MATHEMATICAL BIOSCIENCES
AND ENGINEERING
Volume **10**, Number **2**, April **2013**

doi:10.3934/mbe.2013.10.463

pp. **463–481**

ON LATENCIES IN MALARIA INFECTIONS AND THEIR IMPACT ON THE DISEASE DYNAMICS

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(Communicated by Jia Li)

Abstract. In this paper, we modify the classic Ross-Macdonald model for malaria disease dynamics by incorporating latencies both for human beings and female mosquitoes. One novelty of our model is that we introduce two general probability functions ($P_1(t)$ and $P_2(t)$) to reflect the fact that the latencies differ from individuals to individuals. We justify the well-posedness of the new model, identify the basic reproduction number $\mathcal{R}_0$ for the model and analyze the dynamics of the model. We show that when $\mathcal{R}_0 < 1$, the disease free equilibrium E_0 is globally asymptotically stable, meaning that the malaria disease will eventually die out; and if $\mathcal{R}_0 > 1$, E_0 becomes unstable. When $\mathcal{R}_0 > 1$, we consider two specific forms for $P_1(t)$ and $P_2(t)$: (i) $P_1(t)$ and $P_2(t)$ are both exponential functions; (ii) $P_1(t)$ and $P_2(t)$ are both step functions. For (i), the model reduces to an ODE system, and for (ii), the long term disease dynamics are governed by a DDE system. In both cases, we are able to show that when $\mathcal{R}_0 > 1$ then the disease will persist; moreover if there is no recovery ($\gamma_1 = 0$), then all admissible positive solutions will converge to the unique endemic equilibrium. A significant impact of the latencies is that they reduce the basic reproduction number, regardless of the forms of the distributions.

1. **Introduction.** Malaria is an infectious disease that is widely spread in tropical and subtropical regions for thousands of years and causes deaths in human beings. It is due to infection by one or more of a family of protozoa called Plasmodium, mainly consisting of four species: Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae and Plasmodium ovale. The pathogen can parasite in the blood cells and other tissues of both human beings and mosquitoes. The infection between human beings and mosquitoes is through biting by female mosquitoes to human beings. Based on such a transmission mechanism, it was initially widely believed that the disease could be wiped out only by eradicating all vector mosquitoes, which turned out to be impossible in practice.

It was Ross [19] who firstly used a mathematical model to quantitatively investigated the spread of malaria. Ross' model was later further extended and studies

2010 *Mathematics Subject Classification.* Primary: 92D25, 92D30; Secondary: 37G99.

Key words and phrases. Malaria, latency, delay, basic reproduction number, stability, Lyapunov function/functional, persistence.

Research supported by NSERC and NCE-MITACS of Canada, and by a Premier's Research Excellence Award of Ontario.

by Macdonald [16, 17, 18], leading to the following system which has been referred to as the Ross-Macdonald model

$$\begin{cases} \frac{\mathrm{d}I_1}{\mathrm{d}t} = ae_1 I_2(1 - \frac{I_1}{N}) - d_1 I_1, \\ \frac{\mathrm{d}I_2}{\mathrm{d}t} = ae_2(M - I_2)\frac{I_1}{N} - d_2 I_2. \end{cases} \tag{1}$$

Here I_1 and I_2 represent the populations of the infectious classes of human beings and female mosquitoes respectively, N and M are the total populations of human beings and female mosquitoes respectively, which are assumed to be constants. The constant a is the mosquito biting rate; e_1 is the probability that a biting by an infective mosquito to a susceptible person will cause infection to the person; and e_2 is the probability that a biting by an susceptible mosquito to a infective human individual will cause infection to the mosquito. The parameters d_1 and d_2 are the death rates of infectious human beings and mosquitoes respectively. By analyzing this mathematical model, both Ross and Macdonald found that it is possible to eradicate the disease without killing all vector mosquitoes. Indeed, by looking at basic reproduction number for this model given by

$$\mathcal{R}_0 = \frac{ae_1 M}{d_1 N}\frac{ae_2}{d_2}, \tag{2}$$

one knows that any measure(s) that can bring $\mathcal{R}_0$ to a value less than 1 would eventually drive the disease to extinction, including controlling the mosquito population M to a sufficiently lower level. Obviously, the approach of mathematically modeling provides much insight into the spread of malaria, by which, effective means to control the disease can be suggested. For example, in addition to decreasing M to certain level (by spraying mosquito pesticides) which was Ross and Macdonald's finding, decreasing the biting rate (achievable by using mosquito nets) can also help eradicate malaria.

