Global Dynamics of Some Vector-Borne Infectious Disease Models with Seasonality

by

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Abstract

Vector-borne infectious diseases such as malaria, dengue, West Nile fever, Zika fever and Lyme disease remain a threat to public health and economics. Both vector life cycle and parasite development are greatly influenced by climatic factors. Understanding the role of seasonal climate in vector-borne infectious disease transmission is particularly important in light of global warming.

This PhD thesis is devoted to the study of global dynamics of four vector-borne infectious disease models. We start with a periodic vector-bias malaria model with constant extrinsic incubation period (EIP). To explore the temperature sensitivity of the EIP of malaria parasites, we also formulate a functional differential equations model with a periodic time delay. Moreover, we incorporate the use of insecticide-treated bed nets (ITNs) into a climate-based mosquito-stage-structured malaria model. Lastly, we develop a time-delayed Lyme disease model with seasonality. By using the theory of basic reproduction ratio, R_0, and the theory of dynamical systems, we derive R_0 and establish a threshold type result for the global dynamics in terms of R_0 for each model. By conducting numerical simulations of case studies, we propose some practical strategies for the control of the diseases.

To my dearest parents

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Statement of contribution

Chapters 2-5 of this thesis consist of the following papers:

Chapter 2: Xiunan Wang and Xiao-Qiang Zhao, A periodic vector-bias malaria model with incubation period, SIAM J. Appl. Math., 2017 (77) 1, 181-201.

Chapter 3: Xiunan Wang and Xiao-Qiang Zhao, A malaria transmission model with temperature-dependent incubation period, Bull. Math. Biol., 2017 (79) 1155-1182.

Chapter 4: Xiunan Wang and Xiao-Qiang Zhao, A climate-based malaria model with the use of bed nets, in review.

Chapter 5: Xiunan Wang and Xiao-Qiang Zhao, Dynamics of a time-delayed Lyme disease model with seasonality, SIAM J. Appl. Dyn. Syst., 2017 (16) 2, 853-881.

The work of the above papers was performed by the author under the supervision of Professor Xiao-Qiang Zhao.

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Chapter 1

Preliminaries

In this chapter, we present some terminologies and known results which will be used in this thesis. They are involved in chain transitivity and attractivity, uniform persistence and coexistence states, monotone dynamics, and the theory of basic reproduction ratio.

1.1 Chain transitivity and attractivity

Let X be a metric space with metric d and $f : X \to X$ a continuous map. A bounded set A is said to attract a bounded set B in X if $\lim_{n\to\infty} \sup_{x\in B}\{d(f^n(x), A)\} = 0$. A subset $A \subset X$ is said to be an attractor for f if A is nonempty, compact, and invariant ($f(A) = A$), and A attracts some open neighborhood U of itself. A global attractor for $f : X \to X$ is an attractor that attracts every point in X. For a nonempty invariant set M, the set $W^s(M) := \{x \in X : \lim_{n\to\infty} d(f^n(x), M) = 0\}$ is called the stable set of M. The omega limit set of x is defined as $\omega(x) = \{y \in X : f^{n_k}(x) \to y, \text{for some } n_k \to \infty\}$ [109, Section 1.1].

Definition 1.1.1. *Let $A \subset X$ be a nonempty invariant set (i.e., $f(A) = A$). We call*

A internally chain transitive if for any $a, b \in A$ and any $\epsilon > 0$, there is a finite sequence $x_1, \ldots, x_m$ in A with $x_1 = a$, $x_m = b$ such that $d(f(x_i), x_{i+1}) < \epsilon$, $1 \leq i \leq m-1$. The sequence $\{x_1, \ldots, x_m\}$ is called an ϵ-chain in A connecting a and b.

Lemma 1.1.2. *[109, Lemma 1.2.1] Let $f : X \to X$ be a continuous map. Then the omega (alpha) limit set of any precompact positive (negative) orbit is internally chain transitive.*

Theorem 1.1.3. *[109, Theorem 1.2.1] Let A be an attractor and C a compact internally chain transitive set for $f : X \to X$. If $C \cap W^s(A) \neq \emptyset$, then $C \subset A$.*

Theorem 1.1.4. *[109, Theorem 1.2.2] Assume that each fixed point of f is an isolated invariant set, that there is no cyclic chain of fixed points, and that every precompact orbit converges to some fixed point of f. Then any compact internally chain transitive set is a fixed point of f.*

1.2 Uniform persistence and coexistence states

Let $f : X \to X$ be a continuous map and $X_0 \subset X$ an open set. Define $\partial X_0 := X \setminus X_0$, and $M_\partial := \{x \in \partial X_0 : f^n(x) \in \partial X_0, n \geq 0\}$, which may be empty.

Theorem 1.2.1. *[109, Theorem 1.3.1 and Remark 1.3.1] Assume that*

(C1) $f(X_0) \subset X_0$ and f has a global attractor A;

(C2) There exists a finite sequence $\mathcal{M} = \{M_1, \ldots, M_k\}$ of disjoint, compact, and isloated invariant sets in ∂X_0 such that

  (a) $\Omega(M_\partial) := \cup_{x \in M_\partial} \omega(x) \subset \cup_{i=1}^{k} M_i$;

  (b) no subset of $\mathcal{M}$ forms a cycle in ∂X_0;

(c) Each M_i *is isolated in* X*;*

(d) $W^s(M_i) \cap X_0 = \emptyset$ *for each* $1 \leq i \leq k$*.*

Then there exists $\delta > 0$ *such that for any compact internally chain transitive set* L *with* $L \not\subset M_i$ *for all* $1 \leq i \leq k$*, we have* $\inf_{x \in L} d(x, \partial X_0) > \delta$*.*

Definition 1.2.2. *A function* $f : X \to X$ *is said to be uniformly persistent with respect to* $(X_0, \partial X_0)$ *if there exists* $\eta > 0$ *such that* $\liminf_{n\to\infty} d(f^n(x), \partial X_0) \geq \eta$ *for all* $x \in X_0$*.*

Recall that the Kuratowski measure of noncompactness, α, is defined by

$$\alpha(B) = \inf\{r : B \text{ has a finite cover of diameter } < r\},$$

for any bounded set B of X. A continuous map $f : X \to X$ is said to be compact (completely continous) is f maps any bounded set to a precompact set in X.

Definition 1.2.3. *A continuous mapping* $f : X \to X$ *is said to be point dissipative if there is a bounded set* B_0 *in* X *such that* B_0 *attracts each point in* X*;* α*-condensing if* f *takes bounded sets to bounded sets and* $\alpha(f(B)) < \alpha(B)$ *for any nonempty closed bounded set* $B \subset X$ *with* $\alpha(B) > 0$*.*

Let (M, d) be a complete metric space, and let $\rho : M \to [0, +\infty)$ be a continuous function. We define

$$M_0 := \{x \in M : \rho(x) > 0\} \text{ and } \partial M_0 := \{x \in M : \rho(x) = 0\}.$$

Assume that $f : M \to M$ is a continuous map with $f(M_0) \subset M_0$.

Definition 1.2.4. f *is said to be* ρ*-uniformly persistent if there exists* $\epsilon > 0$ *such that* $\liminf_{n\to+\infty} \rho(f^n(x)) \geq \epsilon, \forall x \in M_0$*.*

For a given open subset $M_0 \subset M$, let $\partial M_0 := M \setminus M_0$. Then we can use the continuous function $\rho : M \to [0, \infty)$, defined by $\rho(x) = d(x, \partial M_0), \forall x \in M$, to obtain the traditional definition of persistence [52].

Next, we assume that M is a closed and convex subset of a Banach space $(X, \|\cdot\|)$, that $\rho : M \to [0, +\infty)$ is a continuous function such that $M_0 = \{x \in M : \rho(x) > 0\}$ is nonempty and convex, and that $f : M \to M$ is a continuous map with $f(M_0) \subset M_0$ [52].

Theorem 1.2.5. *[52, Theorem 4.5] Assume that*

(1) $f : X \to X$ is point dissipative and ρ-uniformly persistent.

(2) f^{n_0} is compact for some integer $n_0 \geq 1$.

(3) f is α-condensing.

Then $f : X_0 \to X_0$ admits a global attractor A_0, and f has a fixed point in A_0.

Suppose $T > 0$, a family of mappings $\Phi(t) : X \to X, t \geq 0$, is called a T-periodic semiflow on X if it possesses the following properties:

(1) $\Phi(0) = I$, where I is the identity map on X.

(2) $\Phi(t + T) = \Phi(t) \circ \Phi(T)$, $\forall t \geq 0$.

(3) $\Phi(t)x$ is continuous in $(t, x) \in [0, \infty) \times X$.

The mapping $\Phi(T)$ is called the Poincaré map associated with this periodic semiflow. In particular, if (2) holds for any $T > 0$, $\Phi(t)$ is called an autonomous semiflow.

1.3 Monotone dynamics

1.3.1 The comparison principle

For $x, y \in \mathbb{R}^n$, we define

$$x \leq y \Leftrightarrow x_i \leq y_i \text{ for } i \in N \quad \text{and} \quad x \ll y \Leftrightarrow x_i < y_i \quad \text{for } i \in N,$$

where $N = \{1, \dots, n\}$. The spaces $AC(J)$ and $L(J)$ consist of all functions from J to $\mathbb{R}^n$ that are absolutely continuous or integrable in J, respectively. Here and below, $J = [a, b]$, $J_0 = (a, b]$. A measurable set $M \subset J$ is said to be dense at a if the set $M \cap [a, a + \epsilon]$ has positive measure for every $\epsilon > 0$. For measurable vector-valued functions φ, ψ we write $\varphi \ll \psi$ at $a+$ if the set $\{t \in J : \varphi(t) \ll \psi(t)\}$ is dense at a.

We consider the nonlinear equation

$$u'(t) = f(t, u(t)) \quad \text{a.e. in } J \tag{1.1}$$

and assume for simplilcity that $f(t, x)$ is defined in the strip $S = J \times \mathbb{R}^n$ and satisfies the following conditions: $f(t, \cdot)$ is continuous in $\mathbb{R}^n$ for almost all (fixed) $t \in J$, $f(\cdot, x)$ is measurable in J for all (fixed) $x \in \mathbb{R}^n$, $f(\cdot, 0) \in L(\mathbb{R})$, and for each constant $A > 0$ there is a function $m(\cdot) \in L(J)$ such that

$$|f(t, x) - f(t, y)| \leq m_A(t)|x - y| \quad \text{for } t \in J \text{ and } |x|, |y| \leq A.$$

The defect P of a function $v \in AC(J)$ with respect to equation (1.1) is defined by

$$(Pv)(t) = v'(t) - f(t, v(t)).$$

The function f is said to be quasimonotone increasing in x if $f_i(t,x)$ is (weakly) increasing in x_j for all $j \neq i$, or equivalently, if

$$x \leq y, x_i = y_i \Rightarrow f_i(t,x) \leq f_i(t,y) \quad \text{a.e. in } J \quad (i = 1, \ldots, n).$$

Theorem 1.3.1. *[91, Theorem 4] Assume that the function $f(t,x)$ satisfies the conditions given above and is quasimonotone inceasing in x, and let $v, w \in AC(J)$ satisfy*

$$v(a) \leq w(a) \text{ and } Pv \leq Pw \quad \text{a.e. in } J.$$

Then each of the following conditions is sufficient for the strong inequality $v \ll w$ in J_0:

(i) $v(a) \ll w(a)$.

(ii) $Pv \ll Pw$ at $a+$.

(iii) For every pair (α, β) of nonempty, disjoint index sets with $\alpha \cup \beta = N$, there are $j \in \beta, k \in \alpha$ such that $f_j(t,x)$ is strictly increasing in x_k for $t \in M, x \in U$, where $M \subset J$ is dense at a and U is a neighborhood of $v(a)$.

1.3.2 Global attractivity and convergence

Let E be an ordered Banach space with positive cone P such that $\text{int}(P) \neq \emptyset$. For $x, y \in E$, we write $x \geq y$ if $x - y \in P$, $x > y$ if $x - y \in P \setminus \{0\}$ and $x \gg y$ if $x - y \in \text{int}(P)$. If $a < b$, we define the order interval $[a,b] := \{x \in E : a \leq x \leq b\}$. The cone P is said to be normal if there exists a constant M such that $0 \leq x \leq y$ implies that $\|x\| \leq M\|y\|$.

Definition 1.3.2. *Let U be a subset of E, and $f : U \to U$ be a continuous map. The* *map f is said to be monotone if $x \geq y$ implies that $f(x) \geq f(y)$; strictly monotone if $x > y$ implies that $f(x) > f(y)$; strongly monotone if $x > y$ implies that $f(x) \gg f(y)$.*

Lemma 1.3.3. *[109, Lemma 2.2.1] Let P be normal, and $S : E \to E$ a continuous and monotone map. Assume that S has a fixed point $x^* \in E$ such that*

(1) $S(x) \ll x^* \ll S(y)$ whenever $x \ll x^* \ll y$.

(2) x^* attracts every point in some open neighborhood W of x^*.

Then x^* is Liapunov stable for S.

Recall that a continuous mapping $f : X \to X$ is said to be asymptotically smooth if for any nonempty closed bounded set $B \subset X$ for which $f(B) \subset B$, there is a compact set $J \subset B$ such that J attracts B. Denote the Fréchet derivative of f at $u = a$ by $Df(a)$ if it exists, and let $r(Df(a))$ be the spectral radius of the linear operator $Df(a) : E \to E$.

Theorem 1.3.4. *[109, Theorem 2.3.4] Let $V = [0, b]$ with $b \gg 0$, and $f : V \to V$ be a continuous map. Assume that*

(1) $f : V \to V$ satisfies either

  (i) f is monotone and strongly subhomogeneous, or

  (ii) f is strongly monotone and strictly subhomogeneous.

(2) $f : V \to V$ is asymptotically smooth, and every positive orbit of f in V is bounded.

(3) $f(0) = 0$, and $Df(0)$ is compact and strongly positive.

Then there exists threshold dynamics:

(a) If $r(Df(0)) \leq 1$, then every positive orbit in V converges to 0.

(b) If $r(Df(0)) > 1$, then there exists a unique fixed point $u^* \gg 0$ in V such that every positive orbit in $V \setminus \{0\}$ converges to u^*.

1.4 Basic reproduction ratio

In epidemiology, the basic reproduction number (ratio) R_0 is the expected number of secondary cases produced, in a completely susceptible population, by a typical infective individual [90]. R_0 serves as a threshold value to measure the effort needed to control the infectious disease. Ever since the celebrated works by Diekmann et al. [24] and by van den Driessche and Watmough [90], there have been numerous papers on the analysis of R_0 for various autonomous epidemic models. Recently, there are also quite a few investigations on the theory and applications of R_0 for models in a periodic environment (see, e.g., [6, 7, 8, 32, 88, 94] and the references therein). More recently, the theory of basic reproduction ratio R_0 has been developed by Zhao for periodic and time-delayed population models with compartmental structure (see [110]). In this section, we first present the R_0 theory for periodic and time-delayed models which we will use in chapters 2, 3 and 5. Then we introduce the theory of R_0 for periodic models which we will use in chapter 4. At last, we will introduce the algorithm for numerical computation of R_0 for periodic and time-delayed models.

1.4.1 The theory of R_0 for periodic and time-delayed models

In this subsection, we introduce the theory of the basic reproduction ratio for periodic and time-delayed models developed by Zhao [110]. Let τ be a nonnegative real number and m be a positive integer, $C = C([-\tau, 0], \mathbb{R}^m)$, and $C^+ = C([-\tau, 0], \mathbb{R}^m_+)$. Then (C, C^+) is an ordered Banach space equipped with the maximum norm and the positive cone C^+. Let $F : \mathbb{R} \to \mathcal{L}(C, \mathbb{R}^m)$ be a map and $V(t)$ be a continuous $m \times m$ matrix function on $\mathbb{R}$. Assume that $F(t)$ and $V(t)$ are ω-periodic in t for some real number $\omega > 0$. For a continuous function $u : [-\tau, \sigma) \to \mathbb{R}^m$ with $\sigma > 0$, define $u_t \in C$ by

$$u_t(\theta) = u(t + \theta), \quad \forall \theta \in [-\tau, 0]$$

for any $t \in [0, \sigma)$.

We consider a linear and periodic functional differential system on C:

$$\frac{du(t)}{dt} = F(t)u_t - V(t)u(t), \quad t \geq 0. \tag{1.2}$$

System (1.2) may come from the equations of infectious variables in the linearization of a given ω-periodic and time-delayed compartmental epidemic model at a disease-free ω-periodic solution. As such, m is the total number of the infectious compartments, and the newly infected individuals at time t depend linearly on the infectious individuals over the time interval $[t - \tau, t]$, which is described by $F(t)u_t$. Further, the internal evolution of individuals in the infectious compartments (e.g., natural and disease-induced deaths, and movements among compartments) is governed by the linear ordinary differential system:

$$\frac{du(t)}{dt} = -V(t)u(t). \tag{1.3}$$

Let $\Phi(t, s), t \geq s$, be the evolution matrices associated with system (1.3), that is, $\Phi(t, s)$ satisfies

$$\frac{\partial}{\partial t}\Phi(t, s) = -V(t)\Phi(t, s), \forall t \geq s, \quad \text{and} \quad \Phi(s, s) = I, \forall s \in \mathbb{R},$$

and $\omega(\Phi)$ be the exponential growth bound of $\Phi(t,s)$, that is,

$$\omega(\Phi) = \inf\left\{\tilde{\omega} : \exists M \geq 1 \text{ such that } \|\Phi(t+s,s)\| \leq Me^{\tilde{\omega}t}, \forall s \in \mathbb{R}, t \geq 0\right\}.$$

We assume that

(H1) Each operator $F(t) : C \to \mathbb{R}^m$ is positive in the sense that $F(t)C^+ \subseteq \mathbb{R}^m_+$.

(H2) Each matrix $-V(t)$ is cooperative, and $\omega(\Phi) < 0$.

We assume that the ω-periodic function $v(t)$ is the initial distribution of infectious individuals. For any given $s \geq 0$, $F(t-s)v_{t-s}$ is the distribution of newly infected individuals at time $t-s$, which is produced by the infectious individuals who were introduced over the time interval $[t-s-\tau, t-s]$. Then $\Phi(t,t-s)F(t-s)v_{t-s}$ is the distribution of those infected individuals who were newly infected at time $t-s$ and remain in the infected compartments at time t. It follows that

$$\int_0^\infty \Phi(t,t-s)F(t-s)v_{t-s}ds = \int_0^\infty \Phi(t,t-s)F(t-s)v(t-s+\cdot)ds$$

is the distribution of accumulative new infections at time t produced by all those infectious individuals introduced at all previous times to t.

Let C_ω be the ordered Banach space of all continuous and ω-periodic functions from $\mathbb{R}$ to $\mathbb{R}^m$, which is equipped with the maximum norm and the positive cone $C_\omega^+ := \{v \in C_\omega : v(t) \geq 0, \forall t \in \mathbb{R}\}$. Define a linear operator $L : C_\omega \to C_\omega$ by

$$[Lv](t) = \int_0^\infty \Phi(t,t-s)F(t-s)v(t-s+\cdot)ds, \quad \forall t \in \mathbb{R}, v \in C_\omega. \tag{1.4}$$

We define the spectral radius of L as the basic reproduction ratio $R_0 = r(L)$.

Let $U(\omega,0)$ be the Poincaré map of system (1.2) on C. The following result shows that R_0 is a threshold value for the stability of the zero solution for periodic system (1.2).

Theorem 1.4.1. *[110, Theorem 2.1] The following statements are valid:*

(i) $R_0 = 1$ *if and only if* $r(U(\omega, 0)) = 1$.

(ii) $R_0 > 1$ *if and only if* $r(U(\omega, 0)) > 1$.

(iii) $R_0 < 1$ *if and only if* $r(U(\omega, 0)) < 1$.

Thus, $R_0 - 1$ *has the same sign as* $r(U(\omega, 0)) - 1$.

In the case where $\tau = 0$, Theorem 1.4.1 reduces to Theorem 2.2 in [94]. Let $W(t, s, \lambda)$ be the evolution operator of the following system on $\mathbb{R}^m$:

$$\frac{dw}{dt} = \left[-V(t) + \frac{F(t)}{\lambda}\right] w, \quad t \in \mathbb{R}. \tag{1.5}$$

Then we have the result

Theorem 1.4.2. *[94, Theorem 2.1] The following statements are valid:*

(i) If $\rho(W(\omega, 0, \lambda)) = 1$ *has a positive solution* λ_0*, then* λ_0 *is an eigenvalue of* L*, and hence* $R_0 > 0$.

(ii) If $R_0 > 0$*, then* $\lambda = R_0$ *is the unique solution of* $\rho(W(\omega, 0, \lambda)) = 1$.

(iii) $R_0 = 0$ *if and only if* $\rho(W(\omega, 0, \lambda)) < 1$ *for all* $\lambda > 0$.

1.4.2 Numerical computation of R_0

In this subsection, we introduce the method proposed by Posny and Wang [70] to numerically calculate the basic reproduction ratio R_0. Let the operator L be defined as in (1.4). For any given $\phi \in C_\omega$, we have

$$\begin{aligned}
(L\phi)(t) &= \int_0^\infty \Phi(t, t-s)F(t-s)\phi(t-s+\cdot)ds \\
&= \int_0^\infty K(t,s)\phi(t-s)ds \\
&= \sum_{k=0}^{\infty} \int_0^\omega K(t, s+k\omega)\phi(t-s)ds \\
&= \int_0^\omega (\sum_{k=0}^{\infty} K(t, s+k\omega))\phi(t-s)ds \\
&= \int_0^\omega G(t,s)\phi(t-s)ds,
\end{aligned} \tag{1.6}$$

where $G(t,s) = \sum_{k=0}^{\infty} K(t, s+k\omega)$. Our aim is to explicitly determine the maximum eigenvalue λ of the operator L such that $(L\phi)(t) = \lambda\phi(t)$ for all ω-periodic functions $\phi \in C_\omega$.

We approximate G by a finite sum

$$G(t,s) \approx \sum_{k=0}^{M} K(t, s+k\omega), \tag{1.7}$$

for some integer $M > 0$. We find it unnecessary to pick a large value for M, owing to the exponential decay of the terms in the summation.

Let us partition the interval $[0, \omega]$ uniformly into n nodes labeled as $t_i = i \cdot \frac{\omega}{n}$ for $i = 0, \ldots, n-1$. Using the trapezoidal rule, we can approximate the integral in (1.6) with second-order accuracy:

$$(L\phi)(t) \approx \frac{\omega}{n}\left(\sum_{i=1}^{n-1} G(t,t_i)\phi(t-t_i) + \frac{1}{2}G(t,t_0)\phi(t-t_0) + \frac{1}{2}G(t,t_n)\phi(t-t_n)\right).$$

Since $\phi(t)$ is ω-periodic, it is clear that $\phi(t-t_0)=\phi(t-t_n)$. For convenience let

$$\tilde{G}(t,t_0)\equiv\frac{1}{2}[G(t,t_0)+G(t,t_n)].$$

Then

$$(L\phi)(t)\approx\frac{\omega}{n}\left[\tilde{G}(t,t_0)\phi(t-t_0)+\sum_{i=1}^{n-1}G(t,t_i)\phi(t-t_i)\right].$$

Now $(L\phi)(t)=\lambda\phi(t)$ can be written as a matrix equation,

$$\frac{\omega}{n}\left[\tilde{G}(t,t_0)\ G(t,t_1)\ G(t,t_2)\ \dots\ G(t,t_{n-1})\right]\begin{bmatrix}\phi(t-t_0)\\ \phi(t-t_1)\\ \phi(t-t_2)\\ \vdots\\ \phi(t-t_{n-1})\end{bmatrix}=\lambda\phi(t).$$

Setting $t=t_j(0\leq j\leq n-1)$ in the above equation yields

$$\frac{\omega}{n}\left[\tilde{G}(t_j,t_0)\ G(t_j,t_1)\ G(t_j,t_2)\ \dots\ G(t_j,t_{n-1})\right]\begin{bmatrix}\phi(t_j-t_0)\\ \phi(t_j-t_1)\\ \phi(t_j-t_2)\\ \vdots\\ \phi(t_j-t_{n-1})\end{bmatrix}=\lambda\phi(t_j). \tag{1.8}$$

Again, by the periodicity of $\phi(t)$, it follows that

$$\begin{array}{ccc}\phi(t_j-t_0)=\phi(t_j), & \phi(t_j-t_1)=\phi(t_{j-1}), & \dots,\\ \phi(t_j-t_{j-1})=\phi(t_1), & \phi(t_j-t_j)=\phi(t_0), & \phi(t_j-t_{j+1})=\phi(t_{n-1}),\\ \dots, & \phi(t_j-t_{n-2})=\phi(t_{j+2}), & \phi(t_j-t_{n-1})=\phi(t_{j+1}),\end{array}$$

and we can rearrange the terms in equation (1.8) to obtain

$$\frac{\omega}{n}\begin{bmatrix} G(t_j,t_j) \; G(t_j,t_{j-1}) \; \ldots \; \tilde{G}(t_j,t_0) \; \ldots \; G(t_j,t_{j+2}) \; G(t_j,t_{j+1}) \end{bmatrix} \begin{bmatrix} \phi(t_0) \\ \phi(t_1) \\ \vdots \\ \phi(t_j) \\ \vdots \\ \phi(t_{n-2}) \\ \phi(t_{n-1}) \end{bmatrix} = \lambda\phi(t_j). \tag{1.9}$$

Note that this equation holds for all $j = 0, \ldots, n-1$, thus generating a matrix system. The coefficient matrix, denoted by A, is given by

$$A = \begin{bmatrix} \tilde{G}(t_0,t_0) & G(t_0,t_{n-1}) & \ldots & \ldots & \ldots & G(t_0,t_2) & G(t_0,t_1) \\ G(t_1,t_1) & \tilde{G}(t_1,t_0) & \ldots & \ldots & \ldots & G(t_1,t_3) & G(t_1,t_2) \\ \vdots & \vdots & \ddots & \ddots & \ddots & \vdots & \vdots \\ G(t_j,t_j) & G(t_j,t_{j-1}) & \ldots & \tilde{G}(t_j,t_0) & \ldots & G(t_j,t_{j+2}) & G(t_j,t_{j+1}) \\ \vdots & \vdots & \ddots & \ddots & \ddots & \vdots & \vdots \\ G(t_{n-2},t_{n-2}) & G(t_{n-2},t_{n-3}) & \ldots & \ldots & \ldots & \tilde{G}(t_{n-2},t_0) & G(t_{n-2},t_{n-1}) \\ G(t_{n-1},t_{n-1}) & G(t_{n-1},t_{n-2}) & \ldots & \ldots & \ldots & G(t_{n-1},t_1) & \tilde{G}(t_{n-1},t_0) \end{bmatrix}. \tag{1.10}$$

Therefore, equation (1.9) can be put into a compact form,

$$\frac{\omega}{n}A\tilde{\phi} = \lambda\tilde{\phi}, \tag{1.11}$$

where A, defined in equation (1.10), is a matrix of dimension $(nm) \times (nm)$, and $\tilde{\phi} = [\phi(t_0), \phi(t_1), \ldots, \phi(t_{n-1})]^T$ is a vector of dimension $(nm) \times 1$. Hence, to find the basic reproduction ratio defined by $R_0 = \rho(L)$, it is equivalent to find the maximum

λ such that (1.11) is valid; i.e.,

$$R_0 \approx \frac{\omega}{n}\rho(A).$$

In the case where $\tau = 0$, we can use Theorem 1.4.2 (ii) and the standard bisection method to compute R_0 numerically.

Chapter 2

A periodic vector-bias malaria model with incubation period

2.1 Introduction

Malaria is one of the most common infectious diseases which cause public health problems and dampen economics [85]. Although the modern world is continuing to make impressive progress in reducing malaria cases and deaths, an estimated 3.3 billion people in 97 countries and territories are still at risk of being infected with malaria, and 1.2 billion are at high risk. According to the recent estimates, 198 million cases of malaria occurred globally in 2013 and the disease led to 584000 deaths, with 90% of deaths occurring in Africa and most cases and deaths occurring in sub-Saharan Africa [99].

Mathematical models provide powerful tools for explaining and predicting malaria transmission trend, and also for quantifying the effectiveness of different intervention and eradication strategies in malaria endemic regions. The first mathematical model for malaria transmission was introduced by Ross [76] and later extended by MacDonald [50]. Since then great progress has been made in mathematical modeling of malaria transmission dynamics; see, e.g., [17, 18, 25, 47, 103], and references therein.

In this chapter we propose a mathematical model which takes into account the following three aspects:

Climate Factor. Malaria is caused by five species of *Plasmodium* protozoan parasites (*vivax, malariae, ovale, knowlesi* and *falciparum*) and is transmitted among humans by the bites of female *Anopheles* mosquitoes. Environmental factors, such as temperature, humidity, rainfall and wind patterns have great impact on mosquito reproduction, development and longevity and the parasite survival in its life cycle in mosquito. For example, a change in temperature from $12°C$ to $31°C$ reduces the number of days required for breeding from 65 days to 7.3 days [42]. The sporogony of the parasites in vector is completed in 55 days at $16°C$, which reduces to 7 days at $28°C$ [53]. Thus, it is necessary to incorporate seasonal climate factors into a mathematical model.

Extrinsic Incubation Period (EIP). Female *Anopheles* mosquitoes pick up *Plasmodium* parasites in a blood meal taken from an infectious human host. The parasites then go through several developmental stages before they migrate to the mosquito salivary glands. The time parasites spent in completing its development within the mosquito and migrating to the salivary glands is known as the extrinsic incubation period (EIP). Once in the salivary glands the parasites can be transmitted to a susceptible human host when the mosquito takes another blood meal [10, 11]. Transmission of malaria to such a susceptible human host cannot occur until the EIP is completed [69]. The longevity of a female adult mosquito ranges from 3 to 100 days and the EIP takes from 10 to 30 days. For the mosquitoes that live so short that the EIP cannot be completed before they die, they don't transmit malaria at all. While for those that live long enough to survive the EIP, they will remain infectious for the rest of their lives. Thus, the EIP directly influence the number of infectious mosquitoes. An appropriate candidate to depict the EIP in mathematics is time delay.

Vector-bias Effect. According to the experiment result in [39], during their development within the human, malaria parasites make infectious humans more attractive to mosquitoes via chemical substances to enhance their transmission. Another theoretical analysis of optimal feeding behavior and the mechanics of blood sucking indicates that mosquitoes may maximize their rates of protein intake during feeding by choosing malaria-infected human hosts [34]. All these results show that mosquitoes may prefer infectious hosts to susceptible ones. This difference between the probabilities of picking humans is the so called "vector-bias". We will incorporate such a vector-bias term into our model to see what impact it has on the epidemiology of malaria.

The rest of this chapter is organized as follows. In the next section, we present the model and the hypotheses on which it is formulated. We introduce the basic reproduction ratio R_0, and prove a threshold result on the global dynamics in terms of R_0 in section 2.3. In section 2.4, we use some monthly reported data to simulate the malaria transmission trend in Maputo Province, Mozambique. Numerical simulations on the long term behaviour of the infectious compartments are also carried out to illustrate our analytic result. A brief discussion is given in section 2.5.

2.2 Model formulation

Our model is motivated by the malaria transmission models in [17, 47, 103]. The biological interpretations for parameters are listed in Table 2.1. Let the state variables $I_h(t), S_m(t), I_m(t)$ represent the numbers of infectious humans, susceptible and infectious female adult mosquitoes at time t, respectively. Compared with the life span of a mosquito, the longevity of a human is quite long. The climate factor has little impact on human activities. Thus, we treat all the parameters related to humans as constants. We suppose that the total number of humans stabilizes at H. Let ρ be the rate at which humans remove from the infectious compartment due to recovery and disease-induced death. We use d_h to denote the natural death rate of humans. Let $\mu(t)$ be the recruitment rate at which female adult mosquitoes emerge from larvae. Vector-bias effect is a phenomenon that vectors show different preference weights in host selection. To depict such a phenomenon, we introduce the parameters p and l, which are defined as the probabilities that a mosquito arrives at a human at random and picks the human if he is infectious and susceptible, respectively [17]. A larger probability corresponds to a higher preference weight. Since infectious humans are more attractive to mosquitoes, we assume that $p \geq l$. The biting rate $\beta(t)$ of mosquitoes is the number of bites per mosquito per unit time at time t. Then $\beta(t)I_m(t)$ is the number of bites by all infectious mosquitoes per unit time at time t. We suppose that the total number of bites made by mosquitoes equals to the number of bites received by humans. We also assume that a mosquito will not bite the same person for more than once. Then $\beta(t)I_m(t)$ is also the number of humans that are bitten by infectious mosquitoes per unit time at time t . Among all the humans that are bitten by infectious mosquitoes, only those originally susceptible ones may contribute to the increase of $I_h(t)$. Hence, we need to derive the probability that a human is susceptible under the condition that a mosquito picks him. Obviously, this probability equals to $\frac{l(H-I_h(t))}{pI_h(t)+l(H-I_h(t))}$, the ratio between the total bitten susceptible humans and the total bitten humans. We neglect the incubation period within humans which is short compared to the longevity of a human. Thus, the number of newly occurred infectious humans per unit time at time t is

$$c\beta(t)\frac{l(H-I_h(t))}{pI_h(t)+l(H-I_h(t))}I_m(t),$$

where c is the probability of transmission of infection from an infectious mosquito to a susceptible human given that the contact between the two occurs.

Similarly, $\frac{pI_h(t)}{pI_h(t)+l(H-I_h(t))}$ is the probability that a human is infectious under the condition that a mosquito picks him. Then the number of newly occurred infected mosquitoes per unit time at time t is

$$b\beta(t)\frac{pI_h(t)}{pI_h(t)+l(H-I_h(t))}S_m(t),$$

where b is the transmission probability per bite from infectious humans to susceptible mosquitoes. The newly infected mosquitoes need to survive the EIP to become infectious. Let τ be the length of the EIP and $d_m(t)$ be the mortality rate for adult female mosquitoes, then the probability that a mosquito survives the EIP at time t is $e^{-\int_{t-\tau}^{t} d_m(s)ds}$. Thus, the number of newly occurred infectious mosquitoes per unit time at time t is

$$e^{-\int_{t-\tau}^{t} d_m(s)ds}\frac{b\beta(t-\tau)pI_h(t-\tau)}{pI_h(t-\tau)+l(H-I_h(t-\tau))}S_m(t-\tau).$$

Consequently, we have the following model:

$$\begin{aligned}
\frac{dI_h(t)}{dt} &= \frac{c\beta(t)l(H-I_h(t))}{pI_h(t)+l(H-I_h(t))}I_m(t)-(d_h+\rho)I_h(t),\\
\frac{dS_m(t)}{dt} &= \mu(t)-\frac{b\beta(t)pI_h(t)}{pI_h(t)+l(H-I_h(t))}S_m(t)-d_m(t)S_m(t),\\
\frac{dI_m(t)}{dt} &= -d_m(t)I_m(t)+e^{-\int_{t-\tau}^{t} d_m(s)ds}\frac{b\beta(t-\tau)pI_h(t-\tau)S_m(t-\tau)}{pI_h(t-\tau)+l(H-I_h(t-\tau))},
\end{aligned}\tag{2.1}$$

where all constant parameters are positive, and $\beta(t)$,$\mu(t)$,$d_m(t)$ are positive, continuous and ω-periodic functions for some $\omega > 0$ with $\mu(t) > 0$ and $\int_0^\omega d_m(t)dt > 0$. It is easy to see that the function

$$a(t) := e^{-\int_{t-\tau}^{t} d_m(s)ds}$$

is also ω-periodic, and hence, model (2.1) is an ω-periodic and time-delayed system.

Table 2.1: Biological interpretations for parameters in model (2.1)

Parameter	Description
c	Probability of transmission of infection from an infectious mosquito to a susceptible human given that contact between them occurs
$\beta(t)$	Biting rate of mosquitoes to humans
l	Probability that a mosquito arrives at human at random and picks the human if he is susceptible
p	Probability that a mosquito arrives at human at random and picks the human if he is infectious
H	The total number of humans
d_h	Human natural death rate
ρ	Rate at which human is removed from the class of infectious (i.e., recovery and disease-induced death rate)
$\mu(t)$	Recruitment rate at which female adult mosquitoes emerge from larvae.
b	Probability of transmission of infection from an infectious human to a susceptible mosquito given that contact between them occurs
$d_m(t)$	Mortality rate for female adult mosquitoes
τ	Extrinsic Incubation Period

2.3 Threshold dynamics

In this section, we will use the theory in section 1.4 to obtain the basic reproduction ratio for our model. It is easy to see that the scalar linear periodic equation

$$\frac{dS_m(t)}{dt} = \mu(t) - d_m(t)S_m(t) \tag{2.2}$$

has a unique positive ω-periodic solution

$$S_m^*(t) = \left[\int_0^t \mu(r) e^{\int_0^r d_m(s)ds} dr + \frac{\int_0^\omega \mu(r) e^{\int_0^r d_m(s)ds} dr}{e^{\int_0^\omega d_m(s)ds} - 1}\right] e^{-\int_0^t d_m(s)ds},$$

which is globally asymptotically stable.

Linearizing system (2.1) at its disease-free periodic solution $(0, S_m^*(t), 0)$, we then obtain the following system of periodic linear equations for the infective variables I_h and I_m:

$$\begin{aligned} \frac{dI_h(t)}{dt} &= -a_{11}(t) I_h(t) + a_{12}(t) I_m(t), \\ \frac{dI_m(t)}{dt} &= a_{21}(t) I_h(t-\tau) - a_{22}(t) I_m(t), \end{aligned} \tag{2.3}$$

where $a_{11}(t) = d_h + \rho$, $a_{12}(t) = c\beta(t)$, $a_{22}(t) = d_m(t)$, and

$$a_{21}(t) = a(t) \frac{b\beta(t-\tau) p S_m^*(t-\tau)}{lH}.$$

Let $C = C([-\tau, 0], \mathbb{R}^2)$, $C^+ = C([-\tau, 0], \mathbb{R}_+^2)$. Then (C, C^+) is an ordered Banach space equipped with the maximum norm and the positive cone C^+. For any given continuous function $v = (v_1, v_2) : [-\tau, \sigma) \to \mathbb{R}^2$ with $\sigma > 0$, we define $v_t \in C$ by

$$v_t(\theta) = (v_1(t+\theta), v_2(t+\theta)), \quad \forall \theta \in [-\tau, 0],$$

for any $t \in [0, \sigma)$. Let $F : \mathbb{R} \to \mathcal{L}(C, \mathbb{R}^2)$ be a map and $V(t)$ be a continuous 2×2 matrix function on $\mathbb{R}$ defined as follows:

$$F(t)\varphi = \begin{bmatrix} a_{12}(t)\varphi_2(0) \\ a_{21}(t)\varphi_1(-\tau) \end{bmatrix}, \qquad V(t) = \begin{bmatrix} a_{11}(t) & 0 \\ 0 & a_{22}(t) \end{bmatrix}.$$

We assume that the ω-periodic function $v(t)$ is the initial distribution of infectious individuals. For any given $s \geq 0$, $F(t-s)v_{t-s}$ is the distribution of newly infected individuals at time $t - s$, which is produced by the infectious individuals who were introduced over the time interval $[t - s - \tau, t - s]$. Then $\Phi(t, t - s)F(t - s)v_{t-s}$ is the distribution of those infected individuals who were newly infected at time $t - s$ and remain in the infected compartments at time t. It follows that

$$\int_0^\infty \Phi(t, t - s)F(t - s)v_{t-s}ds = \int_0^\infty \Phi(t, t - s)F(t - s)v(t - s + \cdot)ds$$

is the distribution of accumulative new infections at time t produced by all those infectious individuals introduced at all previous times to t.

Let C_ω be the ordered Banach space of all continuous and ω-periodic functions from $\mathbb{R}$ to $\mathbb{R}^2$, which is equipped with the maximum norm and the positive cone $C_\omega^+ := \{v \in C_\omega : v(t) \geq 0, \forall t \in \mathbb{R}\}$. Define a linear operator $L : C_\omega \to C_\omega$ by

$$[Lv](t) = \int_0^\infty \Phi(t, t - s)F(t - s)v(t - s + \cdot)ds, \quad \forall t \in \mathbb{R}, v \in C_\omega,$$

where $\Phi(t, s), t \geq s$, is the evolution matrix associated with the following system

$$\frac{dv(t)}{dt} = -V(t)v(t),$$

that is, $\Phi(t, s)$ satisfies

$$\frac{\partial}{\partial t}\Phi(t, s) = -V(t)\Phi(t, s), \quad \forall t \geq s, \quad \text{and} \quad \Phi(s, s) = I, \quad \forall s \in \mathbb{R}.$$

It then easily follows that

$$\Phi(t, s) = \begin{bmatrix} e^{-\int_s^t a_{11}(r)dr} & 0 \\ 0 & e^{-\int_s^t a_{22}(r)dr} \end{bmatrix}$$

and

$$\begin{aligned}
[Lv](t) &= \int_0^\infty \Phi(t,t-s)F(t-s)v(t-s+\cdot)ds \\
&= \int_0^\infty \Phi(t,t-s)\begin{bmatrix} a_{12}(t-s)v_2(t-s) \\ a_{21}(t-s)v_1(t-s-\tau) \end{bmatrix} ds \\
&= \int_0^\infty \begin{bmatrix} e^{-\int_{t-s}^t a_{11}(r)dr}a_{12}(t-s)v_2(t-s) \\ e^{-\int_{t-s}^t a_{22}(r)dr}a_{21}(t-s)v_1(t-s-\tau) \end{bmatrix} ds \\
&= \begin{bmatrix} \int_0^\infty e^{-\int_{t-s}^t a_{11}(r)dr}a_{12}(t-s)v_2(t-s)ds \\ \int_\tau^\infty e^{-\int_{t-s+\tau}^t a_{22}(r)dr}a_{21}(t-s+\tau)v_1(t-s)ds \end{bmatrix} \\
&= \int_0^\infty K(t,s)v(t-s)ds, \quad \forall t\in\mathbb{R}, \quad v=\begin{bmatrix} v_1 \\ v_2 \end{bmatrix}\in C_\omega,
\end{aligned}$$

where

$$K(t,s)=\begin{bmatrix} 0 & e^{-\int_{t-s}^t a_{11}(r)dr}a_{12}(t-s) \\ e^{-\int_{t-s+\tau}^t a_{22}(r)dr}a_{21}(t-s+\tau) & 0 \end{bmatrix}, \quad \text{if} \quad s\geq\tau,$$

and

$$K(t,s)=\begin{bmatrix} 0 & e^{-\int_{t-s}^t a_{11}(r)dr}a_{12}(t-s) \\ 0 & 0 \end{bmatrix}, \quad \text{if} \quad s<\tau.$$

Following section 1.4, we define $R_0 = r(L)$. Let $\hat{P}(t)$ be the solution maps of system (2.3), that is, $\hat{P}(t)\varphi = u_t(\varphi), t \geq 0$, where $u(t,\varphi)$ is the unique solution of system (2.3) with $u_0 = \varphi \in C([-\tau,0],\mathbb{R}^2)$. Then $\hat{P} := \hat{P}(\omega)$ is the Poincaré map associated with linear system (2.3). Let $r(\hat{P})$ be the spectral radius of $\hat{P}$. By Theorem 1.4.1, we have the following result.

Lemma 2.3.1. *$R_0 - 1$ has the same sign as $r(\hat{P}) - 1$.*

Let

$$W := C([-\tau, 0], [0, H]) \times C([-\tau, 0], \mathbb{R}_+) \times \mathbb{R}_+.$$

Then we have the following preliminary result for system (2.1).

Lemma 2.3.2. *For any* $\varphi \in W$, *system* (2.1) *has a unique nonnegative bounded solution* $u(t, \varphi)$ *on* $[0, \infty)$ *with* $u_0 = \varphi$, *and* $u_t(\varphi) \in W$ *for all* $t \geq 0$.

Proof. For any $\varphi = (\varphi_1, \varphi_2, \varphi_3) \in W$, we define

$$\widetilde{f}(t, \varphi) = \begin{pmatrix} \frac{c\beta(t)l(H-\varphi_1(0))}{(p-l)\varphi_1(0)+lH}\varphi_3 - (d_h + \rho)\varphi_1(0) \\ \mu(t) - \frac{b\beta(t)p\varphi_1(0)}{(p-l)\varphi_1(0)+lH}\varphi_2(0) - d_m(t)\varphi_2(0) \\ -d_m(t)\varphi_3 + e^{-\int_{t-\tau}^{t} d_m(s)ds} \frac{b\beta(t-\tau)p\varphi_1(-\tau)\varphi_2(-\tau)}{(p-l)\varphi_1(-\tau)+lH} \end{pmatrix}.$$

Since $\widetilde{f}(t, \varphi)$ is continuous in $(t, \varphi) \in \mathbb{R}_+ \times W$, and $\widetilde{f}(t, \varphi)$ is Lipschitz in φ on each compact subset of W, it then follows that system (2.1) has a unique solution $u(t, \varphi)$ on its maximal interval $[0, \sigma_\varphi)$ of existence with $u_0 = \varphi$ (see, e.g., [29, Theorems 2.2.1 and 2.2.3]).

Let $\varphi = (\varphi_1, \varphi_2, \varphi_3) \in W$ be given. If $\varphi_i(0) = 0$ for some $i \in \{1, 2\}$, then $\widetilde{f}_i(t, \varphi) \geq 0$. If $\varphi_3 = 0$, then $\widetilde{f}_3(t, \varphi) \geq 0$. If $\varphi_1(0) = H$, then $\widetilde{f}_1(t, \varphi) \leq 0$. By [84, Theorem 5.2.1 and Remark 5.2.1], it follows that for any $\varphi \in W$, the unique solution $u(t, \varphi)$ of system (2.1) with $u_0 = \varphi$ satisfies $u_t(\varphi) \in W$ for all $t \in [0, \sigma_\varphi)$.

