $\delta_{HJ} = \delta_{HA} = 0$ is GAS in $\mathcal{D}_1$ whenever $\mathcal{R}_1 < 1$.*

3.3.4 Existence of endemic equilibrium point (EEP): special case:

In this section, conditions for the existence of endemic equilibria (i.e., equilibria where the infected components of the age-structured model (3.16) are non-zero) will be derived. Owing to the complexity of the model (3.16), the analyses in this section will be carried out for the special case of the model with no disease-induced mortality ($\delta_{HJ} = \delta_{HA} = 0$), and no disease transmission by latently-infected individuals ($\eta = 0$). Substituting $\delta_{HJ} = \delta_{HA} = \eta = 0$ into the model (3.16) gives the following reduced model (it should be noted that setting $\delta_{HJ} = \delta_{HA} = 0$ in (3.16) results in $N_H^* = \frac{\Pi_J}{\mu_H}$):

$$
\begin{aligned}
\frac{dS_{HJ}}{dt} &= \Pi_J + \psi_J R_{HJ} - \frac{\mu_H b_2 \beta_{HJ} I_V}{\Pi_J} S_{HJ} - (\xi + \mu_H) S_{HJ}, \\
\frac{dS_{HA}}{dt} &= \xi S_{HJ} + \psi_A R_{HA} - \frac{\mu_H b_2 \beta_{HA} I_V}{\Pi_J} S_{HA} - \mu_H S_{HA}, \\
\frac{dE_{HJ}}{dt} &= \frac{\mu_H b_2 \beta_{HJ} I_V}{\Pi_J} S_{HJ} - (\sigma_{HJ} + \xi + \mu_H) E_{HJ}, \\
\frac{dE_{HA}}{dt} &= \xi E_{HJ} + \frac{\mu_H b_2 \beta_{HA} I_V}{\Pi_J} S_{HA} - (\sigma_{HA} + \mu_H) E_{HA}, \\
\frac{dI_{HJ}}{dt} &= \sigma_{HJ} E_{HJ} - (\xi + \gamma_J + \mu_H) I_{HJ}, \\
\frac{dI_{HA}}{dt} &= \sigma_{HA} E_{HA} + \xi I_{HJ} - (\gamma_A + \mu_H) I_{HA}, \\
\frac{dR_{HJ}}{dt} &= \gamma_J I_{HJ} - (\xi + \mu_H + \psi_J) R_{HJ}, \\
\frac{dR_{HA}}{dt} &= \gamma_A I_{HA} + \xi R_{HJ} - (\mu_H + \psi_A) R_{HA}, \\
\frac{dS_V}{dt} &= \Pi_V - \frac{\mu_H b_2 \beta_V (I_{HJ} + I_{HA})}{\Pi_J} S_V - \mu_V S_V, \\
\frac{dI_V}{dt} &= \frac{\mu_H b_2 \beta_V (I_{HJ} + I_{HA})}{\Pi_J} S_V - \mu_V I_V.
\end{aligned}
\tag{3.27}
$$

It can be shown that the reproduction number of the reduced model (3.27) is given by

$$
\begin{aligned}
\mathcal{R}_2 &= \mathcal{R}_0|_{\eta=\delta_{HJ}=\delta_{HA}=0} \\
&= \sqrt{\frac{b_2 \beta_V \Pi_V \mu_H \{ b_2 \beta_{HJ} \mu_H \left[\sigma_{HJ} g_3 (g_5 + \xi) + \sigma_{HA} \xi g_4 \right] + b_2 \beta_{HA} \xi \sigma_{HA} g_2 g_4 \}}{\Pi_J \mu_V^2 (\xi + \mu_H) \left(\prod_{i=2}^{5} g_i \right)}},
\end{aligned}
\tag{3.28}
$$

where, now, $g_2 = \sigma_{HJ} + \xi + \mu_H$, $g_3 = \sigma_{HA} + \mu_H$, $g_4 = \xi + \gamma_J + \mu_H$ and $g_5 = \gamma_A + \mu_H$.

Let $\mathcal{E}_1 = (S_{HJ}^{**}, S_{HA}^{**}, E_{HJ}^{**}, E_{HA}^{**}, I_{HJ}^{**}, I_{HA}^{**}, R_{HJ}^{**}, R_{HA}^{**}, S_V^{**}, I_V^{**})$ represents an arbitrary endemic equilibrium of the model (3.27). Furthermore, let

$$
\lambda_{HJ}^{**} = \frac{\mu_H b_2 \beta_{HJ} I_V^{**}}{\Pi_J}, \quad \lambda_{HA}^{**} = \frac{\mu_H b_2 \beta_{HA} I_V^{**}}{\Pi_J} \quad \text{and} \quad \lambda_V^{**} = \frac{\mu_H b_2 \beta_V (I_{HJ}^{**} + I_{HA}^{**})}{\Pi_J},
\tag{3.29}
$$

be the *force of infection* (i.e., rate of infection) for susceptible juveniles, susceptible adults and susceptible mosquitoes at steady-state, respectively. Solving the equations of the reduced model (3.27) at steady-state gives:

$$
\begin{aligned}
S_{HJ}^{**} &= \frac{g_2 g_4 g_6 \Pi_J}{g_1\{[\sigma_{HJ}(\gamma_J + g_6) + g_4 g_6]\lambda_{HJ}^{**} + g_2 g_4 g_6\}}, \\
E_{HJ}^{**} &= \frac{g_4 g_6 \Pi_J \lambda_{HJ}^{**}}{g_1\{[\sigma_{HJ}(\gamma_J + g_6) + g_4 g_6]\lambda_{HJ}^{**} + g_2 g_4 g_6\}}, \\
R_{HJ}^{**} &= \frac{\sigma_{HJ}\gamma_J \Pi_J \lambda_{HJ}^{**}}{g_1\{[\sigma_{HJ}(\gamma_J + g_6) + g_4 g_6]\lambda_{HJ}^{**} + g_2 g_4 g_6\}}, \\
I_{HJ}^{**} &= \frac{\sigma_{HJ}\lambda_{HJ}^{**} g_6 \Pi_J}{g_1\{[\sigma_{HJ}(\gamma_J + g_6) + g_4 g_6]\lambda_{HJ}^{**} + g_2 g_4 g_6\}}, \\
S_{HA}^{**} &= \frac{\xi S_{HJ}^{**} + \psi_A R_{HA}^{**}}{\lambda_{HA}^{**} + \mu_H}, \\
E_{HA}^{**} &= \frac{\xi \Pi_J \lambda_{HJ}^{**}\left\{\beta_{HA}\lambda_{HJ}^{**}[\psi_A \sigma_{HJ}(\gamma_J g_5 + \gamma_A g_6) + \prod_{i=4}^{7} g_i] + q_0\right\}}{g_1 \mu_H q_1 q_2},
\end{aligned}
\tag{3.30}
$$

$$
I_{HA}^{**} = \frac{\xi \Pi_J \lambda_{HJ}^{**}\{\beta_{HA}\lambda_{HJ}^{**}[g_6 g_7(\sigma_{HA} g_4 + \sigma_{HJ} g_3) + \sigma_{HA}\sigma_{HJ}\gamma_J \psi_A] + q_3\}}{g_1 \mu_H q_1 q_2},
$$

$$
R_{HA}^{**} = \frac{\xi \Pi_J \lambda_{HJ}^{**}\{\beta_{HA}\lambda_{HJ}^{**}[g_4 g_6 \sigma_{HA}\gamma_A + \sigma_{HJ} g_3(g_6\gamma_A + g_5\gamma_J)] + q_4\}}{g_1 \mu_H q_1 q_2},
$$

$$
S_V^{**} = \frac{\Pi_V}{\lambda_V^{**} + \mu_V}, \quad I_V^{**} = \frac{\lambda_V^{**}\Pi_V}{\mu_V(\lambda_V^{**} + \mu_V)},
$$

where,

$$
q_0 = (\beta_{HA} g_2 + \beta_{HJ}\mu_H)\left(\prod_{i=4}^{7} g_i\right),
$$

$$
q_1 = [\sigma_{HJ}(\gamma_J + g_6) + g_4 g_6]\lambda_{HJ}^{**} + g_2 g_4 g_6,
$$

$$q_2 = \{\beta_{HA}\lambda_{HJ}^{**}[\sigma_{HA}(\gamma_A + g_7) + g_5 g_7] + g_3 g_5 g_7 \beta_{HJ}\},$$

$$q_3 = g_6 g_7[\beta_{HJ}\mu_H(\sigma_{HA} g_4 + \sigma_{HJ} g_3) + g_2 g_4 \sigma_{HA}\beta_{HA}],$$

$$q_4 = g_4 g_6 \sigma_{HA}\gamma_A(\beta_{HA} g_2 + \beta_{HJ}\mu_H) + g_3 \sigma_{HJ}\beta_{HJ}\mu_H(g_6\gamma_A + g_5\gamma_J),$$

with, $g_6 = \xi + \mu_H + \psi_J$ and $g_7 = \mu_H + \psi_A$.

Substituting the expressions for I_{HJ}^{**} and I_{HA}^{**} in (3.30) into the equation for λ_V^{**} in (3.29), and simplifying, gives

$$\lambda_V^{**} = \frac{\Pi_J \lambda_{HJ}^{**}(a_0 \lambda_{HJ}^{**} + a_1)}{M_0}, \tag{3.31}$$

where,

$$a_0 = \beta_{HA}\{\sigma_{HJ}\mu_H g_6[\sigma_{HA}(\gamma_A + g_7) + g_5 g_7] + \sigma_{HA}\xi(\sigma_{HJ}\gamma_J\psi_A + g_4 g_6 g_7)\},$$

$$a_1 = g_6 g_7\{\beta_{HJ}\mu_H[\sigma_{HJ} g_3(g_5 + \xi) + \sigma_{HA}\xi g_4] + \sigma_{HA}\beta_{HA}\xi g_2 g_4\}.$$

Furthermore, substituting the equation for I_V^{**} in (3.30) into the equation for λ_{HJ}^{**} in (3.29) gives

$$\lambda_{HJ}^{**} = \frac{\mu_H b_2 \beta_{HJ}\Pi_V \lambda_V^{**}}{\Pi_J \mu_V(\lambda_V^{**} + \mu_V)}. \tag{3.32}$$

Finally, solving for λ_V^{**} from (3.32) and substituting the result into (3.31), and simplifying, shows that the non-zero equilibria of the model (3.27) satisfy the following quadratic

$$c_0(\lambda_{HJ}^{**})^2 + c_1\lambda_{HJ}^{**} + c_2 = 0, \tag{3.33}$$

with,

$$c_0 = \Pi_J b_2 \beta_V \beta_{HA} \mu_H \mu_V \xi [\sigma_{HJ} \sigma_{HA} \gamma_J \psi_A + g_6 g_7 (g_3 \sigma_{HJ} + g_4 \sigma_{HA})]$$
$$+ \Pi_J \beta_{HA} \mu_H \mu_V [\sigma_{HA}(\gamma_A + g_7) + g_5 g_7] \{ b_2 \beta_V \sigma_{HJ} \mu_H g_6 + \mu_V g_1 [\sigma_{HJ}(\gamma_J + g_6) + g_4 g_6] \},$$
$$c_2 = \beta_{HJ} \mu_H g_6 g_7 \Pi_J \mu_V^2 \left(\prod_{i=1}^{5} g_i \right) (1 - \mathcal{R}_2^2).$$

The components of the positive equilibrium (or equilibria) of the reduced model (3.27) can then be obtained by solving for λ_{HJ}^{**} in (3.33), and substituting the result in the steady-state expressions in (3.30). Furthermore, it follows from (3.33) that the coefficient c_0 is always positive and c_2 is positive (negative) if $\mathcal{R}_2$ is less than (greater than) unity. These results are summarized below.

Theorem 3.4. *The reduced model (3.27) has a unique endemic equilibrium whenever* $\mathcal{R}_2 > 1$.

Numerical simulations of the model (3.27), depicted in Figure 3.4, show convergence to an endemic equilibrium when $\mathcal{R}_2 > 1$ (suggesting that the unique EEP of the reduced model (3.27) is asymptotically stable when it exists).

3.4 Effect of Age-structure

The effect of age-structure on the dynamics of the age-structured model (3.16) will now be qualitatively assessed by comparing its dynamical features with those for the equivalent model with no age structure. The equivalent model with no age-structure, obtained by setting $S_H = S_{HJ} + S_{HA}$, $E_H = E_{HJ} + E_{HA}$, $I_H = I_{HJ} + I_{HA}$, $R_H = R_{HJ} + R_{HA}$, so that ($N_H = S_H + E_H + I_H + R_H$), $\Pi_H = \Pi_J$, $\beta_H = \beta_{HJ} + \beta_{HA}$, $\sigma_H = \sigma_{HJ} + \sigma_{HA}$, $\psi_H = \psi_{HJ} + \psi_{HA}$, $\delta_H = \delta_{HJ} + \delta_{HA}$, $\xi = 0$ and $\gamma_H = \gamma_{HJ} + \gamma_{HA}$ in (3.16), is given by

$$
\begin{aligned}
\frac{dS_H}{dt} &= \Pi_H + \psi_H R_H - \frac{b_2\beta_H I_V}{N_H} S_H - \mu_H S_H, \\
\frac{dE_H}{dt} &= \frac{b_2\beta_H I_V}{N_H} S_H - (\sigma_H + \mu_H) E_H, \\
\frac{dI_H}{dt} &= \sigma_H E_H - (\gamma_H + \mu_H + \delta_H) I_H, \\
\frac{dR_H}{dt} &= \gamma_H I_H - (\psi_H + \mu_H) R_H, \\
\frac{dS_V}{dt} &= \Pi_V - \frac{b_2\beta_V(\eta E_H + I_H)}{N_H} S_V - \mu_V S_V, \\
\frac{dI_V}{dt} &= \frac{b_2\beta_V(\eta E_H + I_H)}{N_H} S_V - \mu_V I_V.
\end{aligned} \tag{3.34}
$$

The DFE of the model (3.34) is given by

$$
\mathcal{E}_{01} = (S_H^*, E_H^*, I_H^*, R_H^*, S_V^*, I_V^*) = \left(\frac{\Pi_H}{\mu_H}, 0, 0, 0, \frac{\Pi_V}{\mu_V}, 0\right),
$$

and the associated reproduction number is given by

$$
\mathcal{R}_{01} = \sqrt{\mathcal{R}_{V01}\mathcal{R}_{H01}}, \tag{3.35}
$$

where,

$$
\mathcal{R}_{V01} = \frac{b_2\beta_H}{\mu_V} \quad \text{and} \quad \mathcal{R}_{H01} = \frac{\Pi_V\mu_H b_2\beta_V[\eta(\gamma_H + \delta_H + \mu_H) + \sigma_H]}{\Pi_H\mu_V(\sigma_H + \mu_H)(\gamma_H + \delta_H + \mu_H)}.
$$

It can be shown (using the approaches in Sections 3.3 and 3.3.2) that the DFE of the model (3.34) is LAS if $\mathcal{R}_{01} < 1$, and that the model (3.34) undergoes backward bifurcation whenever the associated backward bifurcation coefficient, a, given by

$$
\begin{aligned}
a = \frac{1}{g_4(\Pi_H\mu_V g_2 g_3)^2}\Big\{&\delta_H[g_4(\sigma_H p_3 + \eta p_4) + p_5 + \sigma_H\gamma_H\eta\mu_V] \\
&- \mu_H[\sigma_H\gamma_H\mu_V p_0 + g_4(b_1\beta_V p_1 + \mu_V p_2)]\Big\},
\end{aligned} \tag{3.36}
$$

is positive. In (3.36),

$$p_0 = \eta\psi_H + \gamma_H + \sigma_H, p_1 = (\mu_H\eta)^2 + \sigma_H^2 + \eta\gamma_H,$$

$$p_2 = \sigma_H(3\mu_H + 2\sigma_H + \gamma_H) + \eta[\gamma_H(2\mu_H + \gamma_H) + \mu_H],$$

$$p_3 = 2b_1\beta_V\mu_H\eta + \mu_V[2\mu_H(1+\eta) - g_2],$$

$$p_4 = b_1\beta_V\eta[\delta_H + 2\eta(\gamma_H + \mu_H)],$$

$$p_5 = \mu_V(2\mu_H - g_2)[2(\gamma_H + \mu_H) + \delta_H].$$

It should be mentioned that, as in the case of the age-structured model (3.16), the backward bifurcation property of the reduced model (3.34) disappears whenever the disease-induced mortality rate (δ_H) is set to zero. In particular, setting $\delta_H = 0$ (i.e., $N_H^* = \dfrac{\Pi_H}{\mu_H}$) in model (3.34), it can be shown that the associated backward bifurcation coefficient reduces to:

$$a = \frac{-\mu_H}{g_4(\Pi_H\mu_V g_2 g_3)^2}[\sigma_H\gamma_H\mu_V p_0 + g_4(b_1\beta_V p_1 + \mu_V p_2)] < 0.$$

Hence, it follows, from Theorem 4.1 of [11], that the reduced model (3.34) will not undergo backward bifurcation when $\delta_H = 0$. Furthermore, the following Lyapunov function

$$\mathcal{F} = \frac{\Pi_V\mu_H b_2\beta_V\left(\eta g_4 + \sigma_{HJ}\right)}{\Pi_H\mu_V\hat{\mathcal{R}}_{01}g_2g_4}E_H + \frac{\Pi_V\mu_H b_2\beta_V}{\Pi_H\mu_V\hat{\mathcal{R}}_{01}g_4}I_H + I_V,$$

can be used to prove the GAS property of the DFE, $\mathcal{E}_{01}$, of the model (3.34), for the case when $\hat{\mathcal{R}}_{01} = \mathcal{R}_{01}|_{\delta_H=0} < 1$. Thus, in summary, the analyses in Section 3.4 show that the age-structured model (3.16), and its equivalent model (3.34) without age-structure, have the same qualitative dynamics with respect to the phenomenon of backward bifurcation and the local and global asymptotic stability of the associated

DFE.

The two models, (3.16) and (3.34), will now be compared in terms of the dynamics of their corresponding endemic equilibrium points. Let $\hat{\mathcal{E}}_1 = (S_H^{**}, E_H^{**}, I_H^{**}, R_H^{**}, S_V^{**}, I_V^{**})$ represents an arbitrary endemic equilibrium of the reduced model (3.34) with $\delta_H = \psi_H = \eta = 0$. Furthermore, let

$$\lambda_H^{**} = \frac{\mu_H b_2 \beta_H I_V^{**}}{\Pi_H} \quad \text{and} \quad \lambda_V^{**} = \frac{\mu_H b_2 \beta_V I_H^{**}}{\Pi_H}, \tag{3.37}$$

be the force of infection for susceptible juveniles, adults and mosquitoes at steady-state, respectively. Solving the equations of the reduced model (3.34), with $\delta_H = \psi_H = \eta = 0$, at steady-state, gives:

$$\begin{aligned}
S_H^{**} &= \frac{\Pi_H}{\lambda_H^{**} + \mu_H}, \quad E_H^{**} = \frac{\lambda_H^{**}\Pi_H}{(\lambda_H^{**} + \mu_H)(\sigma_H + \mu_H)}, \\
I_H^{**} &= \frac{\sigma_H \lambda_H^{**}\Pi_H}{(\lambda_H^{**} + \mu_H)(\sigma_H + \mu_H)(\gamma_H + \mu_H)}, \\
R_H^{**} &= \frac{\gamma_H \sigma_H \lambda_H^{**}\Pi_H}{(\psi_H + \mu_H)(\lambda_H^{**} + \mu_H)(\sigma_H + \mu_H)(\gamma_H + \mu_H)}, \\
S_V^{**} &= \frac{\Pi_V}{\lambda_V^{**} + \mu_V}, \quad I_V^{**} = \frac{\lambda_V^{**}\Pi_V}{\mu_V(\lambda_V^{**} + \mu_V)}.
\end{aligned} \tag{3.38}$$

Substituting (3.38) into (3.37) shows that the positive endemic equilibrium of the model (3.34), with $\delta_H = \psi_H = \eta = 0$, satisfy

$$\lambda_H^{**} = \frac{[\mu_H(\sigma_H + \mu_H) + (\gamma_H + \mu_H)](\mathcal{R}_{02} - 1)}{\beta_V \sigma_H b_2 \mu_V \mu_H + (\sigma_H + \mu_H) + (\gamma_H + \mu_H)}, \tag{3.39}$$

where $\mathcal{R}_{02} = \mathcal{R}_{01}|_{\delta_H = \psi_H = \eta = 0}$. Hence, the model (3.34), with $\delta_H = \psi_H = \eta = 0$, has a unique endemic equilibrium (obtained by substituting (3.39) into (3.38)) whenever $\mathcal{R}_{02} > 1$. Define the following invariant region for the model (3.34):

$$\mathcal{D}_2 = \left\{ (S_H, E_H, I_H, R_H, S_V, I_V) \in \mathbb{R}^6_+ : S_H + E_H + I_H + R_H \leq \frac{\Pi_H}{\mu_H}; \quad S_V + I_V \leq \frac{\Pi_V}{\mu_V} \right\}.$$

Let,

$$\mathcal{D}_0 = \{(S_H, E_H, I_H, R_H, S_V, I_V) \in \mathbb{R}^6_+ : E_H = I_H = I_V = 0\}.$$

Theorem 3.5. *The unique endemic equilibrium of the reduced model (3.34), with $\delta_H = \psi_H = \eta = 0$, is GAS in $\mathcal{D}_2 \backslash \mathcal{D}_0$ whenever $\mathcal{R}_{02} > 1$.*

The proof of Theorem 3.5 is given in Appendix D.

In summary, it follows from the analyses in Sections 3.3 and 3.4 that both the age-structured model (3.16) and the reduced model (3.34), without age-structure, have a unique endemic equilibrium whenever their associated reproduction number exceeds unity. The models (3.16) and (3.34) have essentially the same qualitative properties with respect to the existence of their associated unique endemic equilibrium points, as well as with respect to (local and global) asymptotic stability of the associated DFE and the backward bifurcation property observed in malaria transmission dynamics. Consequently, it is shown, in this chapter, that adding age-structure to the basic malaria transmission model (3.34) does not alter its qualitative dynamics with respect to the existence and stability of equilibria, as well as with respect to its backward bifurcation property.

3.5 Numerical Simulations

The single-strain age-structured model (3.16) is simulated, using the parameter values given in Table 3.3 (unless otherwise stated), to assess the impact of various non-pharmaceutical anti-malaria intervention (namely, mosquito-reduction and per-

sonal protection strategies (against mosquito bite)) on the transmission dynamics of malaria in a community. In this thesis, mosquito-reduction measures are modelled using the parameters Π_V, μ_V and b_2. While a reduction in Π_V signifies effective larvaciding (i.e. spraying mosquito breading sites using suitable chemical agents, such as *Israelensis* [25]), reduction in the average lifespan of mosquitoes ($\frac{1}{\mu_V}$) is achieved by effective adulticiding (such as by the use of DDT [51, 69]). Similarly, the use of personal protection against mosquito bites (by using suitable insect repellents and insecticide treated bed nets (ITNs) [50, 69]) is modelled by the parameter b_2 (a reduction in b_2 implies effective personal protection against mosquito bites). In these simulations, the following initial conditions, based on the population of Kenya [64], are used: $(S_{HJ}(0), S_{HA}(0), E_{HJ}(0), E_{HA}(0), I_{HJ}(0), I_{HA}(0), R_{HJ}(0), R_{HA}(0), S_V(0), I_V(0)) = (18,684,000, 18,684,000, 6,000,600, 0, 0, 0, 0, 2,0000, 1,000, 0)$. Furthermore, the associated demographic parameters, Π_J and μ_H, are chosen such that the total population, at the DFE ($N_H^* = \frac{\Pi_J}{\mu_H}$), is 38 million (the current population of Kenya [64]).

Figure 3.5A depicts the cumulative number of new cases of infection for juveniles for various values of the average lifespan of mosquitoes. The figure shows a decrease in the cumulative number of new cases with decreasing mosquito lifespan (as expected). Similar results are obtained for adults (Figure 3.5B). Plots for cumulative mortality, as a function of average lifespans of mosquitoes, are depicted in Figures 3.6, where it is shown that mortality decrease with decreases mosquito lifespan. It is worth noting, from Figure 3.6, that the cumulative mortality in juveniles is higher than in adults. This is in line with the fact that malaria-induced mortality is higher in juveniles than in adults [69]. Furthermore, the decrease in mortality is more pronounced in adults than in juveniles (this may be due to higher initial values of infected juveniles used in the simulations [69]). Unlike in Figure 3.6B, Figure 3.6A shows that a decrease in mosquito lifespan has marginal effect on the cumulative malaria-induced mortality in juveniles.

The effect of larvaciding is monitored by simulating the model (3.16) with various values of Π_V. The results obtained, depicted in Figure 3.7, show a decrease in the cumulative number of new cases in juveniles (Figure 3.7A) and adults (Figure 3.7B) for decreasing values of Π_V, as expected. A contour plot of the reproduction number $\mathcal{R}_1$, as a function of the mosquito biting rate (b_2) and average mosquito lifespan ($\frac{1}{\mu_V}$), is depicted in Figure 3.8. As expected, the plot shows a decrease in $\mathcal{R}_1$ values with decreasing values of the average lifespan and biting rate of mosquitoes. For instance, if the use of insect repellents and ITNs in the community reduces the mosquito biting rate to $b_2 = 2$, malaria will be effectively controlled (or eliminated) in the community if the use of mosquito-reduction strategies can reduce the average lifespan of mosquitoes to about 10 days (since, in this case, $\mathcal{R}_1 < 1$; and, in line with Theorem 3.3, the DFE of the model (3.16), with $\delta_{HJ} = \delta_{HA} = \psi_J = \psi_A = 0$, is globally-asymptotically stable for this case).

It should be mentioned that the simulation results discussed in this chapter are subject to the uncertainties in the estimates of the parameter values (tabulated in Table 3.3) used in the simulations. The effect of such uncertainties on the results obtained can be assessed using a sampling technique, such as Latin Hypercube Sampling [7, 41].

3.6 Summary of the Chapter

A new, single-strain age-structured, deterministic model for the transmission dynamics of malaria in a community is designed and rigorously analysed in this chapter. Some of the main mathematical and numerical simulation results obtained are summarized below:

(i) the model (3.16) undergoes the phenomenon of backward bifurcation at $\mathcal{R}_0 = 1$ whenever a certain inequality holds;

(ii) the backward bifurcation property of the model (3.16) can be removed if the disease-induced mortality in humans is set to zero ($\delta_{HJ} = \delta_{HA} = 0$). That is, it is shown in this chapter that the backward bifurcation property of the model (3.16) is caused by malaria-induced mortality in humans;

(iii) it is shown that the disease-free equilibrium of the model (3.16) is globally-asymptotically stable, in the absence of disease-induced mortality and loss of infection-acquired immunity, whenever the associated reproduction number ($\mathcal{R}_1$) is less than unity;

(iv) a reduced version of the model (3.16) (in the absence of disease-induced mortality and transmission by exposed individuals), given by (3.27), is shown to have a unique endemic equilibrium whenever its associated reproduction number ($\mathcal{R}_2$) exceeds unity. Numerical simulations suggest that this equilibrium is asymptotically-stable;

(v) the equivalent model without age-structure, given by (3.34), exhibits the same essential qualitative dynamics as the age-structured model (3.16), and its unique endemic equilibrium is shown to be globally-asymptotically stable whenever its reproduction number ($\mathcal{R}_{02}$) is greater than unity. Thus, this study shows that adding age-structure to the basic model for malaria transmission in a community does not alter the qualitative dynamics of the basic model (with respect to the existence and asymptotic stability of its equilibria, as well as with respect to its backward bifurcation property);

(vi) numerical simulations of the model (3.16) show that the cumulative number of new cases of infection and malaria-induced mortality increase with increasing average lifespan and birth rate of mosquitoes.

Variable	Description
S_{HJ}	Population of susceptible juveniles
S_{HA}	Population of susceptible adults
E_{HJ}	Population of latently-infected juveniles
E_{HA}	Population of latently-infected adults
I_{HJ}	Population of symptomatic juveniles
I_{HA}	Population of symptomatic adults
R_{HJ}	Population of recovered juveniles
R_{HA}	Population of recovered adults
S_V	Population of susceptible mosquitoes
I_V	Population of infected mosquitoes

Table 3.1: Description of the state variables of the single-strain model (3.16).

Parameters	Description
b_2	Average *per capita* biting rate of mosquitoes
β_{HJ}	Probability of infection of susceptible juveniles *per* mosquito bite
β_{HA}	Probability of infection of susceptible adults *per* mosquito bite
β_V	Probability of infection of susceptible vectors *per* mosquito bite of the infected host
μ_H	Natural death rate of humans
μ_V	Natural death rate of mosquitoes
σ_{HJ}	Rate of development of clinical symptoms of malaria for latently-infected juveniles
σ_{HA}	Rate of development of clinical symptoms of malaria for latently-infected adults
δ_{HJ}	Disease-induced mortality rate for juveniles
δ_{HA}	Disease-induced mortality rate for adults
γ_J	Recovery rate of juveniles
γ_A	Recovery rate of adults
ψ_J	Rate of loss of natural immunity for juveniles
ψ_A	Rate of loss of natural immunity for adults
ξ	Maturation rate for juveniles
η	Modification parameter for reduction in infectiousness of latently-infected humans
Π_J	Recruitment (birth or immigration) rate of juveniles
Π_V	Birth rate of adult mosquitoes

Table 3.2: Description of parameters of the single-strain model (3.16).