The Ross-Macdonald model is mathematically tractable in the sense that long term solution behavior of the model system (1) can be fully determined by the combined parameter $\mathcal{R}_0$. Yet, it is biologically less accurate in the sense that many biological factors are omitted. One of the important factors is the latency in the transmission process. This can be seen from the life cycle of malaria parasite. The life cycle of the Plasmodium begins from a blood meal of female mosquito from human beings. After being bitten by an infected female mosquito, a person receives an inoculum of plasmodium parasite (sporozoites). About half an hour later, liver cells of the person are invaded by sporozoites. The reproduction of parasites (merozoites) occurs in liver cells again and again, releasing more free merozoites to infect more liver cells. The immature trophozoites, the name of the merozoites at this stage, become mature developing either in the sexual or asexual way. Those who undergo the asexual development will go to the erythrocytic cycle producing more immature trophozolie, while others grows to gametocytes in the sexual way waiting for going out to the body of a female mosquito via its biting. Once they are ingested into a female mosquito, the parasite gametocytes taken up in the blood will further differentiate into male or female gametes and then fuse in the mosquito gut. This produces an ookinete that penetrates the gut lining and produces an oocyst in the gut wall. When the oocyst ruptures, it releases sporozoites that migrate through the mosquito's body to the salivary glands, where they are then ready to infect a new human host. See, e.g. [2, 22] for details on this

topic. Both developments inside a mosquito and inside an human host described above take some time.

Some modellers have noticed the missing of latencies in the Ross-Macdonald model and have proposed replacements by delay differential equations, but most of these works only have incorporated *a single delay* denoting the latency of the parasite in mosquitoes, see, e.g., [2, 3, 14]. Recently Ruan et al [20] modified the model (1) by adding *two delays* accounting for the latencies in mosquitoes and humans respectively, resulting in the following delayed and rescaled system

$$\begin{cases} \frac{\mathrm{d}x(t)}{\mathrm{d}t} = ame_1 y(t-\tau_1)[1-x(t-\tau_1)]e^{-d_1\tau_1} - d_1 x(t), \\ \frac{\mathrm{d}y(t)}{\mathrm{d}t} = ae_2[1-y(t-\tau_2)]x(t-\tau_2)e^{-d_2\tau_2} - d_2 y(t), \end{cases} \tag{3}$$

where $m = M/N$, $x = I_1/N$ and $y = I_2/M$, and the term $e^{-d_1\tau_1}$ ($e^{-d_2\tau_2}$ resp.) accounts for the probability that an infected human host (mosquito resp.) can survive the latent period τ_1 (τ_2 resp.). Note that (3) is exactly the subsystem of the model proposed in Anderson and May [1, p.399], consisting of the infectious components only, which is decoupled from the full system there. However no analysis was done in [1]. For this modified model, the basic reproduction number is adjusted to

$$\mathcal{R}_0 = \frac{a^2 e_1 e_2 m e^{-d_1\tau_1} e^{-d_2\tau_2}}{d_1 d_2}. \tag{4}$$

It is shown in [20] that when $\mathcal{R}_0 < 1$, then the disease free equilibrium $(0,0)$ is stable; when $\mathcal{R}_0 \geq 1$, then $(0,0)$ is unstable and there is an endemic equilibrium (x^*, y^*) which is locally asymptotically stable provided that the two delays are small and

$$a^2 e_1 e_2 m < ae_2 d_1 + 2d_1 d_2. \tag{5}$$

This condition is a mathematically technical one, and it does not seem to have a biological explanation. Numerical simulations indicate that solutions of (3) with initial values from the region $[0,1] \times [0,1]$ can go outside this region, causing a confusion since $x(t)$ and $y(t)$ are proportional variables. This confusion suggests a careful revisit to the model. Moreover, the latencies of the malaria parasite in mosquitoes may differ from individual to individual, and so do the latencies in humans. This requires some mechanism in the model to reflect such variances of the latencies.