Clearly, $0 \leq u_1(t, \varphi) \leq H$ for all $t \in [0, \sigma_\varphi)$. In view of the second and third equations of system (2.1), we have

$$\begin{aligned} \frac{du_2(t)}{dt} &\leq \mu(t) - d_m(t)u_2(t), \forall t \in [0, \sigma_\varphi), \\ \frac{du_3(t)}{dt} &\leq -d_m(t)u_3(t) + e^{-\int_{t-\tau}^{t} d_m(s)ds} b\beta(t-\tau)u_2(t-\tau), \forall t \in [0, \sigma_\varphi). \end{aligned}$$

Thus, both $u_2(t)$ and $u_3(t)$ are bounded on $[0, \sigma_\varphi)$, and hence, [29, Theorem 2.3.1] implies that $\sigma_\varphi = \infty$. □

For any given $\varphi \in W$, let $u(t,\varphi) = (u_1(t), u_2(t), u_3(t))$ be the unique solution of system (2.1) satisfying $u_0 = \varphi$. Let

$$w(t) := e^{-\int_{t-\tau}^{t} d_m(s)ds} u_2(t-\tau) + u_3(t).$$

Then $(u_1(t), u_3(t))$ can be regarded as a solution of the following nonautonomous system:

$$\begin{aligned} \frac{du_1(t)}{dt} &= \frac{c\beta(t)l(H-u_1(t))}{(p-l)u_1(t)+lH}u_3(t) - (d_h+\rho)u_1(t), \\ \frac{du_3(t)}{dt} &= -d_m(t)u_3(t) + \frac{b\beta(t-\tau)pu_1(t-\tau)}{(p-l)u_1(t-\tau)+lH}(w(t)-u_3(t)). \end{aligned} \tag{2.4}$$

It easily follows that $w(t)$ satisfies

$$\frac{dw(t)}{dt} = -d_m(t)w(t) + e^{-\int_{t-\tau}^{t} d_m(s)ds}\mu(t-\tau), \tag{2.5}$$

and system (2.5) has a unique positive ω-periodic solution

$$K(t) := e^{-\int_{t-\tau}^{t} d_m(s)ds} S_m^*(t-\tau),$$

which is globally attractive in $\mathbb{R}$. Thus, system (2.4) has a limiting system:

$$\begin{aligned} \frac{dv_1(t)}{dt} &= \frac{c\beta(t)l(H-v_1(t))}{(p-l)v_1(t)+lH}v_2(t) - (d_h+\rho)v_1(t), \\ \frac{dv_2(t)}{dt} &= -d_m(t)v_2(t) + \frac{b\beta(t-\tau)pv_1(t-\tau)}{(p-l)v_1(t-\tau)+lH}(K(t)-v_2(t)). \end{aligned} \tag{2.6}$$

Note that $z(t) = (u_1(t), u_3(t), w(t))$ satisfies the following ω-periodic system:

$$\begin{aligned}
\frac{du_1(t)}{dt} &= \frac{c\beta(t)l(H-u_1(t))}{(p-l)u_1(t)+lH}u_3(t) - (d_h+\rho)u_1(t),\\
\frac{du_3(t)}{dt} &= -d_m(t)u_3(t) + \frac{b\beta(t-\tau)pu_1(t-\tau)}{(p-l)u_1(t-\tau)+lH}(w(t)-u_3(t)),\\
\frac{dw(t)}{dt} &= -d_m(t)w(t) + e^{-\int_{t-\tau}^{t} d_m(s)ds}\mu(t-\tau).
\end{aligned} \tag{2.7}$$

Clearly, system (2.1) is equivalent to (2.7). It suffices to study system (2.7). Let

$$\Omega := C([-\tau, 0], [0, H]) \times \mathbb{R}_+^2.$$

We then have the following preliminary result for system (2.7).

Lemma 2.3.3. *For any $\varphi \in \Omega$, system* (2.7) *has a unique solution $z(t, \varphi)$ with $z_0 = \varphi$, and $z_t(\varphi) \in \Omega, \forall t \geq 0$.*

Proof. For any $\varphi \in \Omega$, define

$$\hat{f}(t,\varphi) = \begin{pmatrix} \frac{c\beta(t)l(H-\varphi_1(0))}{(p-l)\varphi_1(0)+lH}\varphi_2 - (d_h+\rho)\varphi_1(0) \\ -d_m(t)\varphi_2 + \frac{b\beta(t-\tau)p\varphi_1(-\tau)}{(p-l)\varphi_1(-\tau)+lH}(\varphi_3-\varphi_2) \\ -d_m(t)\varphi_3 + e^{-\int_{t-\tau}^{t} d_m(s)ds}\mu(t-\tau) \end{pmatrix}.$$

Since $\hat{f}(t, \varphi)$ is continuous in $(t, \varphi) \in \mathbb{R} \times \Omega$, and $\hat{f}(t, \varphi)$ is Lipschitz in φ on each compact subset of Ω, it then follows that system (2.7) has a unique solution $z(t, \varphi)$ with $z_0 = \varphi$ on its maximal interval $[0, \sigma_\varphi)$ of existence.

Let $\varphi = (\varphi_1, \varphi_2, \varphi_3) \in \Omega$ be given. If $\varphi_1(0) = 0$, then $\hat{f}_1(t, \varphi) \geq 0$. If $\varphi_i = 0$ for some $i = 2, 3$, then $\hat{f}_i(t, \varphi) \geq 0$. If $\varphi_1(0) = H$, then $\hat{f}_1(t, \varphi) \leq 0$. By [84, Theorem 5.2.1 and Remark 5.2.1], it follows that for any $\varphi \in \Omega$, the unique solution $z(t, \varphi)$ of system (2.7) with $u_0 = \varphi$ satisfies $z_t(\varphi) \in \Omega$ for all $t \in [0, \sigma_\varphi)$.

Since equation (2.5) has a globally attractive periodic solution $K(t)$, it follows that $z_3(t,\varphi) = w(t)$ is bounded on $[0,\sigma_\varphi)$, that is, there exists $B > 0$ such that $w(t) \leq B, \forall t \in [0,\sigma_\varphi)$. In view of the second equation of system (2.7), we have

$$\frac{du_3(t)}{dt} \leq -d_m(t)u_3(t) + b\beta(t-\tau)B.$$

Hence, $z_2(t,\varphi) = u_3(t)$ is also bounded on $[0,\sigma_\varphi)$. Then [29, Theorem 2.3.1] implies that $\sigma_\varphi = \infty$. □

Let

$$G(t) := C([-\tau,0],[0,H]) \times [0,K(t)], \quad t \geq 0.$$

Then we have the following result for system (2.6).

Lemma 2.3.4. *For any $\varphi \in G(0)$, system* (2.6) *has a unique solution $v(t,\varphi)$ with $v_0 = \varphi$, and $v_t(\varphi) \in G(t), \forall t \geq 0$.*

Proof. For any $\varphi \in G(0)$, define

$$f(t,\varphi) = \begin{pmatrix} \frac{c\beta(t)l(H-\varphi_1(0))}{(p-l)\varphi_1(0)+lH}\varphi_2 - (d_h+\rho)\varphi_1(0) \\ -d_m(t)\varphi_2 + \frac{b\beta(t-\tau)p\varphi_1(-\tau)}{(p-l)\varphi_1(-\tau)+lH}(K(t)-\varphi_2) \end{pmatrix}.$$

Since f is continuous in $(t,\varphi) \in \mathbb{R} \times G(0)$, and f is Lipschitz in φ on each compact subset of $G(0)$, it then follows that system (2.6) has a unique solution $v(t,\varphi)$ with $v_0 = \varphi$ on its maximal interval $[0,\sigma_\varphi)$ of existence.

Let $\varphi = (\varphi_1,\varphi_2) \in G(0)$ be given. If $\varphi_1(0) = 0$, then $f_1(t,\varphi) \geq 0$. If $\varphi_2 = 0$, then $f_2(t,\varphi) \geq 0$. If $\varphi_1(0) = H$, then $f_1(t,\varphi) \leq 0$. By [84, Theorem 5.2.1 and Remark 5.2.1], it follows that the unique solution $v(t,\varphi)$ of system (2.6) with $v_0 = \varphi$ satisfies $v_t(\varphi) \in C([-\tau,0],[0,H]) \times \mathbb{R}_+$.

It remains to prove that $v_2(t) \leq K(t), \forall t \in [0,\sigma_\varphi)$. Suppose this does not hold.

Then there exists $t_0 \in [0, \sigma_\varphi)$ and $\epsilon_0 > 0$ such that

$$v_2(t_0) = K(t_0) \quad \text{and} \quad v_2(t) > K(t), \quad \forall t \in (t_0, t_0 + \epsilon_0).$$

Since

$$\frac{dv_2(t_0)}{dt} = -d_m(t_0)v_2(t_0) = -d_m(t_0)K(t_0) < \frac{dK(t_0)}{dt},$$

there exists $\epsilon_1 \in (0, \epsilon_0)$ such that $v_2(t) \leq K(t),\ \forall t \in (t_0, t_0 + \epsilon_1)$, which is a contradiction. This proves that $v_t(\varphi) \in G(t), \forall t \in [0, \sigma_\varphi)$. Clearly, $v_t(\varphi)$ is bounded on $[0, \sigma_\varphi)$, and hence, [29, Theorem 2.3.1] implies that $\sigma_\varphi = \infty$. □

Note that the linearized system of (2.6) at (0,0) is

$$\begin{aligned} \frac{dv_1(t)}{dt} &= -(d_h + \rho)v_1(t) + c\beta(t)v_2(t), \\ \frac{dv_2(t)}{dt} &= \frac{b\beta(t-\tau)pK(t)}{lH}v_1(t-\tau) - d_m(t)v_2(t), \end{aligned} \tag{2.8}$$

which is the same as system (2.3).

Let P be the Poincaré map of the linear system (2.8) on the space $C([-\tau, 0], \mathbb{R}) \times \mathbb{R}$, and $r(P)$ be its spectral radius. Then we have the following threshold type result for system (2.6).

Lemma 2.3.5. *The following statements are valid:*

(i) If $r(P) \leq 1$, then $v^*(t) = (0, 0)$ is globally asymptotically stable for system (2.6) *in $G(0)$.*

(ii) If $r(P) > 1$, then system (2.6) *admits a unique positive ω-periodic solution $\bar{v}(t) = (\bar{v}_1(t), \bar{v}_2(t))$ which is globally asymptotically stable for system* (2.6) *in $G(0) \setminus \{0\}$.*

Proof. Let $S(t)$ be the solution maps of system (2.6), that is, $S(t)\varphi = v_t(\varphi), t \geq 0$, where $v(t,\varphi)$ is the unique solution of system (2.6) with $v_0 = \varphi \in G(0)$. It follows from Lemma 2.3.4 that $S(t)$ maps $G(0)$ into $G(t)$, and $S := S(\omega) : G(0) \to G(\omega) = G(0)$ is the Poincaré map associated with system (2.6). By the continuity and differentiability of solutions with respect to initial values, it follows that S is differentiable at zero and the Frechét derivative $DS(0) = P$.

For any given $\varphi, \psi \in G(0)$ with $\varphi \geq \psi$, let $v(t) = v(t,\varphi)$ and $\bar{v}(t) = v(t,\psi)$. Define

$$A(t) := \frac{b\beta(t-\tau)pv_1(t-\tau)}{(p-l)v_1(t-\tau)+lH}, \quad B(t) := \frac{b\beta(t-\tau)p\bar{v}_1(t-\tau)}{(p-l)\bar{v}_1(t-\tau)+lH}.$$

Since $v_1(t-\tau) = \varphi_1(t-\tau)$ and $\bar{v}_1(t-\tau) = \psi_1(t-\tau)$, $\forall t \in [0,\tau]$, we have $A(t) \geq B(t)$, $\forall t \in [0,\tau]$. In view of $v(0) = \varphi(0) \geq \psi(0) = \bar{v}(0)$, the comparison theorem for cooperative ordinary differential systems implies that $v(t) \geq \bar{v}(t)$, $\forall t \in [0,\tau]$. Here we have regarded $A(t)$ and $B(t)$ in system (2.6) as two given functions of t on $[0,\tau]$. Repeating this procedure for $t \in [\tau, 2\tau], [2\tau, 3\tau], \ldots$, it then follows that $v(t,\varphi) \geq v(t,\psi)$, $\forall t \in [0,\infty)$. This implies that $S(t) : G(0) \to G(t)$ is monotone for each $t \geq 0$.

Next we show that the solution map $S(t)$ is eventually strongly monotone. Let $\varphi > \psi$ and denote $v(t,\varphi) = (\bar{y}_1(t), \bar{y}_2(t))$, $v(t,\psi) = (y_1(t), y_2(t))$.

Claim 1. There exists $t_0 \in [0,\tau]$ such that $\bar{y}_2(t) > y_2(t), \forall t \geq t_0$.

We first prove that $\bar{y}_2(t_0) > y_2(t_0)$ for some $t_0 \in [0,\tau]$. Otherwise, we have $\bar{y}_2(t) = y_2(t), \forall t \in [0,\tau]$, and hence, $\frac{d\bar{y}_2(t)}{dt} = \frac{dy_2(t)}{dt}, \forall t \in (0,\tau)$. Thus, we have

$$\left[\frac{b\beta(t-\tau)p\bar{y}_1(t-\tau)}{(p-l)\bar{y}_1(t-\tau)+lH} - \frac{b\beta(t-\tau)py_1(t-\tau)}{(p-l)y_1(t-\tau)+lH}\right][K(t)-y_2(t)] = 0, \ \forall t \in [0,\tau]. \quad (2.9)$$

Since $\varphi > \psi$ and $\varphi_2 = \bar{y}_2(0) = y_2(0) = \psi_2$, $\varphi_1 > \psi_1$. Then there exists an open interval $(a,b) \subset [-\tau, 0]$ such that $\varphi_1(\theta) > \psi_1(\theta), \forall \theta \in (a,b)$. It follows from equation

(2.9) that $y_2(t) = K(t), \forall t \in (a+\tau, b+\tau)$, and hence,

$$\frac{dK(t)}{dt} = \frac{dy_2(t)}{dt} = -d_m(t)K(t), \quad \forall t \in (a+\tau, b+\tau),$$

which contradicts with the fact that

$$\frac{dK(t)}{dt} = -d_m(t)K(t) + e^{-\int_{t-\tau}^{t} d_m(s)ds}\mu(t-\tau).$$

Let

$$g_1(t,y) := -d_m(t)y + \frac{b\beta(t-\tau)py_1(t-\tau)}{(p-l)y_1(t-\tau)+lH}[K(t)-y].$$

Since

$$\begin{aligned}\frac{d\bar{y}_2(t)}{dt} &= -d_m(t)\bar{y}_2(t) + \frac{b\beta(t-\tau)p\bar{y}_1(t-\tau)}{(p-l)\bar{y}_1(t-\tau)+lH}[K(t)-\bar{y}_2(t)]\\ &\geq -d_m(t)\bar{y}_2(t) + \frac{b\beta(t-\tau)py_1(t-\tau)}{(p-l)y_1(t-\tau)+lH}[K(t)-\bar{y}_2(t)]\\ &= g_1(t,\bar{y}_2(t)),\end{aligned}$$

we have

$$\frac{d\bar{y}_2(t)}{dt} - g_1(t,\bar{y}_2(t)) \geq 0 = \frac{dy_2(t)}{dt} - g_1(t,y_2(t)), \ \forall t \geq t_0.$$

Since $\bar{y}_2(t_0) > y_2(t_0)$, the comparison theorem for ODEs (see Theorem 1.3.1) implies that $\bar{y}_2(t) > y_2(t), \forall t \geq t_0$.

Claim 2. $\bar{y}_1(t) > y_1(t), \forall t > t_0$.

We first prove that for any $\epsilon > 0$, there exists an open interval $(c,d) \subset [t_0, t_0+\epsilon]$ such that $H > \bar{y}_1(t), \forall t \in (c,d)$. Otherwise, there exists $\epsilon_0 > 0$ such that $H = \bar{y}_1(t), \forall t \in (t_0, t_0+\epsilon_0)$. It then follows from the first equation of system (2.6) that $0 = -(d_h+\rho)H$, which is a contradiction. Let

$$f_1(t,y) := \frac{c\beta(t)l[H-y]}{(p-l)y+lH}y_2(t) - (d_h+\rho)y.$$

Then we have
$$\begin{aligned}\frac{d\bar{y}_1(t)}{dt} &= \frac{c\beta(t)l[H-\bar{y}_1(t)]}{(p-l)\bar{y}_1(t)+lH}\bar{y}_2(t)-(d_h+\rho)\bar{y}_1(t)\\ &> \frac{c\beta(t)l[H-\bar{y}_1(t)]}{(p-l)\bar{y}_1(t)+lH}y_2(t)-(d_h+\rho)\bar{y}_1(t)\\ &= f_1(t,\bar{y}_1(t)), \quad \forall t\in(c,d),\end{aligned}$$

and hence,

$$\frac{d\bar{y}_1(t)}{dt}-f_1(t,\bar{y}_1(t))>0=\frac{dy_1(t)}{dt}-f_1(t,y_1(t)), \quad \forall t\in(c,d).$$

Since $\bar{y}_1(t_0)\geq y_1(t_0)$, it follows from 1.3.1 that $\bar{y}_1(t)>y_1(t), \forall t>t_0$.

In view of Claims 1 and 2, we obtain

$$(\bar{y}_1(t),\bar{y}_2(t))\gg(y_1(t),y_2(t)), \quad \forall t>t_0.$$

Since $t_0\in[0,\tau]$, it follows that

$$(\bar{y}_{1t},\bar{y}_2(t))\gg(y_{1t},y_2(t)), \quad \forall t>2\tau,$$

that is, $v_t(\varphi)\gg v_t(\psi), \forall t>2\tau$. This shows that $S(t):G(0)\to G(t)$ is strongly monotone for any $t>2\tau$.

For any given $\varphi\in G(0), \varphi\geq 0, 0\leq\lambda\leq 1$, let $v(t,\varphi)$ and $v(t,\lambda\varphi)$ be the solutions of (2.6) satisfying $v_0=\varphi$ and $v_0=\lambda\varphi$, respectively. Denote $x(t)=\lambda v(t,\varphi)$ and $z(t)=v(t,\lambda\varphi)$. Let $f(t,\varphi)$ be defined as in the proof of Lemma 2.3.4. Note that for any $\psi\in G(t)$ and $\lambda\in[0,1]$, we have $f(t,\lambda\psi)\geq\lambda f(t,\psi)$. Then

$$\frac{dx(t)}{dt}=\lambda\frac{dv(t,\varphi)}{dt}=\lambda f(t,v_t(\varphi))\leq f(t,\lambda v_t(\varphi))=f(t,x_t).$$

Clearly, $\frac{dz(t)}{dt}=f(t,z_t)$ and $x_0=\lambda v_0(\varphi)=\lambda\varphi=z_0$. By the comparison theorem for FDEs (see [84, Theorem 5.1.1]), we have $x(t) \le z(t), \forall t \ge 0$, that is, $\lambda v(t,\varphi) \le v(t,\lambda\varphi), \forall t \ge 0$, and hence, $\lambda v_t(\varphi) \le v_t(\lambda\varphi), \forall t \ge \tau$. This shows that the solution map $S(t) : G(0) \to G(t)$ is subhomogeneous. Next, we prove that $S(t) : G(0) \to G(t)$ is strictly subhomogeneous for any $t > \tau$. For any given $\varphi \in G(0)$ with $\varphi \gg 0$ and $\lambda \in (0,1)$, let

$$f_2(t,r) := \frac{c\beta(t)l[H-r]}{(p-l)r+lH} z_2(t) - (d_h+\rho)r,$$
$$g_2(t,r) := \frac{c\beta(t)l[H-r]}{(p-l)r+lH}.$$

Since $g_2(t,r)$ is strictly decreasing in r and $v_1(t,\varphi) > \lambda v_1(t,\varphi), \lambda v_2(t,\varphi) \le v_2(t,\lambda\varphi) = z_2(t), \forall\lambda \in (0,1), \forall t > 0$, it follows that

$$\frac{dx_1(t)}{dt} < g_2(t,x_1(t))z_2(t) - (d_h+\rho)x_1(t) = f_2(t,x_1(t)),$$

and hence,

$$\frac{dx_1(t)}{dt} - f_2(t,x_1(t)) < 0 = \frac{dz_1(t)}{dt} - f_2(t,z_1(t)), \quad \forall t > 0.$$

Note that $x_1(0) = \lambda\varphi_1(0), z_1(0) = \lambda\varphi_1(0)$. By Theorem 1.3.1, we then obtain $x_1(t) < z_1(t), \forall t > 0$. This implies that $v_t(\lambda\varphi) > \lambda v_t(\varphi), \forall t > \tau$.

Now we fix an integer n_0 such that $n_0\omega > 2\tau$. It then follows that $S^{n_0} = S(n_0\omega) : G(0) \to G(0)$ is strongly monotone and strictly subhomogeneous. Note that $DS^{n_0}(0) = DS(n_0\omega)(0) = P(n_0\omega) = P^{n_0}(\omega) = P^{n_0}$, and $r(P^{n_0}) = (r(P))^{n_0}$. By Theorem 1.4.1 and Lemma 1.3.3, as applied to S^{n_0}, we have the following threshold type result:

(a) If $r(P) \le 1$, then $v^*(t) = (0,0)$ is globally asymptotically stable for system (2.6) in $G(0)$.

(b) If $r(P) > 1$, then there exists a unique positive $n_0\omega$-periodic solution $\bar{v}(t) =$

$(\bar{v}_1(t), \bar{v}_2(t))$, which is globally asymptotically stable for system (2.6) in $G(0) \setminus \{0\}$.

It remains to prove that $\bar{v}(t)$ is also an ω-periodic solution of system (2.6). Let $\bar{v}(t) = v(t, \psi)$. By the properties of periodic semiflows, we have $S^{n_0}(S(\psi)) = S(S^{n_0}(\psi)) = S(\psi)$, which implies that $S(\psi)$ is also a positive fixed point of S^{n_0}. By the uniqueness of the positive fixed point of S^{n_0}, it follows that $S(\psi) = \psi$. So $\bar{v}(t)$ is an ω-periodic solution of system (2.6). $\square$

Next, we use the theory of chain transitive sets (see 1.1) to lift the threshold type result for system (2.6) to system (2.7).

Theorem 2.3.6. *The following statements are valid:*

(i) If $r(P) \leq 1$*, then the periodic solution* $(0, 0, K(t))$ *is globally asymptotically stable for system* (2.7) *in* Ω*.*

(ii) If $r(P) > 1$*, then system* (2.7) *admits a unique positive* ω*-periodic solution* $(\bar{v}_1(t), \bar{v}_2(t), K(t))$*, which is globally asymptotically stable for system* (2.7) *in* $\Omega \setminus \{0\} \times \{0\} \times \mathbb{R}_+$*.*

Proof. Let $\tilde{P}(t)$ be the solution maps of system (2.7), that is, $\tilde{P}(t)\varphi = z_t(\varphi), t \geq 0$, where $z(t, \varphi)$ is the unique solution of system (2.7) with $z_0 = \varphi \in \Omega$. Then $\tilde{P} := \tilde{P}(\omega)$ is the Poincaré map of system (2.7). Then $\{\tilde{P}^n\}_{n \geq 0}$ defines a discrete-time dynamical system on Ω. For any given $\bar{\varphi} \in \Omega$, let $\bar{z}(t) = (u_1(t), u_3(t), w(t))$ be the unique solution of system (2.7) with $\bar{z}_0 = \bar{\varphi}$ and let $\omega(\bar{\varphi})$ be the omega limit set of the orbit $\{\tilde{P}^n(\bar{\varphi})\}_{n \geq 0}$ for the discrete-time semiflow $\tilde{P}^n$.

Since equation (2.5) has a unique positive ω-periodic solution $K(t)$, which is globally attractive, we have $\lim_{t \to \infty}(w(t) - K(t)) = 0$, and hence, $\lim_{n \to \infty}(\tilde{P}^n(\bar{\varphi}))_3 = K(0)$. Thus, there exists a subset $\tilde{\omega}$ of $C([-\tau, 0], [0, H]) \times \mathbb{R}_+$ such that $\omega(\bar{\varphi}) = \tilde{\omega} \times \{K(0)\}$.

For any $\phi = (\phi_1, \phi_2, \phi_3) \in \omega(\bar{\varphi})$, there exists a sequence $n_k \to \infty$ such that $\tilde{P}^{n_k}(\bar{\varphi}) \to \phi$, as $k \to \infty$. Since $u_1(n_k\omega) \leq H$ and $u_3(n_k\omega) \leq w(n_k\omega)$, letting $n_k \to \infty$, we obtain $0 \leq \phi_1 \leq H, 0 \leq \phi_2 \leq K(0)$. It then follows that $\tilde{\omega} \subseteq C([-\tau, 0], [0, H]) \times [0, K(0)] = G(0)$. It is easy to see that

$$\tilde{P}^n|_{\omega(\bar{\varphi})}(\phi_1, \phi_2, K(0)) = S^n|_{\tilde{\omega}}(\phi_1, \phi_2) \times \{K(0)\}, \quad \forall (\phi_1, \phi_2) \in \tilde{\omega}, n \geq 0.$$

By Lemma 1.1.2, $\omega(\bar{\varphi})$ is an internally chain transitive set for $\tilde{P}^n$ on Ω. It then easily follows that $\tilde{\omega}$ is an internally chain transitive set for S^n on $G(0)$.

In the case where $r(P) \leq 1$, it follows from Lemma 2.3.5 that $(0, 0)$ is globally asymptotically stable for S^n in $G(0)$. By Theorem 1.1.3, we have $\tilde{\omega} = \{(0, 0)\}$, and hence, $\omega(\bar{\varphi}) = \{(0, 0, K(0))\}$. Then $\tilde{P}^n(0, 0, K(0)) \to (0, 0, K(0))$ as $n \to \infty$. Clearly, $(0, 0, K(0))$ is a fixed point of $\tilde{P}$. This implies that statement (i) is valid.

In the case where $r(P) > 1$, by Lemma 2.3.5 (ii) and Theorem 1.1.4, it follows that either $\tilde{\omega} = \{(0, 0)\}$ or $\tilde{\omega} = \{(\bar{v}_{10}, \bar{v}_2(0))\}$, where $\bar{v}_{10}(\theta) = \bar{v}_1(\theta), \forall \theta \in [-\tau, 0]$. We further claim that $\tilde{\omega} \neq \{(0, 0)\}$. Suppose, by contradiction, that $\tilde{\omega} = \{(0, 0)\}$, then we have $\omega(\bar{\varphi}) = \{(0, 0, K(0))\}$. Thus, $\lim_{t\to\infty}(u_1(t), u_3(t)) = (0, 0)$, and for any $\epsilon > 0$, there exists $T = T(\epsilon) > 0$ such that $|w(t) - K(t)| < \epsilon$ for all $t \geq T$. Then for any $t \geq T(\epsilon)$, we have

$$\begin{aligned}
&\frac{du_1(t)}{dt} \geq \frac{c\beta(t)l(H - u_1(t))}{(p - l)u_1(t) + lH} u_3(t) - (d_h + \rho)u_1(t), \\
&\frac{du_3(t)}{dt} \geq -d_m(t)u_3(t) + \frac{b\beta(t - \tau)pu_1(t - \tau)}{(p - l)u_1(t - \tau) + lH}(K(t) - \epsilon - u_3(t)).
\end{aligned} \tag{2.10}$$

Let r_ϵ be the spectral radius of the Poincaré map associated with the following periodic linear system:

$$\begin{aligned}\frac{du_1(t)}{dt} &= -(d_h+\rho)u_1(t) + c\beta(t)u_3(t),\\ \frac{du_3(t)}{dt} &= \frac{b\beta(t-\tau)pu_1(t-\tau)}{lH}(K(t)-\epsilon) - d_m(t)u_3(t).\end{aligned} \tag{2.11}$$

Since $\lim_{\epsilon\to 0^+} r_\epsilon = r(P) > 1$, we can fix ϵ small enough such that $r_\epsilon > 1$. By similar result to Lemma 2.3.5 (ii), it follows that the Poincaré map of the following system

$$\begin{aligned}\frac{du_1(t)}{dt} &= \frac{c\beta(t)l(H-u_1(t))}{(p-l)u_1(t)+lH}u_3(t) - (d_h+\rho)u_1(t),\\ \frac{du_3(t)}{dt} &= -d_m(t)u_3(t) + \frac{b\beta(t-\tau)pu_1(t-\tau)}{(p-l)u_1(t-\tau)+lH}(K(t)-\epsilon-u_3(t)).\end{aligned} \tag{2.12}$$

admits a globally asymptotically stable fixed point $(\bar{u}_{10}, \bar{u}_3(0)) \gg 0$. In the case where $\bar{\varphi} \in \Omega \setminus \{0\} \times \{0\} \times \mathbb{R}_+$, we have $(u_1(t), u_3(t)) > 0$ in $\mathbb{R}^2$ for all $t > 0$. In view of (3.17) and (3.19), the comparison principle implies that

$$\liminf_{n\to\infty}(u_{1n\omega}(\varphi), u_3(n\omega,\varphi)) \geq (\bar{u}_{10}, \bar{u}_3(0)) \gg 0,$$

which contradicts $\lim_{t\to\infty}(u_1(t), u_3(t)) = (0,0)$. It then follows that $\tilde{\omega} = \{(\bar{v}_{10},\bar{v}_2(0))\}$, and hence, $\omega(\bar{\varphi}) = \{(\bar{v}_{10}, \bar{v}_2(0), K(0))\}$. This implies that $\lim_{t\to\infty}(\bar{z}(t) - (\bar{v}_1(t), \bar{v}_2(t), K(t))) = (0,0,0)$. □

It is easy to see that $u_2(t) = e^{\int_t^{t+\tau} d_m(s)ds}(w(t+\tau) - u_3(t+\tau))$. Then in the case where $r(P) \leq 1$, we have $\lim_{t\to\infty}(u_2(t) - S_m^*(t)) = 0$, and in the case where $r(P) > 1$, we have $\lim_{t\to\infty}(u_2(t) - \hat{u}_2(t)) = 0$, where

$$\hat{u}_2(t) := e^{\int_t^{t+\tau} d_m(s)ds}(K(t+\tau) - \bar{v}_2(t+\tau)) > 0.$$

As a straightforward consequence of Theorem 2.3.6, we have the following result for system (2.1).

Theorem 2.3.7. *The following statements are valid for system* (2.1)*:*

(i) *If* $r(P) \leq 1$, *then* $\lim_{t\to\infty} \|(u(t,\varphi) - (0, S_m^*(t), 0))\| = 0, \forall \varphi \in W$*;*

(ii) *If* $r(P) > 1$, *then* $\lim_{t\to\infty} \|(u(t,\varphi) - (\bar{v}_1(t), \hat{u}_2(t), \bar{v}_2(t)))\| = 0, \forall \varphi \in W \setminus \{0\} \times C([-\tau,0],\mathbb{R}_+) \times \{0\}$.

To describe the global dynamics of system (2.1) in terms of R_0, we need the following result.

Lemma 2.3.8. $r(P) = r(\hat{P})$.

Proof. For any $\psi \in Y := C([-\tau,0],\mathbb{R}) \times \mathbb{R}$, let $v(t,s,\psi) = (v^{(1)}(t,s,\psi), v^{(2)}(t,s,\psi))$ be the unique solution of linear system (2.8) with $v_s(s,\psi) = \psi$, where $v_t(s,\psi) = (v_t^{(1)}(s,\psi), v^{(2)}(t,s,\psi)), \forall t \geq s$. For any $\varphi \in X := C([-\tau,0],\mathbb{R}^2)$, let $u(t,s,\varphi)$ be the unique solution of linear system (2.8) with $u_s(s,\varphi) = \varphi$, where $u_t(s,\varphi)(\theta) = u(t+\theta,s,\varphi), \forall \theta \in [-\tau,0]$. Let $U(t,s)$ and $\hat{U}(t,s)$ be the evolution operators of system (2.8) on Y and X, respectively, that is,

$$U(t,s)\psi = v_t(s,\psi), \quad \forall \psi \in Y, \quad \forall t \geq s,$$
$$\hat{U}(t,s)\varphi = u_t(s,\varphi), \quad \forall \varphi \in X, \quad \forall t \geq s.$$

By the uniqueness of solutions, we have

$$v(t,s,\psi) = u(t,s,\varphi), \quad \forall t \geq s,$$

provided that $\psi = (\psi_1,\psi_2) \in Y$ and $\varphi = (\varphi_1,\varphi_2) \in X$ satisfy $\psi_1 \equiv \varphi_1$ and $\psi_2 = \varphi_2(0)$. Recall that the exponential growth bound of an evolution family $V(t,s)$ $(t \geq s)$ on a

Banach space is defined as

$$\omega(V) = \inf\{\tilde{\omega} : \exists M \geq 1 : \forall s \in \mathbb{R}, t \geq 0 : \|V(t+s,s)\| \leq Me^{\tilde{\omega}t}\}.$$

Let $\omega(U)$ and $\omega(\hat{U})$ be the exponential growth bounds of $U(t,s)$ and $\hat{U}(t,s)$, respectively. Then we have the following two claims.

Claim 1. For any given $\delta > 0$, $\omega(U) \leq \omega(\hat{U}) + \delta$.

Indeed, by the definition of $\omega(\hat{U})$, there exists $M_\delta > 1$ such that

$$\|\hat{U}(t+s,s)\varphi\|_X \leq M_\delta e^{(\omega(\hat{U})+\delta)t}\|\varphi\|_X, \quad \forall t \geq 0, \quad \forall s \in \mathbb{R}, \quad \forall \varphi \in X.$$

This implies that

$$\|u(t+s,s,\varphi)\|_{\mathbb{R}^2} \leq M_\delta e^{(\omega(\hat{U})+\delta)t}\|\varphi\|_X, \quad \forall t \geq 0, \quad \forall s \in \mathbb{R}, \quad \forall \varphi \in X.$$

For any $\psi = (\psi_1, \psi_2) \in Y$, let $\tilde{\psi} = (\psi_1, \tilde{\psi}_2)$, where $\tilde{\psi}_2(\theta) = \psi_2 \in \mathbb{R}, \forall \theta \in [-\tau, 0]$. Clearly, $\tilde{\psi} \in X$. Then $v(t,s,\psi) = u(t,s,\tilde{\psi}), \forall t \geq s, s \in \mathbb{R}$. Since $\|\tilde{\psi}\|_X = \|\psi\|_Y$, we have

$$\begin{aligned}\|v(t+s,s,\psi)\|_{\mathbb{R}^2} &= \|u(t+s,s,\tilde{\psi})\|_{\mathbb{R}^2} \\ &\leq M_\delta e^{(\omega(\hat{U})+\delta)t}\|\tilde{\psi}\|_X \\ &= M_\delta e^{(\omega(\hat{U})+\delta)t}\|\psi\|_Y, \quad \forall t \geq 0, \quad \forall s \in \mathbb{R}.\end{aligned}$$

It follows that there exists $\tilde{M}_\delta \geq M_\delta$ such that

$$\|U(t+s,s)\psi\|_Y = \|v_{t+s}(s,\psi)\|_Y \leq \tilde{M}_\delta e^{(\omega(\hat{U})+\delta)t}\|\psi\|_Y, \quad \forall t \geq 0, \quad \forall s \in \mathbb{R}, \quad \forall \psi \in Y,$$

and hence, $\|U(t+s,s)\| \leq \tilde{M}_\delta e^{(\omega(\hat{U})+\delta)t}$, $\forall t \geq 0$. By the definition of $\omega(U)$, we then obtain $\omega(U) \leq \omega(\hat{U}) + \delta$.

Claim 2. For any given $\delta > 0$, $\omega(\hat{U}) \leq \omega(U) + \delta$.

Indeed, by the definition of $\omega(U)$, there exists $K_\delta > 1$ such that

$$\|U(t+s,s)\psi\|_Y \leq K_\delta e^{(\omega(U)+\delta)t}\|\psi\|_Y, \quad \forall t \geq 0, \quad \forall s \in \mathbb{R}, \quad \forall \psi \in Y.$$

It then follows that

$$\|v(t+s,s,\psi)\|_{\mathbb{R}^2} \leq K_\delta e^{(\omega(U)+\delta)t}\|\psi\|_Y, \quad \forall t \geq 0, \quad \forall s \in \mathbb{R}, \quad \forall \psi \in Y.$$

For any $\varphi = (\varphi_1, \varphi_2) \in X$, let $\hat{\varphi} = (\varphi_1, \varphi_2(0))$. Clearly, $\hat{\varphi} \in Y$. Then $u(t,s,\varphi) = v(t,s,\hat{\varphi}), \forall t \geq s, s \in \mathbb{R}$. Since $\|\hat{\varphi}\|_Y \leq \|\varphi\|_X$, we have

$$\begin{aligned}\|u(t+s,s,\varphi)\|_{\mathbb{R}^2} &= \|v(t+s,s,\hat{\varphi})\|_{\mathbb{R}^2} \\ &\leq K_\delta e^{(\omega(U)+\delta)t}\|\hat{\varphi}\|_Y \\ &\leq K_\delta e^{(\omega(U)+\delta)t}\|\varphi\|_X, \quad \forall t \geq 0, \quad \forall s \in \mathbb{R}.\end{aligned}$$

It follows that there exists $\tilde{K}_\delta \geq K_\delta$ such that

$$\|\hat{U}(t+s,s)\varphi\|_X = \|u_{t+s}(s,\varphi)\|_X \leq \tilde{K}_\delta e^{(\omega(U)+\delta)t}\|\varphi\|_X, \quad \forall t \geq 0, \quad \forall s \in R, \quad \forall \varphi \in X,$$

and hence, $\|\hat{U}(t+s,s)\| \leq \tilde{K}_\delta e^{(\omega(U)+\delta)t}$, $\forall t \geq 0,\ s \in \mathbb{R}$. By the definition of $\omega(\hat{U})$, we then have $\omega(\hat{U}) \leq \omega(U) + \delta$.

In Claims 1 and 2 above, letting $\delta \to 0^+$, we obtain that $\omega(U) \leq \omega(\hat{U})$ and $\omega(\hat{U}) \leq \omega(U)$, and hence, $\omega(U) = \omega(\hat{U})$. Note that $\hat{P} = \hat{U}(\omega, 0)$ and $P = U(\omega, 0)$. By [88, Proposition A.2], we have $\omega(U) = \frac{\ln r(U(\omega,0))}{\omega}$, and $\omega(\hat{U}) = \frac{\ln r(\hat{U}((\omega,0))}{\omega}$. This implies that $r(P) = r(\hat{P})$. □

Combining Lemmas 2.3.1 and 2.3.8 and Theorem 2.3.7, we have the following threshold type result on the global dynamics of system (2.1).

Theorem 2.3.9. *The following statements are valid for system* (2.1)*:*

(i) If $R_0 \leq 1$*, then the disease-free periodic solution* $(0, S_m^*(t), 0)$ *is globally asymptotically stable for system* (2.1) *in* W*.*

(ii) If $R_0 > 1$*, then system* (2.1) *admits a unique positive* ω*-periodic solution* $(\bar{v}_1(t), \hat{u}_2(t), \bar{v}_2(t))$*, which is globally asymptotically stable for system* (2.1) *in* $W \setminus \{0\} \times C([-\tau, 0], \mathbb{R}_+) \times \{0\}$*.*

2.4 A case study

In this section, we first study the malaria transmission case in Maputo province, Mozambique. Then we verify our obtained threshold type result in terms of R_0. We also study how the vector-bias effect and the EIP length influence the disease transmission. The numerical simulations are done in Matlab by using dde23 and CFTOOL.

Mozambique is a sub-Saharan African country. Malaria is the primary cause of mortality in Mozambique, resulting in an estimated $44000 - 67000$ malaria-specific deaths each year for all age groups [60]. The sub-tropical climate of Maputo Province is favorable for malaria transmission. The summer season lasts from October to March, while the winter season goes from April to September. To implement simulations on the seasonal transmission pattern in Maputo Province, we need to evaluate the values of all parameters in our model.

2.4.1 Parameter estimation

According to Mozambique Population Census in September 2007 (see http://www.geohive.com/cntry/mozambique.aspx), Maputo Province has a population of 1205709, which can be chosen as the value of H. According to the CIA WorldFact Book (see https://www.cia.gov/library/publications/the-world-factbook/fields/2102.html), the life expectancy of Mozambique is 52.94 years. Using this number we estimate the human natural death rate as $d_h = \frac{1}{52.94 \times 12} = 0.00157$ Month^{-1}. The values of p and l may vary from 0 to 1 and $p \geq l$ [17, 34, 39]. The estimation of parameters is listed in Table 2.2.

Table 2.2: Parameter values

Parameter	Value	Dimension	Reference
H	1205709	dimensionless	see text
d_h	0.00157	Month^{-1}	see text
ρ	0.0187	Month^{-1}	[18]
c	0.011	dimensionless	[18]
b	0.2	dimensionless	[18]
τ	$[10/30.4, 30/30.4]$	Month	[69]
p	$(0, 1)$	dimensionless	[17]
l	$(0, 1)$	dimensionless	[17]
$\beta(t)$	to be evaluated	Month^{-1}	see text
$\mu(t)$	to be evaluated	Month^{-1}	see text
$d_m(t)$	to be evaluated	Month^{-1}	see text

The results in [107] show that malaria incidence is strongly and positively correlated with temperature of Maputo Province. Thus, we can evaluate the periodic parameters by using the monthly mean temperatures of Maputo Province from 1990 to 2012 (obtained from Climate Change Knowledge Portal website: http: // sdwebx. worldbank. org/ climateportal), as shown in Table 2.3.

Table 2.3: Monthly mean temperatures for Maputo Province (in °C)

Month	Jul	Aug	Sep	Oct	Nov	Dec
Temperature	19.19	20.77	22.23	23.66	24.57	26.08
Month	Jan	Feb	Mar	Apr	May	June
Temperature	26.75	26.65	26.22	24.61	21.94	19.77

By appealing to the method of estimating the biting rate in [46], the temperature-dependent contact rate per unit time in Maputo can be expressed as

$$\bar{\beta}(C) = \frac{30.4 \text{ Month}^{-1}}{107.204 - 13.3523C + 0.677509C^2 - 0.0159732C^3 + 0.000144876C^4},$$

where C is the temperature in $^\circ C$.

The biting rate of mosquitoes in Maputo Province can then be fitted by

$$\begin{aligned}\beta(t) = {} & 6.983 - 1.993\cos(\pi t/6) - 0.4247\cos(\pi t/3) - 0.128\cos(\pi t/2)\\ & - 0.04095\cos(2\pi t/3) + 0.0005486\cos(5\pi t/6) - 1.459\sin(\pi t/6)\\ & - 0.007642\sin(\pi t/3) - 0.0709\sin(\pi t/2) + 0.05452\sin(2\pi t/3)\\ & - 0.06235\sin(5\pi t/6) \text{ Month}^{-1}.\end{aligned}$$

The mortality rate for adult female mosquitoes can be evaluated as

$$\bar{d}_m(\bar{C}) = 3.04 + 29.564\exp\big(-\frac{\bar{C} - 278^\circ K}{2.7035}\big) \text{ Month}^{-1},$$

(see [80, 87]), where $\bar{C}$ is the temperature in degrees Kelvin (K) (The temperature in K equals to the temperature in $^\circ C$ plus 273.15) in the range $[278, 303]$. Thus, the mortality rate for adult female mosquitoes $d_m(t)$ in Maputo Province can be approximated by

$$\begin{aligned}d_m(t) = {} & 3.086 + 0.04788\cos(\pi t/6) + 0.01942\cos(\pi t/3) + 0.007133\cos(\pi t/2)\\ & + 0.0007665\cos(2\pi t/3) - 0.001459\cos(5\pi t/6) + 0.02655\sin(\pi t/6)\\ & + 0.01819\sin(\pi t/3) + 0.01135\sin(\pi t/2) + 0.005687\sin(2\pi t/3)\\ & + 0.003198\sin(5\pi t/6) \text{ Month}^{-1}.\end{aligned}$$

Motivated by [46], we suppose that the recruitment rate of mosquitoes from larvae is proportional to the biting rate, i.e., $\mu(t) = k \times \beta(t)$ Mosquitoes/Month, where k is a positive constant number. We estimate $k = 5 \times 1205709$ to keep the mosquito population at a relatively reasonable level compared with the human population.

2.4.2 Model validation

In this subsection, we simulate the malaria transmission case in Maputo Province based on the data from the second picture of Figure 11 in [83]. From that picture we can observe that the number of monthly malaria cases exhibit an obvious seasonal fluctuation which is consistent with the seasonal variation of temperature in Maputo Province. We can also see that the reported cases decrease dramatically in 2007 since after a series of initiatives in malaria prevention and treatment. However, the cases rise again in 2011 which may be due to the emergence and spread of drug resistance. The monthly new cases correspond to the term $\frac{c\beta(t)l(H-I_h(t))I_m(t)}{(p-l)I_h(t)+lH}$ in the first equation of system (2.1). We choose $l/p = \frac{1}{4}$. Since the period of our system is $\omega = 12$ months, we use the truncation of Fourier series with period 12 to fit the monthly new cases. The fitted results for the endemic periods from July 2007 to June 2009 and from July 2010 to December 2012 are shown by the dotted green curves in Figures 2.1 and 2.2, respectively.

For the endemic period from July 2007 to June 2009, to depict the success of prevention and treatment, we choose the biting rate as $(1-\alpha)\beta(t)$, where $\alpha = 20\%$ is the efficiency in reduction of the biting rate, which may be due to the use of insecticide-treated bed nets. We set the probability of successful transmission from an infectious mosquito to a susceptible human as $0.75c = 0.75 \times 0.011$ and that of successful transmission from an infectious human to a susceptible mosquito as $0.8b = 0.8 \times 0.2$ to estimate the effect of some antimalarial drugs. The EIP is chosen as $15/30.4$ month. The initial functions are chosen as the constant functions $I_h(\theta) =$

$337598, S_m(\theta) = 2712343, I_m(0) = 2000$ for all $\theta \in [-\tau, 0]$. The simulation result is shown by the blue curve in Figure 2.1. For the endemic period from July 2010 to December 2012, to simulate the failure of treatment due to drug resistance, we set the probability of successful transmission from an infectious mosquito to a susceptible human as $c = 0.011$ and that of successful transmission from an infectious human to a susceptible mosquito as $b = 0.2$. The EIP is chosen as 15/30.4 month. The initial functions are $I_h(\theta) = 361713, S_m(\theta) = 2712343, I_m(0) = 2000$ for all $\theta \in [-\tau, 0]$. The simulation result until the year 2020 is shown by the blue curve in Figure 2.2.

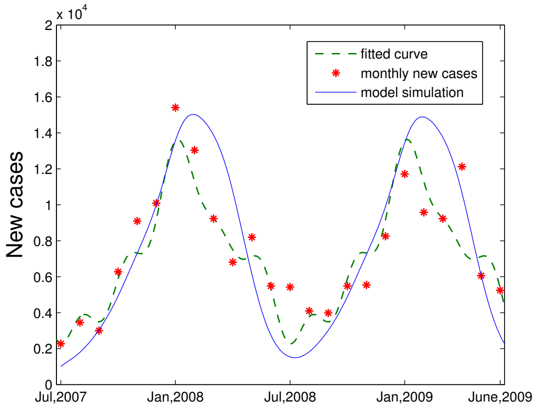

Figure 2.1: The simulation result for the number of new malaria cases from July 2007 to June 2009. The red stars represent data from [83]. The dotted green curve is the fitted result by using CFTOOL. The blue curve is the simulation result of our model.