Parameter	Value	Reference
b_2	$0.5 \quad \text{day}^{-1}$	[23]
β_{HJ}	0.181	[23]
β_{HA}	0.181	[23]
β_V	0.8333	[45]
μ_H	$0.00004 \quad \text{day}^{-1}$	[45]
μ_V	$0.05 \quad \text{day}^{-1}$	[45]
σ_{HJ}	$0.10333 \quad \text{day}^{-1}$	[13]
σ_{HA}	$0.08333 \quad \text{day}^{-1}$	[13]
δ_{HJ}	$0.0003454 \quad \text{day}^{-1}$	[1]
δ_{HA}	$0.0000174 \quad \text{day}^{-1}$	[1]
γ_J	$0.0014 \quad \text{day}^{-1}$	[1]
γ_A	$0.0035 \quad \text{day}^{-1}$	[1]
ψ_J	$0.0027 \quad \text{day}^{-1}$	[1]
ψ_A	$0.0027 \quad \text{day}^{-1}$	[1]
ξ	$0.00000986 \quad \text{day}^{-1}$	[1]
η	$[0, 1)$	Variable
Π_J	$1520 \quad \text{day}^{-1}$	Assumed
Π_V	$500 \quad \text{day}^{-1}$	Assumed

Table 3.3: Parameter values for the single-strain model (3.16).

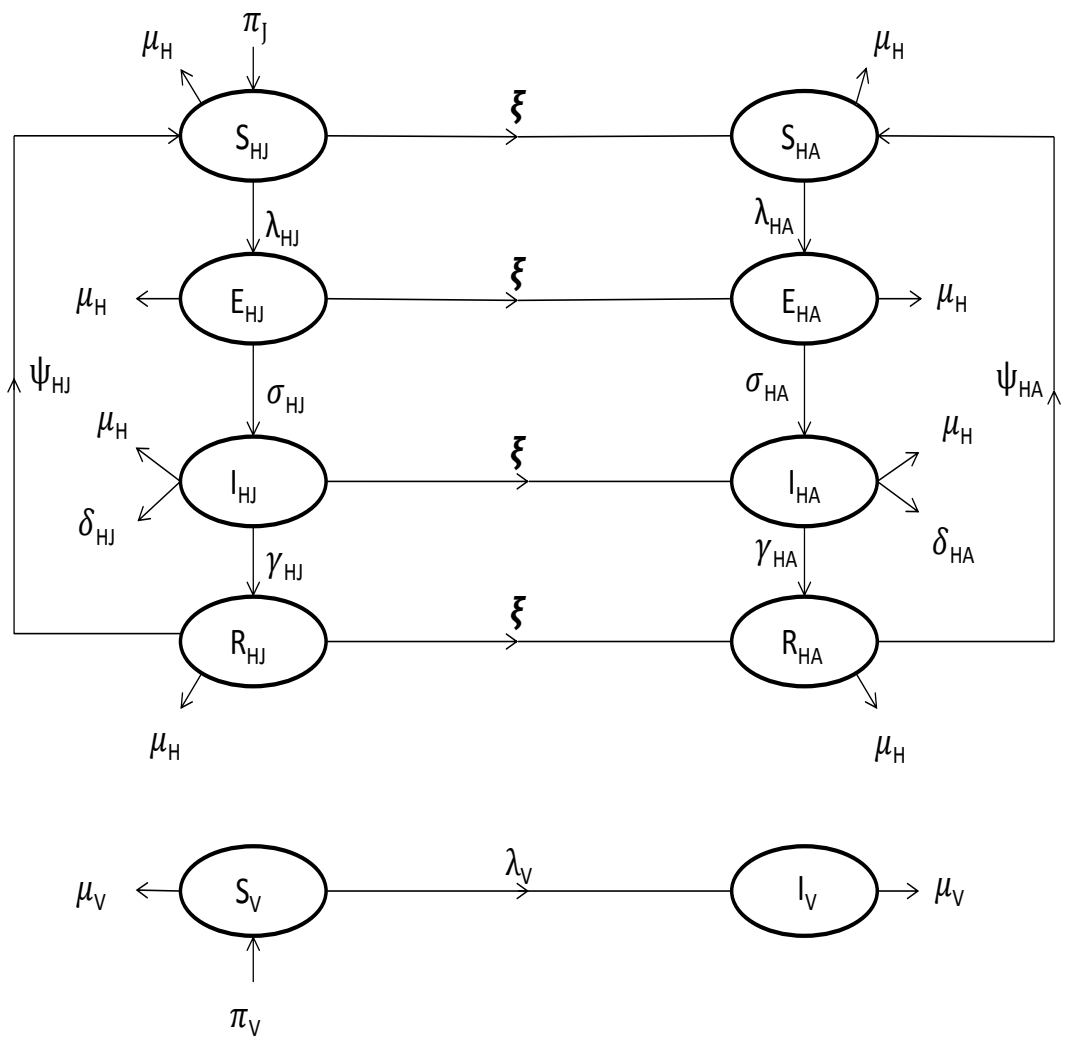

Figure 3.1: Schematic diagram of the single-strain model (3.16).

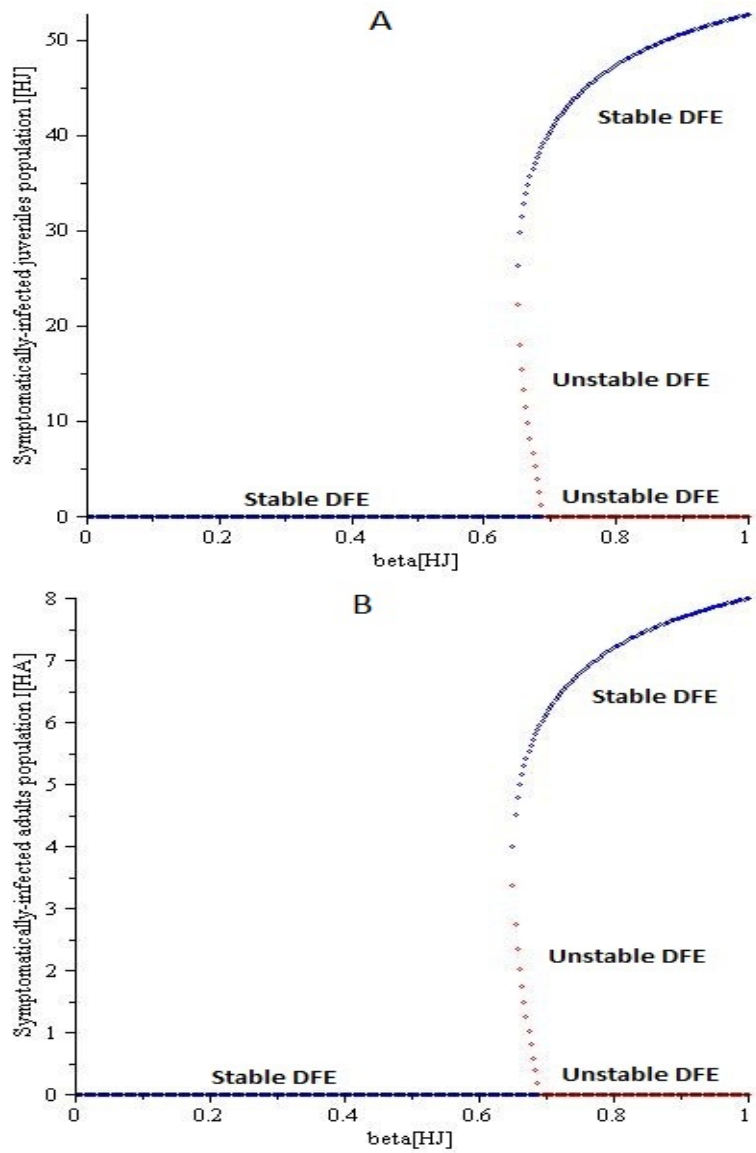

Figure 3.2: Backward bifurcation diagram for the single-strain model (3.16), showing the total number of symptomatic individuals (juveniles and adults) as a function of the backward bifurcation parameter β^*_{HJ}. (A) Symptomatically-infected juveniles (I_{HJ}). (B) Symptomatically-infected adults (I_{HA}). Parameter values used are as given in Table 3.3, with: $\Pi_J = 100$, $\Pi_V = 20000$, $\mu_H = 0.062$, $\mu_V = 0.6$, $\delta_{HJ} = 0.9$, $\delta_{HA} = 0.7$, $\xi = \frac{1}{15}$, $\gamma_J = 1$, $\gamma_A = 1$, $\sigma_{HJ} = 0.6$, $\sigma_{HA} = 0.5$, $\psi_J = 0.8$, $\psi_A = 0.7$, $\beta_{HA} = 0.0001$, $\beta_V = 0.1867$, $\eta = 0$, $b_2 = 1$ (so that, $a = 0.0003225760046 > 0$ and $\mathcal{R}_0 = 1$).

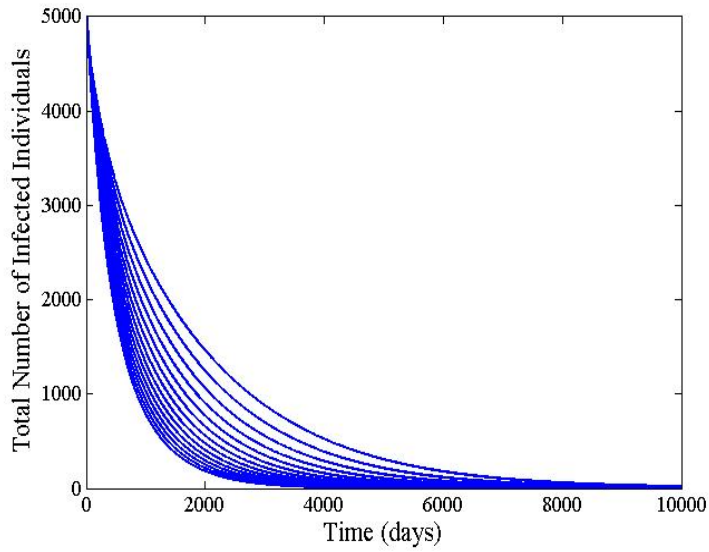

Figure 3.3: Simulations of the single-strain model (3.16), showing the total number of infected individuals as a function of time, using various initial conditions. Parameter values used are as given in Table 3.3, with $\Pi_J = 1520$, $\Pi_V = 1000$, $\mu_V = \frac{1}{20}$, $\mu_H = 0.00004$, $\xi = 0.00000986$, $\gamma_J = 0.0014$, $\gamma_A = 0.0035$, $\sigma_{HJ} = 0.10333$, $\sigma_{HA} = 0.08333$, $\psi_J = \psi_A = \delta_{HJ} = \delta_{HA} = 0$, $\beta_{HA} = 0.1$ $\beta_{HJ} = 0.2$, $\beta_V = 0.6$, $\eta = 0$ and $b_2 = 0.8$ (so that, $\mathcal{R}_1 = 0.6862$).

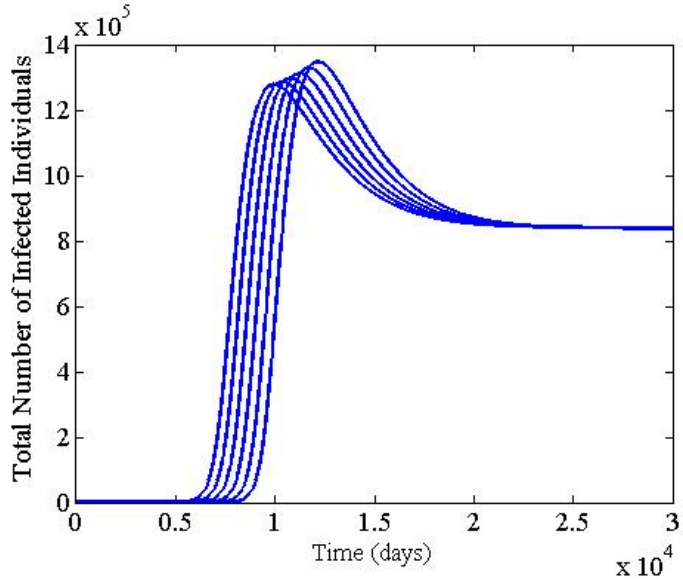

Figure 3.4: Simulations of the single-strain model (3.27), showing the total number of infected individuals as a function of time, using various initial conditions. Parameter values used are as given in Table 3.3, with $\Pi_J = 1520$, $\Pi_V = 1000$, $\mu_V = \frac{1}{20}$, $\mu_H = 0.00004$, $\xi = 0.00000986$, $\gamma_J = 0.0014$, $\gamma_A = 0.0035$, $\sigma_{HJ} = 0.10333$, $\sigma_{HA} = 0.08333$, $\psi_J = \psi_A = \delta_{HJ} = \delta_{HA} = 0$, $\beta_{HA} = 0.1$ $\beta_{HJ} = 0.2$, $\beta_V = 0.9$, $\eta = 0$ and $b_2 = 3$ (so that, $\mathcal{R}_2 = 3.1518$).

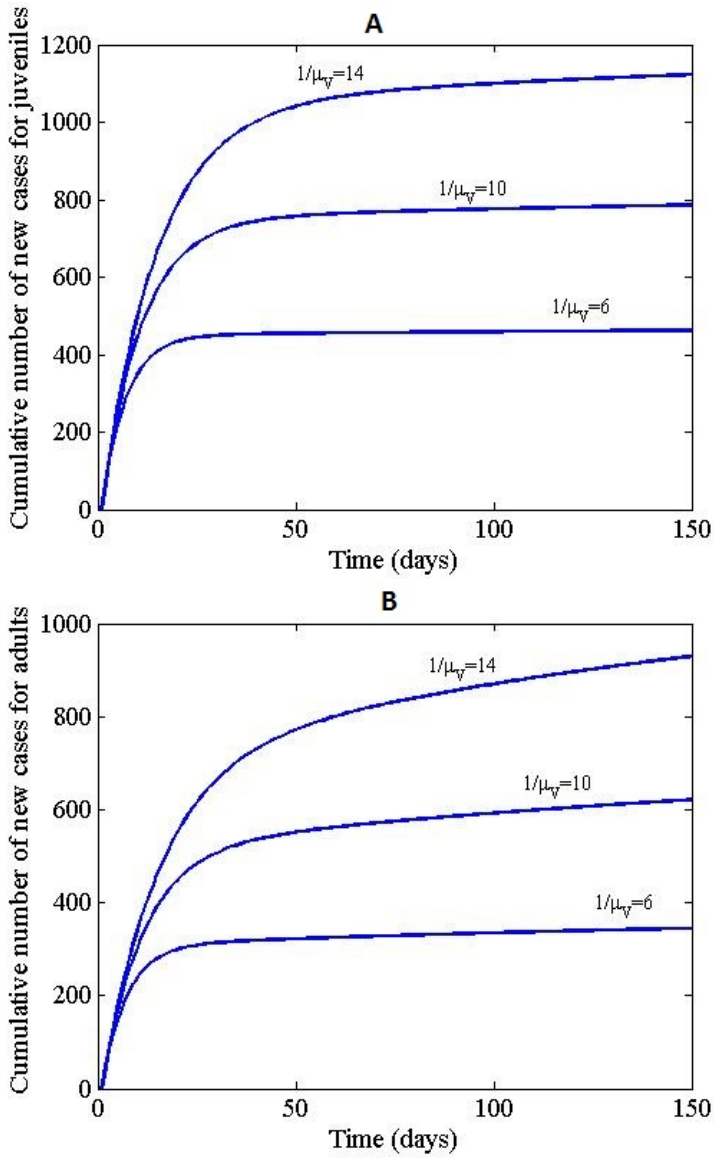

Figure 3.5: Simulations of the single-strain model (3.16), showing the cumulative number of new cases for juveniles and adults as a function of time, for various values of average lifespan of mosquitoes ($\frac{1}{\mu_V}$). (A) Juveniles. (B) Adults. Parameter values used are as given in Table 3.3, with $\Pi_J = 1520$, $\Pi_V = 500$, $\mu_H = 0.00004$, $\delta_{HJ} = 0.0034$, $\delta_{HA} = 0.00034$, $\xi = 0.00000986$, $\gamma_J = 0.0014$, $\gamma_A = 0.0035$, $\sigma_{HJ} = 0.10333$, $\sigma_{HA} = 0.08333$, $\psi_J = 0.0027$, $\psi_A = 0.0027$, $\beta_{HA} = 0.2$ $\beta_{HJ} = 0.3$, $\beta_V = 0.8333$, $\eta = 0$ and $b_2 = 0.5$.

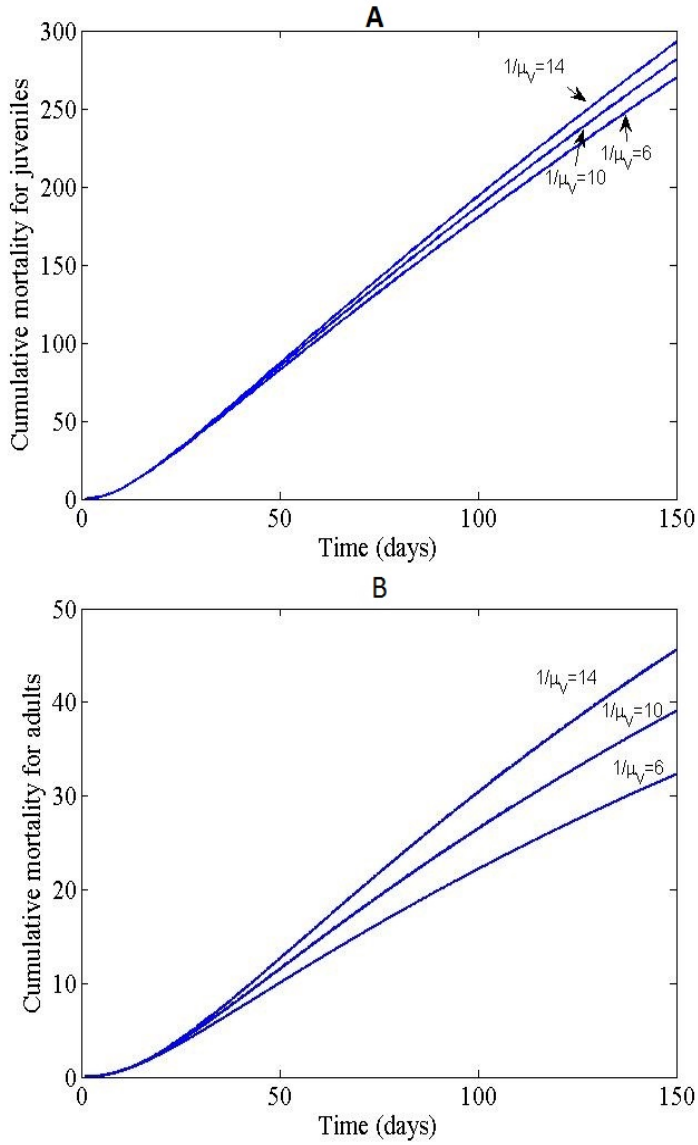

Figure 3.6: Simulations of the single-strain model (3.16), showing the cumulative mortality for juveniles and adults as a function of time, for various values of average lifespan of mosquitoes ($\frac{1}{\mu_V}$). (A) Juveniles. (B) Adults. Parameter values used are as given in Table 3.3, with $\Pi_J = 1520$, $\Pi_V = 500$, $\mu_H = 0.00004$, $\delta_{HJ} = 0.0034$, $\delta_{HA} = 0.00034$, $\xi = 0.00000986$, $\gamma_J = 0.0014$, $\gamma_A = 0.0035$, $\sigma_{HJ} = 0.10333$, $\sigma_{HA} = 0.08333$, $\psi_J = 0.0027$, $\psi_A = 0.0027$, $\beta_{HA} = 0.2$ $\beta_{HJ} = 0.3$, $\beta_V = 0.8333$, $\eta = 0$ and $b_2 = 0.5$.

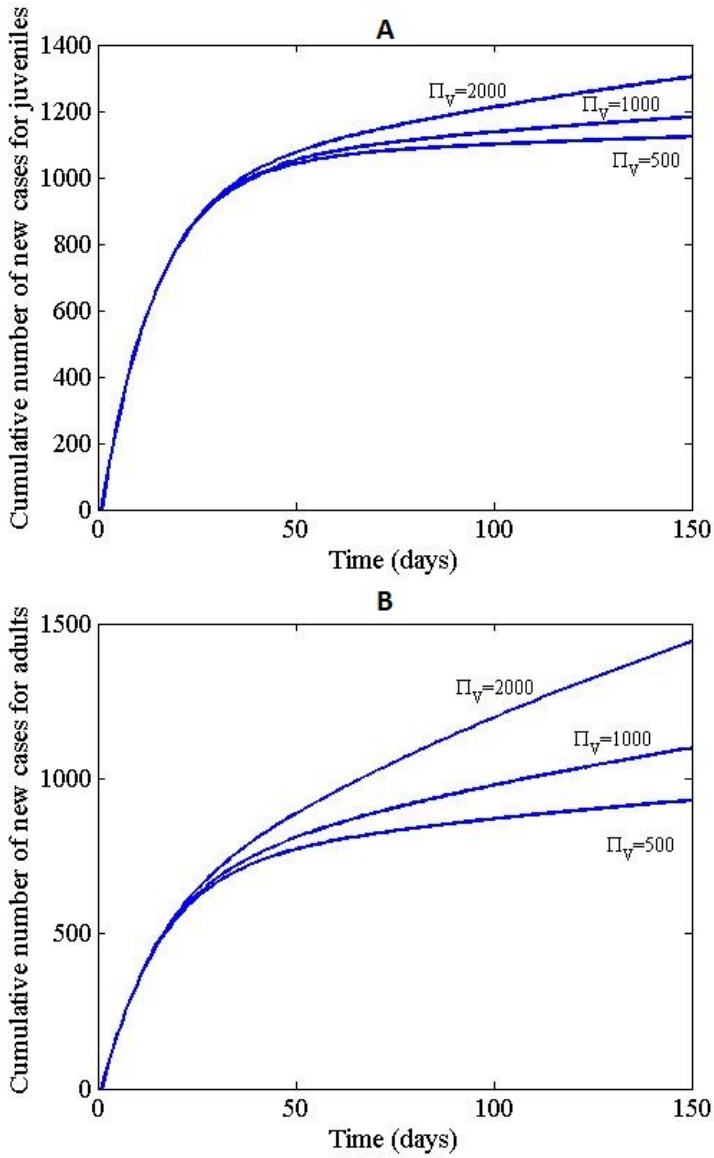

Figure 3.7: Simulations of the single-strain model (3.16), showing the cumulative number of new cases for juveniles and adults as a function of time, for various values of birth rate of adult mosquitoes (Π_V). (A) Juveniles. (B) Adults. Parameter values used are as given in Table 3.3, with $\Pi_J = 1520$, $\mu_V = \frac{1}{14}$, $\mu_H = 0.00004$, $\delta_{HJ} = 0$, $\delta_{HA} = 0$, $\xi = 0.00000986$, $\gamma_J = 0.0014$, $\gamma_A = 0.0035$, $\sigma_{HJ} = 0.10333$, $\sigma_{HA} = 0.08333$, $\psi_J = 0$, $\psi_A = 0$, $\beta_{HA} = 0.2$ $\beta_{HJ} = 0.3$, $\beta_V = 0.8333$, $\eta = 0$ and $b_2 = 0.5$.

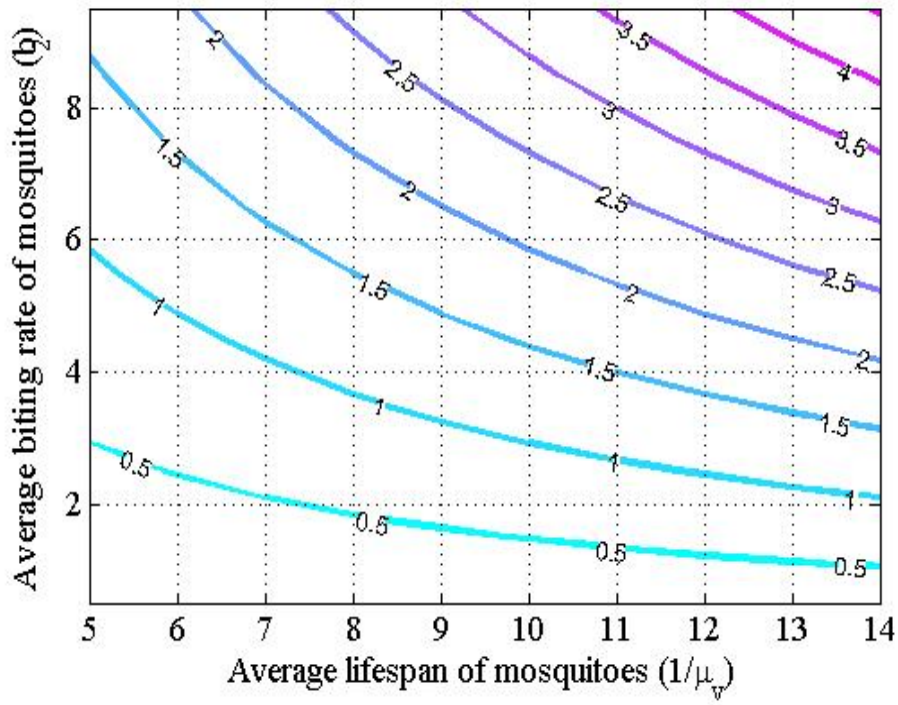

Figure 3.8: Simulations of the single-strain model (3.16), showing a contour plot of $\mathcal{R}_1$ as a function of the biting rate (b_2) and average lifespan ($\frac{1}{\mu_V}$) of mosquitoes. Parameter values used are as given in Table 3.3, with $\Pi_J = 1520$, $\Pi_V = 300$, $\mu_H = 0.00004$, $\delta_{HJ} = \delta_{HA} = 0$, $\xi = 0.00000986$, $\gamma_J = 0.0014$, $\gamma_A = 0.0035$, $\sigma_{HJ} = 0.10333$, $\sigma_{HA} = 0.08333$, $\psi_J = 0.0027$, $\psi_A = 0.0027$, $\beta_{HA} = 0.2$ $\beta_{HJ} = 0.3$, $\beta_V = 0.8333$ and $\eta = 0$.

Chapter 4

Age-structured Treatment Model

4.1 Introduction

In this chapter, the single-strain model in Chapter 3 is extended to assess the community-wide impact of the use of anti-malaria drugs to treat individuals with clinical symptoms of malaria. As stated in Chapter 1, various drugs are currently being used to treat people infected with malaria (such as *Aralen, Chloroquine, Malaraquine and Nivaquine* [6, 46]). The use of these drugs in the community, some of which are administered in combinations (combination therapy), is known to result in the emergence and transmission of drug-resistant malaria strain in the community [6, 46]. Malaria drug resistance is attributed to factors such as [6]:

(a) spontaneous mutations that confer reduced sensitivity to a given drug or class of drugs;

(b) treatment failure (due to incorrect dosing, non-compliance with duration of dosing regimen, poor drug quality, drug interactions, poor or erratic absorption and misdiagnosis etc.).

Anti-malaria drug resistance clearly poses great challenges to the global effort to effectively control the spread of malaria (or to eradicate the disease) [6, 67]. Con-

sequently, it is important to study the qualitative impact of treatment (using the currently-available anti-malaria drugs) on the transmission dynamics of malaria in a population. To achieve this objective, the model in Chapter 3 will now be extended to incorporate the dynamics of two strains of malaria (wild and drug-resistant strains).

4.2 Model Formulation

The age-structured treatment model for malaria is designed by splitting the total human population at time t, denoted by $N_H(t)$, into the mutually-exclusive sub-populations of susceptible juveniles ($S_J(t)$), susceptible adults ($S_A(t)$), latently-infected (asymptomatic) juveniles with the wild strain ($E_{JW}(t)$), latently-infected (asymptomatic) adults with the wild strain ($E_{AW}(t)$), latently-infected (asymptomatic) juveniles with the resistant strain ($E_{JR}(t)$), latently-infected (asymptomatic) adults with the resistant strain ($E_{AR}(t)$), symptomatic juveniles with the wild strain ($I_{JW}(t)$), symptomatic adults with the wild strain ($I_{AW}(t)$), symptomatic juveniles with the resistant strain ($I_{JR}(t)$), symptomatic adults with the resistant strain ($I_{AR}(t)$), effectively-treated juveniles ($T_J(t)$), effectively-treated adults ($T_A(t)$), recovered juveniles ($R_J(t)$) and recovered adults ($R_A(t)$), so that

$$\begin{aligned} N_H(t) = {} & S_J(t) + S_A(t) + E_{JW}(t) + E_{AW}(t) + E_{JR}(t) + E_{AR}(t) + I_{JW}(t) + I_{AW}(t) \\ & + I_{JR}(t) + I_{AR}(t) + T_J(t) + T_A(t) + R_J(t) + R_A(t). \end{aligned}$$

As in Chapter 3, individuals in the latently-infected classes (E_{JW}, E_{AW}, E_{JR} and E_{AR}) are asymptotically-infected (and can transmit malaria infection to susceptible mosquitoes).

The total mosquito population at time t, denoted by $N_V(t)$, is sub-divided into the compartments of susceptible mosquitoes ($S_V(t)$) and mosquitoes infected with

the wild ($V_W(t)$) and resistant ($V_R(t)$) strains, so that

$$N_V(t) = S_V(t) + V_W(t) + V_R(t).$$

The population of susceptible juveniles is generated by the birth (or immigration) of juveniles (at a rate Π_J). Although vertical transmission of malaria can occur (see [22] and some of the references therein), it is assumed, in this study, that all children are born susceptible (so that there is no vertical transmission of malaria from mother-to-child). This population is increased by the loss of infection-acquired immunity by recovered juveniles (at a *per capita* rate ψ_J). It is decreased by infection, following effective contacts with infected mosquitoes, at a rate λ_J, given by

$$\lambda_J = \frac{\beta_J b_1(N_V, N_H)(V_W + \theta_R V_R)}{N_V}. \tag{4.1}$$

In (4.1), β_J is the probability of infection of susceptible juveniles *per* bite by an infected mosquito and $b_1(N_V, N_H)$ is the *per capita* biting rate of mosquitoes on susceptible humans (juveniles and adults) *per* unit time. Furthermore, $\theta_R > 0$ is a modification parameter accounting for the possible variability of infectiousness of mosquitoes infected with the resistant strain (V_R) in comparison to mosquitoes infected with the wild strain. It is further decreased by maturation to adulthood (at a rate ξ; as in Chapter 3, this rate is assumed to be same for all humans compartments) and natural death (at a rate μ_H; it is assumed that natural death occurs in all human epidemiological classes at this rate). Thus,

$$\frac{dS_J}{dt} = \Pi_J + \psi_J R_J - \lambda_J S_J - (\xi + \mu_H) S_J. \tag{4.2}$$

The population of susceptible adults is generated by the maturation of susceptible juveniles (at the rate ξ) and by the loss of infection-acquired immunity by recovered adults (at a rate ψ_A). It is decreased by infection at a rate λ_A, given by

$$\lambda_A = \frac{\beta_A b_1(N_V, N_H)(V_W + \theta_R V_R)}{N_V}, \tag{4.3}$$

where β_A is the probability of infection of susceptible adults *per* bite by an infected mosquito. This population is further decreased by natural death. Hence,

$$\frac{dS_A}{dt} = \xi S_J + \psi_A R_A - \lambda_A S_A - \mu_H S_A. \tag{4.4}$$

The population of latently-infected juveniles with the wild (resistant) strain is generated by the infection of susceptible juveniles with the wild (resistant) strain at the rate $\beta_J b_1(N_V, N_H)$ ($\theta_R \beta_J b_1(N_V, N_H)$). It is decreased by the development of clinical symptoms of malaria at a rate σ_{JW} (σ_{JR}), maturation to adulthood (at the rate ξ) and natural death, so that

$$\frac{dE_{JW}}{dt} = \frac{\beta_J b_1(N_V, N_H) V_W}{N_V} S_J - (\sigma_{JW} + \xi + \mu_H) E_{JW}, \tag{4.5}$$

$$\frac{dE_{JR}}{dt} = \frac{\theta_R \beta_J b_1(N_V, N_H) V_R}{N_V} S_J - (\sigma_{JR} + \xi + \mu_H) E_{JR}. \tag{4.6}$$

Furthermore, the population of latently-infected adults with the wild (resistant) strain is generated by the maturation of latently-infected juveniles with the wild (resistant) strain (at the rate ξ) and by the infection of susceptible adults with the

wild (resistant) strain at the rate $\beta_A b_1(N_V, N_H)$ ($\theta_R \beta_A b_1(N_V, N_H)$). It is diminished by the development of malaria symptoms at a rate σ_{AW} (σ_{AR}) and natural death. Hence,

$$\frac{dE_{AW}}{dt} = \xi E_{JW} + \frac{\beta_A b_1(N_V, N_H) V_W}{N_V} S_A - (\sigma_{AW} + \mu_H) E_{AW}, \tag{4.7}$$

$$\frac{dE_{AR}}{dt} = \xi E_{JR} + \frac{\theta_R \beta_A b_1(N_V, N_H) V_R}{N_V} S_A - (\sigma_{AR} + \mu_H) E_{AR}. \tag{4.8}$$

The population of symptomatic juveniles with the wild strain is generated when latently-infected juveniles with the wild strain develop clinical symptoms of malaria (at the rate σ_{JW}). It is decreased by treatment (at a rate τ_J), maturation to adulthood (at the rate ξ), natural recovery (at a rate γ_J), natural death and disease-induced death (at a rate δ_J). Hence,

$$\frac{dI_{JW}}{dt} = \sigma_{JW} E_{JW} - (\tau_J + \xi + \gamma_J + \mu_H + \delta_J) I_{JW}. \tag{4.9}$$

The population of symptomatic juveniles with the resistant strain is generated by the development of malaria symptoms by latently-infected juveniles with the resistant strain (at the rate σ_{JR}) and by the development of resistance by treated symptomatic juveniles (at a rate $(1 - f_J)\tau_J$, where $0 < f_J < 1$ is the fraction of symptomatic juveniles who are effectively-treated). It is decreased by maturation (at the rate ξ), recovery (at a rate $\phi_1 \gamma_J$, where $\phi_1 > 0$ is a modification parameter accounting for the possible variability of the recovery rate of symptomatic juveniles with the resistant strain in comparison to symptomatic juveniles with the wild strain), natural

death and disease-induced death (at a rate $\theta_1\delta_J$, where $\theta_1 > 0$ is a modification parameter accounting for the possible variability of the mortality rate of symptomatic juveniles with the resistant strain in comparison to symptomatic juveniles with the wild strain). Hence,

$$\frac{dI_{JR}}{dt} = \sigma_{JR}E_{JR} + (1 - f_J)\tau_J I_{JW} - (\xi + \phi_1\gamma_J + \mu_H + \theta_1\delta_J)I_{JR}. \tag{4.10}$$

Similarly, the population of symptomatic adults with the wild strain is generated at the rates ξ and σ_{AW}, and reduced by treatment (at the rate τ_A), natural recovery (at a rate γ_A), natural death and disease-induced death (at a rate δ_A), so that (it should be mentioned that $\delta_J > \delta_A$, since malaria mortality rate is higher in children than in adults [14, 69]),

$$\frac{dI_{AW}}{dt} = \xi I_{JW} + \sigma_{AW}E_{AW} - (\tau_A + \gamma_A + \mu_H + \delta_A)I_{AW}. \tag{4.11}$$

Furthermore, the population of symptomatic adults with the resistant strain is generated at the rates ξ, σ_{AR} and $(1 - f_A)\tau_A$, and reduced by recovery (at a rate $\phi_2\gamma_A$, where $\phi_2 > 0$ is a modification parameter accounting for the possible variability of the recovery rate of symptomatic adults with the resistant strain in comparison to symptomatic adults with the wild strain), natural death and disease-induced death (at a rate $\theta_2\delta_A$, where $\theta_2 > 0$ is a modification parameter accounting for the possible variability of the mortality rate of symptomatic adults with the resistant strain in comparison to those with the wild strain), so that,

$$\frac{dI_{AR}}{dt} = \xi I_{JR} + \sigma_{AR}E_{AR} + (1 - f_A)\tau_A I_{AW} - (\phi_2\gamma_A + \mu_H + \theta_2\delta_A)I_{AR}. \tag{4.12}$$

The population of effectively-treated juveniles is generated at the rate $f_J\tau_J$, and decreased by maturation (at the rate ξ), recovery (at an increased rate $\phi_3\gamma_J$, where $\phi_3 > 1$ is a modification parameter accounting for the assumed increase in the recovery rate of treated juveniles in comparison to the recovery rate of untreated symptomatic juveniles [60]), natural death and disease-induced death (at a rate $\theta_3\delta_J$, where $\theta_3 < 1$ is a modification parameter accounting for the assumed reduction in mortality rate of treated symptomatic juveniles with the wild strain in comparison to untreated symptomatic juveniles [60]), so that,

$$\frac{dT_J}{dt} = f_J\tau_J I_{JW} - (\xi + \phi_3\gamma_J + \mu_H + \theta_3\delta_J)T_J. \tag{4.13}$$

Similarly, the population of effectively-treated adults is generated at a rate $f_A\tau_A$ and by the maturation of treated juveniles (at the rate ξ). It is decreased by recovery (at a rate $\phi_4\gamma_A$, where $\phi_4 > 1$ is a modification parameter accounting for the assumed increase in the recovery rate of treated symptomatic adults with the wild strain in comparison to untreated symptomatic adults), natural death and disease-induced death (at a rate $\theta_4\delta_A$, where $\theta_4 < 1$ is a modification parameter accounting for the reduced mortality rate of treated adults in comparison to untreated symptomatic adults). Thus,

$$\frac{dT_A}{dt} = f_A\tau_A I_{AW} + \xi T_J - (\phi_4\gamma_A + \mu_H + \theta_4\delta_A)T_A. \tag{4.14}$$

The population of recovered juveniles is generated by the recovery of symptomatic juveniles with the wild strain, resistant strain and effectively-treated juveniles (at the rates γ_J, $\phi_1\gamma_J$ and $\phi_3\gamma_J$, respectively). This population is decreased by the loss of infection-acquired immunity (at the rate ψ_J), maturation (at the rate ξ) and natural

death. Thus,

$$\frac{dR_J}{dt} = \gamma_J I_{JW} + \phi_1 \gamma_J I_{JR} + \phi_3 \gamma_J T_J - (\psi_J + \xi + \mu_H) R_J. \tag{4.15}$$

Similarly, the population of recovered adults is generated by the maturation of recovered juveniles (at the rate ξ), recovery of symptomatic adults with the wild and resistant strains as well as the recovery of effectively-treated individuals (at the γ_A, $\phi_2\gamma_A$ and $\phi_4\gamma_A$, respectively). It is decreased by the loss of infection-acquired immunity (at the rate ψ_J) and natural death. Thus,

$$\frac{dR_A}{dt} = \xi R_J + \gamma_A I_{AW} + \phi_2 \gamma_A I_{AR} + \phi_4 \gamma_A T_A - (\psi_A + \mu_H) R_A. \tag{4.16}$$

The population of susceptible mosquitoes is generated by the birth of adult mosquitoes (at a *per capita* rate Π_V). It is reduced by infection, following effective contacts with infected humans, at a rate λ_V, where

$$\lambda_V = \frac{\beta_V b_2(N_V, N_H)[I_{JW} + I_{AW} + \eta_R(I_{JR} + I_{AR})]}{N_H}. \tag{4.17}$$

In (4.17), β_V is the probability of infection of a susceptible mosquito *per* bite on an infected human and $b_2(N_V, N_H)$ is *per capita* biting rate of susceptible mosquitoes on infected humans. Furthermore, the parameter $\eta_R > 0$ accounts for the possible variability of the infectiousness of symptomatic humans with the resistant strain in comparison to symptomatic humans with the wild strain. This population is further decreased by natural death (at a rate μ_V). Hence,

$$\frac{dS_V}{dt} = \Pi_V - \lambda_V S_V - \mu_V S_V. \tag{4.18}$$

The population of infected mosquitoes with the wild strain is generated by the infection of susceptible mosquitoes with the wild strain (at the rate $\beta_V b_2(N_V, N_H)$) and decreased by natural death (at the rate μ_V). Thus,

$$\frac{dV_W}{dt} = \frac{\beta_V b_2(N_V, N_H)(I_{JW} + I_{AW})}{N_H} S_V - \mu_V V_W. \tag{4.19}$$

Similarly, the population of infected mosquitoes with the resistant strain is generated by the infection of susceptible mosquitoes with the resistant strain (at the rate $\eta_R \beta_V b_2(N_V, N_H)$) and decreased by natural death (at the rate μ_V). Thus,

$$\frac{dV_R}{dt} = \frac{\eta_R \beta_V b_2(N_V, N_H)(I_{JR} + I_{AR})}{N_H} S_V - \mu_V V_R. \tag{4.20}$$

As in Chapter 3, the following conservation law of mosquito bites must hold:

$$b_2 N_V = b_1(N_V, N_H) N_H, \tag{4.21}$$

so that,

$$N_V = \frac{b_1(N_V, N_H) N_H}{b_2}. \tag{4.22}$$

It follows, based on the above derivations and assumptions, and using (4.1) and (4.3)

with (4.22) in $\{(4.2), (4.4), (4.5), (4.6), (4.7), (4.8)\}$, that the age-structured model for the transmission dynamics of the wild and resistant strains of malaria in a community is given by the following deterministic system of non-linear differential equations (flow diagrams of the model are depicted in Figures 4.1 and 4.2, and the state variables and parameters of the model are described in Tables 4.1 and 4.2, respectively):

$$
\begin{aligned}
\frac{dS_J}{dt} &= \Pi_J + \psi_J R_J - \frac{\beta_J b_2 (V_W + \theta_R V_R)}{N_H} S_J - (\xi + \mu_H) S_J, \\
\frac{dS_A}{dt} &= \xi S_J + \psi_A R_A - \frac{\beta_A b_2 (V_W + \theta_R V_R)}{N_H} S_A - \mu_H S_A, \\
\frac{dE_{JW}}{dt} &= \frac{\beta_J b_2 V_W}{N_H} S_J - (\sigma_{JW} + \xi + \mu_H) E_{JW}, \\
\frac{dE_{JR}}{dt} &= \frac{\theta_R \beta_J b_2 V_R}{N_H} S_J - (\sigma_{JR} + \xi + \mu_H) E_{JR}, \\
\frac{dE_{AW}}{dt} &= \xi E_{JW} + \frac{\beta_A b_2 V_W}{N_H} S_A - (\sigma_{AW} + \mu_H) E_{AW}, \\
\frac{dE_{AR}}{dt} &= \xi E_{JR} + \frac{\theta_R \beta_A b_2 V_R}{N_H} S_A - (\sigma_{AR} + \mu_H) E_{AR}, \\
\frac{dI_{JW}}{dt} &= \sigma_{JW} E_{JW} - (\tau_J + \xi + \gamma_J + \mu_H + \delta_J) I_{JW}, \\
\frac{dI_{JR}}{dt} &= \sigma_{JR} E_{JR} + (1 - f_J) \tau_J I_{JW} - (\xi + \phi_1 \gamma_J + \mu_H + \theta_1 \delta_J) I_{JR}, \\
\frac{dI_{AW}}{dt} &= \xi I_{JW} + \sigma_{AW} E_{AW} - (\tau_A + \gamma_A + \mu_H + \delta_A) I_{AW}, \\
\frac{dI_{AR}}{dt} &= \sigma_{AR} E_{AR} + \xi I_{JR} + (1 - f_A) \tau_A I_{AW} - (\phi_2 \gamma_A + \mu_H + \theta_2 \delta_A) I_{AR}, \\
\frac{dT_J}{dt} &= f_J \tau_J I_{JW} - (\xi + \phi_3 \gamma_J + \mu_H + \theta_3 \delta_J) T_J, \\
\frac{dT_A}{dt} &= \xi T_J + f_A \tau_A I_{AW} - (\phi_4 \gamma_A + \mu_H + \theta_4 \delta_A) T_A, \\
\frac{dR_J}{dt} &= \gamma_J I_{JW} + \phi_1 \gamma_J I_{JR} + \phi_3 \gamma_J T_J - (\psi_J + \xi + \mu_H) R_J, \\
\frac{dR_A}{dt} &= \xi R_J + \gamma_A I_{AW} + \phi_2 \gamma_A I_{AR} + \phi_4 \gamma_A T_A - (\psi_A + \mu_H) R_A, \\
\frac{dS_V}{dt} &= \Pi_V - \frac{\beta_V b_2 [I_{JW} + I_{AW} + \eta_R (I_{JR} + I_{AR})]}{N_H} S_V - \mu_V S_V, \\
\frac{dV_W}{dt} &= \frac{\beta_V b_2 (I_{JW} + I_{AW})}{N_H} S_V - \mu_V V_W,
\end{aligned}
\tag{4.23}
$$

$$\frac{dV_R}{dt} = \frac{\eta_R \beta_V b_2 (I_{JR} + I_{AR})}{N_H} S_V - \mu_V V_R.$$

The two-strain age-structured malaria model (4.23) is an extension of the single-strain age-structured malaria model (3.16), developed in Chapter 3, by including:

(i) the dynamics of the wild and resistant strains for humans and vectors (single malaria strain was considered in the model (3.16));

(ii) compartments for treated individuals (T_J and T_A).

Furthermore, the model (4.23) extends the two-strain malaria model in [23] by:

(i) adding age-structure (i.e., the dynamics of juveniles and adults in the community);

(ii) adding the dynamics of exposed individuals;

(iii) adding the dynamics of recovered individuals.

The objective of this chapter is to address the following main questions:

(a) What are the main qualitative features of the two-strain age-structured malaria model (4.23)?

(b) In particular, under what conditions can the disease persist, or be effectively-controlled (or eliminated), from the community?

4.2.1 Basic properties

The following two results can be established using the approach in Appendix A and Section 3.2.1.

Theorem 4.1. *Let the initial data be* $S_J(0) > 0$, $S_A(0) > 0$, $E_{JW}(0) \geq 0$, $E_{JR}(0) \geq 0$, $E_{AW}(0) \geq 0$, $E_{AR}(0) \geq 0$, $I_{JW}(0) \geq 0$, $I_{JR}(0) \geq 0$ $I_{AW}(0) \geq 0$, $I_{AR}(0) \geq 0$, $R_J(0) \geq 0$, $R_A(0) \geq 0$, $T_J(0) \geq 0$, $T_A(0) \geq 0$, $S_V(0) > 0$ *and* $V_W(0) \geq 0$, $V_R(0) \geq 0$. *Then the solutions* $(S_J(t), S_A(t), E_{JW}(t), E_{JR}(t), E_{AW}(t), E_{AR}(t), I_{JW}(t), I_{JR}(t), I_{AW}(t), I_{AR}(t), R_J(t), R_A(t), T_J(t), T_A(t), S_V(t), V_W(t), V_R(t))$ *of the model (4.23), with positive initial data, will remain positive for all time* $t > 0$.

Lemma 4.1. *The closed set*

$$\mathcal{D} = \{(S_J, S_A, E_{JW}, E_{JR}, E_{AW}, E_{AR}, I_{JW}, I_{JR}, I_{AW}, I_{AR}, R_J, R_A, S_V, V_W, V_R) \in \mathbb{R}_+^{17} : N_H \leq \frac{\Pi_J}{\mu_H}, N_V \leq \frac{\Pi_V}{\mu_H}\} \tag{4.24}$$

is positively-invariant and attracting for the model (4.23).

4.3 Stability of DFE

The DFE of the two-strain model (4.23) is given by,

$$\mathcal{E}_{0T} = (S_J^*, S_A^*, E_{JW}^*, E_{JR}^*, E_{AW}^*, E_{AR}^*, I_{JW}^*, I_{JR}^*, I_{AW}^*, I_{AR}^*, T_J^*, T_A^*, R_J^*, R_A^*, S_V^*, V_W^*, V_R^*)$$

$$= \left(\frac{\Pi_J}{(\xi + \mu_H)}, \frac{\xi \Pi_J}{\mu_H(\xi + \mu_H)}, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, \frac{\Pi_V}{\mu_V}, 0, 0\right).$$

The associated non-negative matrix $\mathcal{F}$ (of new infection terms) and the matrix $\mathcal{V}$ (of the transition terms) are given, respectively, by:

$$
\mathcal{F} = \begin{bmatrix}
0\,0\,0\,0 & 0 & 0 & 0 & 0 & 0\,0 & \dfrac{b_2\beta_J S_J^*}{N_H^*} & 0 \\
0\,0\,0\,0 & 0 & 0 & 0 & 0 & 0\,0 & 0 & \dfrac{\theta_R b_2\beta_J S_J^*}{N_H^*} \\
0\,0\,0\,0 & 0 & 0 & 0 & 0 & 0\,0 & \dfrac{b_2\beta_A S_A^*}{N_H^*} & 0 \\
0\,0\,0\,0 & 0 & 0 & 0 & 0 & 0\,0 & 0 & \dfrac{\theta_R b_2\beta_A S_A^*}{N_H^*} \\
0\,0\,0\,0 & 0 & 0 & 0 & 0 & 0\,0 & 0 & 0 \\
0\,0\,0\,0 & 0 & 0 & 0 & 0 & 0\,0 & 0 & 0 \\
0\,0\,0\,0 & 0 & 0 & 0 & 0 & 0\,0 & 0 & 0 \\
0\,0\,0\,0 & 0 & 0 & 0 & 0 & 0\,0 & 0 & 0 \\
0\,0\,0\,0 & 0 & 0 & 0 & 0 & 0\,0 & 0 & 0 \\
0\,0\,0\,0 & 0 & 0 & 0 & 0 & 0\,0 & 0 & 0 \\
0\,0\,0\,0 & \dfrac{b_2\beta_V S_V^*}{N_H^*} & 0 & \dfrac{b_2\beta_V S_V^*}{N_H^*} & 0 & 0\,0 & 0 & 0 \\
0\,0\,0\,0 & 0 & \dfrac{\eta_R b_2\beta_V S_V^*}{N_H^*} & 0 & \dfrac{\eta_R b_2\beta_V S_V^*}{N_H^*} & 0\,0 & 0 & 0
\end{bmatrix},
$$

and,

$$
\mathcal{V} = \begin{bmatrix}
g_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & g_3 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
-\xi & 0 & g_4 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & -\xi & 0 & g_5 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
-\sigma_{JW} & 0 & 0 & 0 & g_6 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & -\sigma_{JR} & 0 & 0 & -(1-f_J)\tau_J & g_7 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & -\sigma_{AW} & 0 & -\xi & 0 & g_8 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & -\sigma_{AR} & 0 & -\xi & -(1-f_A)\tau_A & g_9 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & -f_J\tau_J & 0 & 0 & 0 & g_{10} & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & -f_A\tau_A & 0 & -\xi & g_{11} & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \mu_V & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \mu_V
\end{bmatrix},
$$

where, $g_1 = \xi + \mu_H$, $g_2 = \sigma_{JW} + \xi + \mu_H$, $g_3 = \sigma_{JR} + \xi + \mu_H$, $g_4 = \sigma_{AW} + \mu_H$, $g_5 = \sigma_{AR} + \mu_H$, $g_6 = \tau_J + \xi + \gamma_J + \mu_H + \delta_J$, $g_7 = \xi + \phi_1\gamma_J + \mu_H + \theta_1\delta_J$, $g_8 = \tau_A + \gamma_A + \mu_H + \delta_A$, $g_9 = \phi_2\gamma_A + \mu_H + \theta_2\delta_A$, $g_{10} = \xi + \phi_3\gamma_J + \mu_H + \theta_3\delta_J$, $g_{11} = \phi_4\gamma_A + \mu_H + \theta_4\delta_A$, $g_{12} = \psi_J + \xi + \mu_H$, $g_{13} = \psi_A + \mu_H$ and $N_H^* = \dfrac{\Pi_J}{\mu_H}$.

The reproduction number, associated with the DFE ($\mathcal{E}_{0T}$) of the model (4.23), denoted by $\mathcal{R}_T$, is then given by $\mathcal{R}_T = \rho(\mathcal{F}\mathcal{V}^{-1})$. It follows from [65] that $\mathcal{R}_T = \max\{\mathcal{R}_W, \mathcal{R}_R\}$, where

$$\mathcal{R}_W = \sqrt{\frac{b_2^2\beta_V\Pi_V\mu_H\{\beta_J\mu_H[\sigma_{JW}g_4(g_8+\xi)+\sigma_{AW}\xi g_6]+\beta_A\sigma_{AW}\xi g_2 g_6\}}{\Pi_J\mu_V^2 g_1 g_2 g_4 g_6 g_8}}, \tag{4.25}$$

and,

$$\mathcal{R}_R = \sqrt{\frac{b_2^2\beta_V\Pi_V\theta_R\eta_R\mu_H\{\beta_J\mu_H[\sigma_{JR}g_5(g_9+\xi)+\sigma_{AR}\xi g_7]+\beta_A\sigma_{AR}\xi g_3 g_7\}}{\Pi_J\mu_V^2 g_1 g_3 g_5 g_7 g_9}}. \tag{4.26}$$

The threshold quantity, $\mathcal{R}_T$, represents the average number of new malaria infections generated by a single infected individual (or infected mosquito) in a completely-susceptible population. The result below follows from Theorem 2 in [65].

Lemma 4.2. *The DFE, $\mathcal{E}_{0T}$, of the model (4.23) is LAS if $\mathcal{R}_T < 1$, and unstable if $\mathcal{R}_T > 1$.*

In the absence of treatment (i.e., $\tau_1 = \tau_2$=0), $\mathcal{R}_T$ reduces to $\mathcal{R}_{0T} = \mathcal{R}_T \mid_{\tau_1=\tau_2=0}=$ $\max\{\mathcal{R}_{0W}, \mathcal{R}_{0R}\}$, where,

$$\mathcal{R}_{0W} = \sqrt{\frac{b_2^2\beta_V\Pi_V\mu_H\{\beta_J\mu_H[\sigma_{JW}g_4(g_{08}+\xi)+\sigma_{AW}\xi g_{06}]+\beta_A\sigma_{AW}\xi g_2 g_{06}\}}{\Pi_J\mu_V^2 g_1 g_2 g_4 g_{06} g_{08}}}, \tag{4.27}$$

and,

$$\mathcal{R}_{0R} = \sqrt{\frac{b_2^2\beta_V\Pi_V\theta_R\eta_R\mu_H\{\beta_J\mu_H[\sigma_{JR}g_5(g_9+\xi)+\sigma_{AR}\xi g_7]+\beta_A\sigma_{AR}\xi g_3 g_7\}}{\Pi_J\mu_V^2 g_1 g_3 g_5 g_7 g_9}}, \tag{4.28}$$

with, $g_{06} = \xi + \gamma_J + \mu_H + \delta_J$ and $g_{08} = \gamma_A + \mu_H + \delta_A$. It is worth stating that the quantity $\mathcal{R}_{0T}$, defined above, is the same as the reproduction number ($\mathcal{R}_0$) for the single-strain, treatment-free, age-structured model (3.27), given by (3.28). It should

be recalled that, as in the model (4.23), no transmission by exposed individuals was assumed in the model (3.27). That is, the parameter η is set to zero in both models.

4.3.1 Backward bifurcation

Theorem 4.2. *The two-strain model* (4.23) *undergoes backward bifurcation at* $\mathcal{R}_T = 1$ *whenever the Inequality (E-3), given in Appendix E, holds.*

The proof of Theorem 4.2, based on using Centre Manifold theory, is given in Appendix E. Thus, like the single strain model (3.16), the two-strain model (4.23) also undergoes backward bifurcation (under certain conditions).

Non-existence of backward bifurcation

As in Chapter 3, consider the model (4.23) with the associated disease-induced mortality rates, δ_J and δ_A, set to zero. This gives:

$$\frac{dN_H(t)}{dt} = \Pi_J - \mu_H N_H(t),$$

so that $N_H(t) \to \frac{\Pi_J}{\mu_H}$ as $t \to \infty$. It can be shown, by substituting $N_H^* = \frac{\Pi_J}{\mu_H}$ into the model (4.23), that the associated bifurcation coefficient, a, given by equation (E-2) in Appendix E, reduces to

$$a = \frac{2b_2\mu_H}{\Pi_J}\{\beta_J\theta_R w_1 v_4 w_{17} + \beta_A\theta_R w_2 v_6 w_{17} + \beta_V[w_{15}v_{17}\eta(w_8 + w_{10})]\} < 0, \qquad (4.29)$$

where w_1, w_2, w_8, w_{10}, w_{15}, w_{17}, v_4, v_6 and v_{17} are eigenvectors of the linearized system of the model (4.23), and are defined in Appendix E (noting that the eigenvectors w_1, w_2 and w_{15} are negative). Hence, these analyses show, as in Chapter 3, that the two-strain model (4.23) does not undergo backward bifurcation in the absence of malaria-induced mortality in humans.

4.3.2 Global asymptotic stability of DFE: special case

The absence of backward bifurcation in (4.23) when $\delta_J = \delta_A = 0$ suggests that the DFE of the model (4.23) may be globally-asymptotically stable under this setting. Let $\delta_J = \delta_A = 0$. Furthermore, for mathematical convenience, let $\psi_J = \psi_A = 0$ (that is, a special case of the two-strain model (4.23), in the absence of mortality in humans ($\delta_J = \delta_A = 0$) and loss of infection-acquired immunity ($\psi_J = \psi_A = 0$), is considered). Define:

$$\begin{aligned}\mathcal{D}_1 =& \{(S_J, S_A, E_{JW}, E_{JR}, E_{AW}, E_{AR}, I_{JW}, I_{JR}, I_{AW}, I_{AR}, T_J, T_A, R_J, R_A, S_V, V_W, V_R) \\ & \in \mathcal{D} : S_J \leq S_J^*, S_A \leq S_A^*, S_V \leq S_V^*\}.\end{aligned} \tag{4.30}$$

The following result can be shown (using, for example, the approach in Section 3.3.3).

Lemma 4.3. *The region $\mathcal{D}_1$ is positively-invariant for the model (4.23) with $\delta_J = \delta_A = \psi_J = \psi_A = 0$.*

We claim the following.

Theorem 4.3. *The DFE, $\mathcal{E}_{0T}$, of the model (4.23), with $\delta_J = \delta_A = \psi_J = \psi_A = 0$, is GAS in $\mathcal{D}_1$ whenever $\tilde{\mathcal{R}}_T = \mathcal{R}_T \mid_{\delta_J = \delta_A = 0} < 1$.*

The proof of Theorem 4.3 is given in Appendix F. The epidemiological consequence of Theorem 4.3 is that malaria will be effectively-controlled (or eliminated) from the community if the associated reproduction threshold ($\tilde{\mathcal{R}}_T$) can be brought to (and maintained at) a value less than unity. In other words, this study shows that if the use of anti-malaria drugs in the community can lead to $\tilde{\mathcal{R}}_T < 1$, then malaria can be effectively-controlled (or eliminated) from the community. Figure 4.3 depicts the solution profiles of the model (4.23) for the case when $\tilde{\mathcal{R}}_T < 1$, showing convergence to the DFE ($\mathcal{E}_{0T}$) (in line with Theorem 4.3).

4.4 Existence and Stability of Boundary and Endemic Equilibria: Special Case

In this section, conditions for the existence of positive equilibria of the model (4.23) will be explored for the special case with no disease-induced mortality ($\delta_J = \delta_A = 0$). The possible non-trivial equilibria of the model (4.23), with $\delta_J = \delta_A = 0$, are:

(i) resistant strain-only boundary equilibrium (an equilibrium of model (4.23) in the absence of the wild strain in the community), denoted by $\mathcal{E}_R$;

(ii) low-endemicity equilibrium (an endemic equilibrium of model (4.23) for the case where the resistant strain is not transmitted), denoted by $\mathcal{E}_L$;

(iii) high-endemicity equilibrium (an equilibrium of model (4.23) where both the wild and resistant strains are transmitted in the community), denoted by $\mathcal{E}_H$.

It is worth stating that, unlike in other models for the dynamics of two strains of a disease in a certain population (such as some models reported in [56]), the two-strain model (4.23) does not have a wild strain-only boundary equilibrium (i.e., an equilibrium with the wild strain only). This is due to the fact that two infected classes, I_{JR} and I_{AR}, are never zero (asymptotically) in the absence of the resistant strain (since $f_J \neq 1$ and $f_A \neq 1$; which also equivalent to $\tau_J \neq 0$ and $\tau_A \neq 0$). Such a wild strain-only boundary equilibrium is only feasible if treated individuals do not develop resistance (so that $f_J = f_A = 1$), or if anti-malaria drug treatment is not administered in the community (i.e., $\tau_J = \tau_A = 0$).