2.4.3 Long term behaviour

By the ω-periodicity of $K(t, s)$ in t, it easily follows that

$$[L\phi](t) = \int_0^\infty K(t, s)\phi(t - s)ds = \int_0^\omega G(t, s)\phi(t - s)ds, \ \forall t \in \mathbb{R}, \ \phi \in C_\omega,$$

where $G(t, s) = \sum_{k=0}^\infty K(t, s + k\omega)$. Consequently, we can use the numerical method in [70] to calculate R_0. Under the same set of parameter values as that of Figure

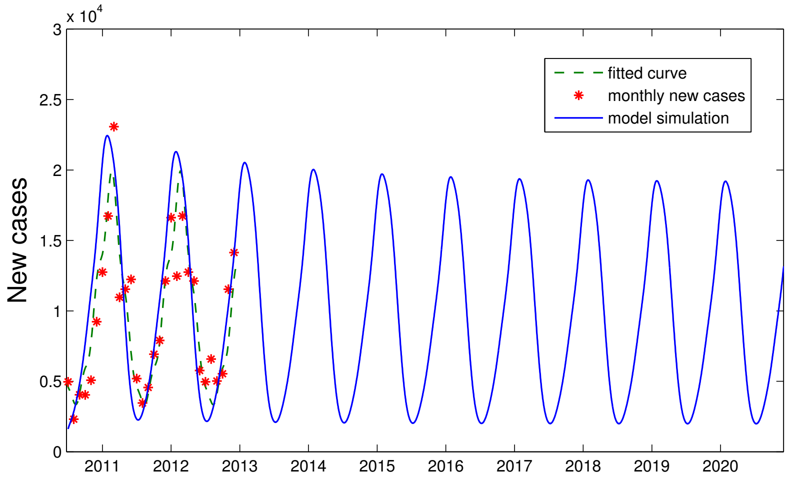

Figure 2.2: The simulation result of new malaria cases from July 2010 to December 2020. The red stars represent data from [83]. The dotted green curve is the fitted result by using CFTOOL. The blue curve is the simulation result of our model.

2.4.2, we get $R_0 = 2.6854$. In this case, a positive periodic solution with period 12 is observed. The periodic fluctuations of the infectious compartments are shown in Figure 2.3. By employing some measures to fight against malaria such as using insecticide-treated nets or clearance of mosquito breeding sites, if we can decrease the biting rate to $0.7\beta(t)$, and increase the mosquito mortality rate and the EIP to $1.6d_m(t)$ and $21/30.4$ months, respectively, then $R_0 = 0.5449$. In this case, we observe that both the infectious human population and the infectious mosquito population tend to 0, which means that the disease dies out eventually (see Figure 2.4). These numerical simulation results consist with our analytic results in the previous section.

The impacts of the length of the EIP and the vector-bias level on malaria transmission are shown in Figures 2.5 and 2.6, respectively. Both figures are obtained in the case of $R_0 > 1$. As can be seen from Figure 2.5, more humans will be infected if the EIP is shorter. This is consistent with our intuition since shortening the EIP may lead to greater population of infectious mosquitoes. To explore the vector bias

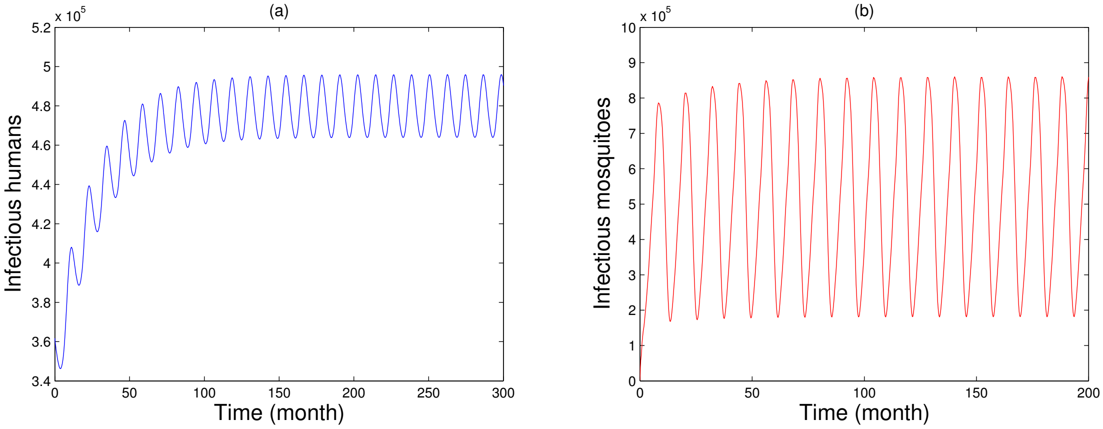

Figure 2.3: Long term behaviour of the infectious compartments where $R_0 = 2.6854$. (a) Time series of I_h. (b) Time series of I_m.

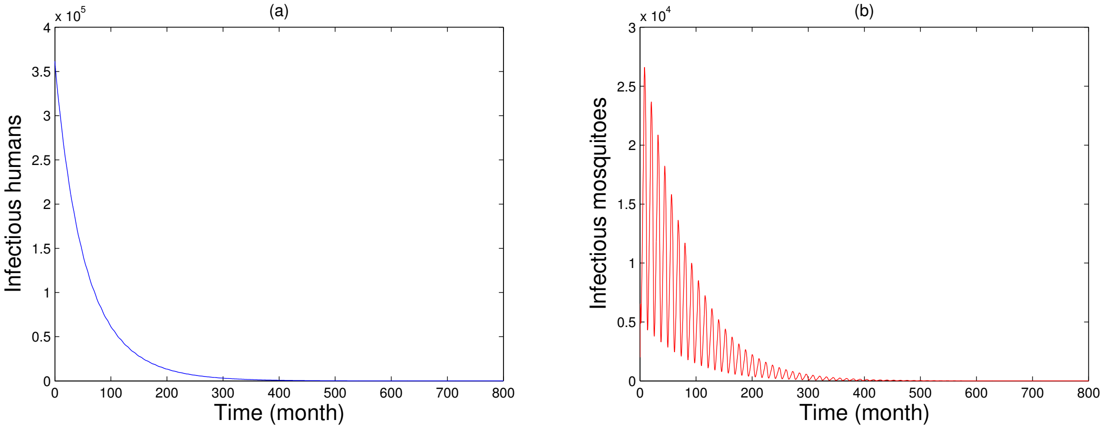

Figure 2.4: Long term behaviour of the infectious compartments where $R_0 = 0.5449$. (a) Time series of I_h. (b) Time series of I_m.

effect, we simulate the number of infectious humans for two different EIP values: $\tau = 15/30.4$ and $\tau = 21/30.4$. For each value of τ, we choose three different values of l/p. From Figure 2.6, we see that the ignorance of the vector-bias effect (i.e., $l/p = 1$) will eventually overestimate and underestimate the number of infectious humans in the case where $\tau = 15/30.4$ and $\tau = 21/30.4$, respectively.

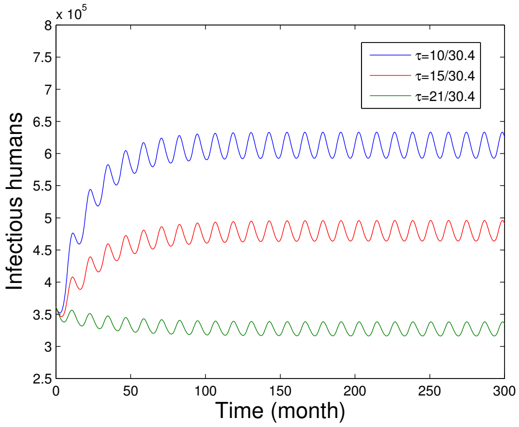

Figure 2.5: The effect of the Extrinsic Incubation Period.

2.5 Discussion

In this chapter, we have proposed a malaria transmission model including three factors: seasonality, the EIP and the vector-bias effect. We incorporated seasonality into the model by assuming that the parameters related to mosquitoes are periodic functions, and employed constant time delay to depict EIP. To investigate the vector-bias effect, we introduced two parameters p and l, that is, the probabilities that a mosquito arrives at a human at random and picks the human if he is infectious and susceptible, respectively. Indeed, letting $q := l/p$, we can write the model system as the following

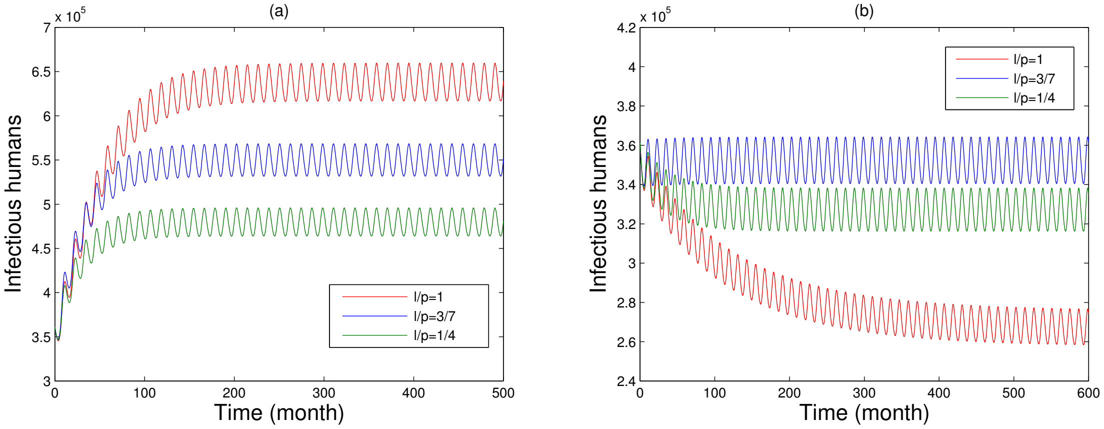

Figure 2.6: The vector-bias effect. (a) $\tau = 15/30.4$; (b) $\tau = 21/30.4$.

one:

$$\begin{aligned}
\frac{dI_h(t)}{dt} &= \frac{c\beta(t)q(H - I_h(t))}{(1-q)I_h(t) + qH} I_m(t) - (d_h + \rho)I_h(t), \\
\frac{dS_m(t)}{dt} &= \mu(t) - \frac{b\beta(t)I_h(t)}{(1-q)I_h(t) + qH} S_m(t) - d_m(t)S_m(t), \\
\frac{dI_m(t)}{dt} &= -d_m(t)I_m(t) + e^{-\int_{t-\tau}^{t} d_m(s)ds} \frac{b\beta(t-\tau)I_h(t-\tau)S_m(t-\tau)}{(1-q)I_h(t-\tau) + qH},
\end{aligned}$$

where q may be interpreted as the relative attractivity of susceptible host versus infectious one. By the definition of the operator L, it easily follows that R_0 depends on q rather than the values of p and l. Using the theory of R_0 recently developed in [110], we have successfully obtained R_0 for our model. By appealing to the theory of monotone and subhomogeneous systems and the theory of chain transitive sets, we have obtained a threshold type result on the global dynamics of the model system in terms of R_0, that is, the disease will die out if $R_0 < 1$ and will eventually stabilize at a positive periodic state if $R_0 > 1$.

We have evaluated all parameters by using some published data and simulated the malaria transmission case in Maputo Province, Mozambique. The simulated curve and the real-data-fitted curve match well. Our simulation result shows that malaria will persist and exhibit seasonal fluctuation in the next few years if no intervention is taken. By employing the algorithm in [70], we numerically calculated the basic reproduction ratio R_0. The numerical simulation results in Figures 2.3 and 2.4 about long term behaviours of the infectious compartments have verified the obtained analytic result.

We have explored the influences of the length of the EIP and the vector-bias effect on the transmission of malaria. We found that a shorter length of the EIP is related to a higher number of the infectious humans. Thus, prolonging the length of the EIP is helpful for the control of the disease. In reality, it is not easy to directly extend the EIP. Possibly we may develop some drugs with such an effect that once a mosquito bites a malaria-infected patient who takes the drugs, then the EIP of this mosquito will be prolonged, that is, the patients who take the drugs serve as a vector to let the drugs make effect on mosquitoes.

The EIP is strongly temperature sensitive, taking from about 10 days to over 30 days. The higher the temperature, the shorter the EIP [50, 69]. Hence, the EIP delay in our model may be modified to a temperature-dependent delay, while this would increase the difficulty of mathematical analysis. We will solve this interesting problem in the next chapter.

Chapter 3

A malaria transmission model with temperature-dependent incubation period

3.1 Introduction

Malaria is the most prevalent human vector-borne disease, with an estimated 214 million malaria cases and about 438 thousand deaths worldwide in 2015 [98]. Both the mosquito life cycle and the parasite development are strongly influenced by seasonally varying temperature. Understanding the role of temperature in malaria transmission is of particular importance in light of climate change [57]. A number of malaria models have been developed to study the climate effects on malaria transmission (see, e.g., [21, 46, 57, 95, 96] and the references therein). Malaria parasites manipulate a host to be more attractive to mosquitoes via the chemical substances [39]. Kingsolver [36] proposed the first malaria model to account for the greater attractiveness of infectious humans to mosquitoes. Chamchod and Britton [17] modeled such vector-bias effect in terms of the different probabilities that a mosquito arrives at a human at random and picks the human if he is infectious or susceptible. Recently, the vector-bias effect has also been incorporated into some climate-based malaria models(see, e.g., [95, 96]).

In Chapter 2, we developed a periodic vector-bias malaria model with incubation period and established the global dynamics in terms of the basic reproduction ratio. We remarked that the constant delay in the model may be modified to a time-dependent delay since the EIP is highly sensitive to temperature. The aim of the current chapter is to solve this problem. We develop a delay differential equations model of malaria transmission in which the delay is periodic in time. To our knowledge, this is the first mosquito-borne disease model that takes into account the time-dependent delay. Several population models with time-dependent delays have been developed (see, e.g., [10, 54, 55, 75, 101]), however, little mathematical analysis is carried out to understand the asymptotic behavior of these models. Recently, Lou and Zhao [49] studied the global dynamics of a host-macroparasite model with seasonal developmental durations by introducing a periodic semiflow on a suitably chosen phase space. We will use the theoretical approach developed in [49] to analyze our model.

The rest of this chapter is organized as follows. In the next section, we give the underlying assumptions and formulate the model. In the following section, we establish the threshold dynamics of the model in terms of the basic reproduction ratio. In section 3.4, we carry out a case study for Maputo Province, Mozambique. A brief discussion concludes the chapter.

3.2 The model

The purpose of this section is to formulate a mathematical model of malaria transmission that incorporates a temperature-dependent delay. The model with a constant EIP is governed by the following system of delay differential equations:

$$\begin{aligned}\frac{dI_h(t)}{dt} &= \frac{c\beta(t)l(H-I_h(t))}{pI_h(t)+l(H-I_h(t))}I_m(t)-(d_h+\rho)I_h(t),\\ \frac{dS_m(t)}{dt} &= \mu(t)-\frac{b\beta(t)pI_h(t)}{pI_h(t)+l(H-I_h(t))}S_m(t)-d_m(t)S_m(t),\\ \frac{dI_m(t)}{dt} &= -d_m(t)I_m(t)+e^{-\int_{t-\tau}^{t}d_m(s)ds}\frac{b\beta(t-\tau)pI_h(t-\tau)S_m(t-\tau)}{pI_h(t-\tau)+l(H-I_h(t-\tau))}.\end{aligned} \tag{3.1}$$

We refer the readers to Chapter 2 of this thesis for more details about the derivation of model (3.1). To introduce the temperature-dependent incubation period, we use the arguments similar to those in [62, 68]. We consider the exposed compartment where mosquitoes are infected but not infectious yet. Let $E_m(t)$ be the number of the exposed mosquitoes at time t, and $M(t)$ the number of newly occured infectious mosquitoes per unit time at time t. Then we have the following system:

$$\begin{aligned}\frac{dI_h(t)}{dt} =&\frac{c\beta(t)l(H-I_h(t))}{pI_h(t)+l(H-I_h(t))}I_m(t)-(d_h+\rho)I_h(t),\\ \frac{dS_m(t)}{dt} =&\mu(t)-B(t,I_h(t),S_m(t))-d_m(t)S_m(t),\\ \frac{dE_m(t)}{dt} =&B(t,I_h(t),S_m(t))-M(t)-d_m(t)E_m(t),\\ \frac{dI_m(t)}{dt} =&M(t)-d_m(t)I_m(t),\end{aligned} \tag{3.2}$$

where $B(t,I_h(t),S_m(t))=\frac{b\beta(t)pI_h(t)S_m(t)}{pI_h(t)+l(H-I_h(t))}$. Let q be the development level of infection such that q increases at a temperature-dependent rate $\gamma(T(t))=\gamma(t)$, $q=q_E=0$ at the transition from S_m to E_m, and $q=q_I$ at the transition from E_m to I_m. The variable q describes how complete the parasite developmental stages are in the mosquito (in other words, how complete the latency stage is). Let $\rho(q,t)$ be the density of mosquitoes with development level q at time t. Then $M(t) = \gamma(t)\rho(q_I,t)$.

Let $J(q,t)$ be the flux, in the direction of increasing q, of mosquitoes with infection development level q at time t. Then we have the following equation (see, e.g., [38])

$$\frac{\partial \rho}{\partial t} = -\frac{\partial J}{\partial q} - d_m(t)\rho.$$

Since $J(q,t) = \gamma(t)\rho(q,t)$, we have

$$\frac{\partial \rho(q,t)}{\partial t} = -\frac{\partial}{\partial q}[\gamma(t)\rho(q,t)] - d_m(t)\rho(q,t). \tag{3.3}$$

For the E_m state, system (3.3) has the boundary condition

$$\rho(q_E,t) = \frac{B(t, I_h(t), S_m(t))}{\gamma(t)}.$$

To solve system (3.3) with this boundary condition, we introduce a new variable

$$\eta = h(t) := q_E + \int_0^t \gamma(s)ds.$$

Let $h^{-1}(\eta)$ be the inverse function of $h(t)$, and define

$$\hat{\rho}(q,\eta) = \rho(q, h^{-1}(\eta)), \quad \hat{d}_m(\eta) = d_m(h^{-1}(\eta)), \quad \hat{\gamma}(\eta) = \gamma(h^{-1}(\eta)).$$

In view of (3.3), we then have

$$\frac{\partial \hat{\rho}(q,\eta)}{\partial \eta} = -\frac{\partial \hat{\rho}(q,\eta)}{\partial q} - \frac{\hat{d}_m(\eta)}{\hat{\gamma}(\eta)}\hat{\rho}(q,\eta). \tag{3.4}$$

This equation is identical in form to the standard von Foerster equation (see [61]).

Let $V(s) = \hat{\rho}(s + q - \eta, s)$. It follows from (3.4) that

$$\frac{dV(s)}{ds} = -\frac{\hat{d}_m(s)}{\hat{\gamma}(s)} V(s).$$

Since $\eta - (q - q_E) \leq \eta$, we have

$$V(\eta) = V(\eta - (q - q_E)) e^{-\int_{\eta-(q-q_E)}^{\eta} \frac{\hat{d}_m(s)}{\hat{\gamma}(s)} ds},$$

and hence,

$$\hat{\rho}(q, \eta) = \hat{\rho}(q_E, \eta - q + q_E) e^{-\int_{\eta-q+q_E}^{\eta} \frac{\hat{d}_m(s)}{\hat{\gamma}(s)} ds}.$$

Define $\tau(q, t)$ to be the time taken to grow from infection development level q_E to level q by a mosquito who arrives at infection development level q at time t. Since $\frac{dq}{dt} = \gamma(t)$, it follows that

$$q - q_E = \int_{t-\tau(q,t)}^{t} \gamma(s) ds, \tag{3.5}$$

and hence,

$$h(t - \tau(q, t)) = h(t) - \int_{t-\tau(q,t)}^{t} \gamma(s) ds = h(t) - (q - q_E).$$

By a change of variable $s = h(\xi)$, we then see that

$$\int_{\eta-q+q_E}^{\eta} \frac{\hat{d}_m(s)}{\hat{\gamma}(s)} ds = \int_{t-\tau(q,t)}^{t} d_m(\xi) d\xi.$$

It follows that

$$\begin{aligned}\rho(q,t) =&\hat{\rho}(q,h(t))\\ =&\rho(q_E,t-\tau(q,t))e^{-\int_{t-\tau(q,t)}^{t} d_m(\xi)d\xi}\\ =&\frac{B(t-\tau(q,t),I_h(t-\tau(q,t)),S_m(t-\tau(q,t)))}{\gamma(t-\tau(q,t))}e^{-\int_{t-\tau(q,t)}^{t} d_m(\xi)d\xi}.\end{aligned}$$

Define $\tau(t) := \tau(q_I,t)$. We then obtain

$$\gamma(t)\rho(q_I,t) = B(t-\tau(t),I_h(t-\tau(t)),S_m(t-\tau(t)))\frac{\gamma(t)}{\gamma(t-\tau(t))}e^{-\int_{t-\tau(t)}^{t} d_m(\xi)d\xi}.$$

Letting $q = q_I$ in (3.5), we have

$$q_I - q_E = \int_{t-\tau(t)}^{t} \gamma(s)ds \tag{3.6}$$

Taking the derivative with respect to t on both sides of (3.6), we obtain

$$1-\tau'(t) = \frac{\gamma(t)}{\gamma(t-\tau(t))}.$$

Thus, there holds $1-\tau'(t) > 0$. In virtue of (3.6), it easily follows that if $\gamma(t)$ is a periodic function, then so is $\tau(t)$ with the same period. Substituting $M(t) =$

$\gamma(t)\rho(q_I, t)$ into system (3.2), we arrive at the following model system:

$$\begin{aligned}
\frac{dI_h(t)}{dt} =& \frac{c\beta(t)l(H - I_h(t))}{pI_h(t) + l(H - I_h(t))} I_m(t) - (d_h + \rho)I_h(t), \\
\frac{dS_m(t)}{dt} =& \mu(t) - B(t, I_h(t), S_m(t)) - d_m(t)S_m(t), \\
\frac{dE_m(t)}{dt} =& B(t, I_h(t), S_m(t)) - d_m(t)E_m(t) \\
& - (1 - \tau'(t))B(t - \tau(t), I_h(t - \tau(t)), S_m(t - \tau(t)))e^{-\int_{t-\tau(t)}^{t} d_m(\xi)d\xi}, \\
\frac{dI_m(t)}{dt} =& (1 - \tau'(t))B(t - \tau(t), I_h(t - \tau(t)), S_m(t - \tau(t)))e^{-\int_{t-\tau(t)}^{t} d_m(\xi)d\xi} \\
& - d_m(t)I_m(t),
\end{aligned} \tag{3.7}$$

where all constant parameters are positive, and $\mu(t)$, $\beta(t)$, $d_m(t)$, $\tau(t)$ are positive, continuous and ω-periodic functions for some $\omega > 0$. The biological interpretations for parameters of model (3.14) is listed in Table 3.1. It is easy to see that the function

$$a(t) := e^{-\int_{t-\tau(t)}^{t} d_m(\xi)d\xi}$$

is also ω-periodic. Thus, model (3.7) can be written as $u'(t) = F(t, u_t)$ with $F(t + \omega, \phi) = F(t, \phi)$ (see the proof of Lemma 2.3.2), and hence, it is an ω-periodic functional differential system. Note that the term $1 - \tau'(t)$ is involved in the development rate from the E_m state to the I_m state, which is different from previous works with constant time delays (see, e.g., system (1) in [95]).

3.3 Global dynamics

In this section we study the global dynamics of system (3.7). We will use the theory in section 1.4 to derive the basic reproduction ratio R_0. Since the third equation of system (3.7) is decoupled from the other equations, it suffices to study the following

Table 3.1: Biological interpretations for parameters of model (3.7)

Parameters	Description
$\tau(t)$	Extrinsic Incubation Period
b	transmission probability per bite from infectious humans to mosquitoes
c	transmission probability per bite from infectious mosquitoes to humans
$\beta(t)$	mosquito biting rate
$\mu(t)$	recruitment rate at which female adult mosquitoes emerge from larvae
$d_m(t)$	natural death rate of female adult mosquitoes
d_h	natural death rate of humans
ρ	removal rate of humans from the infectious compartment (i.e., recovery rate and disease-induced death rate)
p	probability that a mosquito arrives at a human at random and picks the human if he is infectious
l	probability that a mosquito arrives at a human at random and picks the human if he is susceptible
H	the total number of humans

system:

$$\begin{aligned} \frac{dI_h(t)}{dt} &= \frac{c\beta(t)l(H-I_h(t))}{pI_h(t)+l(H-I_h(t))}I_m(t)-(d_h+\rho)I_h(t), \\ \frac{dS_m(t)}{dt} &= \mu(t)-B(t,I_h(t),S_m(t))-d_m(t)S_m(t), \\ \frac{dI_m(t)}{dt} &= (1-\tau'(t))B(t-\tau(t),I_h(t-\tau(t)),S_m(t-\tau(t)))e^{-\int_{t-\tau(t)}^{t} d_m(\xi)d\xi} \\ &\quad -d_m(t)I_m(t). \end{aligned} \tag{3.8}$$

It is easy to see that the scalar linear periodic equation

$$\frac{dS_m(t)}{dt} = \mu(t)-d_m(t)S_m(t) \tag{3.9}$$

has a unique positive ω-periodic solution

$$S_m^*(t) = \left[\int_0^t \mu(r)e^{\int_0^r d_m(s)ds}dr + \frac{\int_0^\omega \mu(r)e^{\int_0^r d_m(s)ds}dr}{e^{\int_0^\omega d_m(s)ds}-1}\right]e^{-\int_0^t d_m(s)ds},$$

which is globally attractive in $\mathbb{R}$.

Linearizing system (3.8) at its disease-free periodic solution $(0, S_m^*(t), 0)$, we then obtain the following system of periodic linear equations for the infective variables I_h and I_m:

$$\begin{aligned} \frac{dI_h(t)}{dt} &= -a_{11}(t)I_h(t) + a_{12}(t)I_m(t), \\ \frac{dI_m(t)}{dt} &= a_{21}(t)I_h(t-\tau(t)) - a_{22}(t)I_m(t), \end{aligned} \tag{3.10}$$

where $a_{11}(t) = d_h + \rho$, $a_{12}(t) = c\beta(t)$, $a_{22}(t) = d_m(t)$, and

$$a_{21}(t) = \frac{(1-\tau'(t))b\beta(t-\tau(t))pS_m^*(t-\tau(t))e^{-\int_{t-\tau(t)}^{t} d_m(\xi)d\xi}}{lH}.$$

Let $\hat{\tau} = \max_{0\le t\le\omega} \tau(t)$, $C = C([-\hat{\tau}, 0], \mathbb{R}^2)$, $C^+ = C([-\hat{\tau}, 0], \mathbb{R}_+^2)$. Then (C, C^+) is an ordered Banach space equipped with the maximum norm and the positive cone C^+. For any given continuous function $v = (v_1, v_2) : [-\hat{\tau}, \sigma) \to \mathbb{R}^2$ with $\sigma > 0$, we define $v_t \in C$ by

$$v_t(\theta) = (v_1(t+\theta), v_2(t+\theta)), \quad \forall \theta \in [-\hat{\tau}, 0],$$

for any $t \in [0, \sigma)$. Let $F : \mathbb{R} \to \mathcal{L}(C, \mathbb{R}^2)$ be a map and $V(t)$ be a continuous 2×2 matrix function on $\mathbb{R}$ defined as follows:

$$F(t)\varphi = \begin{bmatrix} a_{12}(t)\varphi_2(0) \\ a_{21}(t)\varphi_1(-\tau(t)) \end{bmatrix}, \qquad V(t) = \begin{bmatrix} a_{11}(t) & 0 \\ 0 & a_{22}(t) \end{bmatrix}.$$

Then the internal evolution of the infective compartments I_h and I_m can be expressed by

$$\frac{dv(t)}{dt} = -V(t)v(t).$$

Let $\Phi(t,s), t \ge s$, be the evolution matrix of the above linear system. That is, $\Phi(t,s)$ satisfies

$$\frac{\partial}{\partial t}\Phi(t,s) = -V(t)\Phi(t,s), \quad \forall t \ge s,$$

and

$$\Phi(s,s)=I,\quad \forall s\in\mathbb{R},$$

where I is the 2×2 identity matrix. It then easily follows that

$$\Phi(t,s)=\left[\begin{array}{cc} e^{-\int_s^t a_{11}(r)dr} & 0 \\ 0 & e^{-\int_s^t a_{22}(r)dr} \end{array}\right].$$

Let C_ω be the ordered Banach space of all continuous and ω-periodic functions from $\mathbb{R}$ to $\mathbb{R}^2$, which is equipped with the maximum norm and the positive cone $C_\omega^+ := \{v\in C_\omega : v(t)\geq 0 \text{ for all } t\in\mathbb{R}\}$.

Suppose that $v\in C_\omega$ is the initial distribution of infectious individuals. Then for any given $s\geq 0$, $F(t-s)v_{t-s}$ is the distribution of newly infectious individuals at time $t-s$, which is produced by the infectious individuals who were introduced over the time interval $[t-s-\hat{\tau}, t-s]$. Then $\Phi(t,t-s)F(t-s)v_{t-s}$ is the distribution of those infectious individuals who newly became infectious at time $t-s$ and remain in the infectious compartments at time t. It follows that

$$\int_0^\infty \Phi(t,t-s)F(t-s)v_{t-s}ds=\int_0^\infty \Phi(t,t-s)F(t-s)v(t-s+\cdot)ds$$

is the distribution of accumulative new infections at time t produced by all those infectious individuals introduced at all previous time to t.

Define a linear operator $L: C_\omega\to C_\omega$ by

$$[Lv](t)=\int_0^\infty \Phi(t,t-s)F(t-s)v(t-s+\cdot)ds,\quad \forall t\in\mathbb{R},\quad v\in C_\omega.$$

Following 1.4, we define $R_0=r(L)$, the spectral radius of L. Let $\hat{P}(t)$ be the solution maps of system (3.10), that is, $\hat{P}(t)\varphi=u_t(\varphi), t\geq 0$, where $u(t,\varphi)$ is the unique solution of (3.10) with $u_0 = \varphi \in C$. Then $\hat{P} := \hat{P}(\omega)$ is the Poincaré map associated with linear system (3.10). Let $r(\hat{P})$ be the spectral radius of $\hat{P}$. By Theorem 1.4.1, we have the following result.

Lemma 3.3.1. *$R_0 - 1$ has the same sign as $r(\hat{P}) - 1$.*

Let

$$W := C([-\hat{\tau}, 0], [0, H]) \times C([-\hat{\tau}, 0], \mathbb{R}_+) \times \mathbb{R}_+.$$

Then we have the following preliminary result for system (3.8).

Lemma 3.3.2. *For any $\varphi \in W$, system (3.8) has a unique nonnegative bounded solution $u(t,\varphi)$ on $[0,\infty)$ with $u_0 = \varphi$, and $u_t(\varphi) := (u_{1t}(\varphi), u_{2t}(\varphi), u_3(t,\varphi)) \in W$ for all $t \geq 0$.*

Proof. For any $\varphi = (\varphi_1, \varphi_2, \varphi_3) \in W$, we define

$$\widetilde{f}(t,\varphi) = \begin{pmatrix} \frac{c\beta(t)l(H-\varphi_1(0))}{(p-l)\varphi_1(0)+lH}\varphi_3 - (d_h+\rho)\varphi_1(0) \\ \mu(t) - \frac{b\beta(t)p\varphi_1(0)}{(p-l)\varphi_1(0)+lH}\varphi_2(0) - d_m(t)\varphi_2(0) \\ -d_m(t)\varphi_3 + (1-\tau'(t))\frac{b\beta(t-\tau(t))p\varphi_1(-\tau(t))\varphi_2(-\tau(t))}{(p-l)\varphi_1(-\tau(t))+lH}e^{-\int_{t-\tau(t)}^{t} d_m(\xi)d\xi} \end{pmatrix}.$$

Since $\widetilde{f}(t,\varphi)$ is continuous in $(t,\varphi) \in \mathbb{R}_+ \times W$, and $\widetilde{f}(t,\varphi)$ is Lipschitz in φ on each compact subset of W, it then follows that system (3.8) has a unique solution $u(t,\varphi)$ on its maximal interval $[0,\sigma_\varphi)$ of existence with $u_0 = \varphi$ (see, e.g., [29, Theorems 2.2.1 and 2.2.3]).

Let $\varphi = (\varphi_1, \varphi_2, \varphi_3) \in W$ be given. If $\varphi_i(0) = 0$ for some $i \in \{1,2\}$, then $\widetilde{f}_i(t,\varphi) \geq 0$. If $\varphi_3 = 0$, then $\widetilde{f}_3(t,\varphi) \geq 0$. If $\varphi_1(0) = H$, then $\widetilde{f}_1(t,\varphi) \leq 0$. By [84, Theorem 5.2.1 and Remark 5.2.1], it follows that for any $\varphi \in W$, the unique solution $u(t,\varphi)$ of system (3.1) with $u_0 = \varphi$ satisfies $u_t(\varphi) \in W$ for all $t \in [0,\sigma_\varphi)$.

Clearly, $0 \leq u_1(t,\varphi) \leq H$ for all $t \in [0,\sigma_\varphi)$. In view of the second and third equations of system (3.8), we have

$$\begin{aligned}
\frac{du_2(t)}{dt} &\leq \mu(t) - d_m(t)u_2(t),\\
\frac{du_3(t)}{dt} &\leq -d_m(t)u_3(t) + (1-\tau'(t))b\beta(t-\tau(t))u_2(t-\tau(t))e^{-\int_{t-\tau(t)}^{t} d_m(\xi)d\xi},
\end{aligned}$$

for all $t \in [0,\sigma_\varphi)$. Thus, both $u_2(t)$ and $u_3(t)$ are bounded on $[0,\sigma_\varphi)$, and hence, [29, Theorem 2.3.1] implies that $\sigma_\varphi = \infty$. □

For any given $\varphi \in W$, let $u(t,\varphi) = (u_1(t), u_2(t), u_3(t))$ be the unique solution of system (3.8) satisfying $u_0 = \varphi$. Let

$$w(t) := e^{-\int_{t-\tau(t)}^{t} d_m(s)ds}u_2(t-\tau(t)) + u_3(t).$$

Then $(u_1(t), u_3(t))$ can be regarded as a solution of the following nonautonomous system:

$$\begin{aligned}
\frac{du_1(t)}{dt} &= \frac{c\beta(t)l(H-u_1(t))}{(p-l)u_1(t)+lH}u_3(t) - (d_h+\rho)u_1(t),\\
\frac{du_3(t)}{dt} &= -d_m(t)u_3(t) + (1-\tau'(t))\frac{b\beta(t-\tau(t))pu_1(t-\tau(t))}{(p-l)u_1(t-\tau(t))+lH}[w(t)-u_3(t)].
\end{aligned} \tag{3.11}$$

It easily follows that $w(t)$ satisfies

$$\frac{dw(t)}{dt} = -d_m(t)w(t) + \mu(t-\tau(t))(1-\tau'(t))e^{-\int_{t-\tau(t)}^{t} d_m(s)ds}, \tag{3.12}$$

and system (3.12) has a unique positive ω-periodic solution

$$K(t) := e^{-\int_{t-\tau(t)}^{t} d_m(s)ds}S_m^*(t-\tau(t)),$$

which is globally attractive in $\mathbb{R}$. Thus, system (3.11) has a limiting system:

$$\begin{aligned}
\frac{dv_1(t)}{dt} &= \frac{c\beta(t)l(H-v_1(t))}{(p-l)v_1(t)+lH}v_2(t)-(d_h+\rho)v_1(t),\\
\frac{dv_2(t)}{dt} &= -d_m(t)v_2(t)+(1-\tau'(t))\frac{b\beta(t-\tau(t))pv_1(t-\tau(t))}{(p-l)v_1(t-\tau(t))+lH}(K(t)-v_2(t)).
\end{aligned} \tag{3.13}$$

Note that $z(t)=(u_1(t),u_3(t),w(t))$ satisfies the following ω-periodic system:

$$\begin{aligned}
\frac{du_1(t)}{dt} &= \frac{c\beta(t)l(H-u_1(t))}{(p-l)u_1(t)+lH}u_3(t)-(d_h+\rho)u_1(t),\\
\frac{du_3(t)}{dt} &= -d_m(t)u_3(t)+(1-\tau'(t))\frac{b\beta(t-\tau(t))pu_1(t-\tau(t))}{(p-l)u_1(t-\tau(t))+lH}(w(t)-u_3(t)),\\
\frac{dw(t)}{dt} &= -d_m(t)w(t)+\mu(t-\tau(t))(1-\tau'(t))e^{-\int_{t-\tau(t)}^{t}d_m(s)ds}.
\end{aligned} \tag{3.14}$$

Clearly, system (3.8) is equivalent to (3.14). It suffices to study system (3.14). Let

$$\Omega := C([-\hat{\tau},0],[0,H])\times\mathbb{R}_+^2.$$

We then have the following preliminary result for system (3.14).

Lemma 3.3.3. *For any $\varphi\in\Omega$, system (3.14) has a unique solution $z(t,\varphi)$ with $z_0=\varphi$, and $z_t(\varphi):=(z_{1t}(\varphi),z_2(t,\varphi),z_3(t,\varphi))\in\Omega$ for all $t\geq 0$.*

Proof. For any $\varphi\in\Omega$, define

$$\hat{f}(t,\varphi)=\begin{pmatrix}\frac{c\beta(t)l(H-\varphi_1(0))}{(p-l)\varphi_1(0)+lH}\varphi_2-(d_h+\rho)\varphi_1(0)\\ -d_m(t)\varphi_2+(1-\tau'(t))\frac{b\beta(t-\tau(t))p\varphi_1(-\tau(t))}{(p-l)\varphi_1(-\tau(t))+lH}(\varphi_3-\varphi_2)\\ -d_m(t)\varphi_3+\mu(t-\tau(t))(1-\tau'(t))e^{-\int_{t-\tau(t)}^{t}d_m(s)ds}\end{pmatrix}.$$

Since $\hat{f}(t,\varphi)$ is continuous in $(t,\varphi)\in\mathbb{R}\times\Omega$, and $\hat{f}(t,\varphi)$ is Lipschitz in φ on each compact subset of Ω, it then follows that system (3.14) has a unique solution $z(t,\varphi)$ with $z_0=\varphi$ on its maximal interval $[0,\sigma_\varphi)$ of existence.

Let $\varphi = (\varphi_1, \varphi_2, \varphi_3) \in \Omega$ be given. If $\varphi_1(0) = 0$, then $\hat{f}_1(t, \varphi) \geq 0$. If $\varphi_i = 0$ for some $i = 2, 3$, then $\hat{f}_i(t, \varphi) \geq 0$. If $\varphi_1(0) = H$, then $\hat{f}_1(t, \varphi) \leq 0$. By [84, Theorem 5.2.1 and Remark 5.2.1], it follows that for any $\varphi \in \Omega$, the unique solution $z(t, \varphi)$ of system (3.14) with $u_0 = \varphi$ satisfies $z_t(\varphi) \in \Omega$ for all $t \in [0, \sigma_\varphi)$.

Since system (3.12) has a globally attractive periodic solution $K(t)$, it follows that $z_3(t, \varphi) = w(t)$ is bounded on $[0, \sigma_\varphi)$, that is, there exists $B > 0$ such that $w(t) \leq B$ for all $t \in [0, \sigma_\varphi)$. In view of the second equation of system (3.14), we have

$$\frac{du_3(t)}{dt} \leq -d_m(t)u_3(t) + b(1 - \tau'(t))\beta(t - \tau(t))B, \quad \forall t \in [0, \sigma_\varphi).$$

Hence, $z_2(t, \varphi) = u_3(t)$ is also bounded on $[0, \sigma_\varphi)$. Then [29, Theorem 2.3.1] implies that $\sigma_\varphi = \infty$. $\square$ $\square$

Let

$$Y(t) := C([-\hat{\tau}, 0], [0, H]) \times [0, K(t)], \quad t \geq 0.$$

Then we have the following result for system (3.13).

Lemma 3.3.4. *For any $\varphi \in Y(0)$, system (3.13) has a unique solution $w(t, \varphi)$ with $w_0 = \varphi$, and $w_t(\varphi) := (w_{1t}(\varphi), w_2(t, \varphi)) \in Y(t)$ for all $t \geq 0$.*

Proof. For any $\varphi \in Y(0)$, define

$$f(t, \varphi) = \begin{pmatrix} \frac{c\beta(t)l(H-\varphi_1(0))}{(p-l)\varphi_1(0)+lH}\varphi_2 - (d_h + \rho)\varphi_1(0) \\ -d_m(t)\varphi_2 + (1 - \tau'(t))\frac{b\beta(t-\tau(t))p\varphi_1(-\tau(t))}{(p-l)\varphi_1(-\tau(t))+lH}(K(t) - \varphi_2) \end{pmatrix}.$$

Since f is continuous in $(t, \varphi) \in \mathbb{R} \times Y(0)$, and f is Lipschitz in φ on each compact subset of $Y(0)$, it then follows that system (3.13) has a unique solution $w(t, \varphi)$ with $w_0 = \varphi$ on its maximal interval $[0, \sigma_\varphi)$ of existence.

Let $\varphi = (\varphi_1, \varphi_2) \in Y(0)$ be given. If $\varphi_1(0) = 0$, then $f_1(t, \varphi) \geq 0$. If $\varphi_2 = 0$, then $f_2(t, \varphi) \geq 0$. If $\varphi_1(0) = H$, then $f_1(t, \varphi) \leq 0$. By [84, Theorem 5.2.1 and Remark 5.2.1], it follows that the unique solution $w(t, \varphi)$ of system (3.13) with $w_0 = \varphi$ satisfies $w_t(\varphi) \in C([-\hat{\tau}, 0], [0, H]) \times \mathbb{R}_+$.

It remains to prove that $w_2(t) \leq K(t)$ for all $t \in [0, \sigma_\varphi)$. Suppose this does not hold. Then there exists $t_0 \in [0, \sigma_\varphi)$ and $\epsilon_0 > 0$ such that

$$w_2(t_0) = K(t_0) \quad \text{and} \quad w_2(t) > K(t), \quad \forall t \in (t_0, t_0 + \epsilon_0).$$

Since

$$\frac{dw_2(t_0)}{dt} = -d_m(t_0) w_2(t_0) = -d_m(t_0) K(t_0) < \frac{dK(t_0)}{dt},$$

there exists $\epsilon_1 \in (0, \epsilon_0)$ such that $w_2(t) \leq K(t)$ for all $t \in (t_0, t_0 + \epsilon_1)$, which is a contradiction. This proves that $w_t(\varphi) \in Y(t)$ for all $t \in [0, \sigma_\varphi)$. Clearly, $w_t(\varphi)$ is bounded on $[0, \sigma_\varphi)$, and hence, [29, Theorem 2.3.1] implies that $\sigma_\varphi = \infty$. □ □

Let

$$G(t) := C([-\tau(0), 0], [0, H]) \times [0, K(t)], \quad t \geq 0.$$

Lemma 3.3.5. *For any $\varphi \in G(0)$, system (3.13) has a unique solution $v(t, \varphi)$ with $v_0 = \varphi$, and $v_t(\varphi) := (v_{1t}(\varphi), v_2(t, \varphi)) \in G(t)$ for all $t \geq 0$.*

Proof. Let $\bar{\tau} = \min_{t \in [0, \omega]} \tau(t)$. For any $t \in [0, \bar{\tau}]$, since $t - \tau(t)$ is strictly increasing in t, we have

$$-\tau(0) = 0 - \tau(0) \leq t - \tau(t) \leq \bar{\tau} - \tau(\bar{\tau}) \leq \bar{\tau} - \bar{\tau} = 0,$$

and hence,

$$v_1(t - \tau(t)) = \varphi_1(t - \tau(t)).$$

Therefore, we have the following ordinary differential equations for $t \in [0, \bar{\tau}]$:

$$\begin{aligned}\frac{dv_1(t)}{dt} &= \frac{c\beta(t)l(H - v_1(t))}{(p-l)v_1(t) + lH}v_2(t) - (d_h + \rho)v_1(t),\\ \frac{dv_2(t)}{dt} &= -d_m(t)v_2(t) + (1 - \tau'(t))\frac{b\beta(t-\tau(t))p\varphi_1(t-\tau(t))}{(p-l)\varphi_1(t-\tau(t)) + lH}(K(t) - v_2(t)).\end{aligned}$$

Given $\varphi \in G(0)$, the solution $(v_1(t), v_2(t))$ of the above system exists for $t \in [0, \bar{\tau}]$. In other words, we have obtained values of $\psi_1(\theta) = v_1(\theta)$ for $\theta \in [-\tau(0), \bar{\tau}]$ and $\psi_2(\theta) = v_2(\theta)$ for $\theta \in [0, \bar{\tau}]$. It is easy to see that $v_1(t) \le H$ and $v_2(t) \le K(t)$ for all $t \in [0, \bar{\tau}]$.

For any $t \in [\bar{\tau}, 2\bar{\tau}]$, we have

$$-\tau(0) = 0 - \tau(0) \le \bar{\tau} - \tau(\bar{\tau}) \le t - \tau(t) \le 2\bar{\tau} - \tau(2\bar{\tau}) \le 2\bar{\tau} - \bar{\tau} = \bar{\tau},$$

and hence, $v_1(t - \tau(t)) = \psi_1(t - \tau(t))$. Solving the following system of ordinary differential equations for $t \in [\bar{\tau}, 2\bar{\tau}]$ with $v_1(\bar{\tau}) = \psi_1(\bar{\tau})$ and $v_2(\bar{\tau}) = \psi_2(\bar{\tau})$:

$$\begin{aligned}\frac{dv_1(t)}{dt} &= \frac{c\beta(t)l(H - v_1(t))}{(p-l)v_1(t) + lH}v_2(t) - (d_h + \rho)v_1(t),\\ \frac{dv_2(t)}{dt} &= -d_m(t)v_2(t) + (1 - \tau'(t))\frac{b\beta(t-\tau(t))p\psi_1(t-\tau(t))}{(p-l)\psi_1(t-\tau(t)) + lH}(K(t) - v_2(t)).\end{aligned}$$

We then get the solution $(v_1(t), v_2(t))$ on $[\bar{\tau}, 2\bar{\tau}]$. We also have $v_1(t) \le H$ and $v_2(t) \le K(t)$ for all $t \in [\bar{\tau}, 2\bar{\tau}]$. Repeating this procedure for $t \in [2\bar{\tau}, 3\bar{\tau}]$, $[3\bar{\tau}, 4\bar{\tau}]$,..., it then follows that for any $\varphi \in G(0)$, system (3.13) has a unique solution $v(t, \varphi)$ with $v_0 = \varphi$, and $v_t(\varphi) := (v_{1t}(\varphi), v_2(t, \varphi)) \in G(t)$ for all $t \ge 0$. □ □

Remark 3.3.6. *By the uniqueness of solutions in Lemmas 3.3.4 and 3.3.5, it follows that for any* $\psi \in Y(0)$ *and* $\phi \in G(0)$ *with* $\psi_1(\theta) = \phi_1(\theta)$ *for all* $\theta \in [-\tau(0), 0]$ *and* $\psi_2 = \phi_2$, *we have* $w(t, \psi) = v(t, \phi)$ *for all* $t \ge 0$, *where* $w(t, \psi)$ *and* $v(t, \phi)$ *are solutions* *of system* (3.13) *satisfying* $w_0 = \psi$ *and* $v_0 = \phi$*, respectively. Similarly, we define*

$$\Pi := C([-\tau(0), 0], [0, H]) \times \mathbb{R}_+^2,$$

and

$$\Psi := C([-\tau(0), 0], [0, H]) \times C([-\tau(0), 0], \mathbb{R}_+) \times \mathbb{R}_+.$$

For any $\psi \in \Omega$ *and* $\phi \in \Pi$ *with* $\psi_1(\theta) = \phi_1(\theta)$ *for all* $\theta \in [-\tau(0), 0]$ *and* $\psi_2 = \phi_2$, $\psi_3 = \phi_3$*, we have* $z(t, \psi) = \tilde{z}(t, \phi)$ *for all* $t \geq 0$*, where* $z(t, \psi)$ *and* $\tilde{z}(t, \phi)$ *are solutions of system* (3.14) *satisfying* $z_0 = \psi$ *and* $\tilde{z}_0 = \phi$*, respectively. It follows that* Π *is positively invariant for system* (3.14)*. For any* $\psi \in W$ *and* $\phi \in \Psi$ *with* $\psi_1(\theta) = \phi_1(\theta), \psi_2(\theta) = \phi_2(\theta)$ *for all* $\theta \in [-\tau(0), 0]$ *and* $\psi_3 = \phi_3$*, we have* $u(t, \psi) = \tilde{u}(t, \phi)$ *for all* $t \geq 0$*, where* $u(t, \psi)$ *and* $\tilde{u}(t, \phi)$ *are solutions of system* (3.8) *satisfying* $u_0 = \psi$ *and* $\tilde{u}_0 = \phi$*, respectively. It then follows that* Ψ *is positively invariant for system* (3.8)*.*

Let $S(t)$ be the solution maps of system (3.13), that is, $S(t)\varphi = v_t(\varphi)$, $t \geq 0$, where $v(t, \varphi)$ is the unique solution of system (3.13) with $v_0 = \varphi \in G(0)$. By similar arguments to those in [49, Lemma 3.5], we have the following result.