4.4.1 Resistant-strain-only boundary equilibrium

Let,

$$\mathcal{E}_R = (S_J^{**}, S_A^{**}, E_{JW}^{**}, E_{AW}^{**}, E_{JR}^{**}, E_{AR}^{**}, I_{JW}^{**}, I_{AW}^{**}, I_{JR}^{**}, I_{AR}^{**}, T_J^{**}, T_A^{**}, R_J^{**}, R_A^{**}, S_V^{**}, V_W^{**},$$
$$V_R^{**}) = (S_J^{**}, S_A^{**}, 0, E_{JR}^{**}, 0, E_{AR}^{**}, 0, I_{JR}^{**}, 0, I_{AR}^{**}, 0, 0, R_J^{**}, R_A^{**}, S_V^{**}, 0, V_R^{**}),$$

represents a resistant strain-only boundary equilibrium of the model (4.23) (i.e., an equilibrium of the model (4.23) in the absence of the wild strain). To investigate the existence of the boundary equilibrium $\mathcal{E}_R$, a special case of the model (4.23) with $\delta_J = \delta_A = 0$ is considered (this assumption is made to ensure mathematical tractability of the ensuing algebraic manipulation). In the absence of the wild strain, the model (4.23), with $\delta_J = \delta_A = 0$, reduces to the following resistant strain-only age-structured system:

$$\begin{aligned}
\frac{dS_J}{dt} &= \Pi_J + \psi_J R_J - \frac{\mu_H b_2 \beta_J \theta_R V_R}{\Pi_J} S_J - (\xi + \mu_H) S_J, \\
\frac{dS_A}{dt} &= \xi S_J + \psi_A R_A - \frac{\mu_H b_2 \beta_A \theta_R V_R}{\Pi_J} S_A - \mu_H S_A, \\
\frac{dE_{JR}}{dt} &= \frac{\mu_H b_2 \beta_J \theta_R V_R}{\Pi_J} S_J - (\sigma_{JR} + \xi + \mu_H) E_{JR}, \\
\frac{dE_{AR}}{dt} &= \xi E_{JR} + \frac{\mu_H b_2 \beta_A \theta_R V_R}{\Pi_J} S_A - (\sigma_{AR} + \mu_H) E_{AR}, \\
\frac{dI_{JR}}{dt} &= \sigma_{JR} E_{JR} - (\xi + \phi_1 \gamma_J + \mu_H) I_{JR}, \\
\frac{dI_{AR}}{dt} &= \xi I_{JR} + \sigma_{AR} E_{AR} - (\phi_2 \gamma_A + \mu_H) I_{AR}, \\
\frac{dR_J}{dt} &= \phi_1 \gamma_J I_{JR} - (\xi + \mu_H + \psi_J) R_J, \\
\frac{dR_A}{dt} &= \xi R_J + \phi_2 \gamma_A I_{AR} - (\mu_H + \psi_A) R_A, \\
\frac{dS_V}{dt} &= \Pi_V - \frac{\mu_H b_2 \beta_V \eta_R (I_{JR} + I_{AR})}{\Pi_J} S_V - \mu_V S_V, \\
\frac{dV_R}{dt} &= \frac{\mu_H b_2 \beta_V \eta_R (I_{JR} + I_{AR})}{\Pi_J} S_V - \mu_V I_V.
\end{aligned} \tag{4.31}$$

The reproduction number of the resistant strain-only age-structured model (4.31) is given by

$$\tilde{\mathcal{R}}_R = \sqrt{\frac{b_2^2\beta_V\Pi_V\theta_R\eta_R\mu_H\{\beta_J\mu_H[\sigma_{JR}g_5(g_9+\xi)+\sigma_{AR}\xi g_7]+\beta_A\sigma_{AR}\xi g_3 g_7\}}{\Pi_J\mu_V^2 g_1 g_3 g_5 g_7 g_9}}, \quad (4.32)$$

where, now, $g_1 = \xi + \mu_H, g_3 = \sigma_{JR} + \xi + \mu_H$, $g_5 = \sigma_{AR} + \mu_H$, $g_7 = \xi + \phi_1\gamma_J + \mu_H$ and $g_9 = \phi_2\gamma_A + \mu_H$. It is convenient to let

$$\lambda_{JR}^{**} = \frac{\mu_H b_2\beta_J\theta_R V_R^{**}}{\Pi_J}, \quad \lambda_{AR}^{**} = \frac{\mu_H b_2\beta_A\theta_R V_R^{**}}{\Pi_J} \quad \text{and} \quad \lambda_{VR}^{**} = \frac{\mu_H b_2\beta_V\theta_R(I_{JR}^{**}+I_{AR}^{**})}{\Pi_J}. \quad (4.33)$$

Solving the equations of the resistant strain-only model (4.31) at steady-state gives:

$$\begin{aligned}
S_{HJ}^{**} &= \frac{g_3 g_7 g_{12}\Pi_J}{g_1\{[\sigma_{JR}(\phi_1\gamma_J+g_{12})+g_7 g_{12}]\lambda_{JR}^{**}+g_3 g_7 g_{12}\}},\\
E_{HJ}^{**} &= \frac{g_7 g_{12}\Pi_J\lambda_{JR}^{**}}{g_1\{[\sigma_{JR}(\phi_1\gamma_J+g_{12})+g_7 g_{12}]\lambda_{JR}^{**}+g_3 g_7 g_{12}\}},\\
R_{HJ}^{**} &= \frac{\sigma_{JR}\phi_1\gamma_J\Pi_J\lambda_{JR}^{**}}{g_1\{[\sigma_{JR}(\phi_1\gamma_J+g_{12})+g_7 g_{12}]\lambda_{JR}^{**}+g_3 g_7 g_{12}\}},\\
I_{HJ}^{**} &= \frac{\sigma_{JR}\lambda_{JR}^{**}g_{12}\Pi_J}{g_1\{[\sigma_{JR}(\phi_1\gamma_J+g_{12})+g_7 g_{12}]\lambda_{JR}^{**}+g_3 g_7 g_{12}\}},
\end{aligned}$$

$$S_{HA}^{**} = \frac{\xi S_{HJ}^{**}+\psi_A R_{HA}^{**}}{\lambda_{AR}^{**}+\mu_H},$$

$$E_{HA}^{**} = \frac{\xi\Pi_J\lambda_{JR}^{**}\{\beta_A\lambda_{JR}^{**}[\psi_A\sigma_{JR}(\phi_1\gamma_J g_9+\phi_2\gamma_A g_{12})+q_0]+q_0(\beta_A g_3+\beta_J\mu_H)\}}{g_1\mu_H q_1 q_2},$$

$$I_{HA}^{**} = \frac{\xi\Pi_J\lambda_{JR}^{**}\{\beta_A\lambda_{JR}^{**}[g_{12}g_{13}(\sigma_{AR}g_7+\sigma_{JR}g_5)+\sigma_{AR}\sigma_{JR}\phi_1\gamma_J\psi_A]+q_3\}}{g_1\mu_H q_1 q_2}, \quad (4.34)$$

$$R_{HA}^{**} = \frac{\xi \Pi_J \lambda_{JR}^{**}\{\beta_A \lambda_{JR}^{**}[g_7 g_{12} \sigma_{AR} \phi_2 \gamma_A + \sigma_{JR} g_5 (g_{12} \phi_2 \gamma_A + g_9 \phi_1 \gamma_J)] + q_4\}}{g_1 \mu_H q_1 q_2},$$

$$S_V^{**} = \frac{\Pi_V}{\lambda_{VR}^{**} + \mu_V}, \quad I_V^{**} = \frac{\lambda_{VR}^{**} \Pi_V}{\mu_V(\lambda_{VR}^{**} + \mu_V)},$$

where,

$$q_0 = g_7 g_9 g_{12} g_{13},$$

$$q_1 = [\sigma_{JR}(\phi_1 \gamma_J + g_{12}) + g_7 g_{12}]\lambda_{JR}^{**} + g_3 g_7 g_{12},$$

$$q_2 = \beta_A \lambda_{JR}^{**}[\sigma_{AR}(\phi_2 \gamma_A + g_{13}) + g_9 g_{13}] + g_5 g_9 g_{13} \beta_J,$$

$$q_3 = g_{12} g_{13}[\beta_J \mu_H (\sigma_{AR} g_7 + \sigma_{JR} g_5) + g_3 g_7 \sigma_{AR} \beta_A],$$

$$q_4 = g_7 g_{12} \sigma_{AR} \phi_2 \gamma_A (\beta_A g_3 + \beta_J \mu_H) + g_5 \sigma_{JR} \beta_J \mu_H (g_{12} \phi_2 \gamma_A + g_9 \phi_1 \gamma_J),$$

with, $g_1 = \xi + \mu_H$, $g_3 = \sigma_{JR} + \xi + \mu_H$, $g_5 = \sigma_{AR} + \mu_H$, $g_7 = \xi + \phi_1 \gamma_J + \mu_H$, $g_9 = \phi_2 \gamma_A + \mu_H$, $g_{12} = \xi + \mu_H + \psi_J$ and $g_{13} = \mu_H + \psi_A$.

Substituting the expressions for I_{JR}^{**} and I_{AR}^{**} in (4.34) into the equation for λ_{VR}^{**} in (4.33), and simplifying, gives

$$\lambda_V^{**} = \frac{\Pi_J \lambda_{JR}^{**}(a_0 \lambda_{JR}^{**} + a_1)}{M_1}, \tag{4.35}$$

where,

$$a_0 = \beta_A\{\sigma_{JR} \mu_H g_{12}[\sigma_{HA}(\phi_2 \gamma_A + g_{13}) + g_9 g_{13}] + \sigma_{AR} \xi (\sigma_{JR} \phi_1 \gamma_J \psi_A + g_7 g_{12} g_{13})\},$$

$$a_1 = g_{12} g_{13}\{\beta_J \mu_H [\sigma_{JR} g_5 (g_9 + \xi) + \sigma_{AR} \xi g_7] + \sigma_{AR} \beta_A \xi g_3 g_7\}.$$

Furthermore, substituting the equation for I_V^{**} in (4.34) into the equation for λ_{JR}^{**} in (4.33) gives

$$\lambda_{JR}^{**} = \frac{\mu_H b_2 \beta_J \Pi_V \lambda_V^{**}}{\Pi_J \mu_V (\lambda_V^{**} + \mu_V)}. \tag{4.36}$$

Finally, solving for λ_{VR}^{**} from (4.36) and substituting the result into (4.35), and simplifying, shows that the non-zero equilibria of the resistant strain-only model (4.31) satisfy the following quadratic (in terms of λ_{JR}^{**})

$$c_0(\lambda_{JR}^{**})^2 + c_1 \lambda_{JR}^{**} + c_2 = 0, \tag{4.37}$$

where,

$$\begin{aligned}
c_0 &= \Pi_J b_2 \beta_V \beta_A \mu_H \mu_V \xi [\sigma_{JR} \sigma_{AR} \gamma_J \psi_A + g_{12} g_{13} (g_5 \sigma_{JR} + g_7 \sigma_{AR})] \\
&\quad + \Pi_J \beta_A \mu_H \mu_V [\sigma_{AR} (\phi_2 \gamma_A + g_{12}) + g_9 g_{12}] \\
&\quad \{b_2 \beta_V \sigma_{JR} \mu_H g_{12} + \mu_V g_1 [\sigma_{JR} (\phi_1 \gamma_J + g_{12}) + g_7 g_{12}]\}, \\
c_2 &= \beta_J \mu_H g_{12} g_{13} (\Pi_J \mu_V^2 g_1 g_3 g_7 g_9)[1 - (\tilde{\mathcal{R}}_R)^2].
\end{aligned}$$

Hence, as in Chapter 3, the following result is obtained.

Theorem 4.4. *The resistant strain-only model (4.31) has a unique positive equilibrium if* $\tilde{\mathcal{R}}_R > 1$.

4.4.2 Low-endemicity equilibrium

In the absence of malaria transmission by individuals or vectors infected with the resistant strain (i.e., $\lambda_{JR} = \lambda_{AR} = \lambda_{VR} = 0$), the model (4.23) has endemic equilibria (low-endemicity equilibria) of the general form:

$$\mathcal{E}_L = (S_J^{**}, S_A^{**}, E_{JW}^{**}, E_{JR}^{**}, E_{AW}^{**}, E_{AR}^{**}, I_{JW}^{**}, I_{JR}^{**}, I_{AW}^{**}, I_{AR}^{**}, T_J^{**}, T_A^{**}, R_J^{**}, R_A^{**}, S_V^{**}, V_W^{**},$$
$$V_R^{**}) = (S_J^{**}, S_A^{**}, E_{JW}^{**}, 0, E_{AW}^{**}, 0, I_{JW}^{**}, 0, I_{AW}^{**}, T_J^{**}, T_A^{**}, R_J^{**}, R_A^{**}, S_V^{**}, V_W^{**}, 0).$$

Setting $\lambda_{JR} = \lambda_{AR} = \lambda_{VR} = 0$ (and using $\delta_J = \delta_A = 0$ for simplicity; so that $N_H^* = \dfrac{\Pi_J}{\mu_H}$) in (4.23) gives the following reduced (low-endemicity) two-strain model:

$$\begin{aligned}
\frac{dS_J}{dt} &= \Pi_J + \psi_J R_J - \frac{\mu_H b_2 \beta_J V_W}{\Pi_J} S_J - (\xi + \mu_H) S_J, \\
\frac{dS_A}{dt} &= \xi S_J + \psi_A R_A - \frac{\mu_H b_2 \beta_A V_W}{\Pi_J} S_A - \mu_H S_A, \\
\frac{dE_{JW}}{dt} &= \frac{\mu_H b_2 \beta_J V_W}{\Pi_J} S_J - (\sigma_{JW} + \xi + \mu_H) E_{JW}, \\
\frac{dE_{AW}}{dt} &= \xi E_{JW} + \frac{\mu_H b_2 \beta_A V_W}{\Pi_J} S_A - (\sigma_{AW} + \mu_H) E_{AW}, \\
\frac{dI_{JW}}{dt} &= \sigma_{JW} E_{JW} - (\tau_J + \xi + \gamma_J + \mu_H) I_{JW}, \\
\frac{dI_{JR}}{dt} &= (1 - f_J)\tau_J I_{JW} - (\xi + \phi_1 \gamma_J + \mu_H) I_{JR}, \\
\frac{dI_{AW}}{dt} &= \xi I_{JW} + \sigma_{AW} E_{AW} - (\tau_A + \gamma_A + \mu_H) I_{AW}, \\
\frac{dI_{AR}}{dt} &= \xi I_{JR} + (1 - f_A)\tau_A I_{AW} - (\phi_2 \gamma_A + \mu_H) I_{AR}, \\
\frac{dT_J}{dt} &= f_J \tau_J I_{JW} - (\xi + \phi_3 \gamma_J + \mu_H) T_J, \\
\frac{dT_A}{dt} &= \xi T_J + f_A \tau_A I_{AW} - (\phi_4 \gamma_A + \mu_H) T_A, \\
\frac{dR_J}{dt} &= \gamma_J I_{JW} + \phi_1 \gamma_J I_{JR} + \phi_3 \gamma_J T_J - (\xi + \mu_H + \psi_J) R_J, \\
\frac{dR_A}{dt} &= \xi R_J + \gamma_A I_{AW} + \phi_2 \gamma_A I_{AR} + \phi_4 \gamma_A T_A - (\mu_H + \psi_A) R_A, \\
\frac{dS_V}{dt} &= \Pi_V - \frac{\mu_H b_2 \beta_V (I_{JW} + I_{AW})}{\Pi_J} S_V - \mu_V S_V, \\
\frac{dV_R}{dt} &= \frac{\mu_H b_2 \beta_V (I_{JW} + I_{AW})}{\Pi_J} S_V - \mu_V I_V.
\end{aligned} \tag{4.38}$$

The reproduction number of the low-endemicity model (4.38) is given by

$$\tilde{\mathcal{R}}_L = \sqrt{\frac{b_2^2\beta_V\Pi_V\mu_H\{\beta_J\mu_H[\sigma_{JW}g_4(g_8+\xi)+\sigma_{AW}\xi g_6]+\beta_A\sigma_{AW}\xi g_2 g_6\}}{\Pi_J\mu_V^2 g_1 g_2 g_4 g_6 g_8}}, \tag{4.39}$$

where, now, $g_1 = \xi + \mu_H, g_2 = \sigma_{JW} + \xi + \mu_H$, $g_4 = \sigma_{AW} + \mu_H$, $g_6 = \tau_J + \xi + \gamma_J + \mu_H$ and $g_8 = \tau_A + \gamma_A + \mu_H$. It is convenient to let:

$$\lambda_{JW}^{**} = \frac{\mu_H b_2 \beta_J V_W^{**}}{\Pi_J}, \quad \lambda_{AW}^{**} = \frac{\mu_H b_2 \beta_A V_W^{**}}{\Pi_J} \quad \text{and} \quad \lambda_{VW}^{**} = \frac{\mu_H b_2 \beta_V (I_{JW}^{**} + I_{AW}^{**})}{\Pi_J}. \tag{4.40}$$

It can be shown, using the approach in Section 4.4.1, that the non-zero equilibria of the low-endemicity model (4.38) satisfy:

$$c_0(\lambda_{JW}^{**})^2 + c_1\lambda_{JW}^{**} + c_2 = 0, \tag{4.41}$$

where,

$$c_0 = \Pi_J b_2 \beta_V \beta_A \mu_H \mu_V \xi[\sigma_{HJ}\sigma_{HA}\gamma_J\psi_A + g_6 g_7(g_3\sigma_{HJ} + g_4\sigma_{HA})]$$
$$+\Pi_J\beta_{HA}\mu_H\mu_V[\sigma_{HA}(\gamma_A + g_7) + g_5 g_7]\{b_2\beta_V\sigma_{HJ}\mu_H g_6 + \mu_V g_1[\sigma_{HJ}(\gamma_J + g_6) + g_4 g_6]\},$$
$$c_2 = \beta_{HJ}\mu_H g_6 g_7 \Pi_J \mu_V^2 \left(\prod_{i=1}^{5} g_i\right)[1 - (\tilde{\mathcal{R}}_L)^2],$$

with, $g_1 = \xi + \mu_H$, $g_2 = \sigma_{JW} + \xi + \mu_H$, $g_4 = \sigma_{AW} + \mu_H$, $g_6 = \tau_J + \xi + \gamma_J + \mu_H$, $g_8 = \tau_A + \gamma_A + \mu_H$, $g_{10} = \xi + \phi_3\gamma_J + \mu_H$, $g_{11} = \phi_A\gamma_A + \mu_H$, $g_{12} = \xi + \mu_H + \psi_J$. The result below follows from (4.41).

Theorem 4.5. *The low-endemicity model (4.38) has a unique positive equilibrium if* $\tilde{\mathcal{R}}_L > 1$.

High-endemicity equilibria

The non-zero equilibria of the system (4.23) are called high-endemicity equilibria to distinguish them from the low-endemicity equilibria (where the resistant strain is not transmitted in the community). The complexity of the system (4.23) makes the analysis of its associated non-zero equilibria not mathematically tractable (and not reported in the thesis).

4.5 Effect of Development of Drug Resistance

The effect of the emergence of drug resistance on the transmission dynamics of malaria in the community will now be qualitatively analysed. Consider the model (4.23) in the absence of resistance development by treated individuals (so that, $f_J = f_A = 1$). Furthermore, for computational convenience, let $\delta_J = \delta_A = 0$.

Consequently, the model (4.23), with $f_J = f_A = 1$ and $\delta_J = \delta_A = 0$, reduces to:

$$
\begin{aligned}
\frac{dS_J}{dt} &= \Pi_J + \psi_J R_J - \frac{\mu_H \beta_J b_2 (V_W + \theta_R V_R)}{\Pi_J} S_J - (\xi + \mu_H) S_J, \\
\frac{dS_A}{dt} &= \xi S_J + \psi_A R_A - \frac{\mu_H \beta_A b_2 (V_W + \theta_R V_R)}{\Pi_J} S_A - \mu_H S_A, \\
\frac{dE_{JW}}{dt} &= \frac{\mu_H \beta_J b_2 V_W}{\Pi_J} S_J - (\sigma_{JW} + \xi + \mu_H) E_{JW}, \\
\frac{dE_{JR}}{dt} &= \frac{\mu_H \theta_R \beta_J b_2 V_R}{\Pi_J} S_J - (\sigma_{JR} + \xi + \mu_H) E_{JR}, \\
\frac{dE_{AW}}{dt} &= \xi E_{JW} + \frac{\mu_H \beta_A b_2 V_W}{\Pi_J} S_A - (\sigma_{AW} + \mu_H) E_{AW}, \\
\frac{dE_{AR}}{dt} &= \xi E_{JR} + \frac{\mu_H \theta_R \beta_A b_2 V_R}{\Pi_J} S_A - (\sigma_{AR} + \mu_H) E_{AR}, \\
\frac{dI_{JW}}{dt} &= \sigma_{JW} E_{JW} - (\tau_J + \xi + \gamma_J + \mu_H) I_{JW}, \\
\frac{dI_{JR}}{dt} &= \sigma_{JR} E_{JR} - (\xi + \phi_1 \gamma_J + \mu_H) I_{JR}, \\
\frac{dI_{AW}}{dt} &= \xi I_{JW} + \sigma_{AW} E_{AW} - (\tau_A + \gamma_A + \mu_H) I_{AW}, \\
\frac{dI_{AR}}{dt} &= \sigma_{AR} E_{AR} + \xi I_{JR} - (\phi_2 \gamma_A + \mu_H) I_{AR}, \\
\frac{dT_J}{dt} &= \tau_J I_{JW} - (\xi + \phi_3 \gamma_J + \mu_H) T_J, \\
\frac{dT_A}{dt} &= \xi T_J + \tau_A I_{AW} - (\phi_4 \gamma_A + \mu_H) T_A, \\
\frac{dR_J}{dt} &= \gamma_J I_{JW} + \phi_1 \gamma_J I_{JR} + \phi_3 \gamma_J T_J - (\psi_J + \xi + \mu_H) R_J, \\
\frac{dR_A}{dt} &= \xi R_J + \gamma_A I_{AW} + \phi_2 \gamma_A I_{AR} + \phi_4 \gamma_A T_A - (\psi_A + \mu_H) R_A, \\
\frac{dS_V}{dt} &= \Pi_V - \frac{\mu_H \beta_V b_2 [I_{JW} + I_{AW} + \eta_R (I_{JR} + I_{AR})]}{\Pi_J} S_V - \mu_V S_V, \\
\frac{dV_W}{dt} &= \frac{\mu_H \beta_V b_2 (I_{JW} + I_{AW})}{\Pi_J} S_V - \mu_V V_W, \\
\frac{dV_R}{dt} &= \frac{\mu_H \eta_R \beta_V b_2 (I_{JR} + I_{AR})}{\Pi_J} S_V - \mu_V V_R.
\end{aligned}
\tag{4.42}
$$

Define $\hat{\mathcal{R}}_W = \mathcal{R}_W \mid_{f_J = f_A = 1, \delta_J = 0} < 1$, $\hat{\mathcal{R}}_R = \mathcal{R}_R \mid_{f_J = f_A = 1, \delta_J = \delta_A = 0} < 1$ and the positively-invariant region:

$$\mathcal{D}_W = \{(S_J, S_A, E_{JW}, E_{JR}, E_{AW}, E_{AR}, I_{JW}, I_{JR}, I_{AW}, I_{AR}, R_J, R_A, S_V, V_W, V_R) \in \mathcal{D} : S_J \leq S_J^*, S_A \leq S_A^*, S_V \leq S_V^*\}. \tag{4.43}$$

The DFE of the wild strain-only component of the system (4.42) is given by

$$(S_J^*, S_A^*, E_{JW}^*, E_{AW}^*, I_{JW}^*, I_{AW}^*, S_V^*, V_W^*) = \left[\frac{\Pi_J}{\xi + \mu_H}, \frac{\xi \Pi_J}{\mu_H(\xi + \mu_H)}, 0, 0, 0, 0, \frac{\Pi_V}{\mu_V}, 0\right].$$

Theorem 4.6. *The DFE of the wild strain-only component of the model (4.42) is GAS in $\mathcal{D}_W$ if $\hat{\mathcal{R}}_W < 1$.*

Proof. Consider the following Lyaponuv function

$$\mathcal{F} = f_1 E_{JW} + f_2 E_{AW} + f_3 I_{JW} + f_4 I_{AW} + V_W,$$

with,

$$f_1 = \frac{\Pi_V \mu_H b_2 \beta_V [\sigma_{JW} g_4 (g_8 + \xi) + \sigma_{AW} \xi g_6]}{\Pi_J \mu_V \hat{\mathcal{R}}_W g_2 g_4 g_6 g_8}, f_2 = \frac{\Pi_V \mu_H b_2 \beta_V \sigma_{AW}}{\Pi_J \mu_V \hat{\mathcal{R}}_W g_4 g_8},$$
$$f_3 = \frac{\Pi_V \mu_H b_2 \beta_V (g_8 + \xi)}{\Pi_J \mu_V \hat{\mathcal{R}}_W g_6 g_8}, f_4 = \frac{\Pi_V \mu_H b_2 \beta_V}{\Pi_J \mu_V \hat{\mathcal{R}}_W g_8},$$

where, now, $g_2 = \sigma_{JW} + \xi + \mu_H$, $g_4 = \sigma_{AW} + \mu_H$, $g_6 = \tau_J + \xi + \gamma_J + \mu_H$, $g_8 = \tau_A + \gamma_A + \mu_H$. The Lyapunov derivative of $\mathcal{F}$ is given by

$$\dot{\mathcal{F}} = f_1 \dot{E}_{JW} + f_2 \dot{E}_{AW} + f_3 \dot{I}_{JW} + f_4 \dot{I}_{AW} + \dot{V}_W,$$

$$
\begin{aligned}
&= f_1\left[\frac{\mu_H b_2 \beta_J V_W}{\Pi_J} S_J - (\sigma_{JW} + \xi + \mu_H) E_{JW}\right] \\
&+ f_2\left[\xi E_{JW} + \frac{\mu_H b_2 \beta_{AW} V_W}{\Pi_J} S_A - (\sigma_{AW} + \mu_H) E_{AW}\right] \\
&+ f_3\left[\sigma_{JW} E_{JW} - (\gamma_J + \xi + \mu_H) I_{JW}\right] \\
&+ f_4\left[\xi I_{JW} + \sigma_{AW} E_{AW} - (\gamma_A + \mu_H) I_{AW}\right] \\
&+ \left[\frac{\mu_H b_2 \beta_V (I_{JW} + I_{AW})}{\Pi_J} S_V - \mu_V V_W\right],
\end{aligned}
$$

which can be simplified to

$$
\begin{aligned}
\dot{\mathcal{F}} = &\Bigg[- \frac{\Pi_V \mu_H b_2 \beta_V [\sigma_{JW} g_4 (g_8 + \xi) + \sigma_{AW} \xi g_6]}{\Pi_J \mu_V \hat{\mathcal{R}}_W g_2 g_4 g_6 g_8} (\sigma_{JW} + \xi + \mu_H) \\
&+ \frac{\Pi_V \mu_H b_2 \beta_V \sigma_{AW}}{\Pi_J \mu_V \hat{\mathcal{R}}_W g_4 g_8} \xi + \frac{\Pi_V \mu_H b_2 \beta_V (g_8 + \xi)}{\Pi_J \mu_V \hat{\mathcal{R}}_W g_6 g_8} \sigma_{JW} \Bigg] E_{JW} \\
&+ \left[- \frac{\Pi_V \mu_H b_2 \beta_V \sigma_{AW}}{\Pi_J \mu_V \hat{\mathcal{R}}_W g_4 g_8} (\sigma_{AW} + \mu_H) + \frac{\Pi_V \mu_H b_2 \beta_V}{\Pi_J \mu_V \hat{\mathcal{R}}_W g_8} \sigma_{AW} \right] E_{AW} \\
&+ \left[- \frac{\Pi_V \mu_H b_2 \beta_V (g_8 + \xi)}{\Pi_J \mu_V \hat{\mathcal{R}}_W g_6 g_8} (\gamma_J + \xi + \mu_H) + \frac{\Pi_V \mu_H b_2 \beta_V}{\Pi_J \mu_V \hat{\mathcal{R}}_W g_8} \xi + \frac{\mu_H b_2 \beta_V}{\Pi_J} S_V \right] I_{JW} \\
&+ \left[- \frac{\Pi_V \mu_H b_2 \beta_V}{\Pi_J \mu_V \hat{\mathcal{R}}_W g_8} (\gamma_A + \mu_H) + \frac{\mu_H b \beta_V}{\Pi_J} S_V \right] I_{AW} \\
&+ \Bigg[\frac{\Pi_V \mu_H b_2 \beta_V [\sigma_{JW} g_4 (g_8 + \xi) + \sigma_{AW} \xi g_6]}{\Pi_J \mu_V \hat{\mathcal{R}}_W g_2 g_4 g_6 g_8} \left(\frac{\mu_H b_2 \beta_J}{\Pi_J} S_J \right) \\
&+ \frac{\Pi_V \mu_H b_2 \beta_V \sigma_{AW}}{\Pi_J \mu_V \hat{\mathcal{R}}_W g_4 g_8} \left(\frac{\mu_H b_2 \beta_A}{\Pi_J} S_A \right) - \mu_V \Bigg] V_W.
\end{aligned}
\tag{4.44}
$$

Since $S_J \leq S_J^*$, $S_A \leq S_A^*$, and $S_V \leq S_V^*$ in $\mathcal{D}_W$, it follows from (4.44), after some algebraic manipulations, that

$$
\dot{\mathcal{F}} \leq \left(1 - \frac{1}{\hat{\mathcal{R}}_W}\right) \left(\frac{\Pi_V \mu_H b_2 \beta_V}{\Pi_J \mu_V} I_{JW} + \frac{\Pi_V \mu_H b_2 \beta_V}{\Pi_J \mu_V} I_{AW} + \mu_V \hat{\mathcal{R}}_W V_W \right) \leq 0
$$

for $\hat{\mathcal{R}}_W \leq 1$. Thus, $\dot{\mathcal{F}} \leq 0$ if $\hat{\mathcal{R}}_w \leq 1$ with $\dot{\mathcal{F}} = 0$ if and only if $E_{JW} = E_{AW} =$

$I_{JW} = I_{AW} = V_W = 0$. Substituting $I_{JW} = I_{AW} = 0$ into the eleventh and twelfth equations of (4.42) implies that $(T_J(t), T_A(t)) \longrightarrow (0,0)$ as t$\longrightarrow \infty$. The proof is completed as in Appendix C. $\square$

Theorem 4.6 shows that the wild strain component of the model (4.42) becomes zero asymptotically if $\hat{\mathcal{R}}_W < 1$ (that is, the wild strain is eliminated from community whenever $\hat{\mathcal{R}}_W < 1$). It should be recalled that the model (4.23), with $\delta_J = \delta_A = 0$, has a unique resistant strain-only boundary equilibrium, in the absence of the wild strain, where $\tilde{\mathcal{R}}_R > 1$ (Theorem 4.4). Extensive numerical simulations of the model (4.42) suggest the following conjecture.

Conjecture 4.1. *The unique positive equilibrium of the resistant strain-only component of the model (4.42) is GAS whenever $\hat{\mathcal{R}}_W < 1 < \hat{\mathcal{R}}_R$.*

The epidemiological implication of Conjecture 4.1 is that the system (4.42) will undergo competitive exclusion, where the resistant strain drives out the wild strain to extinction (as depicted in Figure 4.4). Thus, this study shows (*via* qualitative analysis and numerical simulations) that, for the case when treatment does not cause resistance, the two-strain model (4.23) undergoes competitive exclusion (where the malaria strain with the higher reproduction number greater than unity drives the other, with reproduction number less than one, to extinction).

The DFE of the resistant strain-only component of the system (4.42) is given by

$$(S_J^*, S_A^*, E_{JR}^*, E_{AR}^*, I_{JR}^*, I_{AR}^*, S_V^*, V_R^*) = \left[\frac{\Pi_J}{\xi + \mu_H}, \frac{\xi \Pi_J}{\mu_H(\xi + \mu_H)}, 0, 0, 0, 0, \frac{\Pi_V}{\mu_V}, 0\right].$$

Theorem 4.7. *The DFE of the resistant strain-only component of the model (4.42) is GAS in $\mathcal{D}_W$ if $\hat{\mathcal{R}}_R < 1$.*

Theorem 4.7 can be proved using the following Lyapunov function:

$$\mathcal{F} = f_1 E_{JR} + f_2 E_{AR} + f_3 I_{JR} + f_4 I_{AR} + V_R,$$

with,

$$f_1 = \frac{\Pi_V \mu_H b_2 \beta_V [\sigma_{JR} g_5 (g_9 + \xi) + \sigma_{AR} \xi g_7]}{\Pi_J \mu_V \hat{\mathcal{R}}_R g_3 g_5 g_7 g_9}, f_2 = \frac{\Pi_V \mu_H b_2 \beta_V \sigma_{AW}}{\Pi_J \mu_V \hat{\mathcal{R}}_R g_5 g_9},$$
$$f_3 = \frac{\Pi_V \mu_H b_2 \beta_V (g_9 + \xi)}{\Pi_J \mu_V \hat{\mathcal{R}}_R g_7 g_9}, f_4 = \frac{\Pi_V \mu_H b_2 \beta_V}{\Pi_J \mu_V \hat{\mathcal{R}}_R g_9},$$

where, now, $g_3 = \sigma_{JR} + \xi + \mu_H$, $g_5 = \sigma_{AR} + \mu_H$, $g_7 = \xi + \phi_1 \gamma_J + \mu_H$, $g_9 = \phi_2 \gamma_A + \mu_H$. It is worth recalling that in the absence of the resistance strain, the model (4.23), with $\delta_J = \delta_A = 0$, has a unique wild strain-only equilibrium whenever $\tilde{\mathcal{R}}_L > 1$ (Theorem 4.5). Numerical simulations (see Figure 4.5) suggest the following conjecture.

Conjecture 4.2. *The unique positive equilibrium of the wild strain-only component of the model (4.42) is GAS whenever* $\hat{\mathcal{R}}_R < 1 < \hat{\mathcal{R}}_W$.

Simulations of the model (4.42), for the case when treatment does not cause resistance (i.e., $f_J = f_A = 1$), shows that (for the case when each of the reproduction number of the two strain exceeds unity) the strain with the higher reproduction number drive the other to extinction (Figures 4.6 and 4.7). These simulations suggest the following conjecture (similar result was established for the two-strain model in [23]).

Conjecture 4.3. *The model (4.42) has no co-existence equilibria if* $\hat{\mathcal{R}}_i > \hat{\mathcal{R}}_j > 1$ *(* $i, j = \{W, R\}$*;* $i \neq j$*).*

4.6 Assessment of Treatment Strategies

The model (4.23) is simulated to assess the impact of anti-malaria drug treatment on the transmission dynamics of malaria in a community. The following effectiveness levels of the treatment strategy are considered (these levels are arbitrary chosen to account for the uncertainty in the estimate of the treatment-related parameters of the model):

(i) low effectiveness level: $\tau_J = \tau_A = 0.009, f_J = f_A = 0.05$;

(ii) moderate effectiveness level: $\tau_J = \tau_A = 0.05, f_J = f_A = 0.1$;

(iii) high effectiveness level: $\tau_J = \tau_A = 5, f_J = f_A = 0.9$.

The simulation results obtained, depicted in Figure 4.8, show a reduction in the cumulative number of new infections (for both juveniles and adults) for increasing effectiveness levels of the treatment strategy. Similar results were obtained for the cumulative malaria-induced mortality (Figure 4.9).

4.7 Summary of the Chapter

The model in Chapter 3 is extended, in Chapter 4, to assess the effect of drug treatment on the transmission dynamics of malaria in a population. The resulting 17-dimensional, age-structured, two-strain deterministic model is rigorously analysed. Some of the main mathematical and numerical simulation results obtained are:

(i) the model (4.23) undergoes the phenomenon of backward bifurcation at $\mathcal{R}_T = 1$ under certain conditions. As in Chapter 3, the backward bifurcation phenomenon arises due to disease-induced mortality in humans;

(ii) it is shown that the disease-free equilibrium of the model (4.23) is globally-asymptotically stable, in the absence of disease-induced mortality and loss

of infection-acquired immunity, whenever the associated reproduction number ($\tilde{\mathcal{R}}_T$) is less than unity;

(iii) for the case when anti-malaria treatment causes drug resistance, the model (4.23) (with $\delta_J = \delta_A = 0$) can have resistant-only boundary equilibrium, low-endemicity equilibrium or high-endemicity equilibrium. On the other hand, when such treatment does not cause drug resistance, the low-endemicity equilibrium reduces to a wild strain-only boundary equilibrium;

(iv) the reduced model (4.42) undergoes competitive exclusion, where the strain with the higher reproduction number (greater than unity) drives the other (with reproduction number less than unity) to extinction;

(v) numerical simulations show that, for the case when treatment does not cause drug resistance, the model (with $\delta_J = \delta_A = 0$) undergoes competitive exclusion when the associated reproduction numbers of the two strains exceed unity. In this case, the strain with the higher reproduction number drives the other to extinction;

(vi) in the absence of disease-induced mortality, the model (4.23) has a unique resistant strain-only boundary equilibrium whenever the associated reproduction number ($\tilde{\mathcal{R}}_R$) exceeds unity;

(vii) numerical simulations of the model (4.23) show (as expected) that the cumulative number of new cases and malaria-related mortality decrease with increasing effectiveness levels of the treatment strategy.

Variable	Description
S_J	Population of susceptible juveniles
S_A	Population of susceptible adults
E_{JW}	Population of latently-infected juveniles with the wild strain
E_{JR}	Population of latently-infected juveniles with the resistant strain
E_{AW}	Population of latently-infected adults with the wild strain
E_{AR}	Population of latently-infected adults with the resistant strain
I_{JW}	Population of symptomatic juveniles with the wild strain
I_{JR}	Population of symptomatic juveniles with the resistant strain
I_{AW}	Population of symptomatic adults with the wild strain
I_{AR}	Population of symptomatic adults with the resistant strain
T_J	Population of effectively-treated juveniles
T_A	Population of effectively-treated adults
R_{HJ}	Population of recovered juveniles
R_{HA}	Population of recovered adults
S_V	Population of susceptible mosquitoes
V_W	Population of mosquitoes infected with the wild strain
V_R	Population of mosquitoes infected with the resistant strain

Table 4.1: Description of the state variables of the two-strain model (4.23).

Table 4.2: Description of parameters of the two-strain model (4.23).

Parameters	Description
b_2	Average *per capita* biting rate of mosquitoes
β_J	Probability of infection of susceptible juveniles *per* mosquito bite
β_A	Probability of infection of susceptible adults *per* mosquito bite
β_V	Probability of infection of susceptible vectors *per* mosquito bite of the infected host
μ_H	Natural death rate of humans
μ_V	Natural death rate of mosquitoes
σ_{JW}	Rate of development of clinical symptoms of malaria of wild strain for latently-infected juveniles
σ_{JR}	Rate of development of clinical symptoms of malaria of resistant strain for latently-infected juveniles
σ_{AW}	Rate of development of clinical symptoms of malaria of wild strain for latently-infected adults
σ_{JR}	Rate of development of clinical symptoms of malaria of resistant strain for latently-infected adults
δ_J	Disease-induced mortality rate for juveniles
δ_A	Disease-induced mortality rate for adults
γ_J	Recovery rate of juveniles
γ_A	Recovery rate of adults
φ_1	Modification parameter for recovery rate in juveniles with the resistant strain
φ_2	Modification parameter for recovery rate in adults with the resistant strain
φ_3	Modification parameter for recovery rate in treated juveniles

Parameters	Description
φ_4	Modification parameter for recovery rate in treated adults
θ_1	Modification parameter for disease-induced mortality rate for juveniles with the resistant strain
θ_2	Modification parameter for disease-induced mortality rate for adults with the resistant strain
θ_3	Modification parameter for disease-induced mortality rate for treated juveniles
θ_4	Modification parameter for disease-induced mortality rate for treated adults
θ_R	Modification parameter for reduction in infectiousness of resistant individuals
η_R	Modification parameter for reduction in infectiousness of treated individuals
τ_J	Treatment rate for juveniles
τ_A	Treatment rate for adults
f_J	Fraction of symptomatic juveniles who are effectively treated
f_A	Fraction of symptomatic adults who are effectively treated
ψ_J	Rate of loss of natural immunity for juveniles
ψ_A	Rate of loss of natural immunity for adults
ξ	Maturation rate for juveniles
Π_J	Recruitment (birth or immigration) rate of juveniles
Π_V	Birth rate of adult mosquitoes

Table 4.3: Parameter values for the two-strain model (4.23).

Parameter	Value	Reference
b_2	$0.5 \quad \text{day}^{-1}$	[23]
β_J	0.181	[23]
β_A	0.181	[23]
β_V	0.8333	[45]
μ_H	$0.00004 \quad \text{day}^{-1}$	[45]
μ_V	$0.05 \quad \text{day}^{-1}$	[45]
σ_{JW}	$0.10333 \quad \text{day}^{-1}$	[13]
σ_{AW}	$0.08333 \quad \text{day}^{-1}$	[13]
σ_{JR}	$0.10333 \quad \text{day}^{-1}$	[13]
σ_{AR}	$0.08333 \quad \text{day}^{-1}$	[13]
δ_J	$0.0003454 \quad \text{day}^{-1}$	[1]
δ_A	$0.0000174 \quad \text{day}^{-1}$	[1]
γ_J	$0.0014 \quad \text{day}^{-1}$	[1]
γ_A	$0.0035 \quad \text{day}^{-1}$	[1]
ϕ_1	$0.8 \quad \text{day}^{-1}$	Assumed
ϕ_2	$0.8 \quad \text{day}^{-1}$	Assumed
ϕ_3	$> 1 \quad \text{day}^{-1}$	Assumed
ϕ_4	$> 1 \quad \text{day}^{-1}$	Assumed
θ_1	$1 \quad \text{day}^{-1}$	Assumed
θ_2	$1 \quad \text{day}^{-1}$	Assumed

Parameter	Value	Reference
θ_3	$(0,1) \quad \text{day}^{-1}$	Assumed
θ_4	$(0,1) \quad \text{day}^{-1}$	Assumed
θ_R	$> 0 \quad \text{day}^{-1}$	variable
η_R	$> 0 \quad \text{day}^{-1}$	Variable
τ_J	$> 0 \quad \text{day}^{-1}$	variable
τ_A	$> 0 \quad \text{day}^{-1}$	variable
f_J	$[0,1] \quad \text{day}^{-1}$	variable
f_A	$[0,1] \quad \text{day}^{-1}$	variable
ψ_J	$0.0027 \quad \text{day}^{-1}$	[1]
ψ_A	$0.0027 \quad \text{day}^{-1}$	[1]
ξ	$0.00000986 \quad \text{day}^{-1}$	[1]
Π_J	$1520 \quad \text{day}^{-1}$	Assumed
Π_V	$500 \quad \text{day}^{-1}$	Assumed

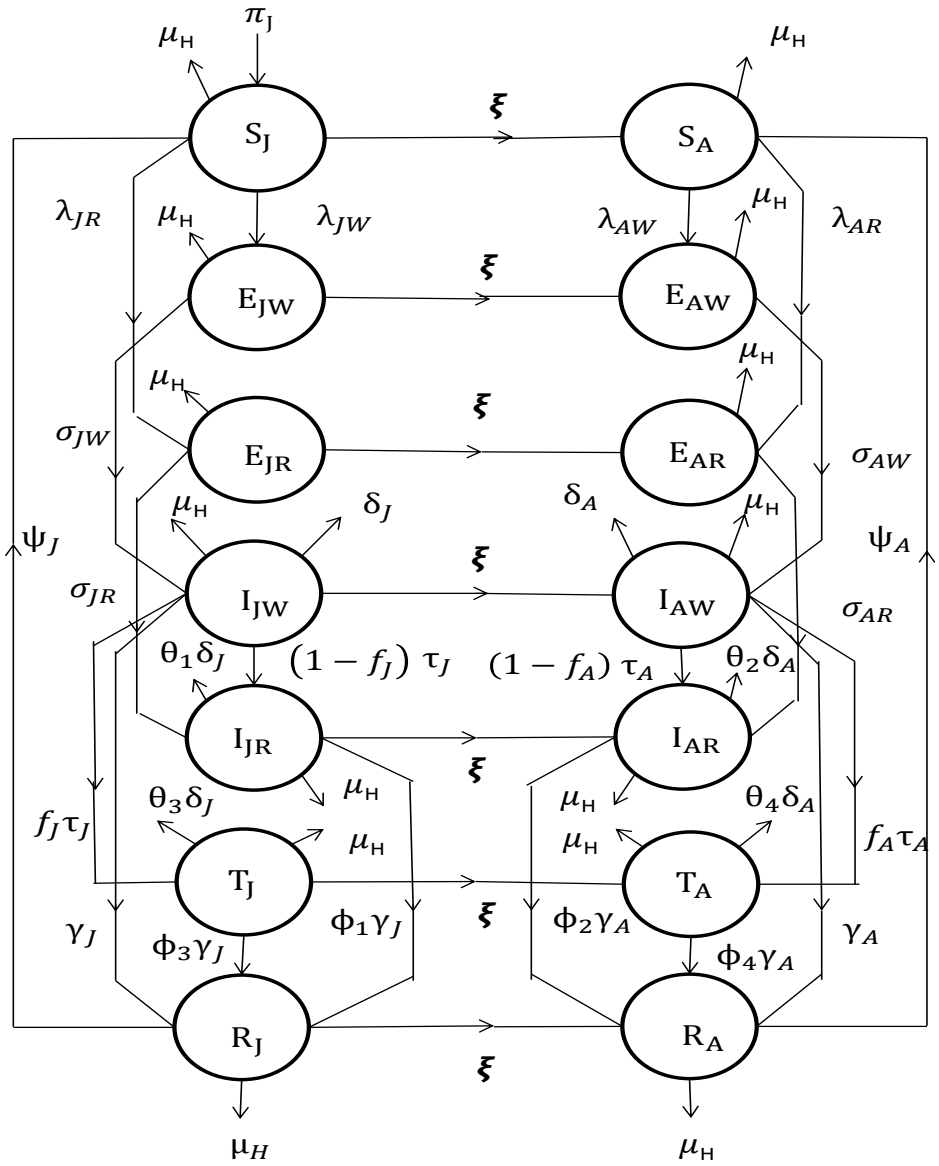

Figure 4.1: Schematic diagram of the human component of the two-strain model (4.23).

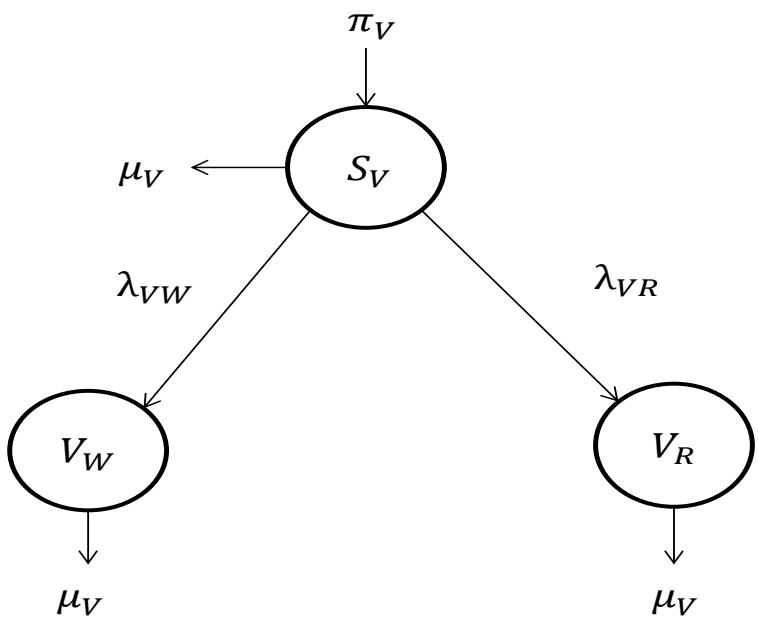

Figure 4.2: Schematic diagram of the mosquito component of the two-strain model (4.23).

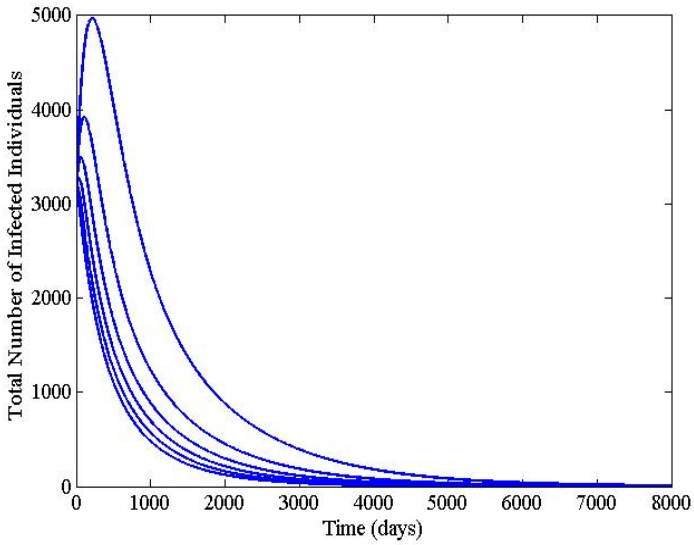

Figure 4.3: Simulations of the two-strain model (4.23), showing the total number of infected individuals as a function of time using various initial conditions. Parameter values used are as given in Table 4.3, with $\Pi_J = 40$, $\Pi_V = 1000$, $\mu_V = \frac{1}{20}$, $\mu_H = 0.00004$, $\delta_J = 0$, $\delta_A = 0$, $\xi = 0.00000986$, $\gamma_J = 0.0014$, $\gamma_A = 0.0035$, $\sigma_{JW} = 0.10333$, $\sigma_{AW} = 0.08333$, $\sigma_{JR} = 0.10333$, $\sigma_{AW} = 0.08333$, $\psi_J = 0$, $\psi_A = 0$, $\beta_A = 0.3$ $\beta_J = 0.4$, $\beta_V = 0.9$, $\eta_R = 0.05$, $\theta_R = 0.05$, $\theta_1 = 1$, $\theta_2 = 1$, $\theta_3 = 0.5$, $\theta_4 = 0.5$, $\phi_1 = 0.8$, $\phi_2 = 0.8$, $\phi_3 = 1.5$, $\phi_4 = 1.5$ $\tau_J = 0.3$, $\tau_A = 0.3$, $f_J = 0.5$, $f_A = 0.5$, and $b_2 = 1$ (so that, $\tilde{\mathcal{R}}_T = \max\{0.6734, 0.5162\} = 0.6734$).

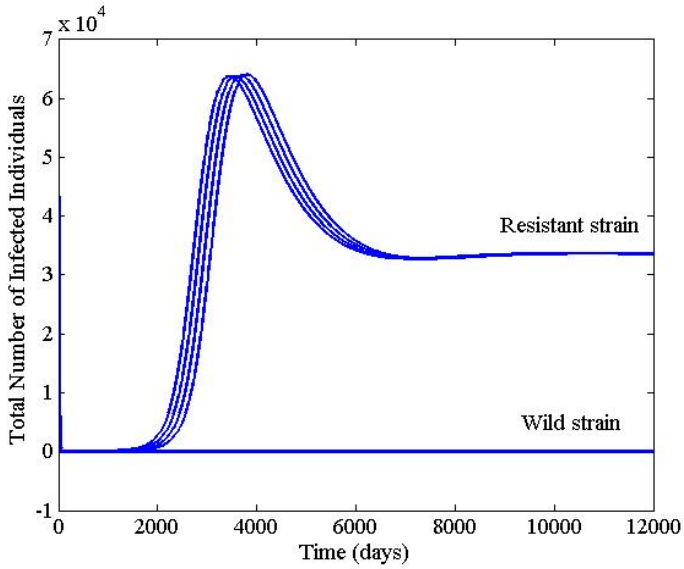

Figure 4.4: Simulations of the two-strain model (4.42), showing the total number of infected individuals as a function of time using various initial conditions. Parameter values used are as given in Table 4.3, with $\Pi_J = 40$, $\Pi_V = 1000$, $\mu_V = \frac{1}{20}$, $\mu_H = 0.00004$, $\delta_J = 0$, $\delta_A = 0$, $\xi = 0.00000986$, $\gamma_J = 0.0014$, $\gamma_A = 0.0035$, $\sigma_{JW} = 0.10333$, $\sigma_{AW} = 0.08333$, $\sigma_{JR} = 0.10333$, $\sigma_{AW} = 0.08333$, $\psi_J = 0$, $\psi_A = 0$, $\beta_A = 0.3$ $\beta_J = 0.4$, $\beta_V = 0.9$, $\eta_R = 0.8$, $\theta_R = 0.8$, $\theta_1 = 1$, $\theta_2 = 1$, $\theta_3 = 0.5$, $\theta_4 = 0.5$, $\phi_1 = 0.8$, $\phi_2 = 0.8$, $\phi_3 = 1.5$, $\phi_4 = 1.5$ $\tau_J = 0.15$, $\tau_A = 0.15$, $f_J = 1$, $f_A = 1$, and $b_2 = 0.8$ (so that, $\hat{\mathcal{R}}_W = 0.7596$ and $\hat{\mathcal{R}}_R = 6.6068$).

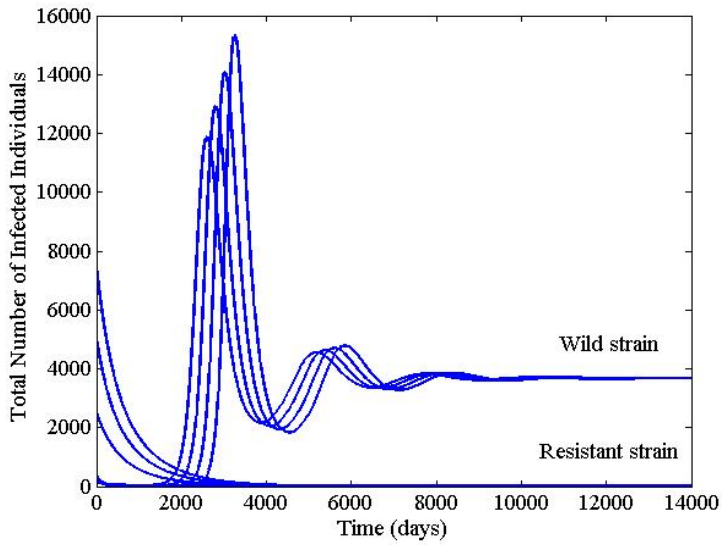

Figure 4.5: Simulations of the two-strain model (4.42), showing the total number of infected individuals as a function of time using various initial conditions. Parameter values used are as given in Table 4.3, with $\Pi_J = 40$, $\Pi_V = 1000$, $\mu_V = \frac{1}{20}$, $\mu_H = 0.00004$, $\delta_J = 0$, $\delta_A = 0$, $\xi = 0.00000986$, $\gamma_J = 0.0014$, $\gamma_A = 0.0035$, $\sigma_{JW} = 0.10333$, $\sigma_{AW} = 0.08333$, $\sigma_{JR} = 0.10333$, $\sigma_{AW} = 0.08333$, $\psi_J = 0$, $\psi_A = 0$, $\beta_A = 0.2$ $\beta_J = 0.3$, $\beta_V = 0.9$, $\eta_R = 0.07$, $\theta_R = 0.07$, $\theta_1 = 1$, $\theta_2 = 1$, $\theta_3 = 0.5$, $\theta_4 = 0.5$, $\phi_1 = 0.8$, $\phi_2 = 0.8$, $\phi_3 = 1.5$, $\phi_4 = 1.5$ $\tau_J = 0.01$, $\tau_A = 0.01$, $f_J = 1$, $f_A = 1$, and $b_2 = 1.5$ (so that, $\hat{\mathcal{R}}_W = 4.4041$ and $\hat{\mathcal{R}}_R = 0.9350$).

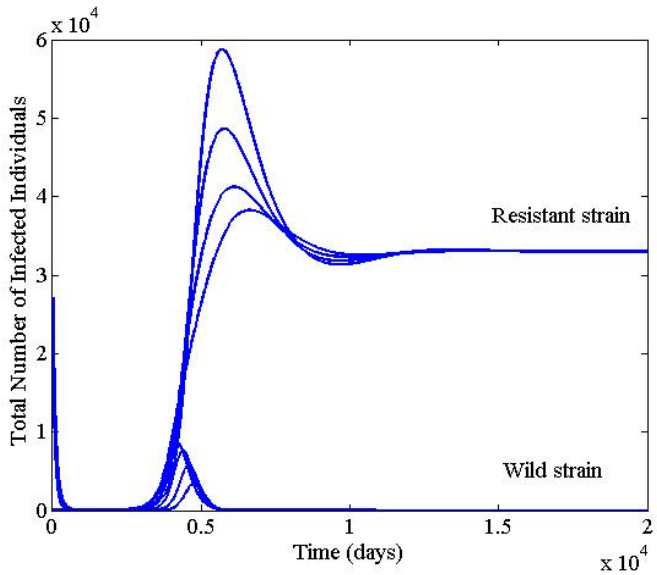

Figure 4.6: Simulations of the two-strain model (4.42), showing the total number of infected individuals as a function of time using various initial conditions. Parameter values used are as given in Table 4.3, with $\Pi_J = 40$, $\Pi_V = 1000$, $\mu_V = \frac{1}{20}$, $\mu_H = 0.00004$, $\delta_J = 0$, $\delta_A = 0$, $\xi = 0.00000986$, $\gamma_J = 0.0014$, $\gamma_A = 0.0035$, $\sigma_{JW} = 0.10333$, $\sigma_{AW} = 0.08333$, $\sigma_{JR} = 0.10333$, $\sigma_{AW} = 0.08333$, $\psi_J = 0$, $\psi_A = 0$, $\beta_A = 0.3$ $\beta_J = 0.4$, $\beta_V = 0.9$, $\eta_R = 0.5$, $\theta_R = 0.5$, $\theta_1 = 1$, $\theta_2 = 1$, $\theta_3 = 0.5$, $\theta_4 = 0.5$, $\phi_1 = 0.8$, $\phi_2 = 0.8$, $\phi_3 = 1.5$, $\phi_4 = 1.5$ $\tau_J = 0.01$, $\tau_A = 0.01$, $f_J = 1$, $f_A = 1$, and $b_2 = 1$ (so that, $\hat{\mathcal{R}}_W = 3.4161$ and $\hat{\mathcal{R}}_R = 5.1615$).