Lemma 3.3.7. $S(t) : G(0) \to G(t)$ *is an* ω*-periodic semiflow in the sense that* (*i*) $S(0) = I$*;* (*ii*) $S(t + \omega) = S(t) \circ S(\omega)$ *for all* $t \geq 0$*;* (*iii*) $S(t)\varphi$ *is continuous in* $(t, \varphi) \in [0, \infty) \times G(0)$*.*

Note that the linearized system of (3.13) at $(0, 0)$ is

$$\begin{aligned}
\frac{dv_1(t)}{dt} &= -(d_h + \rho)v_1(t) + c\beta(t)v_2(t), \\
\frac{dv_2(t)}{dt} &= \frac{(1 - \tau'(t))b\beta(t - \tau(t))pK(t)}{lH} v_1(t - \tau(t)) - d_m(t)v_2(t).
\end{aligned} \tag{3.15}$$

Let P be the Poincaré map of the linear system (3.15) on the space $C([-\tau(0), 0], \mathbb{R}) \times \mathbb{R}$, and $r(P)$ be its spectral radius. Then we have the following threshold type result for system (3.13).

Lemma 3.3.8. *The following statements are valid:*

(i) *If* $r(P) \leq 1$, *then* $v^*(t) = (0,0)$ *is globally asymptotically stable for system* (3.13) *in* $G(0)$.

(ii) *If* $r(P) > 1$, *then system* (3.13) *admits a unique positive* ω*-periodic solution* $\tilde{v}(t) = (\tilde{v}_1(t), \tilde{v}_2(t))$ *which is globally asymptotically stable for system* (3.13) *in* $G(0) \setminus \{0\}$.

Proof. It follows from Remark 3.3.6 that $S(t)$ maps $G(0)$ into $G(t)$, and $S := S(\omega) : G(0) \to G(\omega) = G(0)$ is the Poincaré map associated with system (3.13). By the continuity and differentiability of solutions with respect to initial values, it follows that S is differentiable at zero and the Frechét derivative $DS(0) = P$.

For any given $\varphi, \psi \in G(0)$ with $\varphi \geq \psi$, let $\bar{v}(t) = v(t,\varphi)$ and $v(t) = v(t,\psi)$ be the unique solutions of system (3.13) with $v_0 = \varphi$ and $v_0 = \psi$, respectively. Let $\bar{\tau} = \min_{t\in[0,\omega]} \tau(t)$. Define

$$A(t) =: \frac{\bar{v}_1(t-\tau(t))}{(p-l)\bar{v}_1(t-\tau(t)) + lH}, \quad B(t) := \frac{v_1(t-\tau(t))}{(p-l)v_1(t-\tau(t)) + lH}.$$

Since

$$-\tau(0) = 0 - \tau(0) \leq t - \tau(t) \leq \bar{\tau} - \tau(\bar{\tau}) \leq \bar{\tau} - \bar{\tau} = 0, \quad \forall t \in [0, \bar{\tau}],$$

we have

$$\bar{v}_1(t-\tau(t)) = \varphi_1(t-\tau(t)) \quad \text{and} \quad v_1(t-\tau(t)) = \psi_1(t-\tau(t)), \quad \forall t \in [0,\bar{\tau}],$$

and hence, $A(t) \geq B(t)$ for all $t \in [0,\bar{\tau}]$. In view of $\bar{v}(0) = \varphi(0) \geq \psi(0) = v(0)$, the comparison theorem for cooperative ordinary differential systems implies that $\bar{v}(t) \geq v(t)$ for all $t \in [0, \bar{\tau}]$.

Repeating this procedure for $t \in [\bar{\tau}, 2\bar{\tau}], [2\bar{\tau}, 3\bar{\tau}], \ldots$, it follows that $v(t, \varphi) \geq v(t, \psi)$ for all $t \in [0, \infty)$. This implies that $S(t) : G(0) \to G(t)$ is monotone for each $t \geq 0$. Next we show that the solution map $S(t)$ is eventually strongly monotone. Let $\varphi > \psi$, and denote $v(t, \varphi) = (\bar{y}_1(t), \bar{y}_2(t))$, $v(t, \psi) = (y_1(t), y_2(t))$.

Claim 1. There exists $t_0 \in [0, \bar{\tau}]$ such that $\bar{y}_2(t) > y_2(t)$ for all $t \geq t_0$.

We first prove that $\bar{y}_2(t_0) > y_2(t_0)$ for some $t_0 \in [0, \bar{\tau}]$. Otherwise, we have $\bar{y}_2(t) = y_2(t)$ for all $t \in [0, \bar{\tau}]$, and hence, $\frac{d\bar{y}_2(t)}{dt} = \frac{dy_2(t)}{dt}$ for all $t \in (0, \bar{\tau})$. Thus, we have

$$\left[\frac{b\beta(t-\tau(t))p\bar{y}_1(t-\tau(t))}{(p-l)\bar{y}_1(t-\tau(t))+lH} - \frac{b\beta(t-\tau(t))py_1(t-\tau(t))}{(p-l)y_1(t-\tau(t))+lH}\right](1-\tau'(t))(K(t)-y_2(t)) = 0, \forall t \in [0, \bar{\tau}]. \tag{3.16}$$

Since $\varphi > \psi$ and $\varphi_2 = \bar{y}_2(0) = y_2(0) = \psi_2$, we have $\varphi_1 > \psi_1$. Then there exists an open interval $(a, b) \subset [-\tau(0), 0]$ such that $\varphi_1(\theta) > \psi_1(\theta)$ for all $\theta \in (a, b)$. Let $h(t) = t - \tau(t)$. Since $h'(t) > 0$, the inverse function $h^{-1}(t)$ exists. It follows from (3.16) that $y_2(t) = K(t)$ for all $t \in (h^{-1}(a), h^{-1}(b))$, and hence,

$$\frac{dK(t)}{dt} = \frac{dy_2(t)}{dt} = -d_m(t)K(t), \quad \forall t \in (h^{-1}(a), h^{-1}(b)),$$

which contradicts the fact that

$$\frac{dK(t)}{dt} = -d_m(t)K(t) + \mu(t-\tau(t))(1-\tau'(t))e^{-\int_{t-\tau(t)}^{t} d_m(s)ds}.$$

Let

$$g_1(t, y) := -d_m(t)y + (1-\tau'(t))\frac{b\beta(t-\tau(t))py_1(t-\tau(t))}{(p-l)y_1(t-\tau(t))+lH}(K(t)-y).$$

Since

$$\begin{aligned}\frac{d\bar{y}_2(t)}{dt} &= -d_m(t)\bar{y}_2(t) + (1-\tau'(t))\frac{b\beta(t-\tau(t))p\bar{y}_1(t-\tau(t))}{(p-l)\bar{y}_1(t-\tau(t))+lH}(K(t)-\bar{y}_2(t))\\ &\geq -d_m(t)\bar{y}_2(t) + (1-\tau'(t))\frac{b\beta(t-\tau(t))py_1(t-\tau(t))}{(p-l)y_1(t-\tau(t))+lH}(K(t)-\bar{y}_2(t))\\ &= g_1(t,\bar{y}_2(t)),\end{aligned}$$

we have

$$\frac{d\bar{y}_2(t)}{dt} - g_1(t,\bar{y}_2(t)) \geq 0 = \frac{dy_2(t)}{dt} - g_1(t,y_2(t)),\ \forall t \geq t_0.$$

Since $\bar{y}_2(t_0) > y_2(t_0)$, the comparison theorem for ordinary differential equations (see Theorem 1.3.1) implies that $\bar{y}_2(t) > y_2(t)$ for all $t \geq t_0$.

Claim 2. $\bar{y}_1(t) > y_1(t)$ for all $t > t_0$.

We first prove that for any $\epsilon > 0$, there exists an open interval $(c,d) \subset [t_0, t_0+\epsilon]$ such that $H > \bar{y}_1(t)$ for all $t \in (c,d)$. Otherwise, there exists $\epsilon_0 > 0$ such that $H = \bar{y}_1(t)$ for all $t \in (t_0, t_0+\epsilon_0)$. It then follows from the first equation of system (3.13) that $0 = -(d_h+\rho)H$, which is a contradiction. Let

$$f_1(t,y) := \frac{c\beta(t)l(H-y)}{(p-l)y+lH}y_2(t) - (d_h+\rho)y.$$

Then we have

$$\begin{aligned}\frac{d\bar{y}_1(t)}{dt} &= \frac{c\beta(t)l(H-\bar{y}_1(t))}{(p-l)\bar{y}_1(t)+lH}\bar{y}_2(t) - (d_h+\rho)\bar{y}_1(t)\\ &> \frac{c\beta(t)l(H-\bar{y}_1(t))}{(p-l)\bar{y}_1(t)+lH}y_2(t) - (d_h+\rho)\bar{y}_1(t)\\ &= f_1(t,\bar{y}_1(t)), \quad \forall t \in (c,d),\end{aligned}$$

and hence,

$$\frac{d\bar{y}_1(t)}{dt} - f_1(t,\bar{y}_1(t)) > 0 = \frac{dy_1(t)}{dt} - f_1(t,y_1(t)), \quad \forall t \in (c,d).$$

Since $\bar{y}_1(t_0) \geq y_1(t_0)$, it follows from Theorem 1.3.1 that $\bar{y}_1(t) > y_1(t)$ for all $t > t_0$.

In view of Claims 1 and 2, we obtain

$$(\bar{y}_1(t), \bar{y}_2(t)) \gg (y_1(t), y_2(t)), \quad \forall t > t_0.$$

Since $t_0 \in [0, \bar{\tau}]$, it follows that

$$(\bar{y}_{1t}, \bar{y}_2(t)) \gg (y_{1t}, y_2(t)), \quad \forall t > \bar{\tau} + \tau(0),$$

that is, $v_t(\varphi) \gg v_t(\psi)$ for all $t > \bar{\tau} + \tau(0)$. This shows that $S(t) : G(0) \to G(t)$ is strongly monotone for any $t > \bar{\tau} + \tau(0)$.

For any given $\varphi \gg 0$ in $G(0)$ and $\lambda \in (0, 1)$, let $v(t, \varphi)$ and $v(t, \lambda\varphi)$ be the solutions of system (3.13) satisfying $v_0 = \varphi$ and $v_0 = \lambda\varphi$, respectively. Denote $x(t) = \lambda v(t, \varphi)$ and $z(t) = v(t, \lambda\varphi)$. As in the proof of Lemma 3.3.5, by the comparison theorem for ordinary differential equations, we have $x(t) > 0$ and $z(t) > 0$ for all $t \geq 0$. Moreover, for all $\theta \in [-\tau(0), 0]$, we have

$$x_1(\theta) = \lambda\varphi_1(\theta) = z_1(\theta), \quad x_2(0) = \lambda\varphi_2 = z_2(0).$$

For any $t \in [0, \bar{\tau}]$, we have $-\tau(0) \leq t - \tau(t) \leq \bar{\tau} - \bar{\tau} = 0$, and hence, $z_1(t - \tau(t)) = x_1(t - \tau(t)) = \lambda\varphi_1(t - \tau(t))$. Thus, $x(t)$ satisfies the following differential inequality:

$$\begin{aligned}
\frac{dx_1(t)}{dt} &< \frac{c\beta(t)l(H - x_1(t))}{(p-l)x_1(t) + lH} x_2(t) - (d_h + \rho)x_1(t), \\
\frac{dx_2(t)}{dt} &< -d_m(t)x_2(t) + (1 - \tau'(t)) \frac{b\beta(t - \tau(t))pz_1(t - \tau(t))}{(p-l)z_1(t - \tau(t)) + lH} (K(t) - x_2(t)),
\end{aligned}$$

for all $t \in [0, \bar{\tau}]$. Since $x(0) = z(0)$, it follows from the comparison theorem for ordinary differential systems (see Theorem 1.3.1) that $x_1(t) < z_1(t)$ and $x_2(t) < z_2(t)$

for all $t \in (0, \bar{\tau}]$. By similar arguments for any interval $(n\bar{\tau}, (n+1)\bar{\tau}]$, $n = 1, 2, 3, \cdots$, we can get $x_1(t) < z_1(t)$ and $x_2(t) < z_2(t)$ for all $t > 0$, that is, $v(t, \lambda\varphi) \gg \lambda v(t, \varphi)$ for all $t > 0$. Therefore, $v_t(\lambda\varphi) \gg \lambda v_t(\varphi)$ for all $t > \tau(0)$.

Now we fix an integer n_0 such that $n_0\omega > \bar{\tau} + \tau(0)$. It then follows that $S^{n_0} = S(n_0\omega) : G(0) \to G(0)$ is strongly monotone and strictly subhomogeneous. Note that $DS^{n_0}(0) = DS(n_0\omega)(0) = P(n_0\omega) = P^{n_0}(\omega) = P^{n_0}$, and $r(P^{n_0}) = (r(P))^{n_0}$. By Theorem 1.3.4 and Lemma 1.3.3 as applied to S^{n_0}, we have the following threshold type result:

(a) If $r(P) \leq 1$, then $v^*(t) = (0, 0)$ is globally asymptotically stable for system (3.13) in $G(0)$.

(b) If $r(P) > 1$, then there exists a unique positive $n_0\omega$-periodic solution $\tilde{v}(t) = (\tilde{v}_1(t), \tilde{v}_2(t))$, which is globally asymptotically stable for system (3.13) in $G(0) \setminus \{0\}$.

It remains to prove that $\tilde{v}(t)$ is also an ω-periodic solution of system (3.13). Let $\tilde{v}(t) = v(t, \psi)$. By the properties of periodic semiflows, we have $S^{n_0}(S(\psi)) = S(S^{n_0}(\psi)) = S(\psi)$, which implies that $S(\psi)$ is also a positive fixed point of S^{n_0}. By the uniqueness of the positive fixed point of S^{n_0}, it follows that $S(\psi) = \psi$. So $\tilde{v}(t)$ is an ω-periodic solution of system (3.13). $\square$ $\square$

Next, we use the theory of chain transitive sets (see section 1.1) to lift the threshold type result for system (3.13) to system (3.14).

Theorem 3.3.9. *The following statements are valid:*

(i) If $r(P) \leq 1$, *then the periodic solution* $(0, 0, K(t))$ *is globally asymptotically stable for system* (3.14) *in* Π*;*

(ii) If $r(P) > 1$, *then system* (3.14) *admits a unique positive* ω*-periodic solution* $(\tilde{v}_1(t),\, \tilde{v}_2(t),\, K(t))$, *which is globally asymptotically stable for system* (3.14) *in* $\Pi \setminus (\{0\} \times \{0\} \times \mathbb{R}_+)$.

Proof. Let $\tilde{P}(t)$ be the solution maps of system (3.14), that is, $\tilde{P}(t)\varphi = z_t(\varphi), t \geq 0$, where $z(t, \varphi)$ is the unique solution of system (3.14) with $z_0 = \varphi \in \Pi$. Then $\tilde{P} := \tilde{P}(\omega)$ is the Poincaré map of system (3.14). Then $\{\tilde{P}^n\}_{n\geq 0}$ defines a discrete-time dynamical system on Π. For any given $\bar{\varphi} \in \Pi$, let $\bar{z}(t) = (u_1(t), u_3(t), w(t))$ be the unique solution of system (3.14) with $\bar{z}_0 = \bar{\varphi}$ and let $\omega(\bar{\varphi})$ be the omega limit set of the orbit $\{\tilde{P}^n(\bar{\varphi})\}_{n\geq 0}$ for the discrete-time semiflow $\tilde{P}^n$.

Since equation (3.12) has a unique positive ω-periodic solution $K(t)$, which is globally attractive, we have $\lim_{t\to\infty}(w(t) - K(t)) = 0$, and hence, $\lim_{n\to\infty} (\tilde{P}^n(\bar{\varphi}))_3 = K(0)$. Thus, there exists a subset $\tilde{\omega}$ of $C([-\tau(0), 0], [0, H]) \times \mathbb{R}_+$ such that $\omega(\bar{\varphi}) = \tilde{\omega} \times \{K(0)\}$.

For any $\phi = (\phi_1, \phi_2, \phi_3) \in \omega(\bar{\varphi})$, there exists a sequence $n_k \to \infty$ such that $\tilde{P}^{n_k}(\bar{\varphi}) \to \phi$, as $k \to \infty$. Since $u_{1n_k\omega} \leq H$ and $u_3(n_k\omega) \leq w(n_k\omega)$, letting $n_k \to \infty$, we obtain $0 \leq \phi_1 \leq H, 0 \leq \phi_2 \leq K(0)$. It then follows that $\tilde{\omega} \subseteq C([-\tau(0), 0], [0, H]) \times [0, K(0)] = G(0)$. It is easy to see that

$$\tilde{P}^n|_{\omega(\bar{\varphi})}(\phi_1, \phi_2, K(0)) = S^n|_{\tilde{\omega}}(\phi_1, \phi_2) \times \{K(0)\}, \quad \forall (\phi_1, \phi_2) \in \tilde{\omega}, \quad n \geq 0,$$

where S is the Poincaré map associated with system (3.13). By Lemma 1.1.2, $\omega(\bar{\varphi})$ is an internally chain transitive set for $\tilde{P}^n$ on Π. It then follows that $\tilde{\omega}$ is an internally chain transitive set for S^n on $G(0)$.

In the case where $r(P) \leq 1$, it follows from Lemma 3.3.8 (i) that $(0, 0)$ is globally asymptotically stable for S^n in $G(0)$. By Theorem 1.1.3, we have $\tilde{\omega} = \{(0, 0)\}$, and hence, $\omega(\bar{\varphi}) = \{(0, 0, K(0))\}$. Then $\tilde{P}^n(\bar{\varphi}) \to (0, 0, K(0))$ as $n \to \infty$. Clearly,

$(0, 0, K(0))$ is a fixed point of $\tilde{P}$. This implies that statement (i) is valid.

In the case where $r(P) > 1$, by Lemma 3.3.8 (ii) and Theorem 1.1.4, it follows that either $\tilde{\omega} = \{(0,0)\}$ or $\tilde{\omega} = \{(\tilde{v}_{10}, \tilde{v}_2(0))\}$, where $\tilde{v}_{10}(\theta) = \tilde{v}_1(\theta)$ for all $\theta \in [-\tau(0), 0]$. We further claim that $\tilde{\omega} \neq \{(0,0)\}$. Suppose, by contradiction, that $\tilde{\omega} = \{(0,0)\}$, then we have $\omega(\bar{\varphi}) = \{(0, 0, K(0))\}$. Thus, $\lim_{t\to\infty}(u_1(t), u_3(t)) = (0, 0)$, and for any $\epsilon > 0$, there exists $T = T(\epsilon) > 0$ such that $|w(t) - K(t)| < \epsilon$ for all $t \geq T$. Then for any $t \geq T$, we have

$$\begin{aligned}
\frac{du_1(t)}{dt} &\geq \frac{c\beta(t)l(H - u_1(t))}{(p-l)u_1(t) + lH} u_3(t) - (d_h + \rho)u_1(t),\\
\frac{du_3(t)}{dt} &\geq -d_m(t)u_3(t) + (1 - \tau'(t))\frac{b\beta(t-\tau(t))pu_1(t-\tau(t))}{(p-l)u_1(t-\tau(t)) + lH}(K(t) - \epsilon - u_3(t)).
\end{aligned} \tag{3.17}$$

Let r_ϵ be the spectral radius of the Poincaré map associated with the following periodic linear system:

$$\begin{aligned}
\frac{du_1(t)}{dt} &= -(d_h + \rho)u_1(t) + c\beta(t)u_3(t),\\
\frac{du_3(t)}{dt} &= (1 - \tau'(t))\frac{b\beta(t-\tau(t))pu_1(t-\tau(t))}{lH}(K(t) - \epsilon) - d_m(t)u_3(t).
\end{aligned} \tag{3.18}$$

Since $\lim_{\epsilon\to 0^+} r_\epsilon = r(P) > 1$, we can fix ϵ small enough such that $r_\epsilon > 1$. By similar result to Lemma 3.3.8 (ii), it follows that the Poincaré map of the following system

$$\begin{aligned}
\frac{du_1(t)}{dt} &= \frac{c\beta(t)l(H - u_1(t))}{(p-l)u_1(t) + lH} u_3(t) - (d_h + \rho)u_1(t),\\
\frac{du_3(t)}{dt} &= -d_m(t)u_3(t) + (1 - \tau'(t))\frac{b\beta(t-\tau(t))pu_1(t-\tau(t))}{(p-l)u_1(t-\tau(t)) + lH}(K(t) - \epsilon - u_3(t))
\end{aligned} \tag{3.19}$$

admits a globally asymptotically stable fixed point $(\bar{u}_{10}, \bar{u}_3(0)) \gg 0$. In the case where $\bar{\varphi} \in \Pi \setminus (\{0\} \times \{0\} \times \mathbb{R}_+)$, we have $(u_1(t), u_3(t)) > 0$ in $\mathbb{R}^2$ for all $t > 0$. In view of

(3.17) and (3.19), the comparison principle implies that

$$\liminf_{n\to\infty}(u_{1n\omega}(\bar{\varphi}), u_3(n\omega,\bar{\varphi})) \geq (\bar{u}_{10}, \bar{u}_3(0)) \gg 0,$$

which contradicts $\lim_{t\to\infty}(u_1(t), u_3(t)) = (0,0)$. It then follows that $\tilde{\omega} = \{(\tilde{v}_{10},\tilde{v}_2(0))\}$, and hence, $\omega(\bar{\varphi}) = \{(\tilde{v}_{10}, \tilde{v}_2(0), K(0))\}$. This implies that $\lim_{t\to\infty}\ (\bar{z}(t) - (\tilde{v}_1(t),\ \tilde{v}_2(t),\ K(t))) = (0,0,0)$. $\square$ $\square$

By the definition of $w(t)$, we have $u_2(t-\tau(t)) = (w(t)-u_3(t))e^{\int_{t-\tau(t)}^{t} d_m(s)ds}$. In the case where $r(P) \leq 1$, we have

$$\begin{aligned}&\lim_{t\to\infty}(u_2(t-\tau(t)) - S_m^*(t-\tau(t)))\\ =&\lim_{t\to\infty}(w(t)-u_3(t)-K(t))e^{\int_{t-\tau(t)}^{t} d_m(s)ds}\\ =&0.\end{aligned}$$

It follows that $\lim_{t\to\infty}(u_2(t) - S_m^*(t)) = 0$. In the case where $r(P) > 1$, we have

$$\lim_{t\to\infty}(u_2(t-\tau(t)) - \hat{u}_2(t)) = 0,$$

where $\hat{u}_2(t) := e^{\int_{t-\tau(t)}^{t} d_m(s)ds}(K(t) - \tilde{v}_2(t))$ is a positive ω-periodic function. Let $x = h(t) := t - \tau(t)$. Then we have $\lim_{x\to\infty}(u_2(x) - \hat{u}_2(h^{-1}(x))) = 0$ and $x + \omega = t+\omega-\tau(t) = t+\omega-\tau(t+\omega) = h(t+\omega)$. It follows that $\hat{u}_2(h^{-1}(x+\omega)) = \hat{u}_2(t+\omega) = \hat{u}_2(t) = \hat{u}_2(h^{-1}(x))$. Replacing x by t, we have

$$\lim_{t\to\infty}(u_2(t) - \hat{u}_2(h^{-1}(t))) = 0,$$

where $\hat{u}_2(h^{-1}(t))$ is a positive ω-periodic function.

As a straightforward consequence of Theorem 3.3.9, we have the following result for system (3.8).

Theorem 3.3.10. *The following statements are valid for system* (3.8)*:*

(i) If $r(P) \leq 1$, *then the disease-free periodic solution* $(0, S_m^*(t), 0)$ *is globally asymptotically stable for system* (3.8) *in* Ψ*;*

(ii) If $r(P) > 1$, *then system* (3.8) *admits a positive* ω*-periodic solution* $(\tilde{v}_1(t), \hat{u}_2(h^{-1}(t)), \tilde{v}_2(t))$*, which is globally asymptotically stable for system* (3.8) *in* $\Psi \setminus (\{0\} \times C([-\tau(0), 0], \mathbb{R}_+) \times \{0\})$.

By the same arguments as in [49, Lemma 3.8], we have $r(P) = r(\hat{P})$. Combining Lemma 3.3.1 and Theorem 3.3.10 we have the following result on the global dynamics of system (3.8).

Theorem 3.3.11. *The following statements are valid for system* (3.8)*:*

(i) If $R_0 \leq 1$, *then the disease-free periodic solution* $(0, S_m^*(t), 0)$ *is globally asymptotically stable for system* (3.8) *in* Ψ*;*

(ii) If $R_0 > 1$, *then system* (3.8) *admits a positive* ω*-periodic solution* $(\tilde{v}_1(t), \hat{u}_2(h^{-1}(t)), \tilde{v}_2(t))$*, which is globally asymptotically stable for system* (3.8) *in* $\Psi \setminus (\{0\} \times C([-\tau(0), 0], \mathbb{R}_+) \times \{0\})$.

In the rest of this section, we derive the dynamics for the variable $E_m(t)$ in system (3.7). It is easy to see that

$$E_m(t) = \int_{t-\tau(t)}^{t} B(\xi, I_h(\xi), S_m(\xi)) e^{-\int_\xi^t d_m(s)ds} d\xi. \tag{3.20}$$

In the case where $R_0 \leq 1$, we have

$$\lim_{t \to \infty} [(I_h(t), S_m(t)) - (0, S_m^*(t))] = 0.$$

It then follows from (3.20) that

$$\lim_{t\to\infty} E_m(t) = 0.$$

In the case where $R_0 > 1$, we have

$$\lim_{t\to\infty}[(I_h(t), S_m(t)) - (\tilde{v}_1(t), \hat{u}_2(h^{-1}(t)))] = 0.$$

By using the integral form (3.20), we obtain

$$\lim_{t\to\infty}[E_m(t) - \int_{t-\tau(t)}^{t} B(\xi, \tilde{v}_1(\xi), \hat{u}_2(h^{-1}(\xi)))e^{-\int_\xi^t d_m(s)ds}d\xi] = 0.$$

Let $\xi = \eta + \omega$. It then follows that

$$\begin{aligned}
&\int_{t+\omega-\tau(t+\omega)}^{t+\omega} B(\xi, \tilde{v}_1(\xi), \hat{u}_2(h^{-1}(\xi)))e^{-\int_\xi^{t+\omega} d_m(s)ds}d\xi \\
=&\int_{t+\omega-\tau(t)}^{t+\omega} B(\xi, \tilde{v}_1(\xi), \hat{u}_2(h^{-1}(\xi)))e^{-\int_\xi^{t+\omega} d_m(s)ds}d\xi \\
=&\int_{t-\tau(t)}^{t} B(\eta+\omega, \tilde{v}_1(\eta+\omega), \hat{u}_2(h^{-1}(\eta+\omega)))e^{-\int_{\eta+\omega}^{t+\omega} d_m(s)ds}d\eta \\
=&\int_{t-\tau(t)}^{t} B(\eta, \tilde{v}_1(\eta), \hat{u}_2(h^{-1}(\eta)))e^{-\int_\eta^{t} d_m(s)ds}d\eta \\
=&\int_{t-\tau(t)}^{t} B(\xi, \tilde{v}_1(\xi), \hat{u}_2(h^{-1}(\xi)))e^{-\int_\xi^{t} d_m(s)ds}d\xi
\end{aligned}$$

Thus,

$$E_m^*(t) = \int_{t-\tau(t)}^{t} B(\xi, \tilde{v}_1(\xi), \hat{u}_2(h^{-1}(\xi)))e^{-\int_\xi^{t} d_m(s)ds}d\xi$$

is a positive ω-periodic function. Consequently, we have the following result on the global dynamics of system (3.7).

Theorem 3.3.12. *The following statements are valid for system* (3.7)*:*

(i) If $R_0 \leq 1$*, then the disease-free periodic solution* $(0, S_m^*(t), 0, 0)$ *is globally asymptotically stable;*

(ii) If $R_0 > 1$*, then system* (3.7) *admits a unique positive* ω*-periodic solution* $(\tilde{v}_1(t)$*,* $\hat{u}_2(h^{-1}(t))$*,* $E_m^*(t)$*,* $\tilde{v}_2(t))$*, which is globally asymptotically stable for all nontrivial solutions.*

3.4 A case study

In this section, we study the malaria transmission case in Maputo Province, Mozambique. We will use the same values as those in section 2.4.1 for all the constant and the periodic parameters except $\tau(t)$. The values of p and l may vary from 0 to 1 and $p \geq l$ (see [17, 34, 39]). In the following simulations, we take $p = 0.8$ and $l = 0.6$.

According to [21], the relationship between the EIP and the temperature is given by

$$\tau(T) = \frac{111}{T - 16},$$

where T is temperature in °C, 111 is the total degree days required for parasite development, and 16 is the temperature at which the parasite development ceases. We take July 1 as the starting point. By using the monthly mean temperatures of Maputo Province (see Table 2.3), we obtain the following approximation for the periodic time delay $\tau(t)$ in CFTOOL (see Figure 3.1):

$$\begin{aligned}\tau(t) =& 1/30.4(17.25 + 8.369\cos(\pi t/6) + 4.806\sin(\pi t/6) + 3.27\cos(\pi t/3)\\ &+ 2.857\sin(\pi t/3) + 1.197\cos(\pi t/2) + 1.963\sin(\pi t/2)\\ &+ 0.03578\cos(2\pi t/3) + 1.035\sin(2\pi t/3) - 0.3505\cos(5\pi t/6)\\ &+ 0.6354\sin(5\pi t/6) - 0.3257\cos(\pi t) + 0\sin(\pi t))\text{Month}.\end{aligned}$$

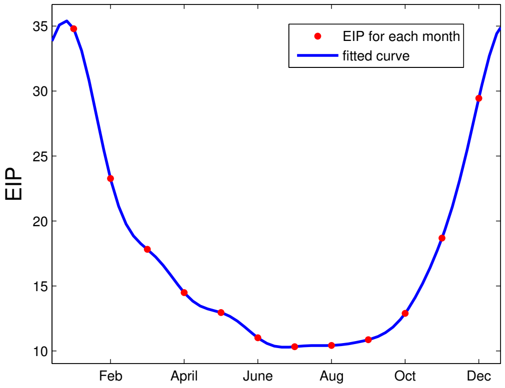

Figure 3.1: The fitted curve of EIP.

To compute R_0 numerically, we first write the operator L into the integral form of [70] by using the similar method to that in [49]. Since

$$F(t-s)\varphi = \begin{pmatrix} a_{12}(t-s)\varphi_2(0) \\ a_{21}(t-s)\varphi_1(-\tau(t-s)) \end{pmatrix},$$

we have

$$\begin{aligned} [Lv](t) &= \int_0^\infty \Phi(t,t-s)F(t-s)v(t-s+\cdot)ds \\ &= \int_0^\infty \begin{pmatrix} e^{-\int_{t-s}^t a_{11}(r)dr} & 0 \\ 0 & e^{-\int_{t-s}^t a_{22}(r)dr} \end{pmatrix} \begin{pmatrix} a_{12}(t-s)v_2(t-s) \\ a_{21}(t-s)v_1(t-s-\tau(t-s)) \end{pmatrix} ds \\ &= \begin{pmatrix} \int_0^\infty e^{-\int_{t-s}^t a_{11}(r)dr} a_{12}(t-s)v_2(t-s)ds \\ \int_0^\infty e^{-\int_{t-s}^t a_{22}(r)dr} a_{21}(t-s)v_1(t-s-\tau(t-s))ds \end{pmatrix}. \end{aligned}$$

Let $t-s-\tau(t-s) = t-s_1$. Since the function $y = h(x) = x-\tau(x)$ is strictly increasing, the inverse function $x = h^{-1}(y)$ exists. Solving $t-s_1 = h(t-s)$, we obtain $s = t-h^{-1}(t-s_1), ds_1 = d(s+\tau(t-s)) = (1-\tau'(t-s))ds$ and $ds = \frac{1}{1-\tau'(h^{-1}(t-s_1))}ds_1$.

Therefore,

$$\begin{aligned}&\int_0^\infty e^{-\int_{t-s}^t a_{22}(r)dr} a_{21}(t-s)v_1(t-s-\tau(t-s))ds\\ =&\int_{\tau(t)}^\infty \frac{e^{-\int_{h^{-1}(t-s_1)}^t a_{22}(r)dr} a_{21}(h^{-1}(t-s_1))v_1(t-s_1)}{1-\tau'(h^{-1}(t-s_1))}ds_1\\ =&\int_{\tau(t)}^\infty \frac{e^{-\int_{h^{-1}(t-s)}^t a_{22}(r)dr} a_{21}(h^{-1}(t-s))v_1(t-s)}{1-\tau'(h^{-1}(t-s))}ds.\end{aligned}$$

Define

$$K_{21}(t,s)=\begin{cases}0, & s<\tau(t),\\ \frac{e^{-\int_{h^{-1}(t-s)}^t a_{22}(r)dr} a_{21}(h^{-1}(t-s))}{1-\tau'(h^{-1}(t-s))}, & s\geq\tau(t),\end{cases}$$

and $K_{12}(t,s)=e^{-\int_{t-s}^t a_{11}(r)dr}a_{12}(t-s)$, $K_{11}(t,s)=K_{22}(t,s)=0$. Then we can rewrite

$$\begin{aligned}[Lv](t) &= \int_0^\infty K(t,s)v(t-s)ds\\ &= \sum_{j=0}^\infty \int_{j\omega}^{(j+1)\omega} K(t,s)v(t-s)ds\\ &= \sum_{j=0}^\infty \int_0^\omega K(t,j\omega+s)v(t-s-j\omega)ds\\ &= \int_0^\omega G(t,s)v(t-s)ds,\end{aligned}$$

where $G(t,s)=\sum_{j=0}^\infty K(t,j\omega+s)$. Consequently, we can use the numerical method in [70] to compute R_0. We set $\omega=12$ months. By using the obtained parameter values above, together with initial functions $I_h(\theta)=337598$, $S_m(\theta)=2712343$, $E_m(0)=1000$, $I_m(0)=2000$ for all $\theta\in[-\hat{\tau},0]$, we get $R_0=3.1471>1$. In this case, the disease will persist and exhibit periodic fluctuation eventually (see Figure 3.2). By employing some malaria control measures such as using insecticide-treated nets, spraying or clearance of mosquito breeding sites, if we can decrease the biting rate to $0.7\beta(t)$, and increase the mosquito mortality rate to $1.5d_m(t)$, then $R_0=0.6591<1$. In this case, we observe that the infectious human population, the exposed and the infectious mosquito populations tend to 0, which means that the disease is eliminated from this area eventually (see Figure 3.3). These numerical simulation results consist with the analytic results in the previous section.

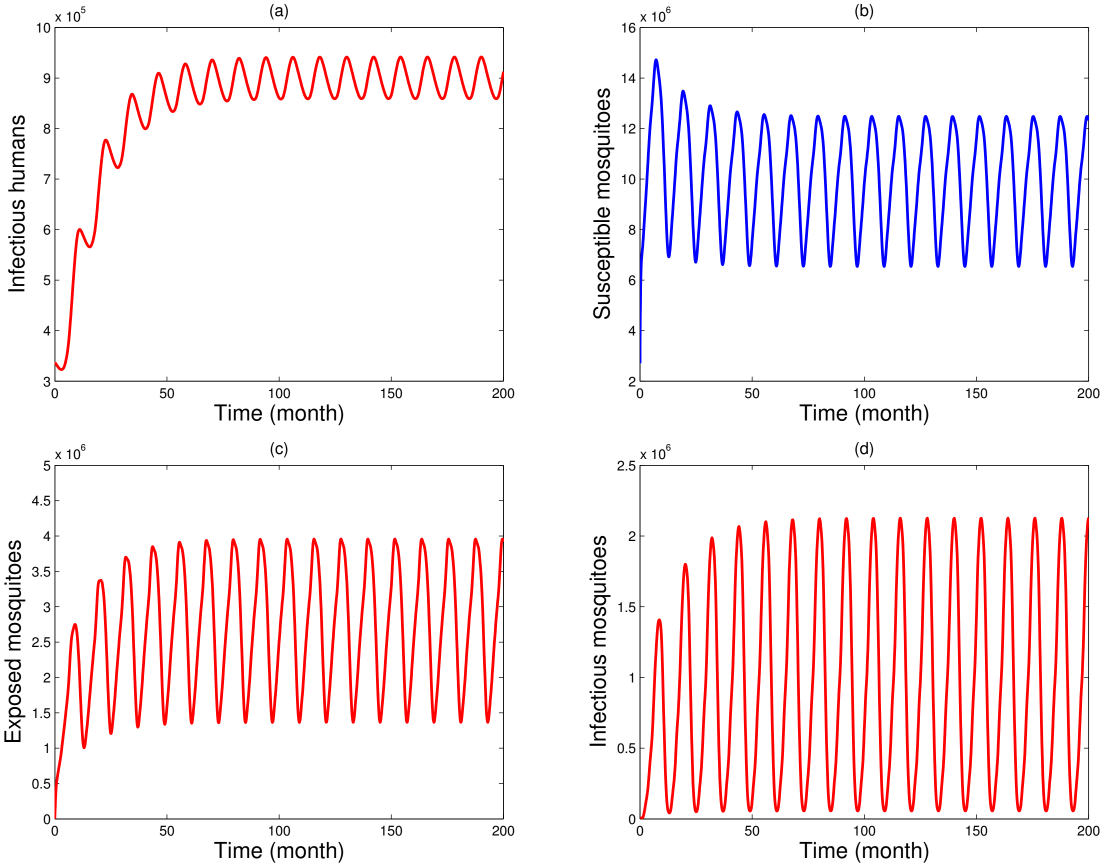

Figure 3.2: Long term behaviour of the solution of system (3.7) when $R_0 = 3.1471 > 1$.

We define the time-averaged EIP duration as

$$[\tau] := \frac{1}{\omega} \int_0^\omega \tau(t) dt.$$

It follows that $[\tau] = 17.2500/30.4$ month. By using this time-averaged EIP duration and keeping all the other parameter values the same as those in Figure 3.2, we obtain $R_0 = 1.8540$, which is less than 3.1471 in Figure 3.2. Figure 3.4 compares the long term behaviour of the infectious compartments of model (3.7) under two different

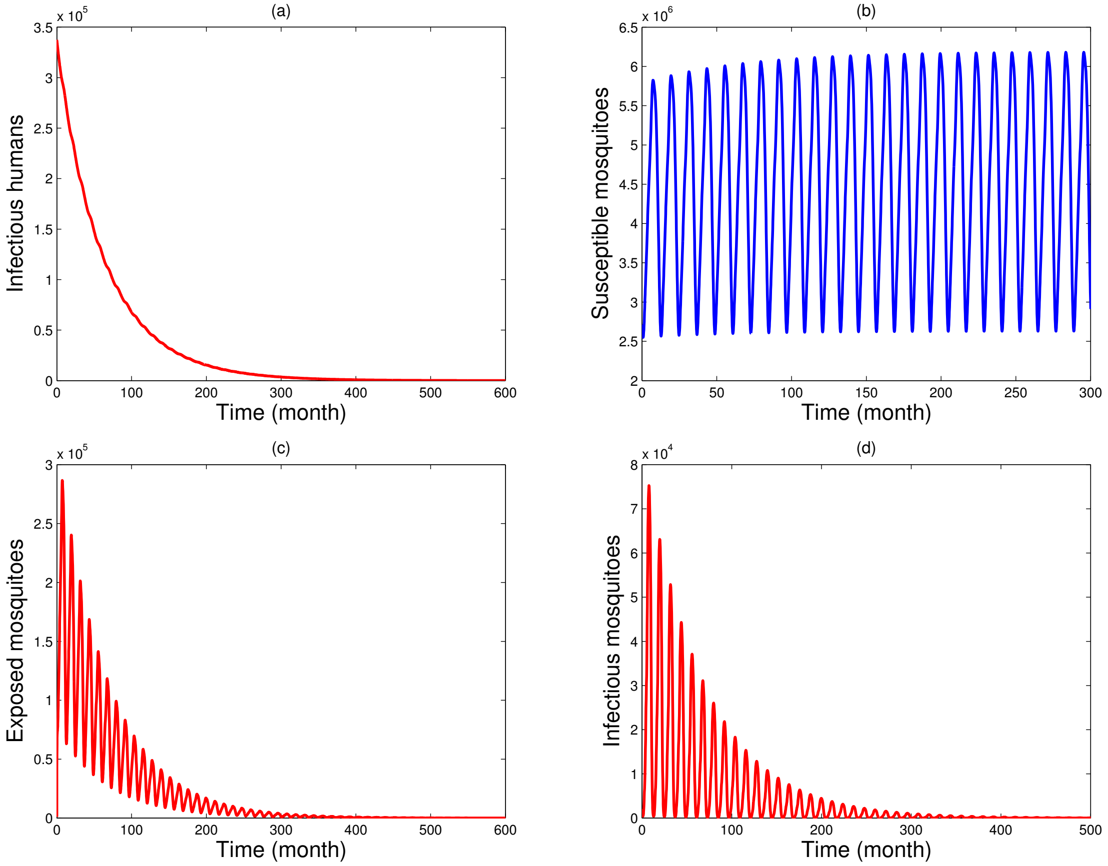

Figure 3.3: Long term behaviour of the solution of system (3.7) when $R_0 = 0.6591 < 1$.

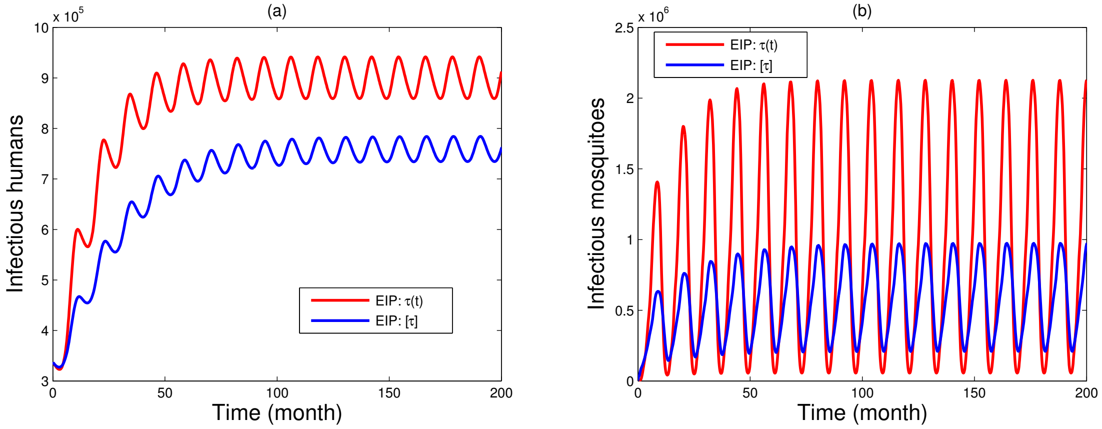

Figure 3.4: Comparison of the long term behaviour of the infectious compartments of model (3.7) under two different EIP durations (red curve: temperature-dependent EIP; blue curve: time-averaged EIP).

values of the EIP durations: the periodic $\tau(t)$ and the constant $[\tau]$. Figure 4(a) indicates that the use of the time-averaged EIP $[\tau]$ may underestimate the number of infectious humans in Maputo. In Figure 4(b), we see that the amplitude of the periodic fluctuation of infectious mosquitoes is obviously smaller when $[\tau]$ is used. In addition, the peak and the nadir of the periodic fluctuation of I_m are underestimated and overestimated, respectively.

3.5 Discussion

Malaria is strongly linked to climate conditions through the impact of climate on the vector and the parasite ecology. Of all the environmental conditions, temperature plays the most important role in malaria transmission. Both the mosquito *Anopheles* and the parasite *Plasmodium* are extremely sensitive to temperature. In particular, the duration of the EIP of *Plasmodium* is determined by temperature (see, e.g., [10, 57]). An increasing number of malaria models have incorporated the effects of temperature on mosquito life cycle. However, none of the existing deterministic malaria transmission models has taken into account the dependence of the EIP on temperature.

In this chapter, we developed a malaria transmission model that, for the first time, incorporates a temperature-dependent EIP. The model is a system of delay differential equations with a periodic time delay. By using the theory recently developed by Zhao [110], we derived the basic reproduction ratio R_0. Incorporation of the periodic delay increases challenges for theoretical analysis. Fortunately, the work by Lou and Zhao [49] throws light on mathematical analysis of delay differential system with periodic delays. Following the theoretical approach in [49] we defined a phase space on which the limiting system generates an eventually strongly monotone periodic semiflow. By employing the theory of monotone and subhomogeneous systems and the theory of chain transitive sets, we established a threshold type result on the global dynamics in terms of the basic reproduction ratio R_0: if $R_0 < 1$, then malaria will be eliminated; if $R_0 > 1$, then the disease will persist and exhibit seasonal fluctuation.

Using some published data from Maputo Province, Mozambique and formula related to mosquito life cycle, we obtained estimations for all the constant and periodic parameters. We fitted the curve of the EIP for Maputo Province by appealing to the Detinova prediction curve. With the algorithm proposed by Posny and Wang [70], we numerically calculated the basic reproduction ratio R_0. The numerical simulation about the long term behaviour of solutions is consistent with the obtained analytic result. To compare our results with those for the constant EIP case, we also conducted numerical simulations for the long term behaviour of infectious compartments by using the time-averaged EIP. It turns out that the adoption of the time-averaged EIP may underestimate both the number of infectious humans and the basic reproduction ratio. Thus, the models incorporating the temperature-dependent EIP are more helpful for the control of the malaria transmission.