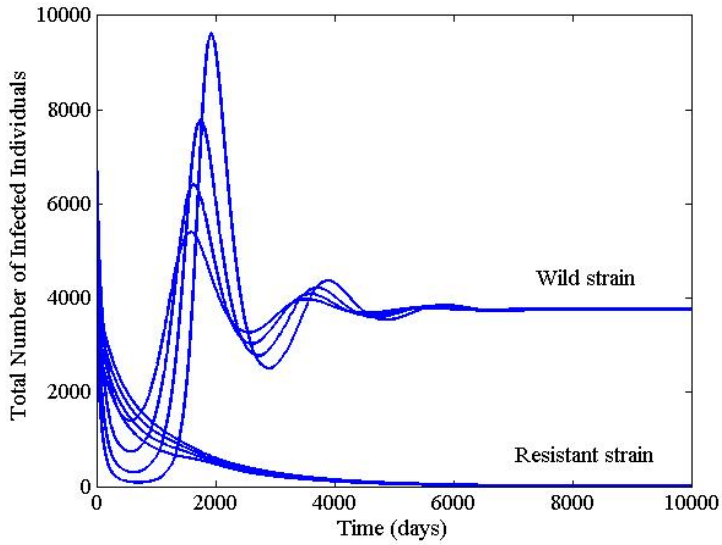

Figure 4.7: Simulations of the two-strain model (4.42), showing the total number of infected individuals as a function of time using various initial conditions. Parameter values used are as given in Table 4.3, with $\Pi_J = 40$, $\Pi_V = 1000$, $\mu_V = \frac{1}{20}$, $\mu_H = 0.00004$, $\delta_J = 0$, $\delta_A = 0$, $\xi = 0.00000986$, $\gamma_J = 0.0014$, $\gamma_A = 0.0035$, $\sigma_{JW} = 0.10333$, $\sigma_{AW} = 0.08333$, $\sigma_{JR} = 0.10333$, $\sigma_{AW} = 0.08333$, $\psi_J = 0$, $\psi_A = 0$, $\beta_A = 0.3$ $\beta_J = 0.4$, $\beta_V = 0.9$, $\eta_R = 0.2$, $\theta_R = 0.2$, $\theta_1 = 1$, $\theta_2 = 1$, $\theta_3 = 0.5$, $\theta_4 = 0.5$, $\phi_1 = 0.8$, $\phi_2 = 0.8$, $\phi_3 = 1.5$, $\phi_4 = 1.5$ $\tau_J = 0.01$, $\tau_A = 0.01$, $f_J = 1$, $f_A = 1$, and $b_2 = 1.7$ (so that, $\hat{\mathcal{R}}_W = 5.8073$ and $\hat{\mathcal{R}}_R = 3.5098$).

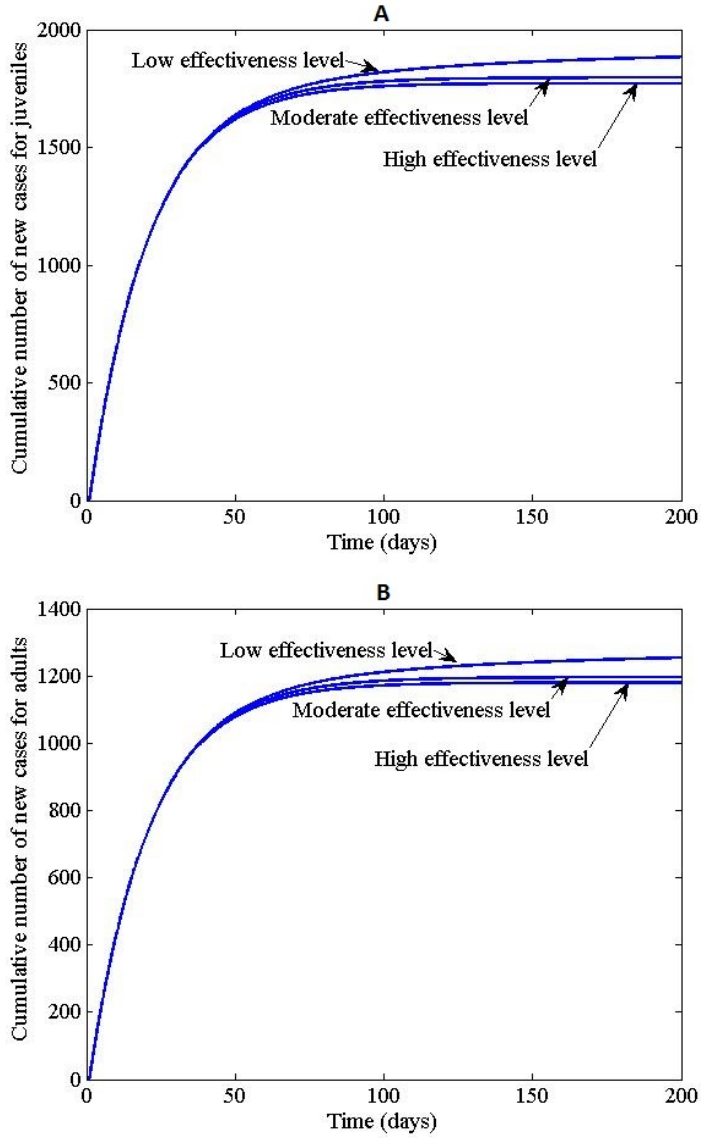

Figure 4.8: Simulations of the two-strain model (4.23) for various effectiveness levels of the treatment strategy, showing the cumulative number of infected individuals as a function of time using various initial conditions. (A) juveniles. (B) adults. Parameter values used are as given in Table 4.3, with $\Pi_J = 1520$, $\Pi_V = 500$, $\mu_V = \frac{1}{20}$, $\mu_H = 0.00004$, $\delta_J = 0.000345$, $\delta_A = 0.000174$, $\xi = 0.00000986$, $\gamma_J = 0.0014$, $\gamma_A = 0.0035$, $\sigma_{JW} = 0.10333$, $\sigma_{AW} = 0.08333$, $\sigma_{JR} = 0.10333$, $\sigma_{AR} = 0.08333$, $\psi_J = 0.0027$, $\psi_A = 0.0027$, $\beta_A = 0.2$ $\beta_J = 0.3$, $\beta_V = 0.9$, $\eta_R = 0.05$, $\theta_R = 0.05$, $\theta_1 = 1$, $\theta_2 = 1$, $\theta_3 = 0.5$, $\theta_4 = 0.5$, $\phi_1 = 0.8$, $\phi_2 = 0.8$, $\phi_3 = 1.5$, $\phi_4 = 1.5$, and $b_2 = 0.5$.

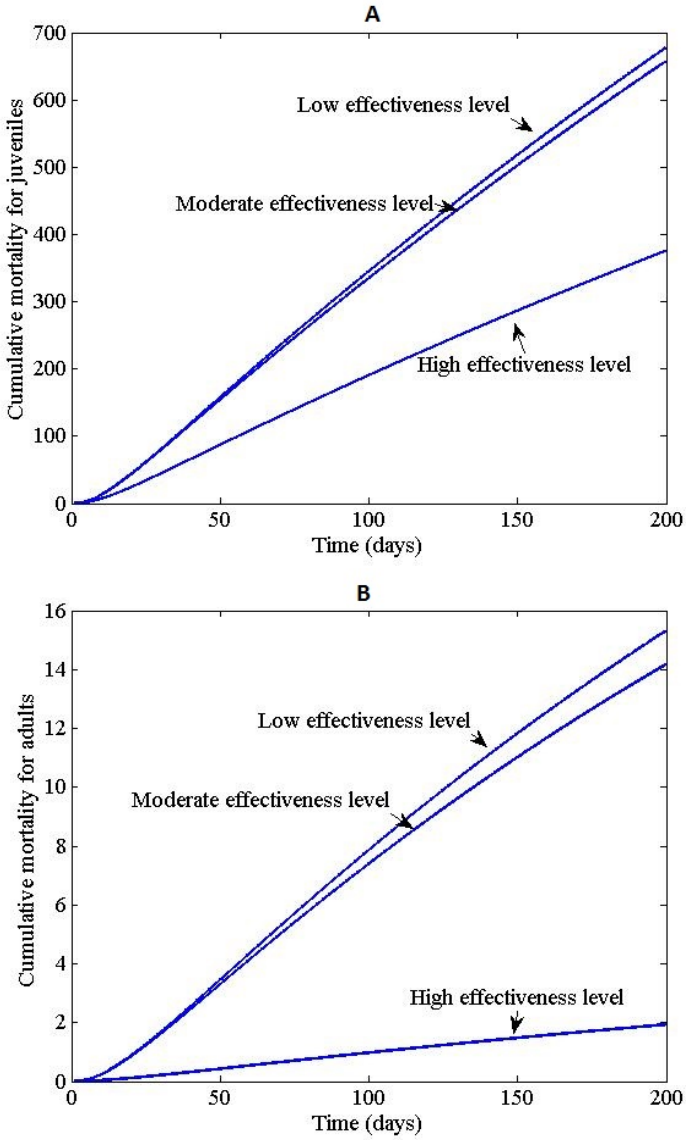

Figure 4.9: Simulations of the two-strain model (4.23) for various effectiveness levels of treatment strategy, showing the cumulative mortality as a function of time using various initial conditions. (A) juveniles. (B) adults. Parameter values used are as given in Table 4.3, with $\Pi_J = 1520$, $\Pi_V = 500$, $\mu_V = \frac{1}{20}$, $\mu_H = 0.00004$, $\delta_J = 0.000345$, $\delta_A = 0.000174$, $\xi = 0.00000986$, $\gamma_J = 0.0014$, $\gamma_A = 0.0035$, $\sigma_{JW} = 0.10333$, $\sigma_{AW} = 0.08333$, $\sigma_{JR} = 0.10333$, $\sigma_{AR} = 0.08333$, $\psi_J = 0$, $\psi_A = 0$, $\beta_A = 0.181$ $\beta_J = 0.281$, $\beta_V = 0.9$, $\eta_R = 0.05$, $\theta_R = 0.05$, $\theta_1 = 1$, $\theta_2 = 1$, $\theta_3 = 0.5$, $\theta_4 = 0.5$, $\phi_1 = 0.8$, $\phi_2 = 0.8$, $\phi_3 = 1.5$, $\phi_4 = 1.5$, and $b_2 = 0.5$.

Chapter 5

Contributions and Future Work

The thesis contributes in three main areas, namely the formulation of new mathematical models for malaria transmission dynamics, qualitative analyses of the models and the provision of some public health insights for effective control of malaria in a community. The specific contributions of the thesis are summarized below.

5.1 Model Formulation

Two new models for the transmission dynamics of malaria in a community are designed in this thesis.

(a) The first model, given by equation (3.16), incorporates the effect of age-structure on the transmission dynamics of malaria. The model extends numerous malaria transmission models published in the literature (such as those in [13, 17, 23, 39, 40, 45, 52]), by adding age-structure. Furthermore, it extends the age-structured malaria model in [49] by including:

  (i) separate compartments for susceptible juveniles and susceptible adults (the two compartments are lumped together in [49]);

  (ii) the dynamics of (and transmission by) latently-infected individuals;

(iii) loss of infection-acquired immunity;

(iv) disease-induced death.

The model (3.16) extends the age-structured malaria model in [1] (which uses mass action incidence for the infection rate) by including:

(i) separate compartments for latently-infected juveniles and latently-infected adults;

(ii) the dynamics of (and transmission by) latently-infected individuals.

(b) The second model, given by (4.23), is an extension of the age-structured model developed in Chapter 3, by including:

(i) the dynamics of the wild and resistant malaria strains for humans and vectors (a single strain was considered in (3.16));

(ii) compartments for treated individuals.

Furthermore, the model (4.23) extends the two-strain malaria model in [23] by:

(i) adding age structure;

(ii) adding the dynamics of exposed and recovered individuals.

5.2 Mathematical Analysis

The thesis further contributes by giving detailed qualitative analyses of the two models, using a diverse collection of theories and techniques from non-linear dynamical systems (such as, comparison theorem, centre manifold theory, Lyapunov function theory, next generation operator method etc.). Some of the main mathematical results obtained are summarized below.

5.2.1 Chapter 3

The age-structured model (3.16) is, first of all, shown to have a locally-asymptotically stable disease-free equilibrium whenever the associated reproduction number is less than unity. The epidemiological implication of this finding is that effective control of malaria in the community is feasible if the initial sizes of the sub-populations of the model are small enough. A notable contribution of this chapter is establishing the presence of the phenomenon of backward bifurcation in the model (3.16). Although models for the transmission dynamics of vector-borne disease are known to exhibit backward bifurcation (see, for instance, [26, 28, 45]), this study is arguably the first to prove the existence of such phenomenon in an age-structured model for malaria transmission in a community. This phenomenon has major epidemiological consequence, since, in a backward bifurcation setting, having the associated reproduction number of the model less than unity is no longer sufficient (*albeit* necessary) for effective disease control. It is further shown that the backward bifurcation property of the model is caused by disease-induced mortality in humans. This chapter shows that more efforts will be required in the quest for effective control of malaria, owing to the presence of backward bifurcation in its transmission dynamics.

It is shown that a reduced version of the model has a unique endemic equilibrium when the associated reproduction number exceeds unity. It should be mentioned that, in general, establishing (rigorously) the existence of an endemic equilibrium of relatively large systems of non-linear equations, such as the age-structured model (3.16), is often a daunting (or impossible) mathematical task. Finally, it is shown that the corresponding malaria transmission model with no age-structure, given by (3.34), has essentially the same qualitative dynamics as the age-structured model (3.16). In other words, one of the main novel contributions of this thesis is establishing that adding age-structure to a basic malaria transmission model does not alter the essential qualitative dynamics of the basic model.

5.2.2 Chapter 4

The model (4.23), for the transmission dynamics of drug-sensitive (wild) and drug-resistant malaria strains in a community, was also rigorously analysed. Results for the local asymptotic stability of the disease-free equilibrium, as well as the mortality-induced backward bifurcation property, of the model were derived. In line with earlier multi-strain models for malaria transmission (such as the model in [23]), it is shown that the model could have resistant strain-only boundary equilibrium and low(high)-endemicity equilibria. Furthermore, it was shown that for the case when anti-malaria treatment does not cause the emergence of drug resistant strain, the low-endemicity equilibrium reduces to a wild strain-only boundary equilibrium. For this (latter) setting, it is shown that the model undergoes the phenomenon of competitive exclusion, where the strain with the higher reproduction number (where both numbers are greater than unity) drives the other to extinction. This result provides insight into which of the two strains will establish itself in the community in the long run.

5.3 Public Health

Extensive numerical simulations of the models developed in this thesis, using a set of parameter values (obtained from the literature), are carried out to gain insight into malaria transmission dynamics in a population. Some of the main public health contributions of the thesis, derived from these simulations, are summarized below:

(a) The cumulative number of new cases of infection and malaria-induced mortality increase with increasing average lifespan and birth rate of mosquitoes;

(b) reduction in mosquito lifespan has marginal effect on cumulative mortality in juveniles;

(c) the cumulative number of new cases and malaria-induced mortality decrease with increasing effectiveness level of the treatment strategy;

(d) disease-induced mortality in humans causes backward bifurcation in malaria transmission dynamics (which makes malaria control in the community difficult);

(e) competitive exclusion occurs in malaria transmission dynamics for the case when drug treatment does not cause resistance.

5.4 Future Work

The work carried out in this thesis can be extended in several directions relevant to malaria transmission dynamics, including:

(i) incorporating the effect of climate change on the dynamics of the malaria vector (mosquito) as well as on the human host. Climatic factors, such as temperature, humidity, rainfall and vapor pressure, are known to significantly affect the incidence of vector-borne diseases, such as malaria (either through changes in the duration of vector and parasite/pathogen life cycles, or by influencing host, vector, or parasite behavior);

(ii) incorporating the effect of vector and host mobility (due to immigration/migration, global travel etc.) This is relevant, considering the cases of incursion of diseases into non-endemic areas (such as the incursion of West Nile virus into North America in the late 1990s [8]);

(iii) assessing the impact of a potential anti-malaria vaccine;

(iv) establishing the global asymptotic stability of the boundary and endemic equilibria of the model in Chapter 4.

Appendix A

Proof of Theorem 3.1

Proof. Let

$$t_1 = sup\{t > 0 : S_{HJ}(t) > 0, S_{HA}(t) > 0, E_{HJ}(t) \geq 0, E_{HA}(t) \geq 0, I_{HJ}(t) \geq 0,$$
$$I_{HA}(t) \geq 0, R_{HJ}(t) \geq 0, R_{HA}(t) \geq 0, S_V(t) > 0, I_V(t) > 0\} > 0.$$

It follows from the first equation of the model (3.16) that

$$\frac{dS_{HJ}}{dt} = \Pi_J + \psi_J R_{HJ} - \lambda_{HJ} S_{HJ} - (\xi + \mu_H) S_{HJ} \geq \Pi_J - \lambda_{HJ} S_{HJ} - (\xi + \mu_H) S_{HJ},$$

which can be written as

$$\frac{d}{dt}\left\{S_{HJ}(t) exp\left[\int_0^t \lambda_{HJ}(u)du + (\xi + \mu_H)t\right]\right\} \geq \Pi_J exp\left[\int_0^t \lambda_{HJ}(u)du + (\xi + \mu_H)t\right],$$

so that,

$$S_{HJ}(t_1)exp\left[\int_0^{t_1}\lambda_{HJ}(u)du+(\xi+\mu_H)t_1\right]-S_{HJ}(0)\geq$$
$$\int_0^{t_1}\Pi_J exp\left[\int_0^{x}\lambda_{HJ}(u)du+(\xi+\mu_H)x\right]dx.$$

Hence,

$$\begin{aligned}S_{HJ}(t_1)\geq S_{HJ}(0)exp&\left[-\int_0^{t_1}\lambda_{HJ}(u)du-(\xi+\mu_H)t_1\right]\\&+exp\left[-\int_0^{t_1}\lambda_{HJ}(u)du-(\xi+\mu_H)t_1\right]\\&\times\int_0^{t_1}\Pi_J exp\left[\int_0^{x}\lambda_{HJ}(u)du+(\xi+\mu_H)x\right]dx>0.\end{aligned}$$

Similarly, it can be shown that $S_{HA}(t)>0$, $E_{HJ}(t)\geq 0$, $E_{HA}(t)\geq 0$, $I_{HJ}(t)\geq 0$, $I_{HA}(t)\geq 0$, $R_{HJ}(t)\geq 0$, $R_{HA}(t)\geq 0$, $S_V(t)>0$ and $I_V(0)\geq 0$ for all time $t>0$. Hence, all solutions of the model (3.16) remain positive for all non-negative initial conditions, as required. □

Appendix B

Proof of Theorem 3.2

Proof. Theorem 3.2 will be proved using Centre Manifold theory [9, 11, 20, 65]. To apply this theory, it is convenient to let $x_1 = S_{HJ}$, $x_2 = S_{HA}$, $x_3 = E_{HJ}$, $x_4 = E_{HA}$, $x_5 = I_{HJ}$, $x_6 = I_{HA}$, $x_7 = R_{HJ}$, $x_8 = R_{HA}$, $x_9 = S_V$ and $x_{10} = I_V$. Furthermore, let $\hat{f} = [f_1, ..., f_{10}]^T$ denote the vector field of the model (3.16). Thus, the model (3.16) can be re-written as:

$$\frac{dx_1}{dt} = f_1 = \Pi_J + \psi_J x_7 - \frac{b_2\beta_{HJ}x_{10}}{\sum\limits_{i=1}^{8} x_i}x_1 - g_1x_1,$$

$$\frac{dx_2}{dt} = f_2 = \xi x_1 + \psi_A x_8 - \frac{b_2\beta_{HA}x_{10}}{\sum\limits_{i=1}^{8} x_i}x_2 - \mu_H x_2,$$

$$\frac{dx_3}{dt} = f_3 = \frac{b_2\beta_{HJ}x_{10}}{\sum\limits_{i=1}^{8} x_i}x_1 - g_2x_3,$$

$$\begin{aligned}
\frac{dx_4}{dt} &= f_4 = \xi x_3 + \frac{b_2\beta_{HA}x_{10}}{\sum\limits_{i=1}^{8} x_i}x_2 - g_3x_4, \\
\frac{dx_5}{dt} &= f_5 = \sigma_{HJ}x_3 - g_4x_5, \\
\frac{dx_6}{dt} &= f_6 = \xi x_5 + \sigma_{HA}x_4 - g_5x_6, \\
\frac{dx_7}{dt} &= f_7 = \gamma_J x_5 - g_6x_7, \\
\frac{dx_8}{dt} &= f_8 = \gamma_A x_6 + \xi x_7 - g_7x_8, \\
\frac{dx_9}{dt} &= f_9 = \Pi_V - \frac{b_2\beta_V[\eta(x_3+x_4)+x_5+x_6]}{\sum\limits_{i=1}^{8} x_i}x_9 - \mu_V x_9,
\end{aligned} \tag{B-1}$$

$$\frac{dx_{10}}{dt} = f_{10} = \frac{b_2\beta_V[\eta(x_3+x_4)+x_5+x_6]}{\sum\limits_{i=1}^{8} x_i}x_9 - \mu_V x_{10},$$

where, $g_1 = \xi + \mu_H$, $g_2 = \sigma_{HJ} + \xi + \mu_H$, $g_3 = \sigma_{HA} + \mu_H$, $g_4 = \xi + \gamma_J + \mu_H + \delta_{HJ}$, $g_5 = \gamma_A + \mu_H + \delta_{HA}$, $g_6 = \psi_J + \xi + \mu_H$ and $g_7 = \psi_A + \mu_H$.

The Jacobian of the transformed system (B-1), evaluated at the DFE ($\mathcal{E}_0$), is given by:

$$J(\mathcal{E}_0) = \begin{bmatrix} -g_1 & 0 & 0 & 0 & 0 & 0 & \psi_J & 0 & 0 & -\dfrac{b_2\beta_{HJ}x_1^*}{x_1^*+x_2^*} \\ \xi & -\mu_H & 0 & 0 & 0 & 0 & 0 & \psi_A & 0 & -\dfrac{b_2\beta_{HA}x_2^*}{x_1^*+x_2^*} \\ 0 & 0 & -g_2 & 0 & 0 & 0 & 0 & 0 & 0 & \dfrac{b_2\beta_{HJ}x_1^*}{x_1^*+x_2^*} \\ 0 & 0 & \xi & -g_3 & 0 & 0 & 0 & 0 & 0 & \dfrac{b_2\beta_{HA}x_2^*}{x_1^*+x_2^*} \\ 0 & 0 & \sigma_{HJ} & 0 & -g_4 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \sigma_{HA} & \xi & -g_5 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \gamma_J & 0 & -g_6 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \gamma_A & \xi & -g_7 & 0 & 0 \\ 0 & 0 & -\dfrac{b_2\beta_V\eta x_9^*}{x_1^*+x_2^*} & -\dfrac{b_2\beta_V\eta x_9^*}{x_1^*+x_2^*} & -\dfrac{b_2\beta_V x_9^*}{x_1^*+x_2^*} & -\dfrac{b_2\beta_V x_9^*}{x_1^*+x_2^*} & 0 & 0 & -\mu_V & 0 \\ 0 & 0 & \dfrac{b_2\beta_V\eta x_9^*}{x_1^*+x_2^*} & \dfrac{b_2\beta_V\eta x_9^*}{x_1^*+x_2^*} & \dfrac{b_2\beta_V x_9^*}{x_1^*+x_2^*} & \dfrac{b_2\beta_V x_9^*}{x_1^*+x_2^*} & 0 & 0 & 0 & -\mu_V \end{bmatrix}.$$

Consider the case when $\mathcal{R}_0 = 1$. Suppose, further, $\beta_{HJ} = \beta_{HJ}^*$ is chosen as a bifurcation parameter. Solving for β_{HJ} from $\mathcal{R}_0 = 1$ gives

$$\beta_{HJ} = \beta_{HJ}^* = \frac{\Pi_J\mu_V^2 g_1 g_3 g_5 - \beta_{HA}\beta_V\Pi_V\mu_H\xi b^2(\eta g_5 + \sigma_{HA})}{\Pi_V\beta_V b^2\mu_H^2\{g_4[\eta g_5(g_3+\xi) + \sigma_{HA}\xi] + \sigma_{HJ}g_3(g_5+\xi)\}}.$$

It is convenient to define:

$$A_0 = -g_3\sigma_{HJ}\{g_1 g_5\gamma_J\mu_H + g_6[\gamma_A\psi_A + n_0(g_1+\delta_{HJ})]\} - g_1 g_4 g_6(\gamma_A\psi_A\mu_H + n_0 g_3) < 0,$$

$$A_1 = -[g_3(\psi_A\sigma_{HA} + g_5\mu_H) + g_5\psi_A\mu_H] < 0,$$

$$A_2 = g_4[\sigma_{HA}\xi + g_5\eta(\xi+g_3)] + g_3\sigma_{HJ}(g_5+\xi) > 0,$$

$$A_3 = \sigma_{HA} + g_5\eta > 0,$$

where $n_0 = g_7(\sigma_{HA} + \mu_H) + \gamma_A\mu_H$.

The right eigenvector of $J(\mathcal{E}_0)|_{\beta_{HJ}=\beta_{HJ}^*}$ is given by

$\mathbf{w} = (w_1, w_2, w_3, w_4, w_5, w_6, w_7, w_8, w_9, w_{10})^T$, where (since $A_0 < 0$, $A_1 < 0$,

$A_2 > 0$ and $A_3 > 0$)

$$w_1 = \frac{-\beta^*_{HJ} b_2 \mu_H \{\psi_J[\gamma_J g_1 + (\xi + \delta_{HJ} + \mu_H) g_2] + g_1 g_2 g_4\}}{g_1^2 g_2 g_4 g_6} w_{10} < 0,$$

$$w_2 = \frac{b_2 \xi (\beta^*_{HJ} \mu_H A_0 + g_1 g_2 g_4 g_6 \beta_{HA} A_1)}{\mu_H g_1^2 \left(\prod_{i=2}^{7} g_i \right)} w_{10} < 0,$$

$$w_3 = \frac{b_2 \beta^*_{HJ} \mu_H}{g_1 g_2} w_{10}, w_4 = \frac{b_2 \xi (g_2 \beta_{HA} + \beta^*_{HJ} \mu_H)}{\prod_{i=1}^{3} g_i} w_{10}, w_5 = \frac{b_2 \sigma_{HJ} \beta^*_{HJ} \mu_H}{g_1 g_2 g_4} w_{10},$$

$$w_6 = \frac{b_2 \xi [g_2 g_4 \sigma_{HA} \beta_{HA} + \beta^*_{HJ} \mu_H (g_4 \sigma_{HA} + g_3 \sigma_{HJ})]}{\prod_{i=1}^{5} g_i} w_{10}, w_7 = \frac{b_2 \sigma_{HJ} \beta^*_{HJ} \gamma_J \mu_H}{g_1 g_2 g_4 g_6} w_{10},$$

$$w_8 = \frac{b_2 \xi [\beta^*_{HJ} (g_3 g_5 \sigma_{HJ} \gamma_J + g_3 g_6 \sigma_{HJ} \gamma_A + g_4 g_6 \sigma_{HA} \gamma_A) + g_2 g_4 g_6 \sigma_{HA} \beta_{HA} \gamma_A \mu_H]}{\prod_{i=1}^{7} g_i} w_{10},$$

$$w_9 = \frac{-(b_2)^2 \beta_V \mu_H \Pi_V (\beta^*_{HJ} \mu_H A_2 + g_2 g_4 \beta_{HA} \xi A_3)}{\mu_V^2 \Pi_J \left(\prod_{i=1}^{5} g_i \right)} w_{10} < 0, w_{10} = w_{10} > 0.$$

Similarly, $J(\mathcal{E}_0)|_{\beta_{HJ} = \beta^*_{HJ}}$ has a left eigenvector $\mathbf{v} = (v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9, v_{10})$, where

$$v_1 = 0, v_2 = 0, v_3 = \frac{b_2 \beta_V \mu_H \Pi_V (g_3 \sigma_{HJ} \xi + g_4 \xi g_5 \eta + g_3 g_5 g_4 \eta + g_3 \sigma_{HJ} g_5 + g_4 \xi \sigma_{HA})}{\mu_V \Pi_J \left(\prod_{i=2}^{5} g_i \right)} v_{10},$$

$$v_4 = \frac{b_2 \beta_V \mu_H \Pi_V (g_5 \eta + \sigma_{HA})}{g_5 g_3 \mu_V \Pi_J} v_{10}, v_5 = \frac{b_2 \beta_V \mu_H \Pi_V (g_5 + \xi)}{g_4 g_5 \mu_V \Pi_J} v_{10}, v_6 = \frac{b_2 \beta_V \mu_H \Pi_V}{g_5 \mu_V \Pi_J} v_{10},$$

$$v_7 = 0, v_8 = 0, v_9 = 0, v_{10} > 0.$$

The transformed system (B-1), with $\beta_{HJ} = \beta^*_{HJ}$, has a simple eigenvalue with zero real part (and all other eigenvalues have negative real part). Hence, Centre Manifold theory can be used to analyse the dynamics of (B-1) near $\beta_{HJ} = \beta^*_{HJ}$ [9, 11, 20, 65]. In particular, Theorem 2.7 will be used.

For the transformed system (B-1), the associated non-zero partial derivatives of the right-hand side functions, f_i $(i = 1...10)$, are given by:

$$\frac{\partial^2 f_1}{\partial x_1 \partial x_{10}} = \frac{\partial^2 f_1}{\partial x_{10} \partial x_1} = \frac{-b_2 \beta^*_{HJ} \mu_H \xi}{\Pi_J g_1}; \frac{\partial^2 f_1}{\partial x_2 \partial x_{10}} = \frac{\partial^2 f_1}{\partial x_3 \partial x_{10}} = \frac{\partial^2 f_1}{\partial x_4 \partial x_{10}} = \frac{\partial^2 f_1}{\partial x_5 \partial x_{10}} =$$
$$\frac{\partial^2 f_1}{\partial x_6 \partial x_{10}} = \frac{\partial^2 f_1}{\partial x_7 \partial x_{10}} = \frac{\partial^2 f_1}{\partial x_8 \partial x_{10}} = \frac{\partial^2 f_1}{\partial x_{10} \partial x_2} = \frac{\partial^2 f_1}{\partial x_{10} \partial x_3} = \frac{\partial^2 f_1}{\partial x_{10} \partial x_4} = \frac{\partial^2 f_1}{\partial x_{10} \partial x_5} =$$
$$\frac{\partial^2 f_1}{\partial x_{10} \partial x_6} = \frac{\partial^2 f_1}{\partial x_{10} \partial x_7} = \frac{\partial^2 f_1}{\partial x_{10} \partial x_8} = \frac{b_2 \beta^*_{HJ} \mu_H^2}{\Pi_J g_1}; \frac{\partial^2 f_2}{\partial x_1 \partial x_{10}} = \frac{\partial^2 f_2}{\partial x_3 \partial x_{10}} = \frac{\partial^2 f_2}{\partial x_4 \partial x_{10}} =$$
$$\frac{\partial^2 f_2}{\partial x_5 \partial x_{10}} = \frac{\partial^2 f_2}{\partial x_6 \partial x_{10}} = \frac{\partial^2 f_2}{\partial x_7 \partial x_{10}} = \frac{\partial^2 f_2}{\partial x_8 \partial x_{10}} = \frac{\partial^2 f_2}{\partial x_{10} \partial x_1} = \frac{\partial^2 f_2}{\partial x_{10} \partial x_3} = \frac{\partial^2 f_2}{\partial x_{10} \partial x_4} =$$
$$\frac{\partial^2 f_2}{\partial x_{10} \partial x_5} = \frac{\partial^2 f_2}{\partial x_{10} \partial x_6} = \frac{\partial^2 f_2}{\partial x_{10} \partial x_7} = \frac{\partial^2 f_2}{\partial x_{10} \partial x_8} = \frac{b_2 \beta_{HA} \mu_H \xi}{\Pi_J g_1};$$
$$\frac{\partial^2 f_2}{\partial x_2 \partial x_{10}} = \frac{\partial^2 f_2}{\partial x_{10} \partial x_2} = \frac{-b_2 \beta_{HA} \mu_H^2}{\Pi_J g_1}; \frac{\partial^2 f_3}{\partial x_1 \partial x_{10}} = \frac{\partial^2 f_3}{\partial x_{10} \partial x_1} = \frac{b_2 \beta^*_{HJ} \mu_H \xi}{\Pi_J g_1};$$
$$\frac{\partial^2 f_3}{\partial x_2 \partial x_{10}} = \frac{\partial^2 f_3}{\partial x_3 \partial x_{10}} = \frac{\partial^2 f_3}{\partial x_4 \partial x_{10}} = \frac{\partial^2 f_3}{\partial x_5 \partial x_{10}} = \frac{\partial^2 f_3}{\partial x_6 \partial x_{10}} = \frac{\partial^2 f_3}{\partial x_7 \partial x_{10}} = \frac{\partial^2 f_3}{\partial x_8 \partial x_{10}} =$$
$$\frac{\partial^2 f_3}{\partial x_{10} \partial x_2} = \frac{\partial^2 f_3}{\partial x_{10} \partial x_3} = \frac{\partial^2 f_3}{\partial x_{10} \partial x_4} = \frac{\partial^2 f_3}{\partial x_{10} \partial x_5} = \frac{\partial^2 f_3}{\partial x_{10} \partial x_6} = \frac{\partial^2 f_3}{\partial x_{10} \partial x_7} = \frac{\partial^2 f_3}{\partial x_{10} \partial x_8} =$$
$$\frac{-b_2 \beta^*_{HJ} \mu_H^2}{\Pi_J g_1}; \frac{\partial^2 f_4}{\partial x_1 \partial x_{10}} = \frac{\partial^2 f_4}{\partial x_3 \partial x_{10}} = \frac{\partial^2 f_4}{\partial x_4 \partial x_{10}} = \frac{\partial^2 f_4}{\partial x_5 \partial x_{10}} = \frac{\partial^2 f_4}{\partial x_6 \partial x_{10}} = \frac{\partial^2 f_4}{\partial x_7 \partial x_{10}} =$$
$$\frac{\partial^2 f_4}{\partial x_8 \partial x_{10}} = \frac{\partial^2 f_4}{\partial x_{10} \partial x_1} = \frac{\partial^2 f_4}{\partial x_{10} \partial x_3} = \frac{\partial^2 f_4}{\partial x_{10} \partial x_4} = \frac{\partial^2 f_4}{\partial x_{10} \partial x_5} = \frac{\partial^2 f_4}{\partial x_{10} \partial x_6} = \frac{\partial^2 f_4}{\partial x_{10} \partial x_7} =$$
$$\frac{\partial^2 f_4}{\partial x_{10} \partial x_8} = \frac{-b_2 \beta_{HA} \mu_H \xi}{\Pi_J g_1}; \frac{\partial^2 f_4}{\partial x_2 \partial x_{10}} = \frac{\partial^2 f_4}{\partial x_{10} \partial x_2} = \frac{b_2 \beta_{HA} \mu_H^2}{\Pi_J g_1}; \frac{\partial^2 f_9}{\partial x_1 \partial x_3} = \frac{\partial^2 f_9}{\partial x_1 \partial x_4} =$$
$$\frac{\partial^2 f_9}{\partial x_2 \partial x_3} = \frac{\partial^2 f_9}{\partial x_2 \partial x_4} = \frac{\partial^2 f_9}{\partial x_3 \partial x_1} = \frac{\partial^2 f_9}{\partial x_3 \partial x_2} = \frac{\partial^2 f_9}{\partial x_3 \partial x_7} = \frac{\partial^2 f_9}{\partial x_3 \partial x_8} = \frac{\partial^2 f_9}{\partial x_4 \partial x_1} =$$
$$\frac{\partial^2 f_9}{\partial x_4 \partial x_2} = \frac{\partial^2 f_9}{\partial x_4 \partial x_7} = \frac{\partial^2 f_9}{\partial x_4 \partial x_8} = \frac{\partial^2 f_9}{\partial x_7 \partial x_3} = \frac{\partial^2 f_9}{\partial x_7 \partial x_4} = \frac{\partial^2 f_9}{\partial x_8 \partial x_3} = \frac{\partial^2 f_9}{\partial x_8 \partial x_4} =$$

$$\frac{b_2\beta_V\eta\mu_H^2\Pi_V}{\Pi_J^2\mu_V}; \frac{\partial^2 f_9}{\partial x_1\partial x_5} = \frac{\partial^2 f_9}{\partial x_1\partial x_6} = \frac{\partial^2 f_9}{\partial x_2\partial x_5} = \frac{\partial^2 f_9}{\partial x_2\partial x_6} = \frac{\partial^2 f_9}{\partial x_4\partial x_5} = \frac{\partial^2 f_9}{\partial x_4\partial x_6} =$$
$$\frac{\partial^2 f_9}{\partial x_4\partial x_6} = \frac{\partial^2 f_9}{\partial x_5\partial x_1} = \frac{\partial^2 f_9}{\partial x_5\partial x_2} = \frac{\partial^2 f_9}{\partial x_5\partial x_7} = \frac{\partial^2 f_9}{\partial x_5\partial x_8} = \frac{\partial^2 f_9}{\partial x_6\partial x_1} = \frac{\partial^2 f_9}{\partial x_6\partial x_2} =$$
$$\frac{\partial^2 f_9}{\partial x_6\partial x_7} = \frac{\partial^2 f_9}{\partial x_6\partial x_8} = \frac{\partial^2 f_9}{\partial x_7\partial x_5} = \frac{\partial^2 f_9}{\partial x_7\partial x_6} = \frac{\partial^2 f_9}{\partial x_8\partial x_5} = \frac{\partial^2 f_9}{\partial x_8\partial x_6} = \frac{b_2\beta_V\mu_H^2\Pi_V}{\Pi_J^2\mu_V};$$
$$\frac{\partial^2 f_9}{\partial x_1\partial x_5} = \frac{\partial^2 f_9}{\partial x_1\partial x_6} = \frac{\partial^2 f_9}{\partial x_2\partial x_5} = \frac{\partial^2 f_9}{\partial x_2\partial x_6} = \frac{\partial^2 f_9}{\partial x_4\partial x_5} = \frac{\partial^2 f_9}{\partial x_4\partial x_6} = \frac{\partial^2 f_9}{\partial x_4\partial x_6} =$$
$$\frac{\partial^2 f_9}{\partial x_5\partial x_1} = \frac{\partial^2 f_9}{\partial x_5\partial x_2} = \frac{\partial^2 f_9}{\partial x_5\partial x_7} = \frac{\partial^2 f_9}{\partial x_5\partial x_8} = \frac{\partial^2 f_9}{\partial x_6\partial x_1} = \frac{\partial^2 f_9}{\partial x_6\partial x_2} = \frac{\partial^2 f_9}{\partial x_6\partial x_7} =$$
$$\frac{\partial^2 f_9}{\partial x_6\partial x_8} = \frac{\partial^2 f_9}{\partial x_7\partial x_5} = \frac{\partial^2 f_9}{\partial x_7\partial x_6} = \frac{\partial^2 f_9}{\partial x_8\partial x_5} = \frac{\partial^2 f_9}{\partial x_8\partial x_6} = \frac{b_2\beta_V\mu_H^2\Pi_V}{\Pi_J^2\mu_V};$$
$$\frac{\partial^2 f_9}{\partial x_3\partial x_3} = \frac{\partial^2 f_9}{\partial x_3\partial x_4} = \frac{\partial^2 f_9}{\partial x_4\partial x_3} = \frac{\partial^2 f_9}{\partial x_4\partial x_4} = \frac{2b_2\beta_V\eta\mu_H^2\Pi_V}{\Pi_J^2\mu_V}; \frac{\partial^2 f_9}{\partial x_5\partial x_5} = \frac{\partial^2 f_9}{\partial x_5\partial x_6} =$$
$$\frac{\partial^2 f_9}{\partial x_6\partial x_5} = \frac{\partial^2 f_9}{\partial x_6\partial x_6} = \frac{2b_2\beta_V\mu_H^2\Pi_V}{\Pi_J^2\mu_V}; \frac{\partial^2 f_9}{\partial x_5\partial x_9} = \frac{\partial^2 f_9}{\partial x_6\partial x_9} = \frac{\partial^2 f_9}{\partial x_9\partial x_5} = \frac{\partial^2 f_9}{\partial x_9\partial x_6} =$$
$$\frac{-b_2\beta_V\mu_H}{\Pi_J}; \frac{\partial^2 f_9}{\partial x_3\partial x_9} = \frac{\partial^2 f_9}{\partial x_4\partial x_9} = \frac{\partial^2 f_9}{\partial x_9\partial x_3} = \frac{\partial^2 f_9}{\partial x_9\partial x_4} = \frac{-b_2\beta_V\eta\mu_H}{\Pi_J}; \frac{\partial^2 f_9}{\partial x_3\partial x_5} =$$
$$\frac{\partial^2 f_9}{\partial x_3\partial x_6} = \frac{\partial^2 f_9}{\partial x_4\partial x_5} = \frac{\partial^2 f_9}{\partial x_4\partial x_6} = \frac{\partial^2 f_9}{\partial x_5\partial x_3} = \frac{\partial^2 f_9}{\partial x_5\partial x_4} = \frac{\partial^2 f_9}{\partial x_6\partial x_3} = \frac{\partial^2 f_9}{\partial x_6\partial x_4} =$$
$$\frac{b_2\beta_V\mu_H\Pi_V(1+\eta)}{\Pi_J\mu_V}; \frac{\partial^2 f_{10}}{\partial x_1\partial x_3} = \frac{\partial^2 f_{10}}{\partial x_1\partial x_4} = \frac{\partial^2 f_{10}}{\partial x_2\partial x_3} = \frac{\partial^2 f_{10}}{\partial x_2\partial x_4} =$$
$$\frac{\partial^2 f_{10}}{\partial x_3\partial x_1} = \frac{\partial^2 f_{10}}{\partial x_3\partial x_2} = \frac{\partial^2 f_{10}}{\partial x_3\partial x_7} = \frac{\partial^2 f_{10}}{\partial x_3\partial x_8} = \frac{\partial^2 f_{10}}{\partial x_4\partial x_1} = \frac{\partial^2 f_{10}}{\partial x_4\partial x_2} = \frac{\partial^2 f_{10}}{\partial x_4\partial x_7} =$$
$$\frac{\partial^2 f_{10}}{\partial x_4\partial x_8} = \frac{\partial^2 f_{10}}{\partial x_7\partial x_3} = \frac{\partial^2 f_{10}}{\partial x_7\partial x_4} = \frac{\partial^2 f_{10}}{\partial x_8\partial x_3} = \frac{\partial^2 f_{10}}{\partial x_8\partial x_4} = \frac{b_2\beta_V\eta\mu_H^2\Pi_V}{\Pi_J^2\mu_V}; \frac{\partial^2 f_{10}}{\partial x_1\partial x_5} =$$
$$\frac{\partial^2 f_{10}}{\partial x_1\partial x_6} = \frac{\partial^2 f_{10}}{\partial x_2\partial x_5} = \frac{\partial^2 f_{10}}{\partial x_2\partial x_6} = \frac{\partial^2 f_{10}}{\partial x_4\partial x_5} = \frac{\partial^2 f_{10}}{\partial x_4\partial x_6} = \frac{\partial^2 f_{10}}{\partial x_4\partial x_6} = \frac{\partial^2 f_{10}}{\partial x_5\partial x_1} =$$
$$\frac{\partial^2 f_{10}}{\partial x_5\partial x_2} = \frac{\partial^2 f_{10}}{\partial x_5\partial x_7} = \frac{\partial^2 f_{10}}{\partial x_5\partial x_8} = \frac{\partial^2 f_{10}}{\partial x_6\partial x_1} = \frac{\partial^2 f_{10}}{\partial x_6\partial x_2} = \frac{\partial^2 f_{10}}{\partial x_6\partial x_7} = \frac{\partial^2 f_{10}}{\partial x_6\partial x_8} =$$
$$\frac{\partial^2 f_{10}}{\partial x_7\partial x_5} = \frac{\partial^2 f_{10}}{\partial x_7\partial x_6} = \frac{\partial^2 f_{10}}{\partial x_8\partial x_5} = \frac{\partial^2 f_{10}}{\partial x_8\partial x_6} = \frac{b_2\beta_V\mu_H^2\Pi_V}{\Pi_J^2\mu_V}; \frac{\partial^2 f_{10}}{\partial x_3\partial x_3} = \frac{\partial^2 f_{10}}{\partial x_3\partial x_4} =$$
$$\frac{\partial^2 f_{10}}{\partial x_4\partial x_3} = \frac{\partial^2 f_{10}}{\partial x_4\partial x_4} = \frac{2b_2\beta_V\eta\mu_H^2\Pi_V}{\Pi_J^2\mu_V}; \frac{\partial^2 f_{10}}{\partial x_5\partial x_5} = \frac{\partial^2 f_{10}}{\partial x_5\partial x_6} = \frac{\partial^2 f_{10}}{\partial x_6\partial x_5} =$$
$$\frac{\partial^2 f_{10}}{\partial x_6\partial x_6} = \frac{2b_2\beta_V\mu_H^2\Pi_V}{\Pi_J^2\mu_V}; \frac{\partial^2 f_{10}}{\partial x_5\partial x_9} = \frac{\partial^2 f_{10}}{\partial x_6\partial x_9} = \frac{\partial^2 f_{10}}{\partial x_9\partial x_5} = \frac{\partial^2 f_{10}}{\partial x_9\partial x_6} = \frac{-b_2\beta_V\mu_H}{\Pi_J};$$
$$\frac{\partial^2 f_{10}}{\partial x_3\partial x_9} = \frac{\partial^2 f_{10}}{\partial x_4\partial x_9} = \frac{\partial^2 f_{10}}{\partial x_9\partial x_3} = \frac{\partial^2 f_{10}}{\partial x_9\partial x_4} = \frac{-b_2\beta_V\eta\mu_H}{\Pi_J}; \frac{\partial^2 f_{10}}{\partial x_3\partial x_5} = \frac{\partial^2 f_{10}}{\partial x_3\partial x_6} =$$
$$\frac{\partial^2 f_{10}}{\partial x_4\partial x_5} = \frac{\partial^2 f_9}{\partial x_4\partial x_6} = \frac{\partial^2 f_{10}}{\partial x_5\partial x_3} = \frac{\partial^2 f_9}{\partial x_5\partial x_4} = \frac{\partial^2 f_{10}}{\partial x_6\partial x_3} = \frac{\partial^2 f_9}{\partial x_6\partial x_4} =$$

$$\frac{b_2\beta_V\mu_H\Pi_V(1+\eta)}{\Pi_J\mu_V}$$

It then follows from Theorem 2.7, and using the above expressions for the non-zero partial derivatives f_i $(i = 1, ..., 10)$ and eigenvectors w_i and v_i $(i = 1, ..., 10)$, that the associated backward bifurcation coefficients, denoted by a and b, are, respectively, given by:

$$a = \sum_{k,i,j=1}^{11} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0),$$

$$= 2\left\{\frac{\mu_H b_2\beta_V}{\Pi_J}\left[\frac{\Pi_V\mu_H}{\Pi_J\mu_V}(h_0 - h_1) - \frac{h_4}{\Pi_J} + h_2 - \eta h_3\right] + \frac{\mu_H^2 b_2\beta_{HJ}^*}{\Pi_J}\left(\frac{h_8}{\Pi_J} - \frac{h_5}{\xi+\mu_H}\right)\right.$$
$$\left. + b_2\beta_{HA}\left(\frac{\mu_H^2}{\Pi_J^2}h_7 - \frac{\xi}{\xi+\mu_H}h_6\right)\right\}, \tag{B-2}$$

and,

$$b = \sum_{k,i,j=1}^{11} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0) = \frac{(b_2\mu_H)^2\beta_V\Pi_V C_0}{\Pi_J\mu_V\left(\prod_{i=1}^{5} g_i\right)} v_{10}w_{10} > 0.$$

In (B-2),

$$h_0 = v_{10}[w_5(w_1 + w_2) + w_6 w_3]\left(\sum_{i=4}^{8} w_i\right),$$

$$h_1 = v_{10}\left[\sum_{i=6}^{8} w_i + w_1 + w_2 + w_4 + w_3(w_3 - w_9) + w_4 w_5\right],$$

$$h_2 = v_{10}[(w_1 + w_2 + w_9) + w_5 w_9], h_3 = v_{10} w_3 w_5, h_4 = v_{10} w_3 w_5,$$

$$h_5 = v_3\left(w_1 + \sum_{i=2}^{8} w_i\right), h_6 = v_4\left(w_2 + \sum_{i=4}^{8} w_i\right), h_7 = v_4 w_2, h_8 = v_3 w_1,$$

$$C_0 = g_3\sigma_{HJ}(g_5 + \xi) + g_4 g_5 \eta(g_3 + \xi) + g_4\sigma_{HA}\xi.$$

It can be shown from (B-2) that the bifurcation coefficient, a, is positive whenever,

$$K_0 > K_1, \tag{B-3}$$

where,

$$\begin{aligned} K_0 = &- \frac{\Pi_V \mu_H^2 b_2 \beta_V}{\Pi_J^2 \mu_V}\left[v_{10}(w_1 + w_2)(w_5 + \eta)\right] \\ &- \left(\frac{b_2}{\xi + \mu_H}\right)\left[\frac{\mu_H^2 \beta_{HJ}^*}{\Pi_J} v_3(w_1 + w_2) + \beta_{HA}\xi v_4 w_2\right], \end{aligned}$$

$$\begin{aligned} K_1 = &- \frac{\Pi_V \mu_H^2 b_2 \beta_V}{\Pi_J^2 \mu_V}\left(\sum_{i=4}^{8} w_i\right) v_{10} w_6 w_3 \\ &- \frac{\Pi_V \mu_H^2 b_2 \beta_V \eta}{\Pi_J^2 \mu_V} v_{10}[w_4 + w_6 + w_7 + w_8 + w_3(w_3 - w_9) + w_4 w_5] \\ &+ \frac{\mu_H b_2 \beta_V}{\Pi_J} v_{10}[(w_1 + w_2 + w_9) + w_5 w_9] - \frac{\mu_H b_2 \beta_V \eta}{\Pi_J} v_{10} w_3 w_5 \\ &- \frac{\Pi_V \mu_H b_2 \beta_V}{\Pi_J \mu_V} v_{10} w_3 w_5 - \frac{\mu_H^2 b_2 \beta_{HJ}^* v_3}{\Pi_J(\xi + \mu_H)}\left(\sum_{i=3}^{8} w_i\right) \\ &- \frac{\Pi_V \mu_H b_2 \beta_V v_4}{\Pi_J \mu_V}\left(\sum_{i=4}^{8} w_i\right) + \frac{\mu_H^2 b_2 \beta_{HA}}{\Pi_J^2} v_4 w_2 + \frac{\mu_H^2 b_2 \beta_{HJ}^*}{\Pi_J^2} v_3 w_1. \end{aligned}$$

Thus, it follows from Theorem 2.7 that the model (3.16) undergoes a backward bifurcation at $\mathcal{R}_0 = 1$ whenever the inequality (B-3) holds. □

Appendix C

Proof of Theorem 3.3

Proof. Consider the model (3.16) with $\delta_{HJ} = \delta_{HA} = \psi_J = \psi_A = 0$ and $\mathcal{R}_1 < 1$. The proof is based on using the following Lyapunov function:

$$\mathcal{F} = f_1 E_{HJ} + f_2 E_{HA} + f_3 I_{HJ} + f_4 I_{HA} + I_V, \tag{C-1}$$

where,

$$\begin{aligned} f_1 &= \frac{\Pi_V \mu_H b_2 \beta_V \left\{ g_3 g_5 (\eta g_4 + \sigma_{HJ}) + \xi [g_4 (\eta g_5 + \sigma_{HA}) + \sigma_{HJ} g_3] \right\}}{\Pi_J \mu_V \mathcal{R}_1 \left(\prod_{i=2}^{5} g_i \right)}, \\ f_2 &= \frac{\Pi_V \mu_H b_2 \beta_V (\eta g_5 + \sigma_{HA})}{\Pi_J \mu_V \mathcal{R}_1 g_3 g_5}, f_3 = \frac{\Pi_V \mu_H b_2 \beta_V (g_5 + \xi)}{\Pi_J \mu_V \mathcal{R}_1 g_4 g_5}, f_4 = \frac{\Pi_V \mu_H b_2 \beta_V}{\Pi_J \mu_V \mathcal{R}_1 g_5}. \end{aligned} \tag{C-2}$$

The Lyapunov derivative of (C-1) is given by

$$\dot{\mathcal{F}} = f_1\dot{E}_{HJ} + f_2\dot{E}_{HA} + f_3\dot{I}_{HJ} + f_4\dot{I}_{HA} + \dot{I}_V,$$

$$\begin{aligned}
&= f_1\left[\frac{\mu_H b_2\beta_{HJ}I_V}{\Pi_J}S_{HJ} - (\sigma_{HJ}+\xi+\mu_H)E_{HJ}\right] \\
&+ f_2\left[\xi E_{HJ} + \frac{\mu_H b_2\beta_{HA}I_V}{\Pi_J}S_{HA} - (\sigma_{HA}+\mu_H)E_{HA}\right] \\
&+ f_3\left[\sigma_{HJ}E_{HJ} - (\gamma_J+\xi+\mu_H)I_{HJ}\right] \\
&+ f_4\left[\xi I_{HJ} + \sigma_{HA}E_{HA} - (\gamma_A+\mu_H)I_{HA}\right] \\
&+ \left\{\frac{\mu_H b_2\beta_V[\eta(E_{HJ}+E_{HA}) + I_{HJ} + I_{HA}]}{\Pi_J}S_V - \mu_V I_V\right\},
\end{aligned}$$

which can be simplified to

$$\begin{aligned}
\dot{\mathcal{F}} = &\Bigg[-\frac{\Pi_V\mu_H b_2\beta_V(\eta g_3g_4g_5 + \eta\xi g_4g_5 + \sigma_{HJ}g_3g_5 + \xi\sigma_{HA}g_4 + \xi\sigma_{HJ}g_3)}{\Pi_J\mu_V\mathcal{R}_1\left(\prod_{i=2}^{5} g_i\right)}(\sigma_{HJ}+\xi+\mu_H) \\
&+ \frac{\Pi_V\mu_H b_2\beta_V g_2g_4(\eta g_5+\sigma_{HA})}{\Pi_J\mu_V\mathcal{R}_1\left(\prod_{i=2}^{5} g_i\right)}\xi + \frac{\Pi_V\mu_H b_2\beta_V g_2g_3(g_5+\xi)}{\Pi_J\mu_V\mathcal{R}_1\left(\prod_{i=2}^{5} g_i\right)}\sigma_{HJ} + \frac{\mu_H\eta b_2\beta_V}{\Pi_J}S_V\Bigg]E_{HJ} \\
&+ \Bigg[-\frac{\Pi_V\mu_H b_2\beta_V g_2g_4(\eta g_5+\sigma_{HA})}{\Pi_J\mu_V\mathcal{R}_1\left(\prod_{i=2}^{5} g_i\right)}(\sigma_{HA}+\mu_H) + \frac{\Pi_V\mu_H b_2\beta_V}{\Pi_J\mu_V\mathcal{R}_1 g_5}\sigma_{HA} + \frac{\mu_H\eta b_2\beta_V}{\Pi_J}S_V\Bigg]E_{HA} \\
&+ \Bigg[-\frac{\Pi_V\mu_H b_2\beta_V g_2g_3(g_5+\xi)}{\Pi_J\mu_V\mathcal{R}_1\left(\prod_{i=2}^{5} g_i\right)}(\gamma_J+\xi+\mu_H) + \frac{\Pi_V\mu_H b_2\beta_V}{\Pi_J\mu_V\mathcal{R}_1 g_5}\xi + \frac{\mu_H b_2\beta_V}{\Pi_J}S_V\Bigg]I_{HJ} \\
&+ \Bigg[-\frac{\Pi_V\mu_H b_2\beta_V}{\Pi_J\mu_V\mathcal{R}_1 g_5}(\gamma_A+\mu_H) + \frac{\mu_H b\beta_V}{\Pi_J}S_V\Bigg]I_{HA}
\end{aligned} \tag{C-3}$$

$$+\left[\frac{\Pi_V\mu_H b_2\beta_V(\eta g_3g_4g_5+\eta\xi g_4g_5+\sigma_{HJ}g_3g_5+\xi\sigma_{HA}g_4+\xi\sigma_{HJ}g_3)}{\Pi_J\mu_V\mathcal{R}_1\left(\prod_{i=2}^{5}g_i\right)}\left(\frac{\mu_H b_2\beta_{HJ}}{\Pi_J}S_{HJ}\right)\right.$$
$$\left.+\frac{\Pi_V\mu_H b_2\beta_V g_2g_4(\eta g_5+\sigma_{HA})}{\Pi_J\mu_V\mathcal{R}_1\left(\prod_{i=2}^{5}g_i\right)}\left(\frac{\mu_H b_2\beta_{HA}}{\Pi_J}S_{HA}\right)-\mu_V\right]I_V.$$

Since $S_{HJ}\leq S^*_{HJ}$, $S_{HA}\leq S^*_{HA}$, and $S_V\leq S^*_V$ in $\mathcal{D}_1$, it follows that

$$\dot{\mathcal{F}}\leq\left(1-\frac{1}{\mathcal{R}_1}\right)\left(\frac{\Pi_V\mu_H\eta b_2\beta_V}{\Pi_J\mu_V}E_{HJ}+\frac{\Pi_V\mu_H\eta b_2\beta_V}{\Pi_J\mu_V}E_{HA}\right.$$
$$\left.+\frac{\Pi_V\mu_H b_2\beta_V}{\Pi_J\mu_V}I_{HJ}+\frac{\Pi_V\mu_H b_2\beta_V}{\Pi_J\mu_V}I_{HA}+\mu_V\mathcal{R}_1I_V\right)\leq 0\quad\text{for}\quad\mathcal{R}_1\leq 1.$$

Thus, $\dot{\mathcal{F}}\leq 0$ if $\mathcal{R}_1\leq 1$ with $\dot{\mathcal{F}}=0$ if and only if $E_{HJ}=E_{HA}=I_{HJ}=I_{HA}=I_V=0$. Furthermore, the largest compact invariant set in

$$\{(S_{HJ},S_{HA},E_{HJ},E_{HA},I_{HJ},I_{HA},R_{HJ},R_{HA},S_V,I_V)\in\mathcal{D}_1:\dot{\mathcal{F}}=0\}$$

is the singleton $\{\mathcal{E}_0\}$. Thus, it follows from the LaSalle′s invariance principle (Theorem 6.4 of [38]) that every solution to the equations of the model (3.16), in the absence of disease-induced (i.e, $\delta_{HJ}=\delta_{HA}=0$) and loss of infection-acquired immunity (i.e., $\psi_J=\psi_A=0$), with initial conditions in $\mathcal{D}_1$ converges to the DFE, $\mathcal{E}_0$, as $t\to\infty$. That is,

$$(E_{HJ}(t),E_{HA}(t),I_{HJ}(t),I_{HA}(t),I_V(t))\to(0,0,0,0,0)\quad\text{as}\quad t\to\infty.$$

Substituting $E_{HJ}=E_{HA}=I_{HJ}=I_{HA}=I_V=0$ into the first, second and ninth equations of the age-structured model (3.16), with $\delta_{HJ}=\delta_{HA}=\psi_J=\psi_A=0$, gives $S_{HJ}(t)\to S^*_{HJ}$, $S_{HA}(t)\to S^*_{HA}$ and $S_V(t)\to S^*_V$ as $t\to\infty$. Thus,

$$[S_{HJ}(t), S_{HA}(t), E_{HJ}(t), E_{HA}(t), I_{HJ}(t), I_{HA}(t), R_{HJ}(t), R_{HA}(t), S_V(t), I_V(t)]$$
$$\to (S^*_{HJ}, S^*_{HA}, 0, 0, 0, 0, 0, 0, S^*_V, 0) \quad \text{as} \quad t \to \infty$$

Thus, the DFE of the model (3.16), is GAS in $\mathcal{D}_1$ if $\mathcal{R}_1 \leq 1$ and $\psi_J = \psi_A = 0$. $\square$