Chapter 4

A climate-based malaria model with the use of bed nets

4.1 Introduction

Malaria remains the most severe and complex health challenge facing the vast majority of the countries in the sub-Saharan Africa [89]. The World Health Organization estimated that there were 214 million malaria cases in 2015, resulting in about 438 thousand deaths [98]. Some commonly used strategies in combatting malaria include antimalarial drugs, larvicides, insecticides and intermittent preventive treatment. Insecticide-treated bed nets (ITNs) is the preferred tool for reducing malaria transmission and alleviating disease burden [22, 41]. In addition to providing a physical barrier between humans and mosquitoes, the insecticide used to treat the bed nets repels mosquitoes, and if a mosquito fails to be repelled, it will often rest on the bed net, and may then be killed by contacting the insecticide [12]. A number of studies in Africa have demonstrated that high coverage of ITNs benefits not only the users but also the whole local community. Since the pioneering work of Ronald Ross

[76], who proved that malaria is transmitted by mosquitoes and proposed the first malaria model, much modeling work has been done to study malaria transmission dynamics (see, e.g., [4, 5, 37, 46, 50, 92] and the references therein). In recent years, several models have been proposed to investigate the impact of bed net use (see, e.g., [2, 19, 35, 58, 59] and the references therein).

As mentioned in [1], most of the existing malaria models include only adult mosquitoes. Indeed, mosquitoes undergo four distinct development stages during a lifetime: egg, larva, pupa, and adult. Quite a few researchers have incorporated the different stages of mosquitoes into their models (see, e.g., [1, 43, 48, 57, 97]). While it is appropriate to assume that only adult mosquitoes are involved in the malaria transmission, the dynamics of the juvenile stage have significant effects on the dynamics of the mosquito population, and hence the disease transmission dynamics [1]. In particular, since larval control is a hot recommended strategy in fighting against malaria, it is necessary to develop a mathematical model which includes the two key stages of mosquitoes (juvenile and adult) so that we can better understand the mosquito population dynamics and gain some insights into the design of disease control strategies.

Recent experimental and field study results indicate that malaria parasites manipulate a host to be more attractive to mosquitoes via chemical substances. (see, e.g., [39]). Only a few mathematical models have accounted for the greater attractiveness of infectious humans to mosquitoes (see, e.g., [17, 36, 59, 95, 103] and the references therein). Incorporating such vector-bias effect in malaria models will give us a better description and a more accurate quantification of the disease dynamics.

The purpose of this chapter is to develop an ordinary differential equations model that, for the first time, incorporates the juvenile mosquito stage, the impact of ITNs use, the vector-bias effect and seasonality simultaneously. This work uses the dynamical systems theory to obtain the qualitative properties of human and mosquito population sizes.

The rest of this chapter is organized as follows. In the next section, we formulate the model and give the underlying assumptions. In section 4.3, we establish the threshold dynamics of the model via the vector reproduction ratio and the basic reproduction ratio. In section 4.4, we do a case study for Port Harcourt, Nigeria. A brief discussion concludes the chapter.

4.2 Model formulation

In order to formulate the model, we consider two stages of mosquitoes: the juvenile stage and the adult one. By juvenile, we mean any of the three aquatic stages: egg, larva and pupa. Let $L_v(t)$ be the number of juvenile mosquitoes at time t. The adult mosquito population is grouped into two compartments, susceptible and infectious, the numbers of which at time t are denoted by $S_v(t)$ and $I_v(t)$, respectively. Letting $N_v(t)$ be the number of all adult mosquitoes at time t, we have $N_v(t) = S_v(t) + I_v(t)$. Let $I_h(t)$ be the number of infectious humans at time t. We assume that the total human population size N_h remains constant for a specified region. Then the number of susceptible humans at time t is $N_h - I_h(t)$. To study the human population dynamics we only need to know how $I_h(t)$ changes with time t. Thus, for the human population we only consider the equation for $I_h(t)$ in our model. Let d_h be the human natural death rate. We use ρ to denote the recovery and disease-induced death rate of humans. Let $\lambda_L(t)$ and $\mu_L(t)$ be the birth rate and the natural death rate of juvenile mosquitoes, respectively. According to [43] and [72], larval crowding and competition for limited resources are quite common in some breeding sites. To account for such a phenomenon, we also incorporate the density-dependent mortality rate of juvenile mosquitoes, denoted by α. We use $\lambda_v(t)$ to denote the birth rate of adult mosquitoes.

Following [2], we model the biting rate of mosquitoes by the linearly decreasing function of the proportion of ITNs use k:

$$\beta(t,k) = \beta_v(t) - k(\beta_v(t) - \beta_r(t)), \quad 0 \leq k \leq 1,$$

where $\beta_v(t)$ is the natural biting rate of mosquitoes, and $\beta_r(t)$ is the reduced biting rate of mosquitoes due to the physical barrier provided by ITNs between the human and the mosquito. If $k = 0$, which means that no one uses ITNs, then the biting rate would remain at its natural level $\beta_v(t)$. The biting rate will be reduced to a minimum value $\beta_r(t)$ if $k = 1$, when everyone uses ITNs. We model the death rate of adult mosquitoes by the following linearly increasing function of k:

$$\mu(t,k) = \mu_v(t) + \bar{\mu}k, \quad 0 \leq k \leq 1,$$

where $\mu_v(t)$ is the natural death rate of adult mosquitoes and $\bar{\mu}k$ is mosquitoes' death rate due to their contact with the insecticide on bed nets.

Let p and l be the probabilities that a mosquito arrives at a human at random and picks the human if he is infectious and susceptible, respectively. Since infectious humans are more attractive to mosquitoes, we assume that $p \geq l$. We denote the biting rate of mosquitoes by $\beta(t,k)$, which is the number of bites per mosquito per unit time at time t. Then $\beta(t,k)I_v(t)$ is the number of bites by all infectious mosquitoes per unit time at time t. We assume that a mosquito does not bite the same person for more than once. Since the total number of bites made by mosquitoes equals to the number of bites received by humans [13], $\beta(t,k)I_v(t)$ is also the number of humans that are bitten by infectious mosquitoes per unit time at time t . Among all the humans that are bitten by infectious mosquitoes, only those originally susceptible ones may contribute to the increase of $I_h(t)$. Hence, we need to derive the probability that a human is susceptible under the condition that a mosquito picks him. Obviously, this probability equals to $\frac{l(N_h-I_h(t))}{pI_h(t)+l(N_h-I_h(t))}$, the ratio between the total bitten susceptible humans and the total bitten humans. For simplicity, we neglect both the intrinsic incubation period within humans and the extrinsic incubation period within mosquitoes. Thus, the number of newly occurred infectious humans per unit time at time t is

$$c\beta(t,k)\frac{l(N_h-I_h(t))}{pI_h(t)+l(N_h-I_h(t))}I_v(t),$$

where c is the probability of transmission of infection from an infectious mosquito to a susceptible human given that the contact between the two occurs. Similarly, $\frac{pI_h(t)}{pI_h(t)+l(N_h-I_h(t))}$ is the probability that a human is infectious under the condition that a mosquito picks him. Then the number of newly occurred infectious mosquitoes per unit time at time t is

$$b\beta(t,k)\frac{pI_h(t)}{pI_h(t)+l(N_h-I_h(t))}S_v(t),$$

where b is the transmission probability per bite from infectious humans to susceptible mosquitoes. The model system is governed by

$$\begin{aligned}
\frac{dL_v(t)}{dt} &= \lambda_L(t)(S_v(t)+I_v(t)) - \mu_L(t)L_v(t) - \alpha L_v(t)^2 - \lambda_v(t)L_v(t),\\
\frac{dS_v(t)}{dt} &= \lambda_v(t)L_v(t) - b\beta(t,k)\frac{pI_h(t)}{pI_h(t)+l(N_h-I_h(t))}S_v(t) - \mu(t,k)S_v(t),\\
\frac{dI_v(t)}{dt} &= b\beta(t,k)\frac{pI_h(t)}{pI_h(t)+l(N_h-I_h(t))}S_v(t) - \mu(t,k)I_v(t),\\
\frac{dI_h(t)}{dt} &= c\beta(t,k)\frac{l(N_h-I_h(t))}{pI_h(t)+l(N_h-I_h(t))}I_v(t) - (d_h+\rho)I_h(t),
\end{aligned} \tag{4.1}$$

where all constant parameters are positive, and $\lambda_L(t)$, $\mu_L(t)$, $\lambda_v(t)$, $\beta(t,k)$, $\mu(t,k)$ are positive, continuous functions ω-periodic in time t for some $\omega > 0$. For reader's convenience, we list all the parameters and their biological interpretations in Table 4.1.

Table 4.1: Biological interpretations for parameters of model (4.1)

Parameters	Description
$L_v(t)$	the number of juvenile mosquitoes (eggs, larvae and pupae)
$S_v(t)$	the number of susceptible adult mosquitoes
$I_v(t)$	the number of infectious adult mosquitoes
$I_h(t)$	the number of infectious humans
$\lambda_L(t)$	birth rate of juvenile mosquitoes
$\mu_L(t)$	natural death rate of juvenile mosquitoes
α	density-dependent death rate of junenile mosquitoes
$\lambda_v(t)$	birth rate of adult mosquitoes
b	transmission probability per bite from infectious humans to mosquitoes
c	transmission probability per bite from infectious mosquitoes to humans
k	proportion of effective ITNs use ($0 \leq k \leq 1$)
$\beta_v(t)$	mosquito biting rate
$\beta_r(t)$	reduced mosquito biting rate due to ITNs
$\mu_v(t)$	natural death rate of adult mosquitoes
$\bar{\mu}k$	death rate of adult mosquitoes due to contact with insecticide on bed nets
d_h	natural death rate of humans
ρ	removal rate of humans from the infectious compartment (i.e., recovery rate and disease-induced death rate)
p	probability that a mosquito arrives at a human at random and picks the human if he is infectious
l	probability that a mosquito arrives at a human at random and picks the human if he is susceptible
N_h	the total number of humans

4.3 Global stability analysis

In what follows, we use the theory developed in [94] to derive two threshold parameters for the model: the vector reproduction ratio R_v and the basic reproduction ratio R_0.

Note that system (4.1) is equivalent to the following one:

$$\begin{aligned}
\frac{dL_v(t)}{dt} &= \lambda_L(t)N_v(t) - \mu_L(t)L_v(t) - \alpha L_v(t)^2 - \lambda_v(t)L_v(t),\\
\frac{dN_v(t)}{dt} &= \lambda_v(t)L_v(t) - \mu(t,k)N_v(t),\\
\frac{dI_v(t)}{dt} &= b\beta(t,k)\frac{pI_h(t)}{pI_h(t)+l(N_h-I_h(t))}(N_v(t)-I_v(t)) - \mu(t,k)I_v(t),\\
\frac{dI_h(t)}{dt} &= c\beta(t,k)\frac{l(N_h-I_h(t))}{pI_h(t)+l(N_h-I_h(t))}I_v(t) - (d_h+\rho)I_h(t).
\end{aligned} \tag{4.2}$$

Then the mosquito population is described by

$$\begin{aligned}
\frac{dL_v(t)}{dt} &= \lambda_L(t)N_v(t) - \mu_L(t)L_v(t) - \alpha L_v(t)^2 - \lambda_v(t)L_v(t),\\
\frac{dN_v(t)}{dt} &= \lambda_v(t)L_v(t) - \mu(t,k)N_v(t).
\end{aligned} \tag{4.3}$$

Linearizing system (4.3) at $(0,0)$, we get the following linear cooperative system:

$$\begin{aligned}
\frac{dL_v(t)}{dt} &= \lambda_L(t)N_v(t) - (\mu_L(t)+\lambda_v(t))L_v(t),\\
\frac{dN_v(t)}{dt} &= \lambda_v(t)L_v(t) - \mu(t,k)N_v(t).
\end{aligned} \tag{4.4}$$

We rewrite system (4.4) as $\frac{dv}{dt} = (\tilde{F}(t) - \tilde{V}(t))v$, where

$$\tilde{F}(t) = \begin{bmatrix} 0 & \lambda_L(t) \\ 0 & 0 \end{bmatrix}, \quad \tilde{V}(t) = \begin{bmatrix} \mu_L(t)+\lambda_v(t) & 0 \\ -\lambda_v(t) & \mu(t,k) \end{bmatrix}.$$

Let $\tilde{Y}(t,s), t \geq s$, be the evolution operator of the linear periodic system

$$\frac{dy}{dt} = -\tilde{V}(t)y.$$

That is, for each $s \in \mathbb{R}$, the 2×2 matrix $\tilde{Y}(t,s)$ satisfies

$$\frac{d}{dt}\tilde{Y}(t,s) = -\tilde{V}(t)\tilde{Y}(t,s), \quad \forall t \geq s, \quad \tilde{Y}(s,s) = I,$$

where I is the 2×2 identity matrix.

Let C_ω be the ordered Banach space of all ω-periodic functions from $\mathbb{R}$ to $\mathbb{R}^2$, equipped with the maximum norm and the positive cone $C_\omega^+ := \{\phi \in C_\omega : \phi(t) \geq 0, \forall t \in \mathbb{R}\}$. According to [94, Section 2], we assume that $\phi(s) \in C_\omega$ is the initial distribution of adult mosquitoes. Then $\tilde{F}(s)\phi(s)$ is the distribution of new juvenile mosquitoes produced by the adult ones who were introduced at time s. Given $t \geq s$, then $\tilde{Y}(t,s)\tilde{F}(s)\phi(s)$ gives the distribution of those mosquitoes who were newly born into the juvenile mosquito compartment at time s and remain alive (either as juvenile mosquitoes or as adult ones) at time t. It follows that

$$\psi(t) := \int_{-\infty}^{t} \tilde{Y}(t,s)\tilde{F}(s)\phi(s)ds = \int_0^\infty \tilde{Y}(t,t-a)\tilde{F}(t-a)\phi(t-a)da$$

is the distribution of accumulative new juvenile and adult mosquitoes at time t produced by all those adult mosquitoes $\phi(s)$ introduced at previous time to t.

We define a linear operator $\tilde{L} : C_\omega \to C_\omega$ by

$$(\tilde{L}\phi)(t) = \int_0^\infty \tilde{Y}(t,t-a)\tilde{F}(t-a)\phi(t-a)da, \quad \forall t \in \mathbb{R}, \quad \phi \in C_\omega.$$

It then follows from [94] that the vector reproduction ratio is $R_v := \rho(\tilde{L})$, the spectral radius of $\tilde{L}$. Let r_1 be the principal Floquét multiplier of system (4.4), that is, the spectral radius of the Poincaré map associated with system (4.4). By [94, Theorem 2.2], $R_v - 1$ has the same sign as $r_1 - 1$. As a straightforward consequence of [109, Theorem 3.1.2], we have the following result.

Lemma 4.3.1. *The following statements are valid:*

- *(i) If* $R_v \le 1$*, then* $(0,0)$ *is globally attractive for system* (4.3) *in* $\mathbb{R}^2_+$.
- *(ii) If* $R_v > 1$*, then system* (4.3) *admits a unique positive* ω*-periodic solution* $(L_v^*(t), N_v^*(t))$*, which is globally attractive for system* (4.3) *in* $\mathbb{R}^2_+ \setminus \{(0,0)\}$.

Let $W := \mathbb{R}^3_+ \times [0, N_h]$. We then have the following result for system (4.2).

Lemma 4.3.2. *For any* $\varphi \in W$*, system* (4.2) *has a unique nonnegative bounded solution* $u(t,\varphi)$ *on* $[0,\infty)$ *with* $u(0)=\varphi$*, and* $u(t,\varphi) \in W$ *for all* $t \ge 0$.

Proof. For any $\varphi = (\varphi_1, \varphi_2, \varphi_3, \varphi_4) \in W$, we define

$$\hat{f}(t,\varphi) = \begin{pmatrix} \lambda_L(t)\varphi_2 - \mu_L(t)\varphi_1 - \alpha\varphi_1^2 - \lambda_v(t)\varphi_1 \\ \lambda_v(t)\varphi_1 - \mu(t,k)\varphi_2 \\ b\beta(t,k)\frac{p\varphi_4(\varphi_2-\varphi_3)}{p\varphi_4 + l(N_h-\varphi_4)} - \mu(t,k)\varphi_3 \\ c\beta(t,k)\frac{l(N_h-\varphi_4)\varphi_3}{p\varphi_4 + l(N_h-\varphi_4)} - (d_h+\rho)\varphi_4 \end{pmatrix}.$$

Since $\hat{f}(t,\varphi)$ is continuous in $(t,\varphi) \in \mathbb{R}_+ \times W$, and $\hat{f}(t,\varphi)$ is Lipschitz in φ on each compact subset of W, it follows that system (4.2) has a unique solution $u(t,\varphi)$ on its maximal interval $[0,\sigma_\varphi)$ of existence with $u(0)=\varphi$ (see, e.g., [29, Theorems 2.2.1 and 2.2.3]).

Let $\varphi = (\varphi_1, \varphi_2, \varphi_3, \varphi_4) \in W$ be given. If $\varphi_i = 0$ for some $i \in \{1,2,3,4\}$, then $\hat{f}_i(t,\varphi) \ge 0$. If $\varphi_4 = N_h$, then $\hat{f}_4(t,\varphi) \le 0$. By [84, Theorem 5.2.1 and Remark 5.2.1], it follows that for any $\varphi \in W$, the unique solution $u(t,\varphi)$ of system (4.2) with $u(0)=\varphi$ satisfies $u(t,\varphi) \in W$ for all $t \in [0,\sigma_\varphi)$.

Clearly, $0 \le u_4(t,\varphi) \le N_h$ for all $t \in [0,\sigma_\varphi)$. It follows from Lemma 4.3.1 that there exists $B_1 > 0$ and $B_2 > 0$ such that $u_1(t,\varphi) \le B_1$, $u_2(t,\varphi) \le B_2, \forall t \in [0,\sigma_\varphi)$.

In view of the third equation of system (4.2), we have

$$\frac{du_3(t,\varphi)}{dt} \leq b\beta(t,k)B_2 - (b\beta(t,k)+\mu(t,k))u_3(t,\varphi).$$

Hence, $u_3(t,\varphi)$ is also bounded on $[0,\sigma_\varphi)$. Then [29, Theorem 2.3.1] implies that $\sigma_\varphi = \infty$. □ □

If $\lim_{t\to\infty}(L_v(t)-L_v^*(t)) = \lim_{t\to\infty}(N_v(t)-N_v^*(t)) = 0$, the last two equations in system (4.2) give rise to the following limiting system:

$$\begin{aligned} \frac{dI_v(t)}{dt} &= b\beta(t,k)\frac{pI_h(t)}{pI_h(t)+l(N_h-I_h(t))}(N_v^*(t)-I_v(t)) - \mu(t,k)I_v(t), \\ \frac{dI_h(t)}{dt} &= c\beta(t,k)\frac{l(N_h-I_h(t))}{pI_h(t)+l(N_h-I_h(t))}I_v(t) - (d_h+\rho)I_h(t). \end{aligned} \tag{4.5}$$

The following result implies that the domain $G(t) := [0,N_v^*(t)]\times[0,N_h]$ is positively invariant for system (4.5).

Lemma 4.3.3. *For any* $\varphi = (\varphi_1,\varphi_2) \in G(0)$*, system* (4.5) *has a unique solution* $v(t,\varphi)$ *with* $v(0)=\varphi$ *and* $(I_v(t,\varphi), I_h(t,\varphi)) \in G(t), \forall t \geq 0$.

Proof. For any $\varphi \in G(0)$, define

$$\tilde{f}(t,\varphi) = \left(\begin{array}{c} b\beta(t,k)\frac{p\varphi_2(N_v^*(t)-\varphi_1)}{p\varphi_2+l(N_h-\varphi_2)} - \mu(t,k)\varphi_1 \\ c\beta(t,k)\frac{l(N_h-\varphi_2)\varphi_1}{p\varphi_2+l(N_h-\varphi_2)} - (d_h+\rho)\varphi_2 \end{array} \right).$$

Since $\tilde{f}$ is continuous in $(t,\varphi) \in \mathbb{R}\times G(0)$ and $\tilde{f}$ is Lipschitz in φ on each compact subset of $G(0)$, it follows that system (4.5) has a unique solution $v(t,\varphi)$ with $v(0)=\varphi$ on its maximal interval $[0,\sigma_\varphi)$ of existence.

Let $\varphi = (\varphi_1,\varphi_2) \in G(0)$ be given. If $\varphi_1 = 0$, then $\tilde{f}_1(t,\varphi) \geq 0$. If $\varphi_2 = 0$, then $\tilde{f}_2(t,\varphi) \geq 0$. If $\varphi_2 = N_h$, then $\tilde{f}_2(t,\varphi) \leq 0$. By [84, Theorem 5.2.1 and Remark

5.2.1], it follows that the unique solution $v(t,\varphi)$ of system (4.5) with $v(0)=\varphi$ satisfies $v(t,\varphi)\in\mathbb{R}_+\times[0,N_h]$.

It remains to prove that $v_1(t)\le N_v^*(t),\forall t\in[0,\sigma_\varphi)$. Suppose this does not hold. Then there exists $t_0\in[0,\sigma_\varphi)$ and $\epsilon_0>0$ such that

$$v_1(t_0)=N_v^*(t_0)\quad\text{and}\quad v_1(t)>N_v^*(t),\quad\forall t\in(t_0,t_0+\epsilon_0).$$

Since

$$\frac{dv_1(t_0)}{dt}=-\mu(t_0,k)v_1(t_0)=-\mu(t_0,k)N_v^*(t_0)<\frac{dN_v^*(t_0)}{dt},$$

there exists $\epsilon_1\in(0,\epsilon_0)$ such that $v_1(t)\le N_v^*(t),\forall t\in(t_0,t_0+\epsilon_1)$, which is a contradiction. This proves that $v(t,\varphi)\in G(t),\forall t\in[0,\sigma_\varphi)$. Clearly, $v(t,\varphi)$ is bounded on $[0,\sigma_\varphi)$, and hence, [29, Theorem 2.3.1] implies that $\sigma_\varphi=\infty$. □ □

Linearizing system (4.5) at $(0,0)$, we get the following linear system

$$\begin{aligned}\frac{dI_v(t)}{dt}&=-\mu(t,k)I_v(t)+b\beta(t,k)\frac{pN_v^*(t)}{lN_h}I_h(t),\\ \frac{dI_h(t)}{dt}&=c\beta(t,k)I_v(t)-(d_h+\rho)I_h(t).\end{aligned}\tag{4.6}$$

We rewrite system (4.6) as $\frac{du}{dt}=(F(t)-V(t))u$, where

$$F(t)=\begin{bmatrix}0 & b\beta(t,k)\frac{pN_v^*(t)}{lN_h}\\ c\beta(t,k) & 0\end{bmatrix},\quad V(t)=\begin{bmatrix}\mu(t,k) & 0\\ 0 & d_h+\rho\end{bmatrix}.$$

Let $Y(t,s),t\ge s$, be the evolution operator of the linear periodic system

$$\frac{dy}{dt}=-V(t)y.$$

That is, for each $s \in \mathbb{R}$, the 2×2 matrix $Y(t,s)$ satisfies

$$\frac{d}{dt}Y(t,s) = -V(t)Y(t,s), \quad \forall t \geq s, \quad Y(s,s) = I,$$

where I is the 2×2 identity matrix.

We assume that $\varphi(s) \in C_\omega$ is the initial distribution of infectious mosquitoes and infectious humans. Then $F(s)\varphi(s)$ is the distribution of new infections produced by the infectious mosquitoes and infectious humans who were introduced at time s. Given $t \geq s$, then $Y(t,s)F(s)\varphi(s)$ gives the distribution of those infectious mosquitoes and infectious humans who were newly infected at time s and remain in the infectious compartments at time t. It follows that

$$\int_{-\infty}^{t} Y(t,s)F(s)\varphi(s)ds = \int_{0}^{\infty} Y(t,t-a)F(t-a)\varphi(t-a)da$$

is the distribution of accumulative new infections at time t produced by all those infectious mosquitoes and infectious humans $\varphi(s)$ introduced at previous time to t.

We define a linear operator $L : C_\omega \to C_\omega$ by

$$(L\varphi)(t) = \int_{0}^{\infty} Y(t,t-a)F(t-a)\varphi(t-a)da, \quad \forall t \in \mathbb{R}, \quad \varphi \in C_\omega.$$

It then follows from [94] that the basic reproduction ratio is $R_0 := \rho(L)$, the spectral radius of L. The following lemma gives a threshold type result for the limiting system (2.6).

Lemma 4.3.4. *The following statements are valid:*

(i) If $R_0 \leq 1$, *then* $(0,0)$ *is globally attractive for system* (4.5) *in* $G(0)$.

(ii) If $R_0 > 1$, *then system* (4.5) *admits a unique positive* ω*-periodic solution* $(I_v^*(t),$

$I_h^*(t)$), which is globally attractive for system (4.5) *in* $G(0) \setminus \{(0,0)\}$.

Proof. Let $S(t)$ be the solution maps of system (4.5), that is, $S(t)(I_v(0), I_h(0)) = (I_v(t), I_h(t)), t \geq 0$, where $(I_v(t), I_h(t))$ is the unique solution of system (4.5) with $(I_v(0), I_h(0)) \in G(0)$. It follows from Lemma 4.3.3 that $S(t)$ maps $G(0)$ into $G(t)$, and $S := S(\omega) : G(0) \to G(\omega) = G(0)$ is the Poincaré map associated with system (4.5).

Let $(\bar{y}_1(0), \bar{y}_2(0)) \geq (y_1(0), y_2(0))$. Let $(\bar{y}_1(t), \bar{y}_2(t))$ and $(y_1(t), y_2(t))$ be the solutions of system (4.5) with initial values $(\bar{y}_1(0), \bar{y}_2(0))$ and $(y_1(0), y_2(0))$, respectively. Then the comparison theorem for cooperative ordinary differential systems implies that $(\bar{y}_1(t), \bar{y}_2(t)) \geq (y_1(t), y_2(t)), \forall t \geq 0$, that is, $S(t) : G(0) \to G(t)$ is monotone for each $t \geq 0$.

Next, we show that $S(t) : G(0) \to G(t)$ is strongly monotone for each $t > 0$. Suppose $(\bar{y}_1(0), \bar{y}_2(0)) > (y_1(0), y_2(0))$. Then the comparison theorem for cooperative ordinary differential systems implies that

$$(\bar{y}_1(t), \bar{y}_2(t)) > (y_1(t), y_2(t)), \quad \forall t \geq 0.$$

We proceed with two cases.

Case 1. $\bar{y}_1(0) > y_1(0)$.

Let

$$g_1(y) := b\beta(t,k)\frac{py_2(t)}{(p-l)y_2(t) + lN_h}(N_v^*(t) - y) - \mu(t,k)y.$$

Since

$$\begin{aligned}\frac{d\bar{y}_1(t)}{dt} &= b\beta(t,k)\frac{p\bar{y}_2(t)}{(p-l)\bar{y}_2(t) + lN_h}(N_v^*(t) - \bar{y}_1(t)) - \mu(t,k)\bar{y}_1(t) \\ &\geq b\beta(t,k)\frac{py_2(t)}{(p-l)y_2(t) + lN_h}(N_v^*(t) - \bar{y}_1(t)) - \mu(t,k)\bar{y}_1(t) \\ &= g_1(\bar{y}_1(t)),\end{aligned}$$

we have

$$\frac{d\bar{y}_1(t)}{dt} - g_1(\bar{y}_1(t)) \geq 0 = \frac{dy_1(t)}{dt} - g_1(y_1(t)), \quad \forall t \geq 0.$$

Since $\bar{y}_1(0) > y_1(0)$, Theorem 1.3.1 implies that $\bar{y}_1(t) > y_1(t), \forall t \geq 0$.

To prove $\bar{y}_2(t) > y_2(t), \forall t > 0$, we first prove that for any $\epsilon > 0$, there exists an open interval $(a, b) \subset [0, \epsilon]$ such that $N_h > \bar{y}_2(t), \forall t \in (a, b)$. Otherwise, there exists $\epsilon_0 > 0$ such that $N_h = \bar{y}_2(t), \forall t \in (0, \epsilon_0)$. It then follows from the second equation of system (2.6) that $0 = -(d_h + \rho)N_h$, which is a contradiction. Let

$$f_1(y) := c\beta(t, k)\frac{l(N_h - y)}{(p - l)y + lN_h}y_1(t) - (d_h + \rho)y.$$

Then we have

$$\begin{aligned}
\frac{d\bar{y}_2(t)}{dt} &= c\beta(t, k)\frac{l(N_h - \bar{y}_2(t))}{(p - l)\bar{y}_2(t) + lN_h}\bar{y}_1(t) - (d_h + \rho)\bar{y}_2(t) \\
&> c\beta(t, k)\frac{l(N_h - \bar{y}_2(t))}{(p - l)\bar{y}_2(t) + lN_h}y_1(t) - (d_h + \rho)\bar{y}_2(t) \\
&= f_1(\bar{y}_2(t)), \quad \forall t \in (a, b),
\end{aligned}$$

and hence,

$$\frac{d\bar{y}_2(t)}{dt} - f_1(\bar{y}_2(t)) > 0 = \frac{dy_2(t)}{dt} - f_1(y_2(t)), \quad \forall t \in (a, b).$$

Since $\bar{y}_2(0) \geq y_2(0)$, it follows from Theorem 1.3.1 that $\bar{y}_2(t) > y_2(t), \forall t > 0$.

Case 2. $\bar{y}_1(0) = y_1(0)$.

Since $(\bar{y}_1(0), \bar{y}_2(0)) > (y_1(0), y_2(0))$ and $\bar{y}_1(0) = y_1(0)$, we must have $\bar{y}_2(0) > y_2(0)$. By similar arguments to those in Case 1, we see that for any $\epsilon > 0$, there exists an open interval $(a, b) \subset [0, \epsilon]$ such that $N_h > \bar{y}_2(t), \forall t \in (a, b)$. Then we have

$$\begin{aligned}
\frac{d\bar{y}_2(t)}{dt} &= c\beta(t,k)\frac{l(N_h - \bar{y}_2(t))}{(p-l)\bar{y}_2(t) + lN_h}\bar{y}_1(t) - (d_h + \rho)\bar{y}_2(t) \\
&\geq c\beta(t,k)\frac{l(N_h - \bar{y}_2(t))}{(p-l)\bar{y}_2(t) + lN_h}y_1(t) - (d_h + \rho)\bar{y}_2(t) \\
&= f_1(\bar{y}_2(t)), \quad \forall t \in (a, b),
\end{aligned}$$

and hence,

$$\frac{d\bar{y}_2(t)}{dt} - f_1(\bar{y}_2(t)) \geq 0 = \frac{dy_2(t)}{dt} - f_1(y_2(t)), \quad \forall t \in (a, b).$$

Since $\bar{y}_2(0) > y_2(0)$, it follows from Theorem 1.3.1 that $\bar{y}_2(t) > y_2(t), \forall t > 0$.

To prove $\bar{y}_1(t) > y_1(t), \forall t > 0$, we first prove that for any $\epsilon > 0$, there exists $(a_1, b_1) \subset [0, \epsilon]$ such that $\bar{y}_1(t) < N_v^*(t), \forall t \in (a_1, b_1)$. Otherwise, there exists $\epsilon_1 > 0$ such that $\bar{y}_1(t) = N_v^*(t), \forall t \in (0, \epsilon_1)$. By the first equation of system (4.5), we have

$$\frac{d\bar{y}_1(t)}{dt} = \frac{dN_v^*(t)}{dt} = -\mu(t,k)N_v^*(t), \quad t \in (0, \epsilon_1),$$

which contradicts the fact that

$$\frac{dN_v^*(t)}{dt} = \lambda_v(t)L_v^*(t) - \mu(t,k)N_v^*(t).$$

Let

$$g_1(t) := b\beta(t,k)\frac{py_2(t)}{(p-l)y_2(t) + lN_h}(N_v^*(t) - y) - \mu(t,k)y.$$

Since

$$\begin{aligned}\frac{d\bar{y}_1(t)}{dt} &= b\beta(t,k)\frac{p\bar{y}_2(t)}{(p-l)\bar{y}_2(t)+lN_h}(N_v^*(t)-\bar{y}_1(t))-\mu(t,k)\bar{y}_1(t)\\ &> b\beta(t,k)\frac{py_2(t)}{(p-l)y_2(t)+lN_h}(N_v^*(t)-\bar{y}_1(t))-\mu(t,k)\bar{y}_1(t)\\ &= g_1(\bar{y}_1(t)), \quad \forall t\in(a_1,b_1),\end{aligned}$$

we have

$$\frac{\bar{y}_1(t)}{dt}-g_1(\bar{y}_1(t))>0=\frac{dy_1(t)}{dt}-g_1(y_1(t)), \quad \forall t\in(a_1,b_1).$$

Since $\bar{y}_1(0)=y_1(0)$, Theorem 1.3.1 implies that $\bar{y}_1(t)>y_1(t), \forall t>0$.

Consequently, $S(t):G(0)\to G(t)$ is strongly monotone for each $t>0$.

For any given $x=(x_1,x_2)\in G(0), \lambda\in[0,1]$, let $v(t,x)$ and $v(t,\lambda x)$ be the solutions of system (4.5) satisfying $v(0)=x$ and $v(0)=\lambda x$, respectively. Denote $u(t)=\lambda v(t,x)$ and $z(t)=v(t,\lambda x)$. Define f by

$$f(t,x)=\begin{bmatrix} b\beta(t,k)\frac{px_2}{(p-l)x_2+lN_h}(N_v^*(t)-x_1)-\mu(t,k)x_1\\ c\beta(t,k)\frac{l(N_h-x_2)}{(p-l)x_2+lN_h}x_1-(d_h+\rho)x_2\end{bmatrix}.$$

Note that for any $\psi\in G(t)$ and $\lambda\in[0,1]$, we have $f(t,\lambda\psi)\geq\lambda f(t,\psi)$. Then

$$\frac{du(t)}{dt}=\lambda\frac{dv(t,x)}{dt}=\lambda f(t,v(t,x))\leq f(t,\lambda v(t,x))=f(t,u(t)).$$

Clearly, $\frac{dz(t)}{dt}=f(t,z(t))$ and $u(0)=\lambda v(0,x)=\lambda x=z(0)$. By the comparison principle we have $u(t)\leq z(t), \forall t\geq 0$, that is, $\lambda v(t,x)\leq v(t,\lambda x), \forall t\geq 0$. This shows that the solution map $S(t):G(0)\to G(t)$ is subhomogeneous.

Next, we prove that for any $t>0$, $S(t):G(0)\to G(t)$ is strictly subhomogeneous.

For any given $x \in G(0)$ with $x \gg 0$ and $\lambda \in (0,1)$, let

$$\begin{aligned} f_2(r) &:= c\beta(t,k)\frac{l(N_h - r)}{(p-l)r + lN_h} z_1(t) - (d_h + \rho)r, \\ g_2(r) &:= c\beta(t,k)\frac{l(N_h - r)}{(p-l)r + lN_h}. \end{aligned}$$

Since $g_2(r)$ is strictly decreasing in r and $\lambda v_1(t,x) \le v_1(t,\lambda x), v_2(t,x) > \lambda v_2(t,x), \forall \lambda \in (0,1), \forall t > 0$, it follows that

$$\begin{aligned} \frac{du_2(t)}{dt} &= \lambda \frac{dv_2(t,x)}{dt} \\ &= \lambda c\beta(t,k)\frac{l(N_h - v_2(t,x))}{(p-l)v_2(t,x) + lN_h} v_1(t,x) - (d_h + \rho)\lambda v_2(t,x) \\ &< c\beta(t,k)\frac{l(N_h - \lambda v_2(t,x))}{(p-l)\lambda v_2(t,x) + lN_h} z_1(t) - (d_h + \rho)\lambda v_2(t,x) \\ &= c\beta(t,k)\frac{l(N_h - u_2(t))}{(p-l)u_2(t) + lN_h} z_1(t) - (d_h + \rho)\lambda v_2(t,x) \\ &= g(u_2(t))z_1(t) - (d_h + \rho)u_2(t) \\ &= f_2(u_2(t)), \end{aligned}$$

and hence,

$$\frac{du_2(t)}{dt} - f_2(u_2(t)) < 0 = \frac{dz_2(t)}{dt} - f_2(z_2(t)), \quad \forall t > 0.$$

Note that $u_2(0) = \lambda v_2(0,x) = \lambda x = v_2(0,\lambda x) = z_2(0)$. By Theorem 1.3.1, we then obtain $u_2(t) < z_2(t), \forall t > 0$. Thus, $\lambda v(t,x) < v(t,\lambda x), \forall t > 0$.

Let P be the Poincaré map associated with system (4.6) on $\mathbb{R}^2$ and $r(P)$ be its spectral radius. By the continuity and differentiability of solutions with respect to initial values, it follows that S is differentiable at zero and the Frechét derivative $DS(0) = P$. By Theorem 1.3.4, as applied to S, we have the following result:

(a) If $r(P) \le 1$, then $(0,0)$ is globally attractive for (4.5) in $G(0)$.

(b) If $r(P) > 1$, then system (4.5) admits a unique positive ω-periodic solution

$(I_v^*(t), I_h^*(t))$, which is globally attractive for system (4.5) in $G(0) \setminus \{(0,0)\}$.

By [94, Theorem 2.2], $R_0 - 1$ has the same sign as $r(P) - 1$. Therefore, we have the desired threshold type result in terms of R_0. □ □

Next, we use the theory of chain transitive sets (see section 1.1) to lift the threshold type result for system (4.5) to system (4.2).

Theorem 4.3.5. *The following statements are valid:*

(i) If $R_v \leq 1$*, then* $(0,0,0,0)$ *is globally attractive for system* (4.2) *in* W*.*

(ii) If $R_v > 1$ *and* $R_0 \leq 1$*, then* $(L_v^*(t), N_v^*(t), 0, 0)$ *is globally attractive for system* (4.2) *in* $W \setminus \{(0,0,0,0)\}$*;*

(iii) If $R_v > 1$ *and* $R_0 > 1$*, then* $(L_v^*(t), N_v^*(t), I_v^*(t), I_h^*(t))$ *is globally attractive for system* (4.2) *in* $W \setminus \mathbb{R}_+^2 \times \{(0,0)\}$*.*

Proof. Let $\{\Psi(t)\}_{t\geq 0}$ be the periodic semiflow associated with system (4.2) on W, that is,

$$\Psi(t)(x) := (L_v(t,x), N_v(t,x), I_v(t,x), I_h(t,x))$$

is the unique solution of system (4.2) with initial value $x \in W$. Then $\Psi := \Psi(\omega)$ is the Poincaré map of system (4.2), and $\{\Psi^n\}_{n\geq 0}$ defines a discrete-time dynamical system on W. For any given $x \in W$, let $\mathcal{L}$ be the omega limit set of the discrete-time orbit $\{\Psi^n(x)\}_{n\geq 0}$. It follows from Lemma 1.1.2 that $\mathcal{L}$ is an internally chain transitive set for Ψ^n on W.

In the case where $R_v \leq 1$, by Lemma 4.3.1(i), we have

$$\lim_{n\to\infty}((\Psi^n(x))_1, (\Psi^n(x))_2, (\Psi^n(x))_3) = (0,0,0).$$

Then there exists a subset $\mathcal{L}_1$ of $\mathbb{R}$ such that

$$\mathcal{L} = \{(0,0,0)\} \times \mathcal{L}_1.$$

For any given $y = (y_1, y_2, y_3, y_4) \in \mathcal{L}$, there exists a sequence $n_k \to \infty$ such that $\Psi^{n_k}(x) \to y$ as $k \to \infty$. Since $0 \leq (\Psi^{n_k}(x))_4 = I_h(n_k\omega, x) \leq N_h$ for all $x \in W$, letting $n_k \to \infty$, we obtain $0 \leq y_4 \leq N_h$. It then follows that $\mathcal{L}_1 \subset [0, N_h]$. It is easy to see that

$$\Psi^n|_{\mathcal{L}}(0,0,0,y_4) = \{(0,0,0)\} \times \Psi_1^n|_{\mathcal{L}_1}(y_4),$$

where $\{\Psi_1(t)\}_{t\geq 0}$ is the solution semiflow associated with the following system:

$$\frac{dI_h(t)}{dt} = -(d_h + \rho)I_h(t). \tag{4.7}$$

Since $\mathcal{L}$ is an internally chain transitive set for Ψ^n, it follows that $\mathcal{L}_1$ is an internally chain transitive set for Ψ_1^n. Since 0 is globally attractive for system (4.7) in $\mathbb{R}$, it follows from Theorem 1.1.3 that $\mathcal{L}_1 = \{0\}$, and hence, $\mathcal{L} = \{(0,0,0,0)\}$. This implies that statement (i) is valid.

In the case where $R_v > 1$, by Lemma 4.3.1(ii), we have

$$\lim_{n\to\infty} ((\Psi^n(x))_1, (\Psi^n(x))_2) = (L_v^*(0), N_v^*(0)).$$

Then there exists a subset $\mathcal{L}_2$ of $\mathbb{R}^2$ such that

$$\mathcal{L} = \{(L_v^*(0), N_v^*(0))\} \times \mathcal{L}_2.$$

For any given $z = (z_1, z_2, z_3, z_4) \in \mathcal{L}$, there exists a sequence $n_j \to \infty$ such that $\Psi^{n_j}(x) \to z$ as $j \to \infty$. Since $0 \leq (\Psi^{n_j}(x))_3 = I_v(n_j\omega, x) \leq N_v(n_j\omega, x)$ and $0 \leq$

$(\Psi^{n_j}(x))_4 = I_h(n_j\omega, x) \leq N_h$ for all $x \in W$, letting $n_j \to \infty$, we obtain $0 \leq z_3 \leq N_v^*(0)$, $0 \leq z_4 \leq N_h$. It then follows that $\mathcal{L}_2 \subset [0, N_v^*(0)] \times [0, N_h] = G(0)$. It is easy to see that

$$\Phi^n|_{\mathcal{L}}(L_v^*(0), N_v^*(0), z_3, z_4) = \{(L_v^*(0), N_v^*(0))\} \times S^n|_{\mathcal{L}_2}(z_3, z_4).$$

Since $\mathcal{L}$ is an internally chain transitive set for Ψ^n, it follows that $\mathcal{L}_2$ is an internally chain transitive set for S^n.

In the case where $R_v > 1$ and $R_0 \leq 1$, by Lemma 4.3.4 (i), we have

$$\lim_{n\to\infty}((\Psi^n(x))_3, (\Psi^n(x))_4) = (0, 0), \quad \forall x \in G(0).$$

It then follows from Theorem 1.1.3 that $\mathcal{L}_2 = \{(0, 0)\}$, and hence, $\mathcal{L} = \{(L_v^*(0), N_v^*(0), 0, 0)\}$. This implies that statement (ii) is valid.

In the case where $R_v > 1$ and $R_0 > 1$, by Lemma 4.3.4 (ii), we have

$$\lim_{n\to\infty}((\Psi^n(x))_3, (\Psi^n(x))_4) = (I_v^*(0), I_h^*(0)), \quad \forall x \in G(0) \setminus \{(0, 0)\}.$$

It follows from Theorem 1.1.4 that

$$\text{either} \quad \mathcal{L}_2 = \{(0, 0)\} \quad \text{or} \quad \mathcal{L}_2 = \{(I_v^*(0), I_h^*(0))\}.$$

We further claim that $\mathcal{L}_2 \neq \{(0, 0)\}$. Suppose, by contradiction, that $\mathcal{L}_2 = \{(0, 0)\}$. Then we have $\lim_{t\to\infty}(I_v(t, x), I_h(t, x)) = (0, 0)$ uniformly for $x \in G(0)$, and for any $\epsilon > 0$, there exists $T = T(\epsilon) > 0$ such that

$$|(L_v(t, x), N_v(t, x)) - (L_v^*(0), N_v^*(0))| < \epsilon$$

for all $t \geq T$ and $x \in G(0)$. Then for any $t \geq T$, we have

$$\begin{aligned} \frac{dI_v(t)}{dt} &\geq b\beta(t,k)\frac{pI_h(t)}{(p-l)I_h(t)+lN_h}(N_v^*(t)-\epsilon-I_v(t))-\mu(t,k)I_v(t), \\ \frac{dI_h(t)}{dt} &= c\beta(t,k)\frac{l(N_h-I_h(t))}{(p-l)I_h(t)+lN_h}I_v(t)-(d_h+\rho)I_h(t). \end{aligned} \tag{4.8}$$

Let r_ϵ be the spectral radius of the Poincaré map associated with the following linear system:

$$\begin{aligned} \frac{d\bar{I}_v(t)}{dt} &= b\beta(t,k)\frac{p\bar{I}_h(t)}{lN_h}(N_v^*(t)-\epsilon)-\mu(t,k)\bar{I}_v(t), \\ \frac{d\bar{I}_h(t)}{dt} &= c\beta(t,k)\bar{I}_v(t)-(d_h+\rho)\bar{I}_h(t). \end{aligned}$$

Since $\lim_{\epsilon\to 0^+} r_\epsilon = r(P) > 1$, we can fix ϵ small enough such that $r_\epsilon > 1$ and $\epsilon < \min_{t\in[0,\omega]} N_v^*(t)$. By similar result to Lemma 4.3.2 (ii), it follows that the Poincaré map of the following system

$$\begin{aligned} \frac{d\bar{I}_v(t)}{dt} &= b\beta(t,k)\frac{p\bar{I}_h(t)}{(p-l)\bar{I}_h(t)+lN_h}(N_v^*(t)-\epsilon-\bar{I}_v(t))-\mu(t,k)\bar{I}_v(t), \\ \frac{d\bar{I}_h(t)}{dt} &= c\beta(t,k)\frac{l(N_h-\bar{I}_h(t))}{(p-l)\bar{I}_h(t)+lN_h}\bar{I}_v(t)-(d_h+\rho)\bar{I}_h(t) \end{aligned} \tag{4.9}$$

admits a globally attractive fixed point $(\bar{I}_v^*(0), \bar{I}_h^*(0)) \gg 0$. Since $x \in W\backslash\mathbb{R}_+^2\times\{(0,0)\}$, $(I_v(t,x), I_h(t,x)) > 0$ for all $t > 0$. In view of (4.8) and (4.9), the comparison principle implies that

$$\liminf_{n\to\infty}(I_v(n\omega,x), I_h(n\omega,x)) \geq (\bar{I}_v^*(0), \bar{I}_h^*(0)) \gg 0,$$

which contradicts $\lim_{t\to\infty}(I_v(t,x), I_h(t,x)) = (0,0)$. It then follows that $\mathcal{L}_2 = \{(I_v^*(0), I_h^*(0))\}$, and hence, $\mathcal{L} = \{(L_v^*(0), N_v^*(0), I_v^*(0), I_h^*(0))\}$. This implies that statement (iii) is valid. □ □

Since system (4.1) is equivalent to (4.2), we have the following result on the global dynamics of our model system.

Theorem 4.3.6. *The following statements are valid:*

(i) If $R_v \leq 1$, then $(0,0,0,0)$ is globally attractive for system (4.1) in W.