Appendix D

Proof of Theorem 3.5

Proof. Consider the reduced model (3.34) with $\mathcal{R}_{02} > 1$ (so that the unique EEP, $\hat{\mathcal{E}}_1$, of the model (3.34), exists). It is clear from (3.34) that, for the case when $\psi_H = 0$, the recovered population $R_H(t) \to 0$ as $t \to \infty$ (this, together with the fact that the state variable $R_H(t)$ does not feature in any of other equations of the model (3.34) when $\psi_H = 0$, imply that the equation for $R_H(t)$ can be temporarily removed form the analyses of the model (3.34) for this special case). Consider, further, the following non-linear Lyapunov function of Goh-Volterra type:

$$\begin{aligned}\mathcal{F} = {} & d_1\left(S_H - S_H^{**} - S_H^{**} log\frac{S_H}{S_H^{**}}\right) + d_2\left(E_H - E_H^{**} - E_H^{**} log\frac{E_H}{E_H^{**}}\right) \\ & + d_3\left(I_H - I_H^{**} - I_H^{**} log\frac{I_H}{I_H^{**}}\right) + d_4\left(S_V - S_V^{**} - S_V^{**} log\frac{S_V}{S_V^{**}}\right) \\ & + d_5\left(I_V - I_V^{**} - I_V^{**} log\frac{I_V}{I_V^{**}}\right),\end{aligned} \tag{D-1}$$

where,

$$\begin{aligned} & d_1 = d_2 = \frac{b_2\beta_V\mu_H I_H^{**} S_V^{**}}{\Pi_H}, d_3 = \frac{(b_2)^2\beta_V\beta_H(\mu_H)^2 I_V^{**} I_H^{**} S_V^{**} S_H^{**}}{\Pi_H^2\sigma_H E_H^{**}}, \\ & d_4 = d_5 = \frac{b_2\beta_H\mu_H I_V^{**} S_H^{**}}{\Pi_H}.\end{aligned} \tag{D-2}$$

The Lyapunov derivative of (D-1) is given by,

$$\begin{aligned}\dot{\mathcal{F}} = {} & d_1\left(1-\frac{S_H^{**}}{S_H}\right)\left(\Pi_H - \frac{b_2\beta_H\mu_H I_V}{\Pi_H}S_H - \mu_H S_H\right) \\ & + d_2\left(1-\frac{E_H^{**}}{E_H}\right)\left[\frac{b_2\beta_H\mu_H I_V}{\Pi_H}S_H - (\sigma_H+\mu_H)E_H\right] \\ & + d_3\left(1-\frac{I_H^{**}}{I_H}\right)\left[\sigma_H E_H - (\gamma_H+\mu_H)I_H\right] \\ & + d_4\left(1-\frac{S_V^{**}}{S_V}\right)\left(\Pi_V - \frac{b_2\beta_V\mu_H I_H}{\Pi_H}S_V - \mu_V S_V\right) \\ & + d_5\left(1-\frac{I_V^{**}}{I_V}\right)\left(\frac{b_2\beta_V\mu_H I_H}{\Pi_H}S_V - \mu_V I_V\right).\end{aligned} \tag{D-3}$$

The following steady-state relations (obtained from (3.34), with $\delta_H = \eta = \psi_H = 0$, at the EEP ($\hat{\mathcal{E}}_1$)) will be used to simplify (D-3):

$$\begin{aligned}\Pi_H &= \frac{b_2\beta_H\mu_H I_V^{**}}{\Pi_H}S_H^{**} + \mu_H S_H^{**}, \\ (\sigma_H+\mu_H) &= \frac{b_2\beta_H\mu_H I_V^{**}}{\Pi_H E_H^{**}}S_H^{**}, \\ (\gamma_H+\mu_H) &= \frac{\sigma_H E_H^{**}}{I_H^{**}}, \\ \Pi_V &= \frac{b_2\beta_V\mu_H I_H^{**}}{\Pi_H}S_V^{**} + \mu_V S_V^{**}, \\ \mu_V &= \frac{b_2\beta_V\mu_H I_H^{**}}{\Pi_H I_V^{**}}S_V^{**}.\end{aligned} \tag{D-4}$$

Substituting (D-2) and (D-4) into (D-3), and simplifying, gives

$$\begin{aligned}\dot{\mathcal{F}} = {} & -\frac{b_2\beta_V\mu_H^2 I_H^{**}S_V^{**}}{\Pi_H}\frac{(S_H-S_H^{**})^2}{S_H} - \frac{b_2\beta_H\mu_H\mu_V I_V^{**}S_H^{**}}{\Pi_H}\frac{(S_V-S_V^{**})^2}{S_V} \\ & + \frac{b_2^2\beta_V\beta_H\mu_H^2 I_V^{**}I_H^{**}S_V^{**}S_H^{**}}{\Pi_H^2\sigma_H E_H^{**}}\left(5-\frac{S_H^{**}}{S_H}-\frac{S_V^{**}}{S_V}-\frac{S_H E_H^{**}I_V}{S_H^{**}E_H I_V^{**}}-\frac{S_V I_H I_V^{**}}{S_V^{**}I_H^{**}I_V}-\frac{E_H I_H^{**}}{E_H^{**}I_H}\right).\end{aligned} \tag{D-5}$$

The first two terms of (D-5) are automatically negative. Furthermore, since the arithmetic mean exceeds the geometric mean, it follows that the third term of (D-5) is also negative. Hence, $\dot{\mathcal{F}} \leq 0$, so that

$$\lim_{t\to\infty}(S_H(t), E_H(t), I_H(t), S_V(t), I_V(t)) \to (S_H^{**}(t), E_H^{**}(t), I_H^{**}(t), S_V^{**}(t), I_V^{**}(t)).$$

Substituting $I_H(t) = I_H^{**}$ into the equation for $R_H(t)$ in (3.34) shows that $R_H(t) \to R_H^{**} = \frac{\gamma_H I_H^{**}}{\psi_H + \mu_H}$ as $t \to \infty$. The proof is concluded as in Appendix C. Thus, the unique EEP, $\hat{\mathcal{E}}_1$, of the reduced model (3.34), is GAS in $\mathcal{D}_2 \backslash \mathcal{D}_0$ whenever $\mathcal{R}_{02} > 1$. $\square$

Appendix E

Proof of Theorem 4.2

Proof. Let $x_1 = S_J$, $x_2 = S_A$, $x_3 = E_{JW}$, $x_4 = E_{JR}$, $x_5 = E_{AW}$, $x_6 = E_{AR}$, $x_7 = I_{JW}$, $x_8 = I_{JR}$, $x_9 = I_{AW}$, $x_{10} = I_{AR}$, $x_{11} = T_J$, $x_{12} = T_A$, $x_{13} = R_J$, $x_{14} = R_A$, $x_{15} = S_V$, $x_{16} = V_W$ and $x_{17} = V_R$. Furthermore, let $\hat{f} = [f_1, ..., f_{10}]^T$ denote the vector field of the model (4.23). Thus, the model (4.23) can be re-written as:

$$\begin{aligned}
\frac{dx_1}{dt} &= \Pi_J + \psi_J x_{13} - \frac{b_2\beta_J(x_{16} + \theta_R x_{17})}{\sum_{i=1}^{14} x_i} x_1 - g_1 x_1, \\
\frac{dx_2}{dt} &= \xi x_1 + \psi_A x_{14} - \frac{b_2\beta_A(x_{16} + \theta_R x_{17})}{\sum_{i=1}^{14} x_i} x_2 - \mu_H x_2, \\
\frac{dx_3}{dt} &= \frac{b_2\beta_J x_{16}}{\sum_{i=1}^{14} x_i} x_1 - g_2 x_3, \\
\frac{dx_4}{dt} &= \frac{b_2\beta_J \theta_R x_{17}}{\sum_{i=1}^{14} x_i} x_1 - g_3 x_4,
\end{aligned} \tag{E-1}$$

$$\frac{dx_5}{dt} = \xi x_3 + \frac{b_2\beta_A x_{16}}{\sum\limits_{i=1}^{14} x_i} x_2 - g_4 x_5,$$

$$\frac{dx_6}{dt} = \xi x_4 + \frac{b_2\beta_A \theta_R x_{17}}{\sum\limits_{i=1}^{14} x_i} x_2 - g_5 x_6,$$

$$\frac{dx_7}{dt} = \sigma_{JW} x_3 - g_6 x_7,$$

$$\frac{dx_8}{dt} = \sigma_{JR} x_4 + (1 - f_J)\tau_J x_7 - g_7 x_8,$$

$$\frac{dx_9}{dt} = \xi x_7 + \sigma_{AW} x_5 - g_8 x_9,$$

$$\frac{dx_{10}}{dt} = \sigma_{AR} x_6 + \xi x_8 + (1 - f_A)\tau_A x_9 - g_9 x_{10},$$

$$\frac{dx_{11}}{dt} = f_J \tau_J x_7 - g_{10} x_{11},$$

$$\frac{dx_{12}}{dt} = \xi x_{11} + f_A \tau_A x_9 - g_{11} x_{12},$$

$$\frac{dx_{13}}{dt} = \gamma_J x_7 + \phi_1 \gamma_J x_8 + \phi_3 \gamma_J x_{11} - g_{12} x_{11},$$

$$\frac{dx_{14}}{dt} = \xi x_{13} + \gamma_A x_9 + \phi_2 \gamma_A x_{10} + \phi_4 \gamma_A x_{12} - g_{13} x_{14},$$

$$\frac{dx_{15}}{dt} = \Pi_V - \frac{b_2\beta_V[x_7 + x_9 + \eta_R(x_8 + x_{10})]}{\sum\limits_{i=1}^{14} x_i} x_{15} - \mu_V x_{15},$$

$$\frac{dx_{16}}{dt} = \frac{b_2\beta_V(x_7 + x_9)}{\sum\limits_{i=1}^{14} x_i} x_{15} - \mu_V x_{16},$$

$$\frac{dx_{17}}{dt} = \frac{b_2\beta_V \eta_R(x_8 + x_{10})}{\sum\limits_{i=1}^{14} x_i} x_{15} - \mu_V x_{17},$$

where, $g_1 = \xi + \mu_H$, $g_2 = \sigma_{JW} + \xi + \mu_H$, $g_3 = \sigma_{JR} + \xi + \mu_H$, $g_4 = \sigma_{AW} + \mu_H$, $g_5 = \sigma_{AR} + \mu_H$, $g_6 = \tau_J + \xi + \gamma_J + \mu_H + \delta_J$, $g_7 = \xi + \phi_1\gamma_J + \mu_H + \theta_1\delta_J$, $g_8 = \tau_A + \gamma_A + \mu_H + \delta_A$, $g_9 = \phi_2\gamma_A + \mu_H + \theta_2\delta_A$, $g_{10} = \phi_3\gamma_J + \mu_H + \theta_3\delta_J$, $g_{11} = \phi_4\gamma_A + \mu_H + \theta_4\delta_A$,

$g_{12} = \psi_J + \xi + \mu_H$, $g_{13} = \psi_A + \mu_H$.

The Jacobian of the transformed system (E-1), evaluated at the DFE ($\mathcal{E}_{0T}$), is given by:

$$J(\mathcal{E}_{0T}) =$$

$$\begin{bmatrix}
-g_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \psi_J & 0 & 0 & -y_1 & -y_2 \\
\xi & -\mu_H & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \psi_A & 0 & -y_3 & -y_4 \\
0 & 0 & -g_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & y_1 & 0 \\
0 & 0 & 0 & -g_3 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & y_2 \\
0 & 0 & \xi & 0 & -g_4 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & y_3 & 0 \\
0 & 0 & 0 & \xi & 0 & -g_5 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & y_4 \\
0 & 0 & \sigma_{JW} & 0 & 0 & 0 & -g_6 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & \sigma_{JR} & 0 & 0 & (1-f_J)\tau_J & -g_7 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & \sigma_{AW} & 0 & \xi & 0 & -g_8 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & \sigma_{AR} & 0 & \xi & (1-f_A)\tau_A & -g_9 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & f_J\tau_J & 0 & 0 & 0 & -g_{10} & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & f_A\tau_A & 0 & \xi & -g_{11} & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & \gamma_J & \phi_1\gamma_J & 0 & 0 & \phi_3\gamma_J & 0 & -g_{12} & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \gamma_A & \phi_2\gamma_A & 0 & \phi_4\gamma_A & \xi & -g_{13} & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & -h_1 & -h_2 & -h_1 & -h_2 & 0 & 0 & -\mu_V & 0 & -\mu_V & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & h_1 & 0 & h_1 & 0 & 0 & 0 & 0 & 0 & 0 & -\mu_V & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & h_2 & 0 & h_2 & 0 & 0 & 0 & 0 & 0 & 0 & -\mu_V
\end{bmatrix},$$

where $y_1 = \frac{b_2\beta_J x_1^*}{x_1^*+x_2^*}$, $y_2 = \frac{b_2\beta_J\theta_R x_1^*}{x_1^*+x_2^*}$, $y_3 = \frac{b_2\beta_A x_2^*}{x_1^*+x_2^*}$, $y_4 = \frac{b_2\beta_A\theta_R x_2^*}{x_1^*+x_2^*}$, $h_1 = \frac{b_2\beta_V\theta_R x_{15}^*}{x_1^*+x_2^*}$ and $h_2 = \frac{b_2\beta_V\eta x_{15}^*}{x_1^*+x_2^*}$. Without loss of generality, consider the case when $\mathcal{R}_W > \mathcal{R}_R$ and $\mathcal{R}_T = 1$ (so that $\mathcal{R}_W = 1$). Furthermore, let $\beta_V = \beta_V^*$ be a bifurcation parameter. Solving for β_V from $\mathcal{R}_W = 1$ gives

$$\beta_V = \beta_V^* = \frac{\Pi_J\mu_V^2 g_1 g_2 g_4 g_6 g_8}{b_2^2\Pi_V\mu_H\{\beta_J\mu_H[\sigma_{JW}g_4(g_8+\xi) + \sigma_{AW}\xi g_6] + \beta_A\sigma_{AW}\xi g_2 g_6\}} > 0.$$

It is convenient to define:

$$
\begin{aligned}
A_0 &= g_{12}\{\psi_A\phi_2\gamma_A(\sigma_{JR}\theta_1\delta_J g_5 + \mu_H g_1 g_7) \\
&\quad + g_5[\psi_A(\theta_2\delta_A + \mu_H) + \mu_H g_9][\sigma_{JR}(\xi + \mu_H + \theta_1\delta_J) + g_1 g_7]\} \\
&\quad + \sigma_{JR}\phi_1\gamma_J\mu_H g_1 g_5 g_9 > 0, \\
A_1 &= \psi_A\phi_2\gamma_A\mu_H + g_5[\gamma_A\phi_2\mu_H + g_{13}(\theta_2\delta_A + \mu_H)] > 0, \\
A_2 &= \sigma_{JW}\tau_J g_4 g_8(1 - f_J)(g_9 + \xi) + \tau_A\xi g_7(1 - f_A)(\sigma_{AW} g_6 + \sigma_{JW} g_4) > 0.
\end{aligned}
$$

The right eigenvector of $J(\mathcal{E}_0)|_{\beta_V=\beta_V^*}$ is given by $\mathbf{w} = (w_1, w_2, w_3, w_4, w_5, w_6, w_7, w_8, w_9, w_{10})^T$, where (since $A_0 > 0$, $A_1 > 0$ and $A_2 > 0$)

$$
\begin{aligned}
w_1 &= \frac{-\beta_J b_2\theta_R\mu_H\{\sigma_{JR}[\phi_1\gamma_J g_1 + g_{12}(\xi + \mu_H + \theta_1\delta_J)] + g_1 g_7 g_{12}\}}{g_1^2 g_3 g_7 g_{12}} w_{17} < 0, \\
w_2 &= -\frac{b_2\xi\theta_R(\beta_J\mu_H A_0 + g_1 g_3 g_7 g_{12}\beta_A A_1)}{\mu_H g_1^2 g_3 g_5 g_7 g_9 g_{12} g_{13}} w_{17} < 0, w_3 = 0, w_4 = \frac{b_2\beta_J\theta_R\mu_H}{g_1 g_3} w_{17}, \\
w_5 &= 0, w_6 = \frac{b_2\xi\theta_R(\beta_A g_3 + \beta_J\mu_H)}{g_1 g_3 g_5} w_{17}, w_7 = 0, w_8 = \frac{b_2\beta_J\sigma_{JR}\theta_R\mu_H}{g_1 g_3 g_7} w_{17}, \\
w_9 &= 0, w_{10} = \frac{b_2\xi\theta_R[\beta_J\mu_H(\sigma_{JR} g_5 + \sigma_{AR} g_7) + \beta_A\sigma_{AR} g_3 g_7]}{g_1 g_3 g_5 g_7 g_9} w_{17}, w_{11} = 0, w_{12} = 0, \\
w_{13} &= \frac{b_2\beta_J\theta_R\sigma_{JR}\gamma_J\phi_1\mu_H}{g_1 g_3 g_7 g_{12}} w_{17}, \\
w_{14} &= \frac{b_2\xi\theta_R\{\beta_J\mu_H[\phi_2\gamma_A g_{12}(\sigma_{JR} g_5 + \sigma_{AR} g_7) + \sigma_{JR}\phi_1\gamma_J g_5 g_9] + \beta_A\sigma_{AR}\phi_2\gamma_A g_3 g_7 g_{12}\}}{g_1 g_3 g_5 g_7 g_9 g_{12} g_{13}} w_{17}, \\
w_{15} &= -\frac{b_2^2\beta_V^*\Pi_V\theta_R\eta\mu_H\{\beta_J\mu_H[\sigma_{JR} g_5(\xi + g_9) + \sigma_{AR}\xi g_7] + \beta_A\sigma_{AR}\xi g_3 g_7\}}{\mu_V^2\Pi_J g_1 g_3 g_5 g_7 g_9} w_{17} < 0, \\
w_{16} &= 0, w_{17} > 0.
\end{aligned}
$$

Similarly, $J(\mathcal{E}_0)|_{\beta_V=\beta_V^*}$ has a left eigenvector $\mathbf{v} = (v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9, v_{10})$, where

$$v_1 = 0, v_2 = 0, v_3 = \frac{\beta_V^* b_2 \Pi_V \mu_H \{v_{16} g_7 g_9 [\sigma_{AW} \xi g_6 + \sigma_{JW} g_4 (g_8 + 1)] + v_{17} \eta A_2\}}{\Pi_J \mu_V g_2 g_4 \left(\prod_{i=6}^{9} g_i \right)},$$

$$v_4 = \frac{b_2 \beta_V^* \Pi_V \eta \mu_H [\sigma_{JR} g_5 (\xi + g_9) + \sigma_{AR} \xi g_7]}{\Pi_J \mu_V g_3 g_5 g_7 g_9} v_{17},$$

$$v_5 = \frac{b_2 \beta_V^* \Pi_V \sigma_{AW} \mu_H [v_{16} g_9 + v_{17} \tau_A \eta (1 - f_A)]}{\Pi_J \mu_V g_4 g_8 g_9}, v_6 = \frac{b_2 \beta_V^* \Pi_V \sigma_{AR} \eta \mu_H}{\Pi_J \mu_V g_5 g_9} v_{17},$$

$$v_7 = \frac{b_2 \beta_V^* \Pi_V \mu_H \{v_{16} g_7 g_9 (g_8 + \xi) + v_{17} \eta [\tau_J g_8 (g_9 + \xi)(1 - f_J) + \tau_A \eta g_7 (1 - f_A)]\}}{\Pi_J \mu_V \left(\prod_{i=6}^{9} g_i \right)},$$

$$v_8 = \frac{b_2 \beta_V^* \Pi_V \eta \mu_H (\xi + g_9)}{\Pi_J \mu_V g_7 g_9} v_{17}, v_9 = \frac{b_2 \beta_V^* \Pi_V \mu_H [v_{16} g_9 + v_{17} \eta \tau_A (1 - f_A)]}{\Pi_J \mu_V g_8 g_9},$$

$$v_{10} = \frac{b_2 \beta_V^* \Pi_V \eta \mu_H}{\Pi_J \mu_V g_9} v_{17}, v_{11} = 0, v_{12} = 0, v_{13} = 0, v_{14} = 0, v_{15} = 0, v_{16} > 0, v_{17} > 0.$$

Using the approach in Appendix B, it can be shown that the backward bifurcation coefficients associated with the model (E-1) are, respectively, given by:

$$a = \sum_{k,i,j=1}^{11} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0),$$

$$= \frac{-2 b_2 \mu_H^2}{\Pi_J^2} \left\{ \frac{\beta_V^* \Pi_J \eta}{\mu_H^2} [-v_{17} w_{15} (w_{10} + w_8)] + \frac{\beta_J \Pi_J \theta_R}{g_1} v_4 w_{17} \left(-\frac{\xi}{\mu_H} w_1 + w_2 + n_0 \right) \right.$$
$$\left. + \frac{\beta_A \Pi_J \theta_R}{g_1} v_6 w_{17} \left[-w_2 + \frac{\xi}{\mu_H} (w_1 + n_0) \right] + \frac{\beta_V \Pi_V \eta}{\mu_V} v_{17} [w_8 (w_1 + w_2 + n_0) + w_{10} n_1] \right\} \tag{E-2}$$

(with, $n_0 = w_4 + w_6 + w_8 + w_{10} + w_{13} + w_{14}, n_1 = w_1 + w_2 + w_4 + w_6 + w_{10} + w_{13} + w_{14}$) and,

$$b = \sum_{k,i,j=1}^{11} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0) = \frac{(b_2 \mu_H)^2 \beta_V^* \Pi_V \eta \theta_R [\sigma_{JR} g_5 (g_9 + \xi) + \sigma_{AR} \xi g_7]}{\Pi_J \mu_V g_1 g_3 g_5 g_7 g_9} v_{17} w_{17} > 0.$$

It follows from (E-2) that the bifurcation coefficient, a, is positive whenever,

$$K_0 > K_1, \tag{E-3}$$

where,

$$K_0 = -\frac{\Pi_J \theta_R}{\mu_H g_1} w_{17}(\beta_J \mu_H v_4 w_2 + \beta_A \xi v_6 w_1) - \frac{\beta_V^* \Pi_V \eta}{\mu_V} v_{17}(w_1 + w_2)(w_8 + w_{10}),$$

$$\begin{aligned} K_1 = &-\frac{\beta_V^* \Pi_J \eta}{\mu_H^2}[v_{17} w_{15}(w_8 + w_{10})] - \frac{\beta_J \Pi_J \theta_R}{\mu_H g_1} w_{17}[v_4(\xi w_1 - \mu_H n_0) + v_6 w_2 - v_{16} n_0] \\ &+ \frac{\beta_V^* \Pi_V \eta}{\mu_V} v_{17}[w_8 n_0 + w_{10}(w_4 + w_6 + w_{10} + w_{13} + w_{14})]. \end{aligned}$$

Thus, it follows from Theorem 2.7 that the model (4.23) undergoes a backward bifurcation at $\mathcal{R}_T = 1$ whenever the inequality (E-3) holds. □

Appendix F

Proof of Theorem 4.3

Proof. It can be shown that the system (4.23) satisfies the Type $\mathcal{K}$ condition (as described in Section 2.7). Hence, comparison theorem [37] can be used. The equations for the infected components of the model (4.23) can be re-written in terms of

$$\frac{d}{dt}\begin{bmatrix} E_{JW} \\ E_{JR} \\ E_{AW} \\ E_{AR} \\ I_{JW} \\ I_{JR} \\ I_{AW} \\ I_{AR} \\ T_J \\ T_A \\ V_W \\ V_R \end{bmatrix} = (\mathcal{F} - \mathcal{V} - \mathcal{S}) \begin{bmatrix} E_{JW} \\ E_{JR} \\ E_{AW} \\ E_{AR} \\ I_{JW} \\ I_{JR} \\ I_{AW} \\ I_{AR} \\ T_J \\ T_A \\ V_W \\ V_R \end{bmatrix}, \tag{F-1}$$

where,

$$\mathcal{S} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & s_1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & s_2 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & s_3 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & s_4 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & s_5 & 0 & s_5 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & s_6 & 0 & s_6 & 0 & 0 & 0 & 0 \end{bmatrix},$$

with, $s_1 = \dfrac{b_2\beta_J(S_J^* - S_J)}{N_H^*}$, $s_2 = \dfrac{b_2\beta_J\theta_R(S_J^* - S_J)}{N_H^*}$, $s_3 = \dfrac{b_2\beta_A(S_A^* - S_A)}{N_H^*}$, $s_4 = \dfrac{b_2\beta_A\theta_R(S_A^* - S_A)}{N_H^*}$, $s_5 = \dfrac{b_2\beta_V(S_V^* - S_V)}{N_H^*}$, $s_6 = \frac{b_2\beta_V\eta_R(S_V^* - S_V)}{N_H^*}$,

$$\mathcal{F} = \begin{bmatrix} 0\,0\,0\,0 & 0 & 0 & 0 & 0 & 0\,0 & \dfrac{b_2\beta_J S_J^*}{N_H^*} & 0 \\ 0\,0\,0\,0 & 0 & 0 & 0 & 0 & 0\,0 & 0 & \dfrac{b_2\beta_J\theta_R S_J^*}{N_H^*} \\ 0\,0\,0\,0 & 0 & 0 & 0 & 0 & 0\,0 & \dfrac{b_2\beta_A S_A^*}{N_H^*} & 0 \\ 0\,0\,0\,0 & 0 & 0 & 0 & 0 & 0\,0 & 0 & \dfrac{b_2\beta_A\theta_R S_A^*}{N_H^*} \\ 0\,0\,0\,0 & 0 & 0 & 0 & 0 & 0\,0 & 0 & 0 \\ 0\,0\,0\,0 & 0 & 0 & 0 & 0 & 0\,0 & 0 & 0 \\ 0\,0\,0\,0 & 0 & 0 & 0 & 0 & 0\,0 & 0 & 0 \\ 0\,0\,0\,0 & 0 & 0 & 0 & 0 & 0\,0 & 0 & 0 \\ 0\,0\,0\,0 & 0 & 0 & 0 & 0 & 0\,0 & 0 & 0 \\ 0\,0\,0\,0 & 0 & 0 & 0 & 0 & 0\,0 & 0 & 0 \\ 0\,0\,0\,0 & \dfrac{b_2\beta_V S_V^*}{N_H^*} & 0 & \dfrac{b_2\beta_V S_V^*}{N_H^*} & 0 & 0\,0 & 0 & 0 \\ 0\,0\,0\,0 & 0 & \dfrac{b_2\beta_V\eta_R S_V^*}{N_H^*} & 0 & \dfrac{b_2\beta_V\eta_R S_V^*}{N_H^*} & 0\,0 & 0 & 0 \end{bmatrix},$$

and,

$$\mathcal{V} = \begin{bmatrix} g_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & g_3 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -\xi & 0 & g_4 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -\xi & 0 & g_5 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -\sigma_{JW} & 0 & 0 & 0 & g_6 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -\sigma_{JR} & 0 & 0 & -(1-f_J)\tau_J & g_7 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\sigma_{AW} & 0 & -\xi & 0 & g_8 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -\sigma_{AR} & 0 & -\xi & -(1-f_A)\tau_A & g_9 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -f_J\tau_J & 0 & 0 & 0 & g_{10} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -f_A\tau_A & 0 & -\xi & g_{11} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \mu_V & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \mu_V \end{bmatrix},$$

with, $g_1 = \xi + \mu_H$, $g_2 = \sigma_{JW} + \xi + \mu_H$, $g_3 = \sigma_{JR} + \xi + \mu_H$, $g_4 = \sigma_{AW} + \mu_H$, $g_5 = \sigma_{AR} + \mu_H$, $g_6 = \tau_J + \xi + \gamma_J + \mu_H$, $g_7 = \xi + \phi_1\gamma_J + \mu_H$, $g_8 = \tau_A + \gamma_A + \mu_H$, $g_9 = \phi_2\gamma_A + \mu_H$,

$g_{10} = \xi + \phi_3\gamma_J + \mu_H$, $g_{11} = \phi_4\gamma_A + \mu_H$, $g_{12} = \psi_J + \xi + \mu_H$, $g_{13} = \psi_A + \mu_H$ and $\dfrac{\Pi_J}{\mu_H}$. Since all the elements of the matrix S are non-negative in $\mathcal{D}_1$, it follows that

$$\frac{d}{dt}\begin{bmatrix} E_{JW} \\ E_{JR} \\ E_{AW} \\ E_{AR} \\ I_{JW} \\ I_{JR} \\ I_{AW} \\ I_{AR} \\ T_J \\ T_A \\ V_W \\ V_R \end{bmatrix} \leq (\mathcal{F} - \mathcal{V}) \begin{bmatrix} E_{JW} \\ E_{JR} \\ E_{AW} \\ E_{AR} \\ I_{JW} \\ I_{JR} \\ I_{AW} \\ I_{AR} \\ T_J \\ T_A \\ V_W \\ V_R \end{bmatrix}.$$

Using the fact that the eigenvalues of the matrix $\mathcal{F} - \mathcal{V}$ all have negative real parts (since when $\tilde{\mathcal{R}}_T < 1$, the DFE, $\mathcal{E}_{0T}$, of the model (4.23) is locally-asymptotically stable; which is equivalent to $\mathcal{F} - \mathcal{V}$ having eigenvalues with negative real parts), it follows that the linearized differential inequality system is stable whenever $\tilde{\mathcal{R}}_T < 1$. Consequently, it follows, by comparison theorem [37], that

$$(E_{JW}(t), E_{JR}(t), E_{AW}(t), E_{AR}(t), I_{JW}(t), I_{JR}(t), I_{AW}(t), I_{AR}(t), T_J(t), T_A(t), V_W(t),$$
$$V_R(t)) \to (0,0,0,0,0,0,0,0,0,0,0,0) \quad \text{as} \quad \text{t} \to \infty.$$

Substituting $E_{JW} = E_{JR} = E_{AW} = E_{AR} = I_{JW} = I_{JR} = I_{AW} = I_{AR} = T_J = T_A = V_W = V_R = 0$ into the first, second and fifteenth equations of the model (4.23) show

that

$$(S_J(t), S_A(t), S_V(t)) \to (S_J^*, S_A^*, S_V^*) \quad \text{as} \quad \text{t} \to \infty.$$

Thus, the DFE, $\mathcal{E}_{0T}$, of the model (4.23), with $\delta_J = \delta_A = \psi_J = \psi_A = 0$, is GAS in $\mathcal{D}_1$ if $\tilde{\mathcal{R}}_T < 1$. $\square$

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