(ii) If $R_v > 1$ and $R_0 \leq 1$, then $(L_v^*(t), N_v^*(t), 0, 0)$ is globally attractive for system (4.1) in $W \setminus \{(0,0,0,0)\}$.

(iii) If $R_v > 1$ and $R_0 > 1$, then $(L_v^*(t), N_v^*(t), I_v^*(t), I_h^*(t))$ is globally attractive for system (4.1) in $W \setminus \mathbb{R}_+^2 \times \{(0,0)\}$.

To finish this section, we remark that when all coefficients are constants, the model system (4.1) reduces to the following autonomous system:

$$\begin{aligned}
\frac{dL_v(t)}{dt} &= \lambda_L N_v(t) - \mu_L L_v(t) - \alpha L_v(t)^2 - \lambda_v L_v(t), \\
\frac{dS_v(t)}{dt} &= \lambda_v L_v(t) - b\beta(k)\frac{pI_h(t)}{pI_h(t) + l(N_h - I_h(t))}S_v(t) - \mu(k)S_v(t), \\
\frac{dI_v(t)}{dt} &= b\beta(k)\frac{pI_h(t)}{pI_h(t) + l(N_h - I_h(t))}S_v(t) - \mu(k)I_v(t), \\
\frac{dI_h(t)}{dt} &= c\beta(k)\frac{l(N_h - I_h(t))}{pI_h(t) + l(N_h - I_h(t))}I_v(t) - (d_h + \rho)I_h(t),
\end{aligned} \tag{4.10}$$

where

$$\beta(k) = \beta_v - k(\beta_v - \beta_r), \quad 0 \leq k \leq 1,$$

$$\mu(k) = \mu_v + \bar{\mu}k, \quad 0 \leq k \leq 1.$$

Then the matrices $\tilde{F}(t)$, $\tilde{V}(t)$, $F(t)$ and $V(t)$, respectively, become

$$\tilde{F} = \begin{bmatrix} 0 & \lambda_L \\ 0 & 0 \end{bmatrix}, \quad \tilde{V} = \begin{bmatrix} \mu_L + \lambda_v & 0 \\ -\lambda_v & \mu(k) \end{bmatrix},$$

$$F = \begin{bmatrix} 0 & \frac{b\beta(k)N_v^* p}{lN_h} \\ c\beta(k) & 0 \end{bmatrix}, \quad V = \begin{bmatrix} \mu(k) & 0 \\ 0 & d_h + \rho \end{bmatrix}.$$

For any given $\omega > 0$, we can regard system (4.10) as an ω-periodic system. By [94, Lemma 2.2 (ii)], we obtain the vector reproduction ratio R_v and the basic reproduction ratio R_0 for system (4.10) as follows:

$$R_v = \rho(\tilde{F}\tilde{V}^{-1}) = \frac{\lambda_L \lambda_v}{\mu(k)(\mu_L + \lambda_v)},$$

$$R_0 = \rho(FV^{-1}) = \sqrt{\frac{c\beta(k)}{\mu(k)} \frac{b\beta(k)p}{lN_h(d_h + \rho)} \frac{\lambda_v}{\alpha\mu(k)} \left(\frac{\lambda_L \lambda_v}{\mu(k)} - (\mu_L + \lambda_v) \right)}. \tag{4.11}$$

By the global attractivity in Theorem 4.3.6, we can easily obtain its analog for autonomous system (4.10), where the ω-periodic solutions are replaced by the corresponding equilibria.

4.4 A case study

In this section, we study the malaria transmission case in Port Harcourt, Nigeria. Nigeria accounts for a quarter of all malaria cases in the 45 malaria endemic countries in Africa [98]. Port Harcourt is the capital and largest city of Rivers State, Nigeria. The topography of Port Harcourt is that of flat plains with a network of rivers, tributaries and creeks which have a high potential for breeding of mosquitoes. Malaria transmission is intense year round with a peak during months of March to November and a nadir during months of December to February [26].

We do the numerical simulations by using ode45 and CFTOOL in Matlab. First, we need to estimate the constant and periodic parameter values. Port Harcourt has a population of 1230000 (see https://en.wikipedia.org/wiki/ List_of_metropolitan_areas_in_Africa), which can be chosen as the value of N_h. The life expectancy of Nigeria is 52.11 years (see http://data.worldbank.org). Using this number we estimate the human natural death rate as $d_h = \frac{1}{52.11 \times 12} = 0.0016$ month^{-1}. The values of p and

l may vary from 0 to 1 and $p \geq l$ [17, 34, 39]. Unless otherwise stated, we use the values listed in Table 4.2 for constant parameters in the simulation.

Table 4.2: Parameter values

Parameter	Value	Dimension	Reference
b	0.2	dimensionless	[18]
c	0.011	dimensionless	[18]
ρ	0.0187	month^{-1}	[18]
p	$(0, 1)$	dimensionless	[17, 34, 39]
l	$(0, 1)$	dimensionless	[17, 34, 39]
α	0.000001	dimensionless	estimated
k	[0,1]	dimensionless	
d_h	0.0016	month^{-1}	see text
N_h	1230000	dimensionless	see text
$\bar{\mu}$	0.01	month^{-1}	estimated
$\beta_v(t)$	to be evaluated	month^{-1}	see text
$\beta_r(t)$	$0.1\beta_v(t)$	month^{-1}	estimated
$\mu_v(t)$	to be evaluated	month^{-1}	see text
$\lambda_L(t)$	to be evaluated	month^{-1}	see text
$\mu_L(t)$	to be evaluated	month^{-1}	see text
$\lambda_v(t)$	to be evaluated	month^{-1}	see text

Since temperature plays a major role in the life cycle of mosquitoes, we evaluate the periodic parameters by using the monthly mean temperatures of Port Harcourt from 1990 to 2012 (obtained from Climate Change Knowledge Portal website: http://sdwebx.worldbank.org /climateportal), as shown in Table 4.3.

Table 4.3: Monthly mean temperatures for Port Harcourt (in °C)

Month	Jan	Feb	Mar	Apr	May	June
Temperature	26.52	28	28.38	27.92	27.18	26.1
Month	Jul	Aug	Sep	Oct	Nov	Dec
Temperature	25.34	25.27	25.49	25.91	26.79	26.34

According to [69], the temperature-dependent mosquito biting rate can be expressed as

$$\beta_v(T) = 30.4 \times 0.000203T(T - 11.7)\sqrt{42.3 - T} \text{ Month}^{-1},$$

where and hereinafter T is the temperature in $^\circ C$. The biting rate of mosquitoes in Port Harcourt can then be fitted by

$$\begin{aligned}\beta_v(t) =&0.1554\cos(\pi t/6) + 0.9065\sin(\pi t/6) - 0.2284\cos(2\pi t/6)\\ &- 0.2764\sin(2\pi t/6) - 0.0578\cos(3\pi t/6) - 0.1473\sin(3\pi t/6)\\ &- 0.0208\cos(4\pi t/6) - 0.1573\sin(4\pi t/6) - 0.0118\cos(5\pi t/6)\\ &- 0.0510\sin(5\pi t/6) + 9.6794 \text{ Month}^{-1}.\end{aligned}$$

Since ITNs are only used at night, even if the entire human population uses ITNs, they can still be bitten by mosquitoes at daytime. We assume that

$$\beta_r(t) = \xi\beta_v(t), \quad \xi \in (0, 1),$$

and we take $\xi = 0.1$ in the simulation.

It follows from [79] that the birth rates of juvenile and adult mosquitoes and the death rate of juvenile mosquitoes can be respectively given by

$$\lambda_L(T) = 2.325\beta_v(T), \quad \lambda_v(T) = \frac{\lambda_L(T)}{10},$$

and

$$\mu_L(T) = 30.4 \times (0.0025T^2 - 0.094T + 1.0257) \text{ Month}^{-1}.$$

Then the birth rates of juvenile and adult mosquitoes and the death rate of juvenile mosquitoes in Port Harcourt can be fitted respectively by

$$\lambda_L(t) = 2.325\beta_v(t), \quad \lambda_v(t) = \frac{\lambda_L(t)}{10},$$

and

$$\begin{aligned}\mu_L(t) =& 0.2240\cos(\pi t/6) + 1.5699\sin(\pi t/6) - 0.4849\cos(2\pi t/6)\\ &- 0.4268\sin(2\pi t/6) - 0.0835\cos(3\pi t/6) - 0.3016\sin(3\pi t/6)\\ &- 0.0210\cos(4\pi t/6) - 0.2684\sin(4\pi t/6) - 0.0051\cos(5\pi t/6)\\ &- 0.0845\sin(5\pi t/6) + 9.0288 \text{ Month}^{-1}.\end{aligned}$$

According to [53, 57], the death rate of adult mosquitoes is evaluated as

$$\mu_v(T) = \frac{30.4}{-0.03T^2 + 1.31T - 4.4} \text{ Month}^{-1}.$$

Then the death rate of adult mosquitoes in Port Harcourt can be approximated by

$$\begin{aligned}\mu_v(t) =& 0.0168\cos(\pi t/6) + 0.1406\sin(\pi t/6) - 0.0503\cos(2\pi t/6)\\ &- 0.0343\sin(2\pi t/6) - 0.0064\cos(3\pi t/6) - 0.0307\sin(3\pi t/6)\\ &- 0.0003\cos(4\pi t/6) - 0.0235\sin(4\pi t/6) + 0.0007\cos(5\pi t/6)\\ &- 0.0070\sin(5\pi t/6) + 3.3136 \text{ Month}^{-1}.\end{aligned}$$

The long term behaviors of solutions of system (4.1) are shown in Figures 4.1, 4.2 and 4.3. Based on Theorem 1.4.2 (ii), we can numerically calculate the vector reproduction ratio R_v and the basic reproduction ratio R_0. Larval source deduction will reduce the rate at which gravid female mosquitoes encounter oviposition sites [104], leading to a decrease in the recruitment rate of larval mosquitoes. In Figure 4.1, we suppose the birth rate of juvenile mosquitoes to be $0.8\lambda_L(t)$, which can be achieved by spraying or eliminating mosquito breeding sites. We also assume that 50% of the humans use ITNs effectively. In this case, $R_v = 0.9041 < 1$ and all compartments converge to 0 eventually meaning that mosquitoes are eliminated from this region. In Figure 4.2, we keep the birth rate of juvenile mosquitoes as $\lambda_L(t)$ and suppose that

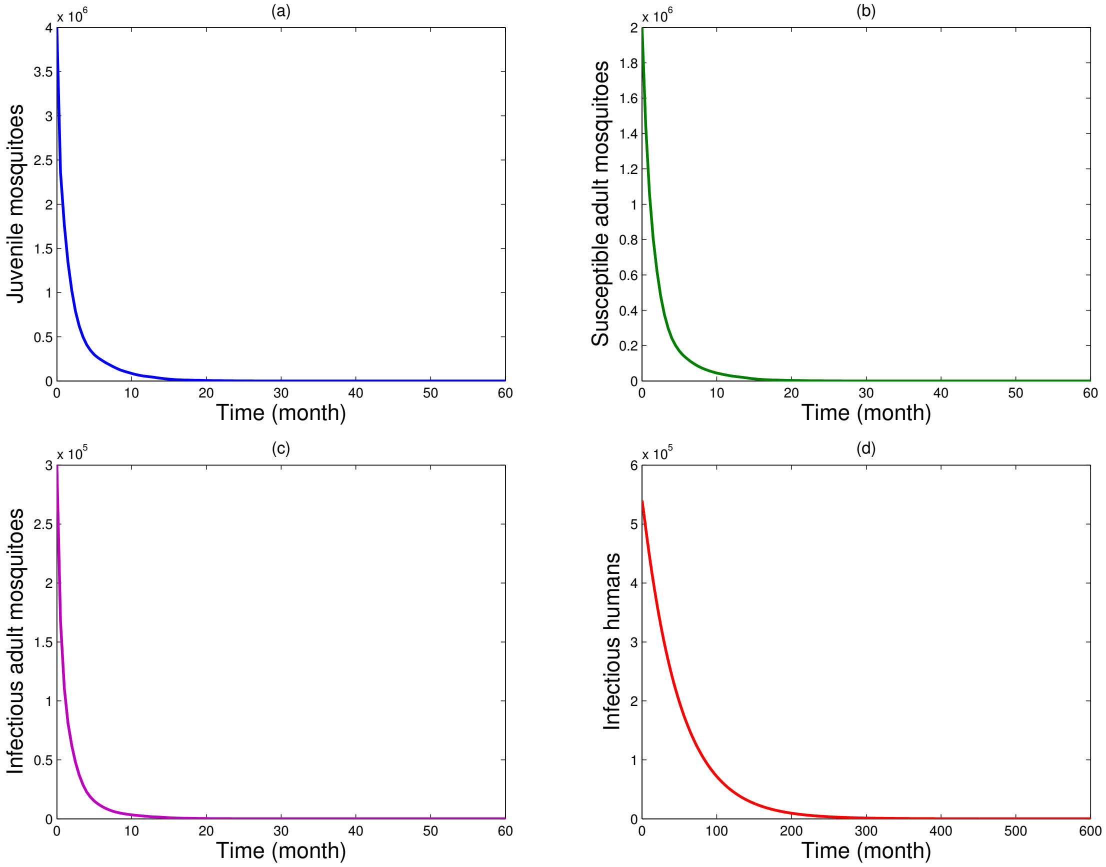

Figure 4.1: Long term behaviour of the solutions of system (4.1). Here the birthrate of juvenile mosquitoes is set to be $0.8\lambda_L(t)$, $k = 0.5$. In this case, $R_v = 0.9041 < 1$.

80% of the humans use ITNs. We calculate $R_v = 1.3549 > 1$ and $R_0 = 0.8620 < 1$. In this case, the juvenile mosquito and susceptible adult mosquito populations exhibit periodic fluctuations. And both the infectious mosquito and infectious human populations converge to 0, which means that malaria is eliminated from this area. In Figure 4.3, we suppose that 50% of the humans use ITNs and keep other parameter values the same as those in Figure 4.2. In this case, we obtain $R_v = 1.3561 > 1$ and $R_0 = 1.6979 > 1$. All compartments fluctuate periodically, which means that the disease will persist. The simulation results shown in Figures 4.1, 4.2 and 4.3 are consistent with the conclusion of Theorem 2. Figure 4.4 shows the relationship between R_0 and k. Clearly, R_0 is a decreasing function of k. We also see that if over

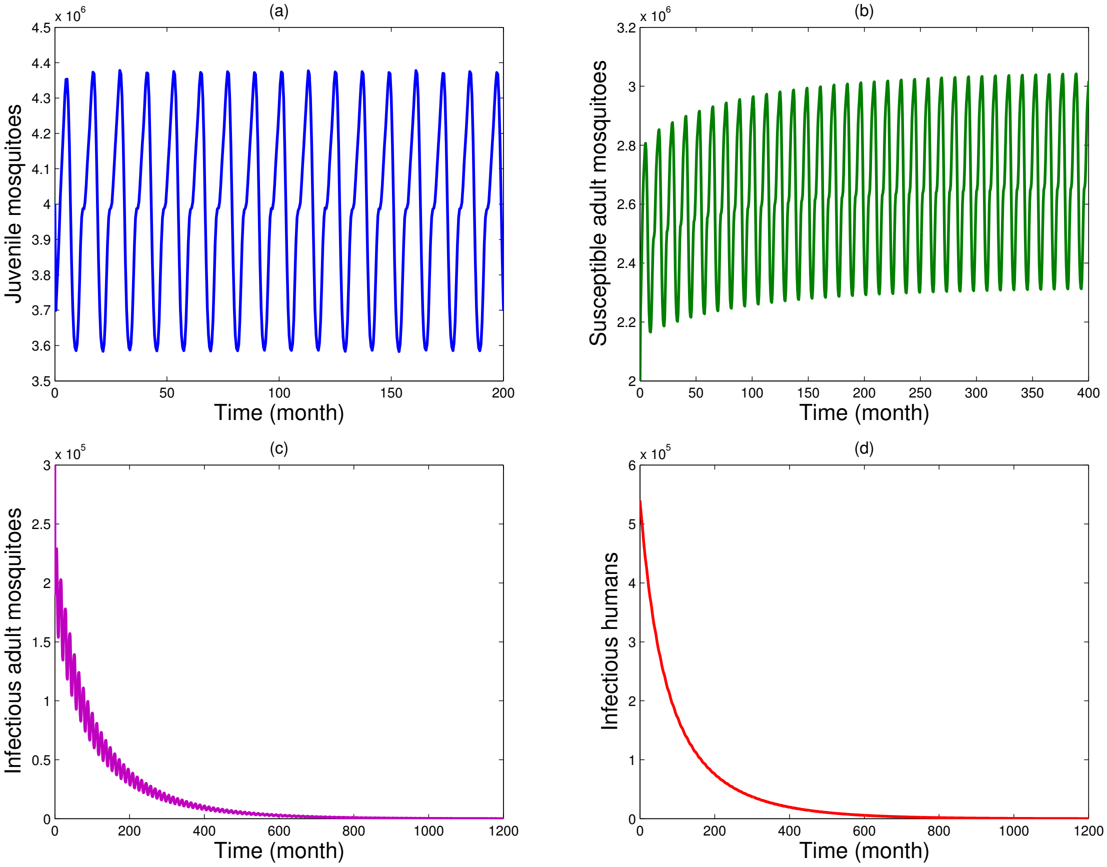

Figure 4.2: Long term behaviour of the solutions of system (4.1). Here $k = 0.8$ and $R_v = 1.3549 > 1$, $R_0 = 0.8620 < 1$.

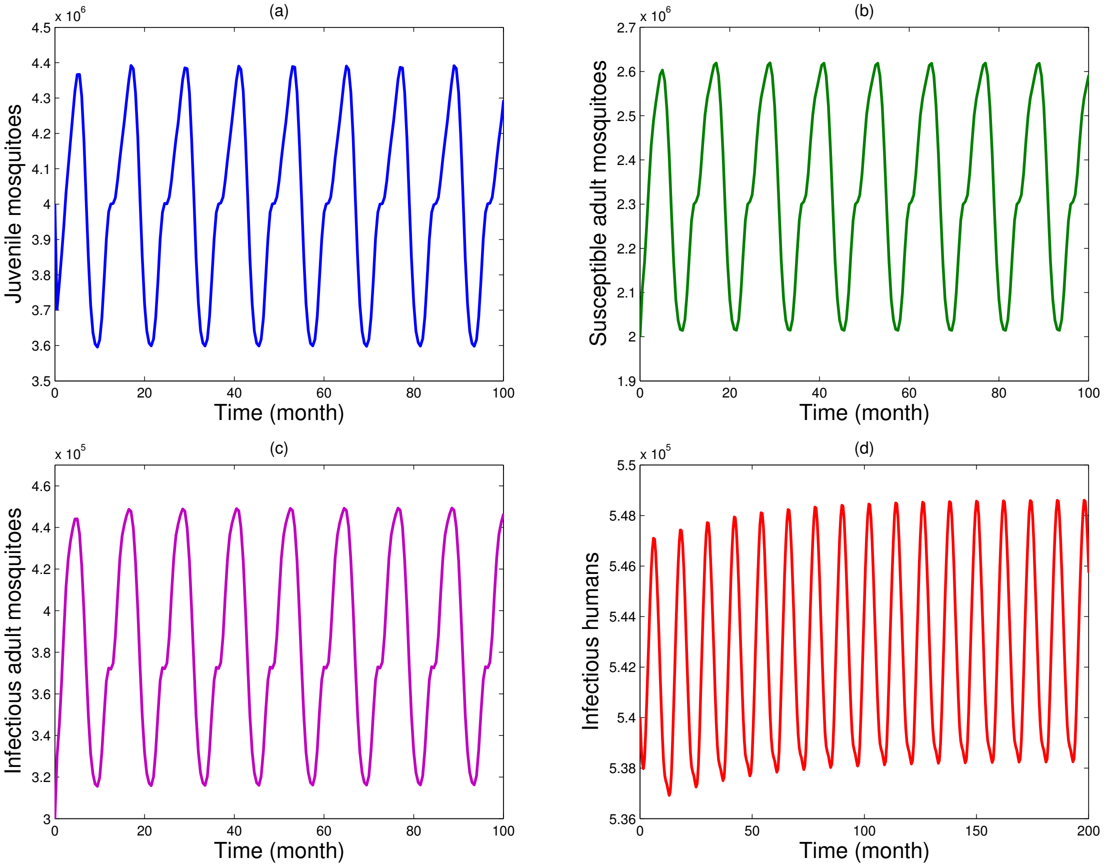

Figure 4.3: Long term behaviour of the solutions of system (4.1). Here $k = 0.5$ and $R_v = 1.3561 > 1$, $R_0 = 1.6979 > 1$.

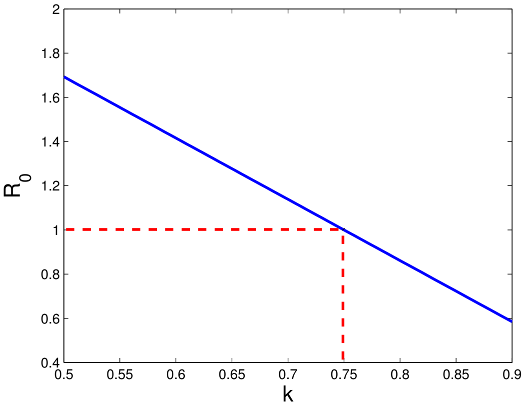

Figure 4.4: The basic reproduction ratio R_0 versus the proportion of bed net use k.

75% of the humans use ITNs in Port Harcourt, then R_0 can be reduced to less than 1, and hence, malaria can be eliminated from this area.

To study the impact of the vector-bias effect, we simulate the relationships between R_0 and k under three different vector-bias levels. As shown in Figure 4.5, for each vector-bias level, R_0 is a decreasing function of k. It is worthwhile to note that the ignorance of the vector-bias effect (i.e., $p = l$) underestimates R_0.

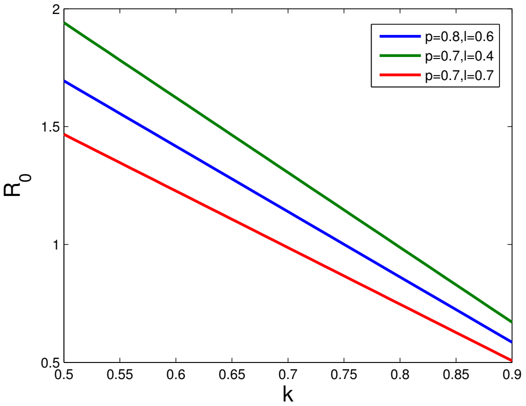

Figure 4.5: R_0 versus k under different vector-bias levels.

Following [94], given a continuous periodic function $g(t)$ with the period ω, we define its average as

$$[g] := \frac{1}{\omega} \int_0^{\omega} g(t)dt.$$

Then the time-averaged parameter values of system (4.1) are $[\beta_v] = 9.6794$, $[\beta_r] = 0.1[\beta_v]$, $[\mu_v] = 3.3136$, $[\mu_L] = 9.0288$, $[\lambda_L] = 2.325[\beta_v]$, $[\lambda_v] = [\lambda_L]/10$. Using these parameter values and formula (4.11), we can calculate the basic reproduction ratio $[R_0]$ of the time-averaged autonomous system (4.10). As can be seen from Figure 4.6, compared with R_0, the basic reproduction ratio $[R_0]$ of the time-averaged autonomous system underestimates the infection risk a little bit. Although the difference between the values of R_0 and $[R_0]$ in Figure 4.6 seems little, sometimes it may lead to great difference in designing disease control strategies, especially when applied to a large community of people.

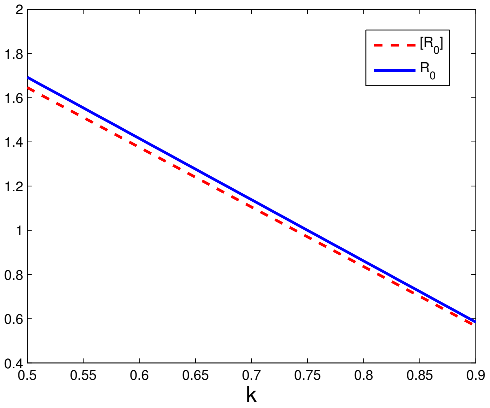

Figure 4.6: R_0 versus k and $[R_0]$ versus k.

4.5 Discussion

An important issue in developing mathematical models is to identify which biological factors are necessary to include and which can be omitted. Usually this is determined by the purpose of a study. Considering that climate factors have a great impact on the mosquito life cycle and the parasite survival in mosquitoes, we incorporated seasonality by developing an ordinary differential equations model with some parameters being periodic functions. In our model, we considered the juvenile stage of mosquitoes in addition to the adult one. This enables us to better understand the mosquito population dynamics, and hence, the malaria transmission dynamics. The incorporation of such juvenile stage may also provide some insights into designing larval control strategies. Insecticide-treated bed net use is one of the effective measures in malaria control. To investigate the effect of ITNs, we modeled the biting rate and the death rate of mosquitoes as functions of the proportion of bed net use. To better understand malaria transmission dynamics and to provide more accurate information for the design of control measures, we also incorporated the effects of different feeding biases by mosquitoes towards humans.

By using the theory of monotone and subhomogeneous systems and the theory of chain transitive sets, we have obtained a complete classification of global dynamics of the model in terms of the vector reproduction ratio R_v and the basic reproduction ratio R_0: (i) If $R_v < 1$, then mosquitoes will die out eventually; (ii) If $R_v > 1$ and $R_0 < 1$, then malaria will be eliminated; (iii) If $R_v > 1$ and $R_0 > 1$, then the disease will persist and exhibit seasonal fluctuation.

By using some published data about Port Harcourt, Nigeria and formula related to mosquito life cycle, we estimated all the constant and periodic parameters. The analytic results are well verified by numerical simulations. Our findings show that if 75% of the human population in Port Harcourt were to use ITNs, then malaria could be eliminated from this area. We have also found that the basic reproduction ratio may be underestimated if we ignore the vector-bias effect. Compared with R_0, the basic reproduction ratio $[R_0]$ of the time-averaged autonomous system underestimates the risk of infection, which confirms the necessity of incorporating seasonality.

In our model, we neglected both the extrinsic incubation period in mosquitoes and the intrinsic incubation period in human hosts. Upon infection, human individuals will move to the exposed compartment, where parasites in their bodies are still in the asexual stages. Since individuals in the exposed class do not have gametocytes in their blood, they are not able to transmit the disease to susceptible mosquitoes until they enter into the infectious class. Susceptible mosquitoes that feed on infectious humans will take gametocytes in blood meals and enter into the exposed class. After fertilisation, sporozoites are produced and migrate to the salivary glands ready to infect any susceptible host, the mosquito is then considered as infectious [57]. It would be interesting to modify our model by incorporating such exposed classes of human hosts and mosquitoes. We leave this as a future work.

Chapter 5

Dynamics of a time-delayed Lyme disease model with seasonality

5.1 Introduction

Lyme disease is one of the most common vector-borne diseases in North America, Europe, and parts of Asia, with thousands of cases reported annually [9, 40]. The disease is caused by the spirochete bacterium *Borrelia burgdorferi* and is transmitted by ticks. *Ixodes scapularis* ticks (also known as black-legged ticks) are the principal vectors of Lyme disease in North America and exhibit a two-year life cycle with four life stages: eggs, larvae, nymphs and adults. Larvae and nymphs mainly attack white-footed mice [86]. Larvae that obtain a blood meal drop off their hosts and then molt into nymphs. At the beginning of the second year, nymphs quest for a second host. After a blood meal, they drop off their hosts and may mature to the adult stage. Adults feed almost exclusively on white-tailed deer, and all mating occurs there. Females eventually drop off the deer they have parasitized, lay their eggs nearby, and die. A female that has engorged and subsequently mated produces around 2000 fertile eggs, and nearly all hatch [81].

There have been a range of modeling works in the study of different aspects of Lyme disease transmission. Some researchers proposed reaction-diffusion models to explore the effect of vectors' stage structure and spatial heterogeneity on the transmission dynamics (see [16, 93, 105, 108, 112]). The models developed in [15, 27, 31, 45, 63, 77] revealed the dilution effects of host population. As mentioned in [3], seasonal variations in temperature, humidity and resource availability have strong effect on tick population dynamics. Climate impacts tick survival mostly during non-parasitic periods of the life cycle: outside certain ranges of temperature and rainfall tick populations cannot survive, because these conditions directly kill the ticks [66] or inhibit host-seeking activity [71]. Within these limits, temperature may also determine development rates [66]. Ogden et. al. [65, 64] proposed simulation models to investigate climate change effects on tick dynamics. Zhang and Zhao [108] developed a reaction-diffusion Lyme disease model with seasonality and studied its global dynamics. Wu et al. [100] established a temperature-driven map of the basic reproduction number of *I. Scapularis* ticks for Canada east of the Rocky Mountains.

The purpose of this chapter is to propose and analyze a time-delayed Lyme disease model with seasonality. Our model is motivated by the Lyme disease models in [93, 108]. We consider three different life stages of tick population: larvae, nymphs, adults, and two host populations: mice and deer. Let $M(t)$ and $m(t)$ be the densities of susceptible and infected mice at time t, respectively. Let $L(t)$, $N(t)$, $n(t)$, $A(t)$, $a(t)$ be the densities of tick larvae, susceptible tick nymphs, infectious tick nymphs, uninfected adult ticks, infected adult ticks at time t, respectively. Let $H(t)$ be the density of deer at time t. Let r_h be the birth rate of deer. Let μ_M, μ_L, μ_N, μ_A, μ_h be the mortality rates per mouse, per tick larva, per tick nymph, per adult tick, and per deer, respectively. Let τ_l be the feeding duration of tick larvae on mice, τ_n be the feeding duration of tick nymphs on mice, and τ_a be the feeding duration of adult ticks on deer. Let β be a mouse's susceptibility to infection when bitten by an infectious tick nymph. Let β_T be a tick's susceptibility to infection when feeding on an infected mouse. Let $\alpha_1(t)$ and $\alpha_2(t)$ be the individual biting rates of tick larvae and nymphs on mice, respectively. Then the drop-off rate of susceptible tick larvae from a mouse, i.e., the recruitment rate of susceptible questing tick nymphs, can be described as

$$e^{-(\mu_L+\mu_M)\tau_l}\alpha_1(t-\tau_l)[M(t-\tau_l)+(1-\beta_T)m(t-\tau_l)]L(t-\tau_l).$$

The drop-off rate of infectious tick larvae from a mouse, i.e., the recruitment rate of infectious questing tick nymphs, is

$$e^{-(\mu_L+\mu_M)\tau_l}\alpha_1(t-\tau_l)\beta_T m(t-\tau_l)L(t-\tau_l).$$

The drop-off rate of susceptible tick nymphs from a mouse, i.e., the recruitment rate of susceptible questing adult ticks, is

$$e^{-(\mu_N+\mu_M)\tau_n}\alpha_2(t-\tau_n)[M(t-\tau_n)+(1-\beta_T)m(t-\tau_n)]N(t-\tau_n).$$

The drop-off rate of infectious tick nymphs from a mouse, i.e., the recruitment rate of infected questing adult ticks, is

$$e^{-(\mu_N+\mu_M)\tau_n}\alpha_2(t-\tau_n)[(M(t-\tau_n)+m(t-\tau_n))n(t-\tau_n)+\beta_T m(t-\tau_n)N(t-\tau_n)].$$

Since it is more reasonable to consider the birth rates of mice and ticks as density dependent, following [77], we suppose that the per capita birth rate of mice is given by

$$B_M(M+m) = r_M \exp(-\frac{M+m}{K_M}),$$

where r_M is the maximal individual birth rate of mice, K_M is the carrying capacity for mice. Let $r(t)$ be the maximal birth rate of ticks and $c(t)$ be the strength of density dependence for adult ticks. We suppose that the per capita birth rate of ticks is given by

$$B_T(t, T_b) = r(t) \exp(-c(t)T_b),$$

where T_b is the density of egg-laying adults, which are exactly those that fall off from deer after blood meals, and it is given by

$$T_b = e^{-(\mu_A+\mu_h)\tau_a} \xi [A(t-\tau_a) + a(t-\tau_a)] H(t-\tau_a),$$

where ξ is the individual biting rate of adult ticks on deer. In the case where there is no competition among ticks, we have $c(t) \equiv 0$, and hence, $B_T(t, T_b) = r(t)$.

Consequently, we have the following model:

$$\begin{aligned}
\frac{dM}{dt} &= (M+m)B_M(M+m) - \mu_M M - \alpha_2(t)\beta M n, \\
\frac{dm}{dt} &= \alpha_2(t)\beta M n - \mu_M m, \\
\frac{dL}{dt} &= T_b B_T(t, T_b) - \mu_L L - \alpha_1(t) L (M+m), \\
\frac{dN}{dt} &= e^{-(\mu_L+\mu_M)\tau_l} K_N(t-\tau_l) - [\gamma + \alpha_2(t)(M+m) + \mu_N] N, \\
\frac{dn}{dt} &= e^{-(\mu_L+\mu_M)\tau_l} K_n(t-\tau_l) - [\gamma + \alpha_2(t)(M+m) + \mu_N] n, \\
\frac{dA}{dt} &= e^{-(\mu_N+\mu_M)\tau_n} K_A(t-\tau_n) - (\mu_A + \xi H) A, \\
\frac{da}{dt} &= e^{-(\mu_N+\mu_M)\tau_n} K_a(t-\tau_n) - (\mu_A + \xi H) a, \\
\frac{dH}{dt} &= r_h - \mu_h H,
\end{aligned} \tag{5.1}$$

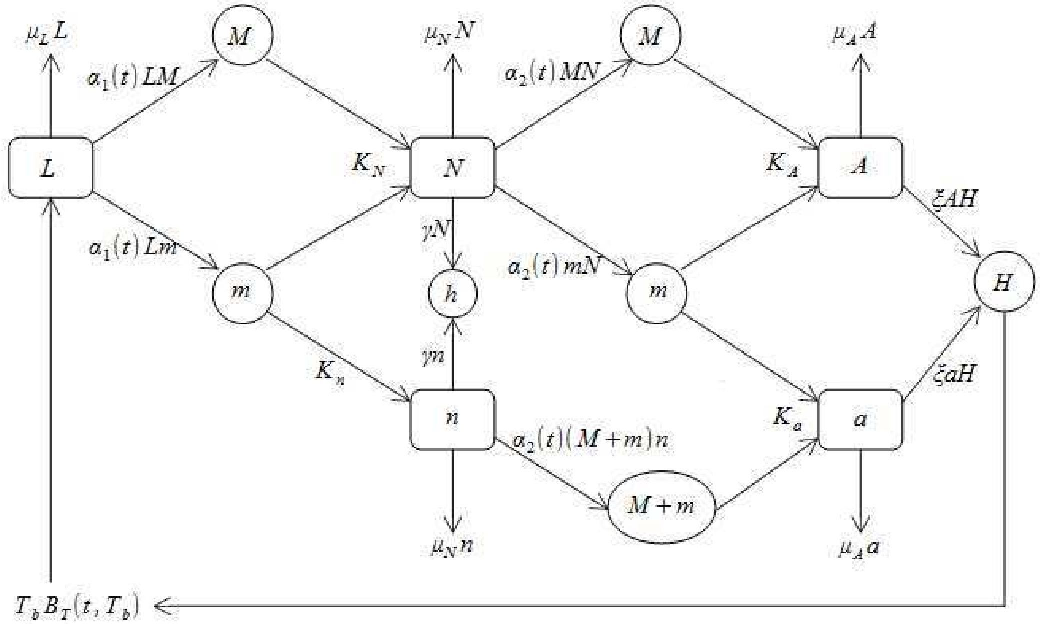

Figure 5.1: The schematic diagram for ticks. Here $K_N = e^{-(\mu_L+\mu_M)\tau_l} K_N(t-\tau_l), K_n = e^{-(\mu_L+\mu_M)\tau_l} K_n(t-\tau_l), K_A = e^{-(\mu_N+\mu_M)\tau_n} K_A(t-\tau_n), K_a = e^{-(\mu_N+\mu_M)\tau_n} K_a(t-\tau_n)$. Notation is defined in Table 5.1.

where

$$\begin{aligned}
K_N(t) &= \alpha_1(t)[M(t) + (1-\beta_T)m(t)]L(t), \\
K_n(t) &= \alpha_1(t)\beta_T m(t)L(t), \\
K_A(t) &= \alpha_2(t)[M(t) + (1-\beta_T)m(t)]N(t), \\
K_a(t) &= \alpha_2(t)[(M(t)+m(t))n(t) + \beta_T m(t)N(t)].
\end{aligned}$$

We incorporate the seasonality into our model by assuming that the birth rate and the biting rate of ticks are time-dependent. More precisely, we suppose that $\alpha_1(t)$, $\alpha_2(t)$, $r(t)$ and $c(t)$ are positive, continuous and ω-periodic functions for some $\omega > 0$, and that all the other parameters are positive constants. Here we do not take into account the case where $c(t) \equiv 0$ because we may use a positive but sufficiently small periodic function to approximate it from the viewpoint of mathematical modeling. Hence, model (5.1) is an ω-periodic and time-delayed system. The biological interpretations for all variables and parameters are also listed in Table 5.1.

Table 5.1: Biological interpretations for variables and parameters in model (5.1)

Parameter	Description
M	the density of susceptible mice
m	the density of infected mice
L	the density of questing tick larvae
N	the density of susceptible questing tick nymphs
n	the density of infectious questing tick nymphs
A	the density of uninfected questing adult ticks
a	the density of infected questing adult ticks
H	the density of deer
τ_l	the feeding duration of tick larvae on mice
τ_n	the feeding duration of tick nymphs on mice
τ_a	the feeding duration of adult ticks on deer
$B_M(M+m)$	the per capita birth rate of mice
r_M	the maximal individual birth rate of mice
K_M	the carrying capacity for mice
$B_T(t,T_b)$	the per capita birth rate of ticks
$r(t)$	the maximal birth rate of ticks
$c(t)$	the strength of density dependence for adult ticks
T_b	the density of egg-laying adult ticks
β	a mouse's susceptibility to infection when bitten by an infectious tick nymph
β_T	a tick's susceptibility to infection when feeding on an infected mouse
$\alpha_1(t)$	individual biting rate of tick larvae on mice
$\alpha_2(t)$	individual biting rate of tick nymphs on mice
γ	biting rate per tick nymph to humans
ξ	individual biting rate of adult ticks on deer
μ_M	mortality rate per mouse
μ_L	mortality rate per questing tick larva
μ_N	mortality rate per questing tick nymph
μ_A	mortality rate per questing adult tick
μ_h	mortality rate per deer
r_h	birth rate of deer

The rest of this chapter is organized as follows. In the next section, we first discuss the disease-free dynamics and then introduce the basic reproduction ratio R_0. In section 5.3, we establish the global dynamics for the model system in terms of R_0. In section 5.4, we do a case study for the Lyme disease transmission in Long Point, Ontario. A brief discussion completes the chapter.

5.2 Basic reproduction ratio

In this section, we study the disease-free periodic solution and derive the basic reproduction ratio for the model. We start with a preliminary result on a system of linear delay differential equations.

Let $r = (r_1, r_2, ..., r_n) \in \mathbb{R}^n_+$. Define

$$C_r = \prod_{i=1}^{n} C([-r_i, 0], \mathbb{R}), \quad C_r^+ = \prod_{i=1}^{n} C([-r_i, 0], \mathbb{R}_+).$$

Then (C_r, C_r^+) is an ordered Banach space. For $\varphi, \psi \in C_r$, we write $\varphi \leq \psi$ if $\psi - \varphi \in C_r^+$; $\varphi < \psi$ if $\psi - \varphi \in C_r^+ \setminus \{0\}$; $\varphi \ll \psi$ if $\psi - \varphi \in \operatorname{int}(C_r^+)$.

Consider the linear periodic system

$$\frac{du(t)}{dt} = L(t)u_t, \tag{5.2}$$

where $u(t) = (u_1(t), u_2(t), ..., u_n(t))$, $u_t = (u_t^1, u_t^2, ..., u_t^n)$ and $u_t^i(s) = u_i(t+s)$ for $s \in [-r_i, 0], 1 \leq i \leq n$. Assume that $L : \mathbb{R} \to \mathcal{L}(C_r, \mathbb{R}^n)$ is continuous, $L(t+T) = L(t)$, $\forall t \in \mathbb{R}$, for some constant $T > 0$, and $L_i(t)\phi \geq 0$ whenever $\phi \geq 0$ and $\phi_i(0) = 0$.

Let $u_t(\varphi)$ be the solution semiflow associated with system (5.2), that is,

$$[u_t(\varphi)]_i(s) = u_i(t+s, \varphi), \quad \forall s \in [-r_i, 0], \quad 1 \leq i \leq n,$$

where $u(t, \varphi) = (u_1(t, \varphi), u_2(t, \varphi), ..., u_n(t, \varphi))$ is the unique solution of (5.2) with $u_0 = \varphi \in C_r$. It follows from [84, Theorem 5.2.1] that $u_t(\varphi) \in C_r^+$ for all $\varphi \in C_r^+, t \geq 0$. Define the Poincaré map $\bar{P} : C_r \to C_r$ by $\bar{P}(\varphi) = u_T(\varphi)$. Then $\bar{P}^n(\varphi) = u_{nT}(\varphi)$ for any integer $n \geq 0$. Motivated by [102, Proposition 2.1], we have the following result.

Lemma 5.2.1. *Assume that μ is a positive eigenvalue of $\bar{P}$ having a strongly positive* *eigenvector* φ^*, *that is,* $\bar{P}\varphi^* = \mu\varphi^*, \mu > 0, \varphi^* \gg 0$. *Then there exists a positive* T-*periodic function* $\bar{v}(t) = (\bar{v}_1(t), \bar{v}_2(t), ..., \bar{v}_n(t))$ *such that* $\bar{u}(t) = e^{\lambda_0 t}\bar{v}(t)$ *is a positive solution of system* (5.2), *where* $\lambda_0 = \frac{\ln\mu}{T}$.

Proof. Let $u(t) = e^{\lambda t}v(t)$. Let E_λ be a map from C_r to C_r defined by

$$[E_\lambda(\varphi)]_i(s) = e^{\lambda s}\varphi_i(s), \quad \forall s \in [-r_i, 0], \quad 1 \le i \le n.$$

Then $(u_t)_i(s) = u_i(t+s) = e^{\lambda(t+s)}v_i(t+s) = e^{\lambda t}e^{\lambda s}(v_t)_i(s) = e^{\lambda t}[E_\lambda(v_t)]_i(s), \forall s \in [-r_i, 0], 1 \le i \le n$. Hence, $u_t = e^{\lambda t}E_\lambda(v_t)$. It follows that

$$\frac{du(t)}{dt} = e^{\lambda t}\frac{dv(t)}{dt} + \lambda e^{\lambda t}v(t) = L(t)e^{\lambda t}E_\lambda(v_t).$$

We then obtain a system of linear periodic equations with parameter λ:

$$\frac{dv(t)}{dt} = -\lambda v(t) + L(t)E_\lambda(v_t). \tag{5.3}$$

Define $\bar{Q}_\lambda : C_r \to C_r$ by $\bar{Q}_\lambda(\varphi) = v_T(\varphi, \lambda)$, where $v(t, \varphi, \lambda)$ is the unique solution of system (5.3) through φ. Then

$$[\bar{Q}_\lambda(\varphi)]_i(s) = [v_T(\varphi, \lambda)]_i(s) = v_i(T+s, \varphi, \lambda) = e^{-\lambda(T+s)}u_i(T+s, E_\lambda(\varphi))$$

for all $s \in [-r_i, 0], 1 \le i \le n$, and hence,

$$[\bar{Q}_\lambda(\varphi)]_i = e^{-\lambda T}[E_{-\lambda}(u_T(E_\lambda(\varphi)))]_i = e^{-\lambda T}[E_{-\lambda}(\bar{P}(E_\lambda(\varphi)))]_i, \quad 1 \le i \le n.$$

Thus,

$$[\bar{Q}_\lambda(E_{-\lambda}(\varphi^*))]_i = e^{-\lambda T}[E_{-\lambda}(\bar{P}(\varphi^*))]_i = \mu e^{-\lambda T}[E_{-\lambda}(\varphi^*)]_i, \quad 1 \le i \le n.$$

Letting $\lambda = \lambda_0 = \frac{\ln \mu}{T}$, we get

$$[\bar{Q}_{\lambda_0}(E_{-\lambda_0}(\varphi^*))]_i = [E_{-\lambda_0}(\varphi^*)]_i, \quad 1 \leq i \leq n,$$

that is, $\bar{Q}_{\lambda_0}(E_{-\lambda_0}(\varphi^*)) = E_{-\lambda_0}(\varphi^*)$. Thus, $E_{-\lambda_0}(\varphi^*)$ is a positive fixed point of $\bar{Q}_{\lambda_0}$. It follows that $\bar{v}(t) := v(t, E_{-\lambda_0}(\varphi^*), \lambda_0)$ is a positive T-periodic solution of (5.3) with $\lambda = \lambda_0$, and hence, $\bar{u}(t) = e^{\lambda_0 t}\bar{v}(t)$ is a positive solution of system (5.2). $\square$

Recently, the theory of basic reproduction ratio has been developed by Zhao [110] for periodic and time-delayed population models with compartmental structure. In what follows, we use this theory to obtain the basic reproduction ratio for our model. We first consider the disease-free periodic solution of (5.1). Letting $m = 0, n = 0, a = 0$ in (5.1), we then get the following system of delay differential equations:

$$\begin{aligned}
\frac{dM}{dt} =& MB_M(M) - \mu_M M,\\
\frac{dL}{dt} =& e^{-(\mu_A+\mu_h)\tau_a}\xi A(t-\tau_a)H(t-\tau_a)r(t)\exp(-c(t)e^{-(\mu_A+\mu_h)\tau_a}\xi A(t-\tau_a)H(t-\tau_a))\\
& - \mu_L L - \alpha_1(t)LM,\\
\frac{dN}{dt} =& e^{-(\mu_L+\mu_M)\tau_l}\alpha_1(t-\tau_l)M(t-\tau_l)L(t-\tau_l) - (\gamma + \alpha_2(t)M + \mu_N)N,\\
\frac{dA}{dt} =& e^{-(\mu_N+\mu_M)\tau_n}\alpha_2(t-\tau_n)M(t-\tau_n)N(t-\tau_n) - (\mu_A + \xi H)A,\\
\frac{dH}{dt} =& r_h - \mu_h H.
\end{aligned} \tag{5.4}$$

In order to avoid the extinction of the mice population, we further assume that

(A1) $r_M > \mu_M$.

It then easily follows that the ordinary differential system $\frac{dM}{dt} = MB_M(M) - \mu_M M$ admits a globally stable positive steady state $M^* := K_M \ln \frac{r_M}{\mu_M}$. Since $\lim_{t\to\infty} H(t) = \frac{r_h}{\mu_h} := H^*$ and $\lim_{t\to\infty} M(t) = M^*$ if $M(0) > 0$, we focus on the following limiting system:

$$\begin{aligned}\frac{dL}{dt} =&H^*e^{-(\mu_A+\mu_h)\tau_a}\xi A(t-\tau_a)r(t)\exp(-c(t)H^*e^{-(\mu_A+\mu_h)\tau_a}\xi A(t-\tau_a))\\ &-(\mu_L+\alpha_1(t)M^*)L,\\ \frac{dN}{dt} =&e^{-(\mu_L+\mu_M)\tau_l}\alpha_1(t-\tau_l)M^*L(t-\tau_l)-(\gamma+\alpha_2(t)M^*+\mu_N)N,\\ \frac{dA}{dt} =&e^{-(\mu_N+\mu_M)\tau_n}\alpha_2(t-\tau_n)M^*N(t-\tau_n)-(\mu_A+\xi H^*)A.\end{aligned} \tag{5.5}$$

Let $Z_1 = C([-\tau_l, 0],\ \mathbb{R})$, $Z_2 = C([-\tau_n, 0],\ \mathbb{R})$, $Z_3 = C([-\tau_a, 0],\ \mathbb{R})$, $Z_1^+ = C([-\tau_l, 0],\ \mathbb{R}_+)$, $Z_2^+ = C([-\tau_n, 0],\ \mathbb{R}_+)$, $Z_3^+ = C([-\tau_a, 0],\ \mathbb{R}_+)$, $Z = Z_1 \times Z_2 \times Z_3$, $Z_+ = Z_1^+ \times Z_2^+ \times Z_3^+$. Define $\tilde{f}(t,\varphi) = (\tilde{f}_1, \tilde{f}_2, \tilde{f}_3)$, where

$$\begin{aligned}\tilde{f}_1 &= H^*e^{-(\mu_A+\mu_h)\tau_a}\xi\varphi_3(-\tau_a)r(t)\exp(-c(t)H^*e^{-(\mu_A+\mu_h)\tau_a}\xi\varphi_3(-\tau_a))\\ &\quad -(\mu_L+\alpha_1(t)M^*)\varphi_1(0),\\ \tilde{f}_2 &= e^{-(\mu_L+\mu_M)\tau_l}\alpha_1(t-\tau_l)M^*\varphi_1(-\tau_l)-(\gamma+\alpha_2(t)M^*+\mu_N)\varphi_2(0),\\ \tilde{f}_3 &= e^{-(\mu_N+\mu_M)\tau_n}\alpha_2(t-\tau_n)M^*\varphi_2(-\tau_n)-(\mu_A+\xi H^*)\varphi_3(0).\end{aligned}$$

It is easy to see that for any $\phi \in Z_+$ with $\phi_i(0) = 0$ for some i, we have $\tilde{f}_i(t,\phi) \geq 0$. It then follows from [84, Theorem 5.2.1] that $w_t(\varphi) \in Z_+$ for all $\varphi \in Z_+$ and $t \in [0, \sigma_\varphi)$, where $[0, \sigma_\varphi)$ is the maximal interval of existence for the solution $w(t,\varphi)$ of (5.5) satisfying $w_0 = \varphi$.

Let $P_1(t)$ be the solution maps of system (5.5), that is, $P_1(t)\psi = w_t(\psi), t \geq 0$, where $w(t,\psi)$ is the unique solution of system (5.5) satisfying $w_0 = \psi \in Z_+$. Then $P_1 := P_1(\omega)$ is the Poincaré map associated with system (5.5) on Z_+. Let $\rho(DP_1(0))$

be the spectral radius of the Frechét derivative of P_1 at 0. Since

$$\begin{aligned}\frac{dL}{dt} &= H^* e^{-(\mu_A+\mu_h)\tau_a}\xi A(t-\tau_a) r(t)\exp(-c(t)H^* e^{-(\mu_A+\mu_h)\tau_a}\xi A(t-\tau_a)) \\ &\quad -(\mu_L+\alpha_1(t)M^*)L, \\ &\le \frac{r(t)}{c(t)}e^{-1} - (\mu_L+\alpha_1(t)M^*)L,\end{aligned}$$

system (5.5) is dominated by the following cooperative system:

$$\begin{aligned}\frac{d\bar{L}}{dt} &= \frac{r(t)}{c(t)}e^{-1} - (\mu_L+\alpha_1(t)M^*)\bar{L}, \\ \frac{d\bar{N}}{dt} &= e^{-(\mu_L+\mu_M)\tau_l}\alpha_1(t-\tau_l)M^*\bar{L}(t-\tau_l) - (\gamma+\alpha_2(t)M^*+\mu_N)\bar{N}, \\ \frac{d\bar{A}}{dt} &= e^{-(\mu_N+\mu_M)\tau_n}\alpha_2(t-\tau_n)M^*\bar{N}(t-\tau_n) - (\mu_A+\xi H^*)\bar{A}.\end{aligned} \tag{5.6}$$

It is easy to see that the linear inhomogeneous equation

$$\frac{d\bar{L}}{dt} = \frac{r(t)}{c(t)}e^{-1} - (\mu_L+\alpha_1(t)M^*)\bar{L}$$

has a globally attractive positive ω-periodic solution $\bar{L}^*(t)$, that is, $\lim_{t\to\infty}(\bar{L}(t) - \bar{L}^*(t)) = 0$. Thus, solutions of (5.6) are bounded and ultimately bounded. By the comparison principle ([84, Theorem 5.1.1]), solutions of system (5.5) exist globally on $[0,\infty)$ and are ultimately bounded. This implies that the discrete-time semiflow $\{P_1^n\}_{n=0}^{\infty}$ is point dissipative on Z_+.

Note that the linearized system of (5.5) at $(0,0,0)$ is

$$\begin{aligned}\frac{dv_1}{dt} &= r(t)H^* e^{-(\mu_A+\mu_h)\tau_a}\xi v_3(t-\tau_a) - (\mu_L+\alpha_1(t)M^*)v_1(t), \\ \frac{dv_2}{dt} &= e^{-(\mu_L+\mu_M)\tau_l}\alpha_1(t-\tau_l)M^*v_1(t-\tau_l) - (\gamma+\alpha_2(t)M^*+\mu_N)v_2(t), \\ \frac{dv_3}{dt} &= e^{-(\mu_N+\mu_M)\tau_n}\alpha_2(t-\tau_n)M^*v_2(t-\tau_n) - (\mu_A+\xi H^*)v_3(t).\end{aligned} \tag{5.7}$$

Let $\tilde{P}$ be the Poincaré map associated with system (5.7) on Z. By the continuity and differentiability of solutions with respect to initial values, it follows that P_1 is differentiable at zero and the Frechét derivative $DP_1(0) = \tilde{P}$. Denote $\tau = \max\{\tau_l, \tau_n, \tau_a\}$. Assume that

(A2) $r(\tilde{P}) > 1$, where $r(\tilde{P})$ is the spectral radius of $\tilde{P}$.

Let $(\bar{L}^*(t), \bar{N}^*(t), \bar{A}^*(t))$ be the unique positive ω-periodic solution of system (5.6). To obtain the global dynamics of system (5.5), we need the following additional assumption:

(A3) $H^* e^{-(\mu_A+\mu_h)\tau_a} \xi \bar{A}^*(t-\tau_a) < \frac{1}{c(t)}$ for all $t \in [0, \omega]$.

Theorem 5.2.2. *Let (A1), (A2) and (A3) hold. Then system* (5.5) *admits a unique positive ω-periodic solution* $(L^*(t),\ N^*(t),\ A^*(t))$ *which is globally attractive in $Z_+ \setminus \{0\}$, and hence, system* (5.1) *admits a unique disease-free periodic solution* $(M^*,\ 0,\ L^*(t),\ N^*(t),\ 0,\ A^*(t),\ 0,\ H^*)$.

Proof. Define

$$Y := [0, \bar{L}_0^*]_{Z_1} \times [0, \bar{N}_0^*]_{Z_2} \times [0, \bar{A}_0^*]_{Z_3},$$

where $\bar{L}_0^* \in Z_1, \bar{N}_0^* \in Z_2, \bar{A}_0^* \in Z_3$, and $\bar{L}_0^*(\theta) = \bar{L}^*(\theta)$ for all $\theta \in [-\tau_l, 0]$, $\bar{N}_0^*(\theta) = \bar{N}^*(\theta)$ for all $\theta \in [-\tau_n, 0]$, $\bar{A}_0^*(\theta) = \bar{A}^*(\theta)$ for all $\theta \in [-\tau_a, 0]$. Recall that P_1 is the Poincaré map associated with system (5.5) on Z_+. For any $\psi \in Z_+$, we have

$$0 \le (L(t,\psi), N(t,\psi), A(t,\psi)) \le (\bar{L}(t,\psi), \bar{N}(t,\psi), \bar{A}(t,\psi)), \quad \forall t \ge 0.$$

Then

$$0 \le (L_t(\psi), N_t(\psi), A_t(\psi)) \le (\bar{L}_t(\psi), \bar{N}_t(\psi), \bar{A}_t(\psi)), \quad \forall t \ge 0.$$

Letting $t = n\omega$, we have

$$0 \leq (L_{n\omega}(\psi), N_{n\omega}(\psi), A_{n\omega}(\psi)) \leq (\bar{L}_{n\omega}(\psi), \bar{N}_{n\omega}(\psi), \bar{A}_{n\omega}(\psi)), \quad \forall n \geq 0,$$

that is,

$$0 \leq P_1^n(\psi) \leq \bar{P}_1^n(\psi), \quad \forall n \geq 0, \tag{5.8}$$

where $\bar{P}_1$ is the Poincaré map associated with (5.6) on Z_+.

Note that $\lim_{t\to\infty}((\bar{L}(t,\psi), \bar{N}(t,\psi), \bar{A}(t,\psi)) - (\bar{L}^*(t), \bar{N}^*(t), \bar{A}^*(t))) = 0$. Then

$$\lim_{t\to\infty} \|(\bar{L}_t(\psi), \bar{N}_t(\psi), \bar{A}_t(\psi)) - (\bar{L}_t^*, \bar{N}_t^*, \bar{A}_t^*)\| = 0.$$

Letting $t = n\omega$, we then have $(\bar{L}_{n\omega}^*, \bar{N}_{n\omega}^*, \bar{A}_{n\omega}^*) = (\bar{L}_0^*, \bar{N}_0^*, \bar{A}_0^*)$, and hence,

$$\lim_{n\to\infty} \|(\bar{L}_{n\omega}(\psi), \bar{N}_{n\omega}(\psi), \bar{A}_{n\omega}(\psi)) - (\bar{L}_0^*, \bar{N}_0^*, \bar{A}_0^*)\| = \lim_{n\to\infty} \|\bar{P}_1^n(\psi) - (\bar{L}_0^*, \bar{N}_0^*, \bar{A}_0^*)\| = 0.$$

This, together with (5.8), implies that $\omega(\psi) \subseteq Y, \forall \psi \in Z_+$.

For any given $\epsilon \in (0,1)$, let $\tilde{P}_\epsilon(t)$ be the solution maps of the following system on Z_+:

$$\begin{aligned}
\frac{dv_1}{dt} &= r(t)(1-\epsilon)H^* e^{-(\mu_A+\mu_h)\tau_a}\xi v_3(t-\tau_a) - (\mu_L + \alpha_1(t)M^*)v_1(t), \\
\frac{dv_2}{dt} &= e^{-(\mu_L+\mu_M)\tau_l}\alpha_1(t-\tau_l)M^* v_1(t-\tau_l) - (\gamma + \alpha_2(t)M^* + \mu_N)v_2(t), \\
\frac{dv_3}{dt} &= e^{-(\mu_N+\mu_M)\tau_n}\alpha_2(t-\tau_n)M^* v_2(t-\tau_n) - (\mu_A + \xi H^*)v_3(t).
\end{aligned} \tag{5.9}$$

Let $\tilde{P}_\epsilon := \tilde{P}_\epsilon(\omega)$. For any given $\varphi, \psi \in Z_+$ with $\varphi \geq \psi$, let $v(t,\varphi)$ and $v(t,\psi)$ be the unique solutions of system (5.9) satisfying $v_0 = \varphi$ and $v_0 = \psi$, respectively. By [84, Theorem 5.1.1], we have $v(t,\varphi) \geq v(t,\psi), \forall t \geq 0$, that is, $\tilde{P}_\epsilon(t) : Z_+ \to Z_+$ is monotone. Next we prove that $\tilde{P}_\epsilon(t) : Z_+ \to Z_+$ is eventually strongly monotone.

Let $\varphi, \psi \in Z$ satisfy $\varphi > \psi$. Denote $v(t, \varphi) = (\bar{y}_1(t), \bar{y}_2(t), \bar{y}_3(t))$ and $v(t, \psi) = (y_1(t), y_2(t), y_3(t))$. Without loss of generality, we assume that $\varphi_1 > \psi_1$.

Claim 1. There exists $t_0 \in [0, \tau_l]$ such that $\bar{y}_2(t) > y_2(t), \forall t \geq t_0$.

We first prove that $\bar{y}_2(t_0) > y_2(t_0)$ for some $t_0 \in [0, \tau_l]$. Otherwise, we have $\bar{y}_2(t) = y_2(t), \forall t \in [0, \tau_l]$, and hence, $\frac{d\bar{y}_2(t)}{dt} = \frac{dy_2(t)}{dt}, \forall t \in (0, \tau_l)$. Thus, we have

$$e^{-(\mu_L+\mu_M)\tau_l}\alpha_1(t-\tau_l)M^*(\bar{y}_1(t-\tau_l) - y_1(t-\tau_l)) = 0, \quad \forall t \in [0, \tau_l].$$

It follows that $\bar{y}_1(t-\tau_l) = y_1(t-\tau_l), \forall t \in [0, \tau_l]$, that is, $\varphi_1(\theta) = \psi_1(\theta), \forall \theta \in [-\tau_l, 0]$, which contradicts the assumption that $\varphi_1 > \psi_1$.

Let

$$g_1(t, y) := e^{-(\mu_L+\mu_M)\tau_l}\alpha_1(t-\tau_l)M^*y_1(t-\tau_l) - (\gamma + \alpha_2(t)M^* + \mu_N)y.$$

Since

$$\begin{aligned}
\frac{d\bar{y}_2(t)}{dt} &= e^{-(\mu_L+\mu_M)\tau_l}\alpha_1(t-\tau_l)M^*\bar{y}_1(t-\tau_l) - (\gamma + \alpha_2(t)M^* + \mu_N)\bar{y}_2(t) \\
&\geq e^{-(\mu_L+\mu_M)\tau_l}\alpha_1(t-\tau_l)M^*y_1(t-\tau_l) - (\gamma + \alpha_2(t)M^* + \mu_N)\bar{y}_2(t) \\
&= g_1(t, \bar{y}_2(t)),
\end{aligned}$$

we have

$$\frac{d\bar{y}_2(t)}{dt} - g_1(t, \bar{y}_2(t)) \geq 0 = \frac{dy_2(t)}{dt} - g_1(t, y_2(t)), \quad \forall t \geq t_0.$$

Since $\bar{y}_2(t_0) > y_2(t_0)$, the comparison theorem for ordinary differential equations (see Theorem 1.3.1) implies that $\bar{y}_2(t) > y_2(t), \forall t \geq t_0$.

Claim 2. $\bar{y}_3(t) > y_3(t), \forall t > t_0 + \tau_n$.

Let

$$g_2(t, y) := e^{-(\mu_N+\mu_M)\tau_n}\alpha_2(t-\tau_n)M^*y_2(t-\tau_n) - (\mu_A + \xi H^*)y.$$

Then we have

$$\begin{aligned}\frac{d\bar{y}_3(t)}{dt} &= e^{-(\mu_N+\mu_M)\tau_n}\alpha_2(t-\tau_n)M^*\bar{y}_2(t-\tau_n) - (\mu_A+\xi H^*)\bar{y}_3(t)\\ &> e^{-(\mu_N+\mu_M)\tau_n}\alpha_2(t-\tau_n)M^*y_2(t-\tau_n) - (\mu_A+\xi H^*)\bar{y}_3(t)\\ &= g_2(t,\bar{y}_3(t)), \quad \forall t > t_0+\tau_n,\end{aligned}$$

and hence,

$$\frac{d\bar{y}_3(t)}{dt} - g_2(t,\bar{y}_3(t)) > 0 = \frac{dy_3(t)}{dt} - g_2(t,y_3(t)), \quad \forall t > t_0+\tau_n.$$

Since $\bar{y}_3(t_0+\tau_n) \geq y_3(t_0+\tau_n)$, it follows from Theorem 1.3.1 that $\bar{y}_3(t) > y_3(t), \forall t > t_0+\tau_n$.

Claim 3. $\bar{y}_1(t) > y_1(t), \forall t > t_0+\tau_n+\tau_a$.

Let

$$g_3(t,y) := r(t)(1-\epsilon)H^*e^{-(\mu_A+\mu_h)\tau_a}\xi y_3(t-\tau_a) - (\mu_L+\alpha_1(t)M^*)y.$$

Then we have

$$\begin{aligned}\frac{d\bar{y}_1(t)}{dt} &= r(t)(1-\epsilon)H^*e^{-(\mu_A+\mu_h)\tau_a}\xi\bar{y}_3(t-\tau_a) - (\mu_L+\alpha_1(t)M^*)\bar{y}_1(t)\\ &> r(t)(1-\epsilon)H^*e^{-(\mu_A+\mu_h)\tau_a}\xi y_3(t-\tau_a) - (\mu_L+\alpha_1(t)M^*)\bar{y}_1(t)\\ &= g_3(t,\bar{y}_1(t)), \quad \forall t > t_0+\tau_n+\tau_a,\end{aligned}$$

and hence,

$$\frac{\bar{y}_1(t)}{dt} - g_3(t,\bar{y}_1(t)) > 0 = \frac{dy_1(t)}{dt} - g_3(t,y_1(t)), \quad \forall t > t_0+\tau_n+\tau_a.$$

Since $\bar{y}_1(t_0+\tau_n+\tau_a) \geq y_1(t_0+\tau_n+\tau_a)$, it follows from Theorem 1.3.1 that

$\bar{y}_1(t) > y_1(t), \forall t > t_0 + \tau_n + \tau_a$.

In view of the above three claims, we obtain

$$(\bar{y}_1(t), \bar{y}_2(t), \bar{y}_3(t)) \gg (y_1(t), y_2(t), y_3(t)), \quad \forall t > t_0 + \tau_n + \tau_a.$$

Since $t_0 \in [0, \tau_l]$, it follows that

$$(\bar{y}_{1t}, \bar{y}_{2t}, \bar{y}_{3t}) \gg (y_{1t}, y_{2t}, y_{3t}), \quad \forall t > 4\tau,$$

that is, $v_t(\varphi) \gg v_t(\psi), \forall t > 4\tau$. This shows that $\tilde{P}_\epsilon(t) : Z_+ \to Z_+$ is strongly monotone for any $t > 4\tau$. It follows from [29, Theorem 3.6.1] that the linear operator $\tilde{P}_\epsilon(t)$ is compact on Z_+. Choose an integer $n_0 > 0$ such that $n_0\omega > 4\tau$. Since $\tilde{P}_\epsilon^{n_0} = \tilde{P}_\epsilon(n_0\omega)$, [44, Lemma 3.1] implies that $r(\tilde{P}_\epsilon)$ is a simple eigenvalue of $\tilde{P}_\epsilon$ having a strongly positive eigenvector, and the modulus of any other eigenvalue is less than $r(\tilde{P}_\epsilon)$. It then follows from Lemma 5.2.1 that there is a positive ω-periodic function $\bar{v}(t) = (\bar{v}_1(t), \bar{v}_2(t), \bar{v}_3(t))^T$ such that $v^*(t) = e^{\frac{\ln r(\tilde{P}_\epsilon)}{\omega}t}\bar{v}(t)$ is a positive solution of system (5.9).

Since $\lim_{\epsilon \to 0^+} r(\tilde{P}_\epsilon) = r(\tilde{P}) > 1$, we can fix an $\epsilon_0 \in (0, 1)$ such that $r(\tilde{P}_{\epsilon_0}) > 1$. Futher, we choose a sufficiently small positive number δ_0 such that

$$r(t)e^{-c(t)v} \geq r(t)(1 - \epsilon_0), \quad \forall t \geq 0, \quad 0 \leq v \leq \delta_0.$$

Since $\lim_{\phi \to 0} P_1(t)(\phi) = 0$ uniformly for $t \in [0, \omega]$, there exists $\delta_1 > 0$ such that

$$\|H^*\xi e^{-(\mu_A + \mu_h)\tau_a} P_1(t)(\phi)\| \leq \delta_0, \quad \forall t \in [0, \omega], \quad \|\phi\| \leq \delta_1.$$

Claim 4. $\limsup_{n \to \infty} \|P_1^n \psi\| \geq \delta_1$ for all $\psi \in Z_+ \setminus \{0\}$.

Suppose, by contradiction, that $\limsup_{n\to\infty} \|P_1^n\phi\| < \delta_1$ for some $\phi \in Z_+ \setminus \{0\}$. Then there exists an integer $N_0 \geq 1$ such that $\|P_1^n\phi\| < \delta_1, \forall n \geq N_0$. For any $t \geq N_0\omega$, we have $t = n\omega + t'$ with $n \geq N_0$, $t' \in [0, \omega]$ and

$$\begin{aligned} \|H^*\xi e^{-(\mu_A+\mu_h)\tau_a} A_t(\phi)\| &\leq \|H^*\xi e^{-(\mu_A+\mu_h)\tau_a} P_1(t)(\phi)\| \\ &= \|H^*\xi e^{-(\mu_A+\mu_h)\tau_a} P_1(t')(P_1^n\phi)\| \\ &\leq \delta_0. \end{aligned}$$

Then for all $t \geq \tau_a + N_0\omega$ we have $0 \leq H^*\xi e^{-(\mu_A+\mu_h)\tau_a} A(t-\tau_a, \phi) \leq \delta_0$. It then follows that

$$\begin{aligned} \frac{dL(t,\phi)}{dt} &= H^* e^{-(\mu_A+\mu_h)\tau_a}\xi A(t-\tau_a) r(t) \exp(-c(t) H^* e^{-(\mu_A+\mu_h)\tau_a}\xi A(t-\tau_a)) \\ &\quad -(\mu_L + \alpha_1(t) M^*) L \\ &\geq r(t)(1-\epsilon_0) H^* e^{-(\mu_A+\mu_h)\tau_a}\xi A(t-\tau_a) - (\mu_L + \alpha_1(t) M^*) L \end{aligned}$$

for all $t \geq \tau_a + N_0\omega$. Since $\phi > 0$, there exists $t_0 \in [0, \tau]$ such that at least one of $L(t_0, \phi) > 0$, $N(t_0, \phi) > 0$, $A(t_0, \phi) > 0$ holds. Without loss of generality, we assume that $L(t_0, \phi) > 0$. It then follows that $L(t, \phi) > 0$ for all $t \geq t_0$, that there exists $t_1 \in [\tau_l, \tau_l + \tau]$ such that $N(t_1, \phi) > 0$, and hence, $N(t, \phi) > 0$ for all $t \geq t_1$, and that there exists $t_2 \in [\tau_l + \tau_n, \tau_l + \tau_n + \tau]$ such that $A(t_2, \phi) > 0$, and hence, $A(t, \phi) > 0$ for all $t \geq t_2$. Hence, $L(t, \phi) > 0$, $N(t, \phi) > 0$, $A(t, \phi) > 0$ for all $t \geq 3\tau$. We can choose a sufficiently small real number $\bar{k} > 0$ such that

$$(L(t,\phi), N(t,\phi), A(t,\phi)) \geq \bar{k}(v_1^*(t), v_2^*(t), v_3^*(t)), \quad \forall t \in [\bar{N}\omega, \bar{N}\omega + \tau],$$

where $\bar{N}\omega \geq \max\{\tau_a + N_0\omega, 3\tau\}$. By [84, Theorem 5.1.1], we have $(L(t, \phi)$, $N(t, \phi)$, $A(t, \phi)) \geq \bar{k}(v_1^*(t)$, $v_2^*(t)$, $v_3^*(t))$, $\forall t > \bar{N}\omega + \tau$. Thus, $\lim_{t\to\infty} L(t, \phi) = \lim_{t\to\infty} N(t, \phi)$

$= \lim_{t\to\infty} A(t,\phi) = \infty$, a contradiction.

For any $\phi \in Y$, we have $\phi \leq (\bar{L}_0^*, \bar{N}_0^*, \bar{A}_0^*)$. Since system (5.5) is dominated by the cooperative system (5.6), it follows from [84, Theorem 5.1.1] that

$$(L(t,\phi), N(t,\phi), A(t,\phi)) \leq (\bar{L}^*(t), \bar{N}^*(t), \bar{A}^*(t)), \quad \forall t \geq 0, \quad \phi \in Y.$$

For any given $\varphi, \psi \in Y$ with $\varphi \geq \psi$, let $w(t,\varphi)$ and $w(t,\psi)$ be the unique solutions of system (5.5) satisfying $w_0 = \varphi$ and $w_0 = \psi$, respectively. Define

$$E(t,x) := r(t)xe^{-c(t)x}.$$

By virtue of (A3), we see that for any $\phi \in Y$,

$$\begin{aligned}
&\frac{\partial E}{\partial x}(t, H^* e^{-(\mu_A+\mu_h)\tau_a}\xi A(t-\tau_a,\phi)) \\
&= [1 - c(t)H^* e^{-(\mu_A+\mu_h)\tau_a}\xi A(t-\tau_a,\phi)]r(t)e^{-c(t)H^* e^{-(\mu_A+\mu_h)\tau_a}\xi A(t-\tau_a,\phi)} \\
&\geq [1 - c(t)H^* e^{-(\mu_A+\mu_h)\tau_a}\xi \bar{A}^*(t-\tau_a)]r(t)e^{-c(t)H^* e^{-(\mu_A+\mu_h)\tau_a}\xi A(t-\tau_a,\phi)} \\
&> 0.
\end{aligned}$$

It then follows that $\tilde{f}_i(t,\varphi) \geq \tilde{f}_i(t,\psi)$ whenever $\varphi \geq \psi$ and $\varphi_i(0) = \psi_i(0)$ holds for some $i \in \{1,2,3\}$. By [84, Theorem 5.1.1], we have $w(t,\varphi) \geq w(t,\psi), \forall t \geq 0$, that is, $P_1(t) : Y \to Y$ is monotone. Next we prove that $P_1(t) : Y \to Y$ is eventually strongly monotone. Let $\varphi, \psi \in Y$ satisfy $\varphi > \psi$. Denote $w(t,\varphi) = (\bar{w}_1(t), \bar{w}_2(t), \bar{w}_3(t))$, $w(t,\psi) = (w_1(t), w_2(t), w_3(t))$. By similar arguments to those in the proof of Claims 1 and 2, we have

Claim 5. There exists $t_0 \in [0, \tau_l]$ such that $\bar{w}_2(t) > w_2(t), \forall t \geq t_0$.

Claim 6. $\bar{w}_3(t) > w_3(t), \forall t > t_0 + \tau_n$.

Now we prove the following claim.

Claim 7. $\bar{w}_1(t) > w_1(t), \forall t > t_0 + \tau_n + \tau_a$.

Let

$$f_1(t, y) := E(t, H^* e^{-(\mu_A+\mu_h)\tau_a} \xi w_3(t - \tau_a)) - (\mu_L + \alpha_1(t) M^*) y.$$

Since $\frac{\partial E}{\partial x}(t, H^* e^{-(\mu_A+\mu_h)\tau_a} \xi A(t - \tau_a, \phi)) > 0$, we have

$$\begin{aligned}\frac{d\bar{w}_1(t)}{dt} &= E(t, H^* e^{-(\mu_A+\mu_h)\tau_a} \xi \bar{w}_3(t - \tau_a)) - (\mu_L + \alpha_1(t) M^*) \bar{w}_1(t) \\ &> E(t, H^* e^{-(\mu_A+\mu_h)\tau_a} \xi w_3(t - \tau_a)) - (\mu_L + \alpha_1(t) M^*) \bar{w}_1(t) \\ &= f_1(t, \bar{w}_1(t)), \quad \forall t > t_0 + \tau_n + \tau_a,\end{aligned}$$

and hence,

$$\frac{d\bar{w}_1(t)}{dt} - f_1(t, \bar{w}_1(t)) > 0 = \frac{dw_1(t)}{dt} - f_1(t, w_1(t)), \quad \forall t > t_0 + \tau_n + \tau_a.$$

Since $\bar{w}_1(t_0 + \tau_n + \tau_a) \geq w_1(t_0 + \tau_n + \tau_a)$, it follows from Theorem 1.3.1 that $\bar{w}_1(t) > w_1(t), \forall t > t_0 + \tau_n + \tau_a$. In view of the above three claims, we obtain

$$(\bar{w}_1(t), \bar{w}_2(t), \bar{w}_3(t)) \gg (w_1(t), w_2(t), w_3(t)), \quad \forall t > t_0 + \tau_n + \tau_a.$$

Since $t_0 \in [0, \tau_l]$, it follows that

$$(\bar{w}_{1t}, \bar{w}_{2t}, \bar{w}_{3t}) \gg (w_{1t}, w_{2t}, w_{3t}), \quad \forall t > 4\tau,$$

that is, $u_t(\varphi) \gg u_t(\psi), \forall t > 4\tau$. This shows that $P_1^n : Y \to Y$ is strongly monotone for $n\omega > 4\tau$.

Since $\tilde{f}(t, \varphi)$ is strictly subhomogeneous in φ, by the same argument as in the proof of [111, Theorem 3.3], we can deduce that P_1 is strictly subhomogeneous on Y. Thus, P_1^n is also strictly subhomogeneous on Y for any integer $n > 0$.

We fix an integer n_0 such that $n_0\omega > 4\tau$. It then follows that $P_1^{n_0} = P_1(n_0\omega) : Y \to Y$ is strongly monotone and strictly subhomogeneous. Let $\tilde{P}(t)$ be the solution map of linear system (5.7) on Z. Note that $DP_1^{n_0}(0) = DP_1(n_0\omega)(0) = \tilde{P}(n_0\omega) = (\tilde{P}(\omega))^{n_0} = \tilde{P}^{n_0}$ and $r(\tilde{P}^{n_0}) = (r(\tilde{P}))^{n_0}$. Since (A2) holds, Theorem 1.3.4, as applied to $P_1^{n_0}$, implies that there exists a unique positive $n_0\omega$-periodic solution $\bar{w}(t) = (L^*(t), N^*(t), A^*(t))$ which is globally attractive for system (5.5) in $Y \setminus \{0\}$.

Now we prove that $\bar{w}(t)$ is also an ω-periodic solution of system (5.5). Let $\bar{w}(t) = w(t, \psi^*)$. By the properties of periodic semiflows, we have $P_1^{n_0}(P_1(\psi^*)) = P_1(P_1^{n_0}(\psi^*)) = P_1(\psi^*)$, which implies that $P_1(\psi^*)$ is also a positive fixed point of $P_1^{n_0}$. By the uniqueness of the positive fixed point of $P_1^{n_0}$, it follows that $P_1(\psi^*) = \psi^*$. So $\bar{w}(t) = (L^*(t), N^*(t), A^*(t))$ is an ω-periodic solution of system (5.5).

By Lemma 1.1.2, for any $\psi \in Z_+$, $\omega(\psi)$ is an internally chain transitive set for $P_1 : Z_+ \to Z_+$. Since $\omega(\psi) \subseteq Y$, it follows from Theorem 1.1.4 that either $\omega(\psi) = 0$ or $\omega(\psi) = \psi^*$, $\forall \psi \in Z_+$. Claim 4 implies that $\omega(\psi) \neq 0, \forall \psi \in Z_+ \setminus \{0\}$. Hence, $\omega(\psi) = \psi^*$, $\forall \psi \in Z_+ \setminus \{0\}$. Thus, system (5.5) admits a unique positive ω-periodic solution $w(t, \psi^*) = (L^*(t), N^*(t), A^*(t))$ which is globally attractive in $Z_+ \setminus \{0\}$. □

Linearizing system (5.1) at its disease-free periodic solution (M^*, 0, $L^*(t)$, $N^*(t)$, 0, $A^*(t)$, 0, H^*), we then obtain the following system of periodic linear equations for the infective variables m, n and a:

$$\begin{aligned}
\frac{dm}{dt} =& -\mu_M m + \alpha_2(t)\beta M^* n,\\
\frac{dn}{dt} =& e^{-(\mu_L+\mu_M)\tau_l}\alpha_1(t-\tau_l)\beta_T L^*(t-\tau_l)m(t-\tau_l) - (\gamma + \alpha_2(t)M^* + \mu_N)n,\\
\frac{da}{dt} =& e^{-(\mu_N+\mu_M)\tau_n}\alpha_2(t-\tau_n)(M^* n(t-\tau_n) + \beta_T N^*(t-\tau_n)m(t-\tau_n)) - (\mu_A + \xi H^*)a.
\end{aligned} \tag{5.10}$$

Since the third equation of system (5.10) is decoupled from the first two equations of system (5.10), it suffices to use the following system to define the basic reproduction ratio:

$$\begin{aligned} \frac{dm}{dt} &= -\mu_M m + \alpha_2(t)\beta M^* n, \\ \frac{dn}{dt} &= e^{-(\mu_L+\mu_M)\tau_l}\alpha_1(t-\tau_l)\beta_T L^*(t-\tau_l)m(t-\tau_l) - (\gamma + \alpha_2(t)M^* + \mu_N)n. \end{aligned} \tag{5.11}$$

Denote $a_{11}(t) = \mu_M$, $a_{12}(t) = \alpha_2(t)\beta M^*$, $a_{22}(t) = \gamma + \alpha_2(t)M^* + \mu_N$, and

$$a_{21}(t) = e^{-(\mu_L+\mu_M)\tau_l}\alpha_1(t-\tau_l)\beta_T L^*(t-\tau_l).$$

Let $C = C([-\tau_l, 0], \mathbb{R}^2)$, $C^+ = C([-\tau_l, 0], \mathbb{R}^2_+)$. Then (C, C^+) is an ordered Banach space equipped with the maximum norm and the positive cone C^+. For any given continuous function $v = (v_1, v_2) : [-\tau_l, \sigma) \to \mathbb{R}^2$ with $\sigma > 0$, we define $v_t \in C$ by

$$v_t(\theta) = (v_1(t+\theta), v_2(t+\theta)), \quad \forall \theta \in [-\tau_l, 0],$$

for any $t \in [0, \sigma)$. Let $F : \mathbb{R} \to \mathcal{L}(C, \mathbb{R}^2)$ be a map and $V(t)$ be a continuous $m \times m$ matrix function on $\mathbb{R}$ defined as follows:

$$F(t)\varphi = \begin{bmatrix} a_{12}(t)\varphi_2(0) \\ a_{21}(t)\varphi_1(-\tau_l) \end{bmatrix}, \qquad V(t) = \begin{bmatrix} a_{11}(t) & 0 \\ 0 & a_{22}(t) \end{bmatrix}.$$

Let $\Phi(t, s), t \geq s$, be the evolution matrix associated with the following system:

$$\frac{dv(t)}{dt} = -V(t)v(t),$$

that is, $\Phi(t, s)$ satisfies

$$\frac{\partial}{\partial t}\Phi(t, s) = -V(t)\Phi(t, s), \quad \forall t \geq s, \quad \text{and} \quad \Phi(s, s) = I, \quad \forall s \in \mathbb{R}.$$

It then easily follows that

$$\Phi(t,s) = \begin{bmatrix} e^{-\int_s^t a_{11}(r)dr} & 0 \\ 0 & e^{-\int_s^t a_{22}(r)dr} \end{bmatrix}.$$

According to section 1.4, we assume that the ω-periodic function $v(t)$ is the initial distribution of infectious individuals. For any given $s \geq 0$, $F(t-s)v_{t-s}$ is the distribution of newly infected individuals at time $t-s$, which is produced by the infectious individuals who were introduced over the time interval $[t-s-\tau_l, t-s]$. Then $\Phi(t,t-s)F(t-s)v_{t-s}$ is the distribution of those infected individuals who were newly infected at time $t-s$ and remain in the infected compartments at time t. It follows that

$$\int_0^\infty \Phi(t,t-s)F(t-s)v_{t-s}ds = \int_0^\infty \Phi(t,t-s)F(t-s)v(t-s+\cdot)ds$$

is the distribution of accumulative new infections at time t produced by all those infectious individuals introduced at all previous times to t.

Let C_ω be the ordered Banach space of all continuous and ω-periodic functions from $\mathbb{R}$ to $\mathbb{R}^2$, which is equipped with the maximum norm and the positive cone $C_\omega^+ := \{v \in C_\omega : v(t) \geq 0, \forall t \in \mathbb{R}\}$. Define a linear operator $L : C_\omega \to C_\omega$ by

$$[Lv](t) = \int_0^\infty \Phi(t,t-s)F(t-s)v(t-s+\cdot)ds, \quad \forall t \in \mathbb{R}, v \in C_\omega.$$

It follows that

$$\begin{aligned}
[Lv](t) &= \int_0^\infty \Phi(t,t-s)F(t-s)v(t-s+\cdot)ds \\
&= \int_0^\infty \Phi(t,t-s)\begin{bmatrix} a_{12}(t-s)v_2(t-s) \\ a_{21}(t-s)v_1(t-s-\tau_l) \end{bmatrix} ds \\
&= \int_0^\infty \begin{bmatrix} e^{-\int_{t-s}^t a_{11}(r)dr}a_{12}(t-s)v_2(t-s) \\ e^{-\int_{t-s}^t a_{22}(r)dr}a_{21}(t-s)v_1(t-s-\tau_l) \end{bmatrix} ds \\
&= \begin{bmatrix} \int_0^\infty e^{-\int_{t-s}^t a_{11}(r)dr}a_{12}(t-s)v_2(t-s)ds \\ \int_{\tau_l}^\infty e^{-\int_{t-s+\tau_l}^t a_{22}(r)dr}a_{21}(t-s+\tau_l)v_1(t-s)ds \end{bmatrix} \\
&= \int_0^\infty K(t,s)v(t-s)ds, \quad \forall t \in \mathbb{R}, \quad v = \begin{bmatrix} v_1 \\ v_2 \end{bmatrix} \in C_\omega,
\end{aligned}$$

where

$$K(t,s) = \begin{bmatrix} 0 & e^{-\int_{t-s}^t a_{11}(r)dr}a_{12}(t-s) \\ e^{-\int_{t-s+\tau_l}^t a_{22}(r)dr}a_{21}(t-s+\tau_l) & 0 \end{bmatrix}, \quad \text{if} \quad s \geq \tau_l,$$

and

$$K(t,s) = \begin{bmatrix} 0 & e^{-\int_{t-s}^t a_{11}(r)dr}a_{12}(t-s) \\ 0 & 0 \end{bmatrix}, \quad \text{if} \quad s < \tau_l.$$

Following section 1.4, we define $R_0 = r(L)$. Let $\hat{P}(t)$ be the solution maps of system (5.11), that is, $\hat{P}(t)\varphi = u_t(\varphi), t \geq 0$, where $u(t,\varphi)$ is the unique solution of (5.11) with $u_0 = \varphi \in C([-\tau_l, 0], \mathbb{R}^2)$. Then $\hat{P} := \hat{P}(\omega)$ is the Poincaré map associated with linear system (5.11) on $C([-\tau_l, 0], \mathbb{R}^2)$. Let $r(\hat{P})$ be the spectral radius of $\hat{P}$. By Theorem 1.4.1, we have the following result.

Lemma 5.2.3. *$R_0 - 1$ has the same sign as $r(\hat{P}) - 1$.*

This result shows that the sign of $R_0 - 1$ determines the stability of the zero solution of linear periodic system (5.11), and hence, R_0 is a threshold value for the local invasion of the disease.

5.3 Threshold dynamics

In this section, we study the global dynamics of system (5.1) in terms of R_0. We first present the following preliminary result.

Lemma 5.3.1. *For any* $\varphi \in C([-\tau, 0], \mathbb{R}_+^8)$*, system* (5.1) *has a unique nonnegative solution through* φ*, and solutions are ultimately bounded.*

Proof. For any $\varphi \in C([-\tau, 0], \mathbb{R}_+^8)$, we define

$$f(t, \varphi) = (f_1, f_2, f_3, f_4, f_5, f_6, f_7, f_8),$$

where

$$\begin{aligned}
f_1 =& (\varphi_1(0) + \varphi_2(0))B_M(\varphi_1(0) + \varphi_2(0)) - \mu_M\varphi_1(0) - \alpha_2(t)\beta\varphi_1(0)\varphi_5(0), \\
f_2 =& \alpha_2(t)\beta\varphi_1(0)\varphi_5(0) - \mu_M\varphi_2(0), \\
f_3 =& e^{-(\mu_A+\mu_h)\tau_a}\xi(\varphi_6(-\tau_a) + \varphi_7(-\tau_a))\varphi_8(-\tau_a)r(t)\exp(-c(t)e^{-(\mu_A+\mu_h)\tau_a}\xi(\varphi_6(-\tau_a) \\
&+ \varphi_7(-\tau_a))\varphi_8(-\tau_a)) - \mu_L\varphi_3(0) - \alpha_1(t)\varphi_3(0)(\varphi_1(0) + \varphi_2(0)), \\
f_4 =& e^{-(\mu_L+\mu_M)\tau_l}\alpha_1(t - \tau_l)[\varphi_1(-\tau_l) + (1 - \beta_T)\varphi_2(-\tau_l)]\varphi_3(-\tau_l) - [\gamma + \alpha_2(t)(\varphi_1(0) \\
&+ \varphi_2(0)) + \mu_N]\varphi_4(0), \\
f_5 =& e^{-(\mu_L+\mu_M)\tau_l}\alpha_1(t - \tau_l)\beta_T\varphi_2(-\tau_l)\varphi_3(-\tau_l) \\
&- [\gamma + \alpha_2(t)(\varphi_1(0) + \varphi_2(0)) + \mu_N]\varphi_5(0),
\end{aligned}$$

$$
\begin{aligned}
f_6 =& e^{-(\mu_N+\mu_M)\tau_n}\alpha_2(t-\tau_n)[\varphi_1(-\tau_n)+(1-\beta_T)\varphi_2(-\tau_n)]\varphi_4(-\tau_n)\\
&-(\mu_A+\xi\varphi_8(0))\varphi_6(0),\\
f_7 =& e^{-(\mu_N+\mu_M)\tau_n}\alpha_2(t-\tau_n)[(\varphi_1(-\tau_n)+\varphi_2(-\tau_n))\varphi_5(-\tau_n)+\beta_T\varphi_2(-\tau_n)\varphi_4(-\tau_n)]\\
&-(\mu_A+\xi\varphi_8(0))\varphi_7(0),\\
f_8 =& r_h-\mu_h\varphi_8(0).
\end{aligned}
$$

Since $f(t,\varphi)$ is continuous in $(t,\varphi)\in\mathbb{R}_+\times C([-\tau,0],\mathbb{R}_+^8)$, and $f(t,\varphi)$ is Lipschitz in φ on each compact subset of $C([-\tau,0],\mathbb{R}_+^8)$, it then follows that system (5.1) has a unique solution $u(t,\varphi)$ on its maximal interval $[0,\sigma_\varphi)$ of existence with $u_0=\varphi$ (see, e.g., [29, Theorem 2.2.1 and 2.2.3]).

Let $\varphi=(\varphi_1,\varphi_2,\varphi_3,\varphi_4,\varphi_5,\varphi_6,\varphi_7,\varphi_8)\in C([-\tau,0],\mathbb{R}_+^8)$ be given. If $\varphi_i(0)=0$ for some $i\in\{1,2,3,4,5,6,7,8\}$, then $f_i(t,\varphi)\geq 0$. By [84, Theorem 5.2.1 and Remark 5.2.1], it follows that for any $\varphi\in C([-\tau,0],\mathbb{R}_+^8)$, the unique solution $u(t,\varphi)$ of system (5.1) with $u_0=\varphi$ satisfies $u_t(\varphi)\in C([-\tau,0],\mathbb{R}_+^8)$ for all $t\in[0,\sigma_\varphi)$.

For the mice population $M(t)+m(t)$, we have

$$\frac{d(M+m)}{dt}=(M+m)r_M\exp(-\frac{M+m}{K_M})-\mu_M(M+m).$$

It follows that for any $M(0)+m(0)>0$, there holds

$$\lim_{t\to\infty}(M(t)+m(t))=M^*.$$

For the larval tick population $L(t)$, we have

$$
\begin{aligned}
\frac{dL}{dt} &= T_b r(t)\exp(-c(t)T_b)-\mu_L L-\alpha_1(t)L(M+m)\\
&\leq \frac{r(t)}{c(t)}e^{-1}-\mu_L L.
\end{aligned}
$$

It is easy to see that the linear inhomogeneous equation

$$\frac{d\bar{L}}{dt} = \frac{r(t)}{c(t)}e^{-1} - \mu_L \bar{L}$$

has a globally attractive positive ω-periodic solution $\bar{L}^*(t)$. Then, by the comparison principle, we have

$$\limsup_{t\to\infty}(L(t) - \bar{L}^*(t)) \leq 0.$$

It follows that there exists $B_1 > 0$ such that

$$\begin{aligned}
\frac{d(N+n)}{dt} &= e^{-(\mu_L+\mu_M)\tau_l}\alpha_1(t-\tau_l)[M(t-\tau_l)+m(t-\tau_l)]L(t-\tau_l) \\
&\quad -[\gamma+\alpha_2(t)(M+m)+\mu_N](N+n) \\
&\leq B_1\alpha_1(t-\tau_l) - (\gamma+\mu_N)(N+n)
\end{aligned}$$

for sufficiently large t. Note that the linear inhomogeneous equation

$$\frac{dU}{dt} = B_1\alpha_1(t-\tau_l) - (\gamma+\mu_N)U$$

has a globally attractive positive ω-periodic solution $U^*(t)$. By the comparison principle, we obtain

$$\limsup_{t\to\infty}(N(t) + n(t) - U^*(t)) \leq 0.$$

Thus, there exists $B_2 > 0$ such that

$$\begin{aligned}
\frac{d(A+a)}{dt} &= e^{-(\mu_N+\mu_M)\tau_n}\alpha_2(t-\tau_n)[M(t-\tau_n)+m(t-\tau_n)][N(t-\tau_n)+n(t-\tau_n)] \\
&\quad -(\mu_A+\xi H)(A+a) \\
&\leq B_2\alpha_2(t-\tau_n) - \mu_A(A+a)
\end{aligned}$$

for sufficiently large t. Since the linear inhomogeneous equation

$$\frac{dV}{dt} = B_2\alpha_2(t-\tau_n) - \mu_A V$$

has a globally attractive positive ω-periodic solution $V^*(t)$, the comparison theorem implies that

$$\limsup_{t\to\infty}(A(t)+a(t)-V^*(t)) \leq 0.$$

For the deer population $H(t)$, it is easy to see that

$$\lim_{t\to\infty} H(t) = H^*.$$

Consequently, solutions of system (5.1) are ultimately bounded. □

Let

$$\begin{aligned} X &= C([-\tau_n,0],\mathbb{R}_+^2)\times C([-\tau_l,0],\mathbb{R}_+)\times C([-\tau_n,0],\mathbb{R}_+^2)\times C([-\tau_a,0],\mathbb{R}_+^3), \\ X_0 &= \{\phi=(\phi_1,\phi_2,\phi_3,\phi_4,\phi_5,\phi_6,\phi_7,\phi_8)\in X : \phi_i(0)>0, i=2,5,7\}. \end{aligned}$$

Let $P(t)$ be the solution maps of system (5.11) on the space $C([-\tau_l,0],\mathbb{R}_+)\times\mathbb{R}_+$. Then $P := P(\omega)$ is the Poincaré map of system (5.11) on the space $C([-\tau_l,0],\mathbb{R})\times\mathbb{R}$. Let $r(P)$ be the spectral radius of P. Then we have the following threshold type result for system (5.1).

Theorem 5.3.2. *Let (A1), (A2) and (A3) hold. Then the following statements are valid:*

(i) If $r(P) < 1$, then the disease-free periodic solution (M^*, 0, $L^*(t)$, $N^*(t)$, 0, $A^*(t)$, 0, H^*) is globally attractive for system (5.1) in X.

(ii) *If* $r(P) > 1$, *then system* (5.1) *admits a positive* ω*-periodic solution and there exists a real number* $\eta > 0$ *such that any solution* $(M(t,\varphi),\ m(t,\varphi),\ L(t,\varphi),\ N(t,\varphi),\ n(t,\varphi),\ A(t,\varphi),\ a(t,\varphi),\ H(t,\varphi))$ *of system* (5.1) *with* $\varphi \in X_0$ *satisfies* $\liminf_{t\to\infty}(m(t), n(t), a(t)) \geq (\eta, \eta, \eta)$.

Proof. We first consider the case where $r(P) < 1$. By arguments similar to those in proving that $\tilde{P}_\epsilon(t)$ is eventually strongly monotone, we can show that $P(t)$ is strongly positive on $C([-\tau_l, 0], \mathbb{R}) \times \mathbb{R}$ for each $t > 2\tau_l$. It follows from [29, Theorem 3.6.1] that the linear operator $P(t)$ is compact on $C([-\tau_l, 0], \mathbb{R}) \times \mathbb{R}$ for each $t > 2\tau_l$. Choose an integer $n_0 > 0$ such that $n_0\omega > 2\tau_l$. Since $P^{n_0} = P(n_0\omega)$, [44, Lemma 3.1] implies that $r(P)$ is a simple eigenvalue of P having a strongly positive eigenvector, and the modulus of any other eigenvalue is less than $r(P)$. Let $\mu = \frac{\ln r(P)}{\omega}$. By Lemma 5.2.1, there exists a positive ω-periodic function $v(t) = (v_1(t), v_2(t))^T$ such that $u(t) = e^{\mu t}v(t)$ is a positive solution of system (5.11).

Let $P_\epsilon(t)$ be the solution maps of the following perturbed linear periodic system on the space $C([-\tau_l, 0], \mathbb{R}) \times \mathbb{R}$:

$$\begin{aligned} \frac{dm}{dt} =& -\mu_M m + \alpha_2(t)\beta(M^* + \epsilon)n, \\ \frac{dn}{dt} =& e^{-(\mu_L+\mu_M)\tau_l}\alpha_1(t-\tau_l)\beta_T(L^*(t-\tau_l) + \epsilon)m(t-\tau_l) - [\gamma + \alpha_2(t)(M^* - \epsilon) + \mu_N]n, \end{aligned} \tag{5.12}$$

and $P_\epsilon := P_\epsilon(\omega)$. Since $\lim_{\epsilon\to 0} r(P_\epsilon) = r(P) < 1$, we can fix a sufficiently small $\epsilon > 0$ such that $r(P_\epsilon) < 1$. It is easy to verify that $P_\epsilon(t)$ is also compact and eventually strongly monotone on $C([-\tau_l, 0], \mathbb{R}) \times \mathbb{R}$ for each $t > 2\tau_l$. As discussed above, there is a positive ω-periodic function $v_\epsilon(t) = (v_{\epsilon 1}(t), v_{\epsilon 2}(t))$ such that $u_\epsilon(t) = e^{\mu_\epsilon t}v_\epsilon(t)$ is a positive solution of (5.12), where $\mu_\epsilon = \frac{\ln r(P_\epsilon)}{\omega} < 0$. Clearly, $\lim_{t\to\infty} u_\epsilon(t) = 0$.

Let $\mathcal{M} = M + m, \mathcal{N} = N + n, \mathcal{A} = A + a$, then we have

$$\begin{aligned}
\frac{d\mathcal{M}}{dt} =& \mathcal{M}B_M(\mathcal{M}) - \mu_M \mathcal{M},\\
\frac{dL}{dt} =& e^{-(\mu_A+\mu_h)\tau_a}\xi\mathcal{A}(t-\tau_a)H(t-\tau_a)r(t)\exp(-c(t)e^{-(\mu_A+\mu_h)\tau_a}\xi\mathcal{A}(t-\tau_a)H(t-\tau_a))\\
&-\mu_L L - \alpha_1(t)L\mathcal{M},\\
\frac{d\mathcal{N}}{dt} =& e^{-(\mu_L+\mu_M)\tau_l}\alpha_1(t-\tau_l)\mathcal{M}(t-\tau_l)L(t-\tau_l) - (\gamma + \alpha_2(t)\mathcal{M} + \mu_N)\mathcal{N},\\
\frac{d\mathcal{A}}{dt} =& e^{-(\mu_N+\mu_M)\tau_n}\alpha_2(t-\tau_n)\mathcal{M}(t-\tau_n)\mathcal{N}(t-\tau_n) - (\mu_A + \xi H)\mathcal{A},\\
\frac{dH}{dt} =& r_h - \mu_h H.
\end{aligned} \tag{5.13}$$

Since $(M^*, L^*(t), N^*(t), A^*(t), H^*)$ is globally attractive for the solutions of system (5.4) in $(C([-\tau_n, 0], \mathbb{R}_+) \setminus \{0\}) \times (Z \setminus \{0\}) \times C([-\tau_a, 0], \mathbb{R}_+)$, $(M^*, L^*(t), N^*(t), A^*(t), H^*)$ is also globally attractive for the solutions of system (5.13) in $(C([-\tau_n, 0], \mathbb{R}_+) \setminus \{0\}) \times (Z \setminus \{0\}) \times C([-\tau_a, 0], \mathbb{R}_+)$. It follows that there exists a sufficiently large integer $n_1 > 0$ such that $n_1\omega \geq \tau_l$ and $M^* - \epsilon \leq \mathcal{M}(t) \leq M^* + \epsilon$, $L(t-\tau_l) \leq L^*(t-\tau_l) + \epsilon$, $\forall t \geq n_1\omega$. We then have

$$\begin{aligned}
\frac{dm}{dt} &= \alpha_2(t)\beta M n - \mu_M m\\
&\leq \alpha_2(t)\beta(M^* + \epsilon)n - \mu_M m,\\
\frac{dn}{dt} &= e^{-(\mu_L+\mu_M)\tau_l}\alpha_1(t-\tau_l)\beta_T m(t-\tau_l)L(t-\tau_l) - (\gamma + \alpha_2(t)(M+m) + \mu_N)n\\
&\leq e^{-(\mu_L+\mu_M)\tau_l}\alpha_1(t-\tau_l)\beta_T m(t-\tau_l)(L^*(t-\tau_l) + \epsilon) - (\gamma + \alpha_2(t)(M^* - \epsilon) + \mu_N)n
\end{aligned}$$

for all $t \geq n_1\omega$. Choose a sufficiently large number $K > 0$ such that $(m(t), n(t))^T \leq K u_\epsilon(t), \forall t \in [n_1\omega, n_1\omega + \tau_l]$. Then [84, Theorem 5.1.1] implies that $(m(t), n(t))^T \leq K u_\epsilon(t)$, $\forall t \geq n_1\omega + \tau_l$. Hence, $\lim_{t\to\infty} m(t) = \lim_{t\to\infty} n(t) = 0$. By using the chain transitive sets arguments (see, e.g., section 1.1), it follows that $\lim_{t\to\infty} a(t) = 0$, $\lim_{t\to\infty} M(t) = M^*$, $\lim_{t\to\infty} H(t) = H^*$, $\lim_{t\to\infty}(L(t) - L^*(t)) = \lim_{t\to\infty}(N(t) -$

$N^*(t)) = \lim_{t\to\infty}(A(t) - A^*(t)) = 0$. This proves statement (i).

In the case where $r(P) > 1$, we appeal to the persistence theory for periodic semiflows. Let $\partial X_0 := X \setminus X_0 = \{\phi \in X : \phi_i(0) = 0 \quad \text{for some} \quad i \in \{2, 5, 7\}\}$. Let $Q(t)$ be the solution maps of system (5.1) on X, that is, $Q(t)\psi = u_t(\psi), t \geq 0$, where $u(t, \psi)$ is the unique solution of system (5.1) satisfying $u_0 = \psi \in X$. Then $Q := Q(\omega)$ is the Poincaré map associated with system (5.1).

From the second, fifth and seventh equations of system (5.1) it is easy to see that $Q(t)X_0 \subseteq X_0$ for all $t \geq 0$. Lemma 5.3.1 implies that the discrete-time system $\{Q^n : X \to X\}_{n\geq 0}$ is point dissipative and Q^n is compact for sufficiently large n. It then follows from [52, Theorem 2.9] that Q admits a global attractor in X. Now we prove that Q is uniformly persistent with respect to X_0.

Let $M_1 = (0, 0, 0, 0, 0, 0, 0, H^*)$, $M_2 = (M^*, 0, 0, 0, 0, 0, 0, H^*)$, $M_3 = (M^*, 0, L_0^*, N_0^*, 0, A_0^*, 0, H^*)$, where $L_0^*(\theta) = L^*(\theta)$ for all $\theta \in [-\tau_l, 0]$, $N_0^*(\theta) = N^*(\theta)$ for all $\theta \in [-\tau_n, 0]$, $A_0^*(\theta) = A^*(\theta)$ for all $\theta \in [-\tau_a, 0]$. Choose a small positive integer δ_0 such that $M^* > 2\delta_0$. Since $\lim_{\phi\to M_1}(Q(t)\phi - M_1) = 0$ uniformly for $t \in [0, \omega]$, there exists $\delta_1 > 0$ such that for any $\phi \in X_0$ with $\|\phi - M_1\| < \delta_1$, we have $\|Q(t)\phi - M_1\| < \delta_0, \forall t \in [0, \omega]$.

Claim 1. $\limsup_{n\to\infty} \|Q(n\omega)\phi - M_1\| \geq \delta_1$ for all $\phi \in X_0$.

Suppose, by contradiction, that $\limsup_{n\to\infty} \|Q(n\omega)\psi - M_1\| < \delta_1$ for some $\psi \in X_0$. Then there exists an integer $N_1 \geq 1$ such that $\|Q(n\omega)\psi - M_1\| < \delta_1$ for all $n \geq N_1$. For any $t \geq N_1\omega$, we have $t = n\omega + t'$ with $n \geq N_1$ and $t' \in [0, \omega]$, and hence, $\|Q(t)\psi - M_1\| = \|Q(t')Q(n\omega)\psi - M_1\| < \delta_0$. It follows that $M(t, \psi) < \delta_0$, $m(t, \psi) < \delta_0$ for all $t \geq N_1\omega$. Since $\psi \in X_0$, $\psi_2(0) > 0$, and hence, $\lim_{t\to\infty}(M(t, \psi) + m(t, \psi)) = M^* > 2\delta_0$, a contradiction.

Since $L^*(t)$ is a positive ω-periodic solution, we can choose $\gamma_0 > 0$ such that $\inf_{t\geq 0} L^*(t) > \gamma_0$. Since $\lim_{\phi\to M_2} \|Q(t)\phi - M_2\| = 0$ uniformly for $t \in [0, \omega]$, there exists $\gamma_1 > 0$ such that for any $\phi \in X_0$ with $\|\phi - M_2\| < \gamma_1$, we have $\|Q(t)\phi - M_2\| < \gamma_0, \forall t \in [0, \omega]$. By similar arguments, we can prove the following claim:

Claim 2. $\limsup_{n\to\infty} \|Q(n\omega)\phi - M_2\| \geq \gamma_1$ for all $\phi \in X_0$.

Since $\lim_{\phi\to M_3} \|Q(t)\phi - Q(t)M_3\| = 0$ uniformly for $t \in [0, \omega]$, for any given $\epsilon > 0$, there exists $\eta_1 > 0$ such that for any $\phi \in X_0$ with $\|\phi - M_3\| < \eta_1$, we have $\|Q(t)\phi - Q(t)M_3\| < \epsilon, \forall t \in [0, \omega]$.

Claim 3. $\limsup_{n\to\infty} \|Q(n\omega)\phi - M_3\| \geq \eta_1$ for all $\phi \in X_0$.

Suppose, by contradiction, that $\limsup_{n\to\infty} \|Q(n\omega)\psi - M_3\| < \eta_1$ for some $\psi \in X_0$. Then there exists $N_3 \geq 1$ such that $\|Q(n\omega)\psi - M_3\| < \eta_1$ for all $n \geq N_3$. For any $t \geq N_3\omega$, we have $t = n\omega + t'$ with $n \geq N_3$, $t' \in [0, \omega]$ and $\|Q(t)\psi - Q(t)M_3\| = \|Q(t')Q(n\omega)\psi - Q(t')Q(n\omega)M_3\| = \|Q(t')Q(n\omega)\psi - Q(t')M_3\| < \epsilon$ for all $t \geq N_3\omega$. Therefore, $M(t) > M^* - \epsilon$, $M(t) + m(t) < M^* + \epsilon$ and $L(t - \tau_l) > L^*(t - \tau_l) - \epsilon$ for all $t \geq N_3\omega + \tau_l$. Let r_ϵ be the spectral radius of the Poincaré map associated with the following system:

$$\begin{aligned}
\frac{dm}{dt} =& - \mu_M m + \alpha_2(t)\beta(M^* - \epsilon)n, \\
\frac{dn}{dt} =& e^{-(\mu_L+\mu_M)\tau_l}\alpha_1(t - \tau_l)\beta_T(L^*(t - \tau_l) - \epsilon)m(t - \tau_l) - (\gamma + \alpha_2(t)(M^* + \epsilon) + \mu_N)n.
\end{aligned} \tag{5.14}$$

Then $\lim_{\epsilon\to 0^+} r_\epsilon = r(P) > 1$. Fix a sufficiently small ϵ such that $r_\epsilon > 1$, $M^* - \epsilon > 0$ and $L^*(t - \tau_l) - \epsilon > 0$ for all $t \geq 0$. By Lemma 5.2.1, system (5.14) has a solution $w(t) = e^{\lambda t}v(t)$, where $v(t) = (v_1(t), v_2(t))$ is positive and ω-periodic, $\lambda = \frac{\ln r_\epsilon}{\omega} > 0$.

Clearly, $\lim_{t\to\infty} w(t) = \infty$. For all $t \geq N_3\omega + \tau_l$, we have

$$\begin{aligned}
\frac{dm}{dt} &= \alpha_2(t)\beta M n - \mu_M m \\
&\geq \alpha_2(t)\beta(M^* - \epsilon)n - \mu_M m, \\
\frac{dn}{dt} &= e^{-(\mu_L+\mu_M)\tau_l}\alpha_1(t-\tau_l)\beta_T m(t-\tau_l)L(t-\tau_l) - (\gamma + \alpha_2(t)(M+m) + \mu_N)n \\
&\geq e^{-(\mu_L+\mu_M)\tau_l}\alpha_1(t-\tau_l)\beta_T m(t-\tau_l)(L^*(t-\tau_l) - \epsilon) - (\gamma + \alpha_2(t)(M^*+\epsilon) + \mu_N)n,
\end{aligned}$$

Since $m(t,\psi) > 0$, $n(t,\psi) > 0$ for all $t \geq 0$, we can choose a sufficiently small $k > 0$ such that

$$(m(t,\psi), n(t,\psi)) \geq kw(t), \quad \forall t \in [N_3\omega + \tau_l, N_3\omega + 2\tau_l].$$

By [84, Theorem 5.1.1], it follows that

$$(m(t,\psi), n(t,\psi)) \geq kw(t) \quad \text{for all} \quad t \geq N_3\omega + 2\tau_l.$$

Hence, $\lim_{t\to\infty} m(t,\psi) = \lim_{t\to\infty} n(t,\psi) = \infty$, a contradiction.

Define

$$M_\partial := \{\phi \in \partial X_0 : Q^n(\phi) \in \partial X_0, \forall n \geq 0\}.$$

For any given $\psi \in \partial X_0$, we have $\psi_2(0) = 0$ or $\psi_5(0) = 0$ or $\psi_7(0) = 0$.

If $\psi_2(0) = 0$, we have the following two cases:

Case 1. $\psi_1(0) = 0$.

Since $\frac{d(M+m)}{dt} = (M+m)B_M(M+m) - \mu_M(M+m)$ and $\psi_1(0) + \psi_2(0) = 0$, $M(t,\psi) = m(t,\psi) = 0$, $\forall t \geq 0$. Then from the fourth, fifth, sixth and seventh equations of (5.1) we have $N(t,\psi) \to 0$, $n(t,\psi) \to 0$, $A(t,\psi) \to 0$, $a(t,\psi) \to 0$ as $t \to \infty$. In view of the third equation of (5.1), we have $L(t,\psi) \to 0$ as $t \to \infty$. In this case, $Q^n(\psi) \to M_1$ as $n \to \infty$.

Case 2. $\psi_1(0) > 0$.

Since $\psi_1(0) > 0$, from the first equation of (5.1) we have $M(t, \psi) > 0$, $\forall t \geq 0$. We proceed with the following two subcases:

Subcase 1. $m(t, \psi) = 0, \forall t \geq 0$.

From the second equation of (5.1) we get $n(t, \psi) = 0$, $\forall t \geq 0$. Then from the seventh equation of (5.1), we have $a(t, \psi) \to 0$ as $t \to \infty$. In this subcase, $Q^n(\psi) \to M_2$ or M_3 as $n \to \infty$.

Subcase 2. $m(t_0, \psi) > 0$ for some $t_0 > 0$.

From the second equation of (5.1) we have $m(t, \psi) > 0$, $\forall t \geq t_0$. We have two possibilities:

(i) $L(t, \psi) = 0$, $\forall t \geq 0$.

From the fourth and fifth equations of (5.1) we get $N(t, \psi) \to 0$, $n(t, \psi) \to 0$ as $t \to \infty$. Then from the sixth and seventh equations of (5.1), we have $A(t, \psi) \to 0$ and $a(t, \psi) \to 0$ as $t \to \infty$. From the second equation of (5.1) we obtain $m(t, \psi) \to 0$ as $t \to \infty$. Thus, $Q^n(\psi) \to M_2$ as $n \to \infty$.

(ii) $L(t_1, \psi) > 0$ for some $t_1 > 0$.

From the third equation of (5.1) we have $L(t, \psi) > 0$, $\forall t \geq t_1$. By the fifth equation of (5.1), it follows that $n(t, \psi) > 0$ for $t > \max\{t_0, t_1\} + \tau_l$. Then from the seventh equation of (5.1), we have $a(t, \psi) > 0$ for $t > \max\{t_0, t_1\} + \tau_l + \tau_n$. Thus, $Q^n(\psi) \in X_0$ for $n\omega > \max\{t_0, t_1\} + \tau_l + \tau_n$.

For the case where $\psi_5(0) = 0$ or $\psi_7(0) = 0$, we can do similar analysis. Finally, we see that for any given $\psi \in M_\partial$, $Q^n(\psi) \to M_1$ as $n \to \infty$, or $Q^n(\psi) \to M_2$ as $n \to \infty$, or $Q^n(\psi) \to M_3$ as $n \to \infty$. Thus, $\bigcup_{\phi \in M_\partial} \omega(\phi) \subseteq \{M_1,\ M_2,\ M_3\}$. Further, no subset of $\{M_1, M_2, M_3\}$ forms a cycle in ∂X_0. With the above three claims, we see that M_1, M_2

and M_3 are isolated invariant sets for Q in X, and $W^s(M_i) \cap X_0 = \emptyset, i = 1, 2, 3$, where $W^s(M_i)$ is the stable set of M_i for Q. By the acyclicity theorem on uniform persistence for maps (see, e.g., Theorem 1.2.1), it follows that $Q : X \to X$ is uniformly persistent with respect to X_0. Note that there exists an equivalent norm for $C([-\tau, 0], \mathbb{R}^8)$ such that for each $t > 0$, the solution map $Q(t)$ of system (5.1) is an κ-contraction on $C([-\tau, 0], \mathbb{R}^8_+)$, where κ is the Kuratowski measure of noncompactness (see, e.g., [29, Theorem 3.6.1]). It then follows from Theorem 1.2.5 that system (5.1) admits an ω-periodic solution $Q(t)\phi^*$ with $\phi^* \in X_0$. Then $M(t, \phi^*) \geq 0$, $m(t, \phi^*) > 0$, $L(t, \phi^*) \geq 0$, $N(t, \phi^*) \geq 0$, $n(t, \phi^*) > 0$, $A(t, \phi^*) \geq 0$, $a(t, \phi^*) > 0$, $H(t, \phi^*) = \frac{r_h}{\mu_h} > 0$. We claim that there exists some $\bar{t} \in [0, \omega]$ such that $M(\bar{t}, \phi^*) > 0$. If it is not the case, then $M(t, \phi^*) \equiv 0$ for all $t \geq 0$, due to the periodicity of $M(t, \phi^*)$. From the first equation of system (5.1) we get $0 = m(t, \phi^*)B_M(m(t, \phi^*)) > 0$, which is a contradiction. Since

$$\frac{dM(t, \phi^*)}{dt} \geq -(\mu_M + \alpha_2(t)\beta \max_{t \in [0,\omega]} n(t, \phi^*))M(t, \phi^*),$$

it follows that $M(t, \phi^*) > 0$ for all $t \geq \bar{t}$. Now the periodicity of $M(t, \phi^*)$ implies that $M(t, \phi^*) > 0$ for all $t \geq 0$. By similar arguments, we can show that $L(t, \phi^*) > 0$, $N(t, \phi^*) > 0$, $A(t, \phi^*) > 0$ for all $t \geq 0$. Therefore, $(M(t, \phi^*)$, $m(t, \phi^*)$, $L(t, \phi^*)$, $N(t, \phi^*)$, $n(t, \phi^*)$, $A(t, \phi^*)$, $a(t, \phi^*)$, $H(t, \phi^*))$ is a positive ω-periodic solution of system (5.1).

By Theorem 1.2.5 with $\rho(x) = d(x, \partial X_0)$, it then follows that $Q : X_0 \to X_0$ has a compact global attractor A_0. For any $\phi \in A_0$, we have $\phi_i(0) > 0$ for all $i = 2, 5, 7$. Let $B_0 := \bigcup_{t \in [0,\omega]} Q(t)A_0$. Then $\psi_i(0) > 0, i = 2, 5, 7$ for all $\psi \in B_0$. Moreover, $B_0 \subseteq X_0$ and $\lim_{t \to \infty} d(Q(t)\phi, B_0) = 0$ for all $\phi \in X_0$. Define a continuous function $p : X \to \mathbb{R}_+$ by

$$p(\phi) = \min_{i=2,5,7} \{\phi_i(0)\}, \quad \forall \phi \in X.$$

Since B_0 is a compact subset of X_0, we have $\inf_{\phi\in B_0} p(\phi) = \min_{\phi\in B_0} p(\phi) > 0$. Consequently, there exists $\eta > 0$ such that

$$\liminf_{t\to\infty} \min(m(t,\phi), n(t,\phi), a(t,\phi)) = \liminf_{t\to\infty} p(Q(t)\phi) \geq \eta.$$

This completes the proof. $\square$

By the same arguments as in Lemma 2.3.8, we have $r(P) = r(\hat{P})$. Combining Lemma 5.2.3 and Theorem 5.3.2, we have the following result.

Theorem 5.3.3. *Let (A1), (A2) and (A3) hold. Then the following statements are valid:*

(i) If $R_0 < 1$, then the disease-free periodic solution $(M^*,\ 0,\ L^*(t),\ N^*(t),\ 0,\ A^*(t),\ 0,\ H^*)$ is globally attractive for system (5.1) in X.

(ii) If $R_0 > 1$, then system (5.1) admits a positive ω-periodic solution and there exists a real number $\eta > 0$ such that any solution $(M(t,\varphi),\ m(t,\varphi),\ L(t,\varphi),\ N(t,\varphi),\ n(t,\varphi),\ A(t,\varphi),\ a(t,\varphi),\ H(t,\varphi))$ of system (5.1) with $\varphi \in X_0$ satisfies $\liminf_{t\to\infty}(m(t), n(t), a(t)) \geq (\eta, \eta, \eta)$.

5.4 A case study

In this section, we investigate the Lyme disease transmission in Long Point, Ontario, which is one of the endemic areas for Lyme disease in Canada.

Values for constant parameters in model (5.1) are obtained and estimated from [15, 16, 51, 64, 65]. We list them in Table 5.2. According to [64, 65, 66], the duration of development and activity of ticks are mainly affected by temperatures. Thus, we evaluate the periodic parameters in model (5.1) by using the monthly mean temperature data from 1981 to 2010 (obtained from the Environment Canada website:

http://www.climate.weatheroffice.gc.ca, see Table 5.3) of Delhi CDA station which is, among all the currently functioning weather stations, the closest to Long Point.

Table 5.2: Values for constant parameters in model (5.1)

Parameter	Value	Dimension	Reference
τ_l	3	day	[64]
τ_n	5	day	[64]
τ_a	10	day	[64]
r_M	2	day^{-1}	[15]
K_M	3000	dimensionless	[51]
β	1	dimensionless	[64]
β_T	0.9	dimensionless	[16]
γ	0.005	day^{-1}	[16]
ξ	0.1/30.4	day^{-1}	Estimated from [64]
μ_M	0.012	day^{-1}	[64]
μ_L	0.006	day^{-1}	[64]
μ_N	0.006	day^{-1}	[64]
μ_A	0.006	day^{-1}	[64]
μ_h	0.01/30.4	day^{-1}	Estimated from [65]
r_h	0.2/30.4	day^{-1}	Estimated from [65]

Table 5.3: Monthly mean temperatures for Delhi CDA (in °C)

Month	Jan	Feb	Mar	Apr	May	June
Temperature	-5.4	-4.7	0	6.9	13.2	18.5
Month	Jul	Aug	Sep	Oct	Nov	Dec
Temperature	21.1	20	15.5	9.4	3.5	-2.2

It follows from Figure 1 in [66] that the preoviposition period of female adults and the preeclosion period for egg masses are given in days, respectively, by

$$Y = 1300C^{-1.42}, \quad Y = 34234C^{-2.27},$$

where $C > 0$ is the temperature in °C. We assume that 5% of adult ticks are pregnant females and the maximum number of eggs produced by each pregnant tick is 3000

[64]. Then the maximal birth rate of ticks per day can be expressed as

$$0.05 \times \frac{3000}{1300C^{-1.42} + 34234C^{-2.27}}.$$

Substituting the temperatures in Table 5.3 into the above formula we can get 12 values, each of which represents the mean maximal birth rate for the corresponding month. For simplicity, we assume that the mean maximal birth rate for a month is also the mean maximal birth rate for each day in that month. Thus, we obtain a vector with 365 elements. After we put this vector into CFTOOL, we can get the following fitted function for the temperature-dependent maximal birth rate of ticks:

$$r(t) = c + \sum_{n=1}^{7} \left(a_n \cos \frac{2n\pi t}{365} + b_n \sin \frac{2n\pi t}{365} \right),$$

where $a_1 = -41.05, b_1 = -13.6, a_2 = 15.3, b_2 = 12.5, a_3 = 0.6696, b_3 = -1.877, a_4 = -1.76, b_4 = -3.236, a_5 = -0.9198, b_5 = -0.03388, a_6 = 0.3419, b_6 = 2.435, a_7 = 0.3846, b_7 = 0.04198, c = 27.04$.

According to [64, 65], the biting rates of larvae and nymphs to mice depend on the mice-finding probability and the activity proportion of immature ticks. The activity proportion of immature ticks is temperature-dependent. The relationship between the activity proportion and temperature is shown in Figure 3 of [65]. By the same method as in getting $r(t)$, we obtain the following fitted function for the temperature-dependent activity proportion of immature ticks:

$$\theta(t) = c + \sum_{n=1}^{7} \left(a_n \cos \frac{2n\pi t}{365} + b_n \sin \frac{2n\pi t}{365} \right),$$

where $a_1 = -0.1057$, $b_1 = -0.0374$, $a_2 = 0.0481$, $b_2 = 0.04018$, $a_3 = -0.009363$, $b_3 = -0.01734$, $a_4 = 0.001915$, $b_4 = 0.001805$, $a_5 = -0.004033$, $b_5 = -0.003589$,

$a_6 = 0.001028$, $b_6 = 0.006714$, $a_7 = 0.001692$, $b_7 = -0.002853$, $c = 0.06712$. In [64], the daily mice-finding probabilities of questing tick larvae and nymphs are given, respectively, by

$$\lambda_{ql} = 0.0013m^{0.515} \quad \text{and} \quad \lambda_{qn} = 0.002m^{0.515},$$

where m is the total number of mice. Then the daily biting rate of larvae and nymphs to one mouse can be given, respectively, by

$$\alpha_1(t) = \frac{0.0013M^{*0.515}}{M^*}\theta(t) \quad \text{and} \quad \alpha_2(t) = \frac{0.002M^{*0.515}}{M^*}\theta(t).$$

Note that for any given $\phi \in C_\omega$, we have

$$\begin{aligned}(L\phi)(t) &= \int_0^\infty K(t,s)\phi(t-s)ds \\ &= \sum_{k=0}^\infty \int_0^\omega K(t,s+k\omega)\phi(t-s)ds \\ &= \int_0^\omega (\sum_{k=0}^\infty K(t,s+k\omega))\phi(t-s)ds \\ &= \int_0^\omega G(t,s)\phi(t-s)ds,\end{aligned}$$

where $G(t,s) = \sum_{k=0}^\infty K(t,s+k\omega)$. Then we can use the method in [70] to calculate R_0. Setting the initial function values as $M(\theta) = 200, m(\theta) = 0, L(\theta) = 100, N(\theta) = 60, n(\theta) = 25, A(\theta) = 50, a(\theta) = 20, H(\theta) = 20$ for $\theta \in [-\tau, 0]$. With the above obtained constant and periodic parameter values, we obtain $R_0 = 2.5530 > 1$. In this case, the solution converges to a positive periodic solution eventually. The time series of $n(t)$ and $a(t)$ are shown in Figure 5.2. If we decrease the maximal birth rate of ticks to $0.1r(t)$, then the solution converges to a disease-free periodic solution, which means that the disease dies out eventually. In this case, we calculate $R_0 = 0.7980 < 1$. The long term behaviour of the questing nymph and adult tick populations are shown in

Figure 5.3 and Figure 5.4, respectively.

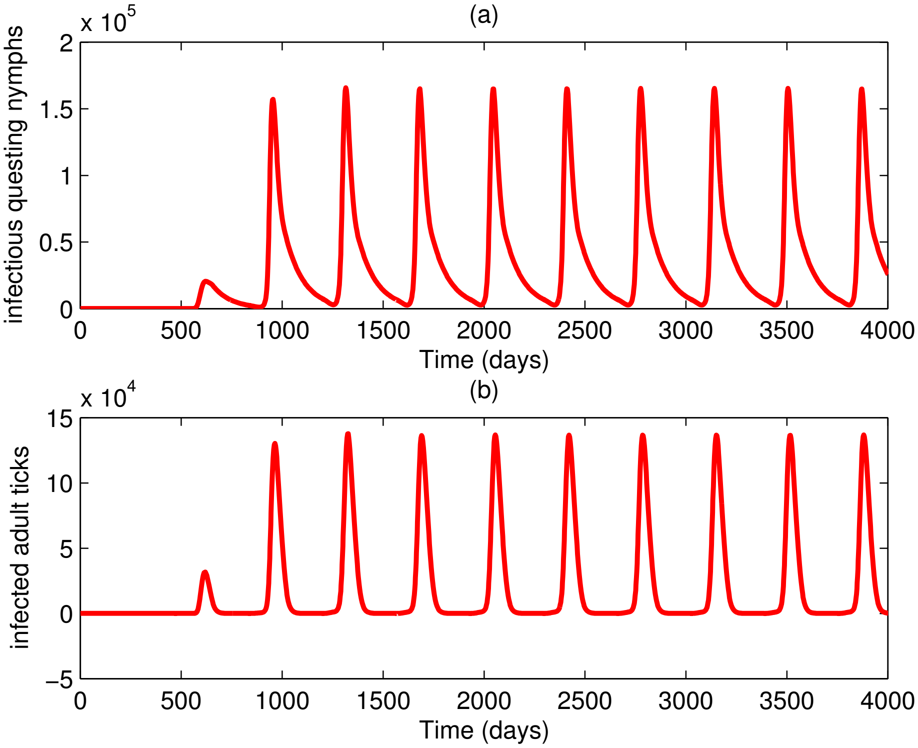

Figure 5.2: Long term behaviour of the solution, where $R_0 = 2.5530$. (a) Time series of $n(t)$; (b) Time series of $a(t)$.

5.5 Discussion

In this project, we have proposed a periodic and time-delayed Lyme disease model. By using the theory developed in [110], we have derived the basic reproduction ratio R_0 for our model. By appealing to the theory of monotone and subhomogeneous systems, the theory of uniform persistence for periodic semiflows and the theory of chain transitive sets, we have obtained a threshold type result on the global dynamics of the model in terms of R_0 under some additional conditions, that is, the disease will die out if $R_0 < 1$ and will persist if $R_0 > 1$.

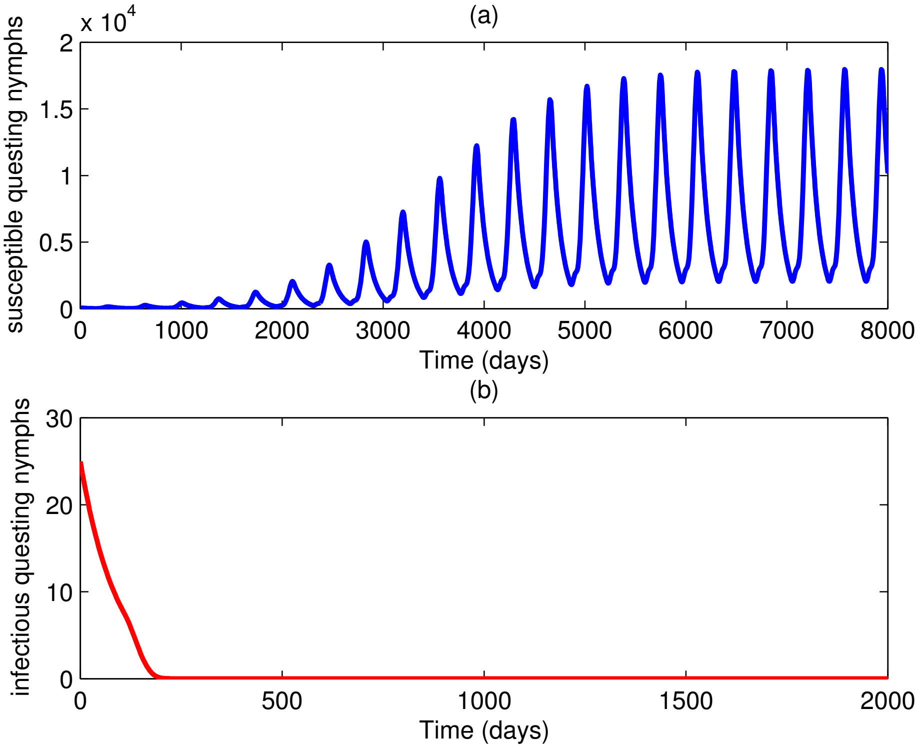

Figure 5.3: Long term behaviour of the solution, where $R_0 = 0.7980$. (a) Time series of $N(t)$; (b) Time series of $n(t)$.

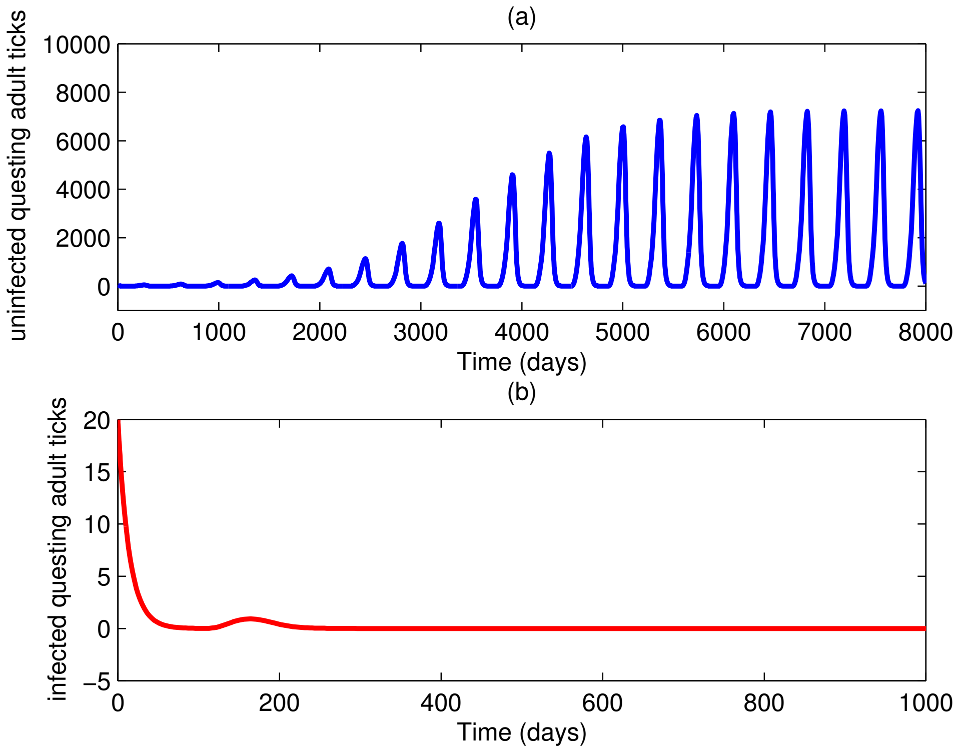

Figure 5.4: Long term behaviour of the solution, where $R_0 = 0.7980$. (a) Time series of $A(t)$; (b) Time series of $a(t)$.

In the case where $c(t) \equiv 0$, the limiting system (5.5) is exactly the linear system (5.7). By the same arguments as those for linear system (5.9) in the proof of Theorem 5.2.2 (just letting $\epsilon = 0$ there), it follows that there is a positive ω-periodic function $\bar{v}(t)$ such that $v^*(t) = e^{\frac{\ln r(\tilde{P})}{\omega}t}\bar{v}(t)$ is a positive solution of linear system (5.7). Note that for any real number $\delta > 0$, $\delta v^*(t)$ is also a solution of system (5.7). Then the standard comparison arguments imply that every positive solution of system (5.7) tends to zero if $r(\tilde{P}) < 1$, and to infinity if $r(\tilde{P}) > 1$, as $t \to \infty$. Thus, under the assumption (A2) (that is, $r(\tilde{P}) > 1$), the tick population grows without bound in the absence of the disease. This also explains why we need to use a positive but sufficiently small periodic function to deal with the case where $c(t) \equiv 0$.

Numerically, we have evaluated all the parameters by using some published data and simulated the Lyme disease transmission case in Long Point, Ontario, Canada. The simulation results show that Lyme disease will persist and exhibit periodic fluctuation in Long Point in the next few years if no further intervention is taken (see Figure 5.2). By employing the algorithm in [70], we numerically calculated the basic reproduction ratio for our model. By using the monthly mean temperatures from 1981 to 2010 in Long Point, we obtain $R_0 = 2.5530 > 1$. After we decrease the maximal birth rate of tick larvae by 90%, we get $R_0 = 0.7980 < 1$. The long term behaviour of the solution in Figures 5.3 and 5.4 indicates that the solution converges to a disease-free periodic solution. This implies that we may eliminate Lyme disease in Long Point by reducing the recruitment rate of tick larvae. Therefore, it may be helpful to regularly search for the spots where adult ticks usually lay eggs, like in sheds, in woodpiles, under rocks and in the crevices of walls. Since tick eggs are static, it is more feasible to focus on the clearance of eggs than to think about killing ticks of the other three life stages.

Chapter 6

Conclusions and future work

In this chapter, we briefly summarize the results of this thesis and present some possible projects as future work.

6.1 Research summary

This PhD thesis is devoted to the study of global dynamics of some climate-based vector-borne infectious disease models. In chapter 2, we proposed a periodic vector-bias malaria model with incubation period. A constant delay is employed to depict the extrinsic incubation period (EIP) in that model. We modified the model by changing the constant delay into a temperature-dependent delay in chapter 3. In chapter 4, we incorporated the control measure of bed net use into a simple mosquito-stage-structured malaria model. In chapter 5, we developed a time-delayed Lyme disease model with seasonality.

By using the recently developed R_0 theory for periodic and time-delayed models by Zhao [110] and the theory of R_0 for periodic models by Wang and Zhao [94], we derived the basic reproduction ratios for these models. By appealing to the theory of monotone and subhomogeneous systems, the theory of chain transitive sets and the theory of uniform persistence (see, e.g., [109]), we obtained the threshold dynamics of these models. For the malaria models in chapters 2 and 3, we proved that the disease-free periodic solution is globally asymptotically stable if $R_0 < 1$ and the positive periodic solution is globally asymptotically stable if $R_0 > 1$. For the malaria model in chapter 4, we obtained the threshold type result in terms of the vector reproduction ratio R_v and the basic reproduction ratio R_0, that is, the mosquito-free equilibrium is globally attractive is $R_v < 1$; the disease-free periodic solution is globally attractive if $R_v > 1$ and $R_0 < 1$; the positive periodic solution is globally attractive if $R_v > 1$ and $R_0 > 1$. For the Lyme disease model in chapter 5, we showed that the disease-free periodic solution is gloablly attractive if $R_0 < 1$; the model system is uniformly persistent and admits a positive periodic solution if $R_0 > 1$.

By conducting case studies, we proposed some practical strategies for the control of the diseases. For the models in chapters 2 and 3, based on data from Maputo Province, we find that prolonging the length of the EIP is helpful for the control of malaria, and the basic reproduction ratio may be underestimated if the time-averaged EIP is used. For the model in chapter 4, we parameterized the model with data from Port Harcourt, Nigeria. The simulation results suggest that the use of ITNs has a positive effect on reducing R_0, and that malaria may be eliminated from this area if over 75% of the human population were to use ITNs. In addition, we find that the ignorance of the vector-bias effect may underestimate the basic reproduction ratio R_0. Another notable result is that the infection risk would be underestimated if the basic reproduction ratio $[R_0]$ of the time-averaged autonomous system were used. In chapter 5, we studied the Lyme disease transmission in Long Point, Ontario, Canada. The simulation result indicates that Lyme disease is endemic in this region. We find that Lyme disease will be eliminated from this area if we decrease the recruitment rate of larvae, which implies that we may control Lyme disease by preventing tick eggs from hatching into larvae.

6.2 Future work

6.2.1 The comprehensive effects of multiple measures in the control of malaria

In recent years, emphasis has been put on integrating multiple strategies for malaria control. However, most mathematical models consider only one control measure (e.g., the bed net use or the vaccine). It is necessary to develop mathematical models which take into account multiple malaria control measures so that we can provide more realistic suggestions for the disease control.

6.2.2 A malaria transmission model with heterogeneous host mixing

The heterogeneity of the population has gained some attention in infectious disease transmission dynamics, that is, a discrete number of types of individuals are distinguished by some epidemiologically significant characteristics such as age groups, species, or routes by which they were infected (see, e.g., [14, 30, 56, 106] and the references therein). Rowe et al. proposed that blood group O protects against severe Plasmodium falciparum malaria through the mechanism of reduced resetting. Their findings provide insights into malaria pathogenesis and suggest that the selective pressure imposed by malaria may contribute to the variable global distribution of ABO blood groups in the human population [78]. We may consider developing a mathematical model for malaria involving different human host blood groups.

6.2.3 Modelling the effect of a double-edged drug on prevention of malaria transmission

At the end of chapter 2, we pointed out that prolonging the length of the EIP is helpful for the control of malaria transmission and we may develop some drugs for malaria-infected people so that once a mosquito bites an infected person who takes the drugs, then the EIP of malaria parasites in that mosquito will be prolonged, that is, the patients who take the drugs serve as a vector to let the drugs make effect on mosquitoes. This kind of drug is double-edged since it can not only alleviate symptoms of patients but also extend the EIP of malaria parasites in mosquitoes. It is interesting to develop a mathematical model to predict the effect of human individuals taking such EIP-extending drugs in a real malaria endemic region, like in a Sub-Saharan African country.

6.2.4 The effects of migratory birds on Lyme disease transmission

In recent years, northward invasive spread of the tick vectors from the United States endemic foci to non-endemic Canadian habitats is a public health concern [23, 67]. Migratory songbirds play an integral role in the wide spread of ticks, especially during northward spring migration [82]. The data reveal that 35% of I. scapularis nymphs removed from northward-migrating birds were infected with B. burgdorferi [82]. We can develop mathematical models to study the roles that the bird migration plays in the geographic distribution of I. scapularis, and hopefully, we may propose some strategies for Lyme disease control.

6.2.5 Dynamics of a sea lice model in a seasonally changing environment

Sea lice cause substantial economic losses on salmon farms [20]. Due to the economic importance of salmons, control of sea lice on salmon farms has been named one of the top priorities in aquaculture research by both scientists and aquaculture practitioners [33]. Sea lice exhibit temperature-dependent development rates and salinity-dependent mortality [74]. A variety of deterministic and stochastic models have been proposed to predict sea lice dynamics (see, e.g., [28, 73] and the references therein). However, little mathematical analysis has been carried out to understand the dynamical behaviors of the solutions. We propose to derive and analyze a sea lice model of functional differential equations with time-periodic delays. We can further consider models involving control measures for sea lice on salmon farms.

6.2.6 Summary

Since the life cycles of mosquitoes, ticks and sea lice are all strongly affected by the seasonally varying temperatures, we can develop non-autonomous ordinary differential equations models with periodic coefficients. Infected mosquitoes will undergo the EIP before they are able to transmit malaria. Larvae, nymphs and adult ticks have different feeding durations on mice and deer. The salmon louse, Lepeophtheirus salmonis, exhibit 8 distinct life stages, consisting of nauplius I/II, coopepodid, chalimus I/II, pre-adult I/II, and adult. The length of time that a nauplius or chalimus requires to mature to their respective next life stages depends on water temperature [74]. One way to depict the EIP of mosquitoes, the feeding duration of ticks, the waiting period of nauplius and chalimus is by time delays. Therefore, we can also develop delay differential equations models for the above projects. To be more realistic, we can even let the delays be periodic in time. The basic reproduction ratio is a key threshold parameter providing information for disease risk and control [90]. We need to derive the basic reproduction ratio and try to obtain the asymptotic behaviour of the model or some bifurcation results. To illustrate the analytic results and to provide insightful suggestions for the disease control, we will also collect some related data and conduct numerical simulations of case studies.

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