The goal of this paper is to derive a more general and more realistic model that incorporates not only the latencies of the malaria parasite in both mosquitoes and humans, but also the variances of the latencies. In Section 2, following the idea in [25], we will formulate a more general model with two probability functions $P_1(t)$ and $P_2(t)$ describing the latency distributions for humans and for mosquitoes respectively. In Section 3, we analyze our new model. Under some reasonable assumptions, we address the well-posedness, identify the basic reproduction number $\mathcal{R}_0$ for the model, and prove that the disease free equilibrium is globally asymptotically stable if $\mathcal{R}_0 < 1$. When $\mathcal{R}_0 > 1$, the disease dynamics is more difficult to determine for general $P_1(t)$ and $P_2(t)$, hence we consider two specific cases for $P_1(t)$ and $P_2(t)$. In Sub-Section 3.2, we consider the case that $P_1(t)$ and $P_2(t)$ are both exponential functions, resulting in an ODE system; in Sub-Section 3.3, we take $P_1(t)$ and $P_2(t)$ as step functions, leading to a system of delay differential equations (DDE). In both cases, we are able to obtain results on the disease dynamics. In Section 4, we summarize our main results and give some remarks discussing the modelling issue.

2. **Model formulation for general latency distributions.** Denote the size of the population of human beings by $N(t)$ and that of the female mosquitoes by $M(t)$. Let $S_1(t)$ and $I_1(t)$ be, respectively, the sub-populations of the susceptible and infectious classes of human hosts and $S_2(t)$ and $I_2(t)$ be the respective sub-populations of the susceptible and infectious classes of female mosquitoes. As mentioned in the introduction, there is a complicated development process within a host as well as within a vector, causing a latency in each half of malaria life cycle. This requires introducing a third class of sub-population: latent (or exposed) class, consisting of those individuals who have been infected but are not infectious yet. Denote by $L_1(t)$ and $L_2(t)$ the sub-populations of the latent host and the latent female mosquito respectively.

We consider a simple demographic scenario by assuming constant natural birth rates and death rates for both humans and the mosquitoes, denoted respectively by $b_1,\ b_2$ and $d_1,\ d_2$. As in the introduction, we use the constant a to denote the mosquito biting rate and let e_1 be the probability that a biting by an infectious mosquito to a susceptible person will cause infection to the person, and e_2 be the probability that a biting by a susceptible mosquito to an infectious human individual will cause infection to the mosquito. The malaria parasite only causes deaths in human beings but not in mosquitoes, and this suggests introducing a disease related death rate for human beings, denoted by d. Infected human beings may recover, either due to the functioning of the immune system or through a treatment including taking anti-malaria drugs such as Chloroquine, Quinine and Amodiaquine. Let γ_1 be the recovery rate which is assumed to be a constant.

Now we introduce the latency distributions by following the idea in [25]. Let $P_1(t)$ denote the probability (without taking death into account) that a latent host individual still remains in the latent class t time units after entering the latent class (i.e., being infected). and similarly, let $P_2(t)$ be the probability that a latent vector individual still remains in the latent class t time units after entering the latent class. It is biologically reasonable to assume that $P_1(t)$ and $P_2(t)$ possess the following properties:

(H) : For $i = 1, 2,\ P_i : [0, \infty) \to [0, 1]$ are non-increasing, piecewise continuous with possibly finitely many jumps and satisfy $P_i(0^+) = 1$, $\lim_{t\to\infty} P_i(t) = 0$ with $\int_0^\infty P_i(u)\,\mathrm{d}u$ positive and finite.

Assume that initially $S_1(0) > 0,\ I_1(0) \geq 0,\ S_2(0) > 0,\ I_2(0) \geq 0$ and $L_1(0) = L_2(0) = 0$. Then the equations governing the subpopulations are given by

$$\begin{cases} \frac{\mathrm{d}S_1}{\mathrm{d}t} = b_1 N(t) - ae_1 I_2(t)\frac{S_1(t)}{N(t)} + \gamma_1 I_1(t) - d_1 S_1(t), \\ L_1(t) = \int_0^t ae_1 I_2(\xi)\frac{S_1(\xi)}{N(\xi)} e^{-(d_1+d)(t-\xi)} P_1(t-\xi)\,\mathrm{d}\xi, \\ I_1(t) = N(t) - S_1(t) - L_1(t), \\ \frac{\mathrm{d}S_2}{\mathrm{d}t} = -ae_2 S_2 \frac{I_1}{N(t)} + b_2 M(t) - d_2 S_2(t), \\ L_2(t) = \int_0^t ae_2 S_2(\xi)\frac{I_1(\xi)}{N(\xi)} e^{-d_2(t-\xi)} P_2(t-\xi)\,\mathrm{d}\xi, \\ I_2(t) = M(t) - S_2(t) - L_2(t). \end{cases} \tag{6}$$

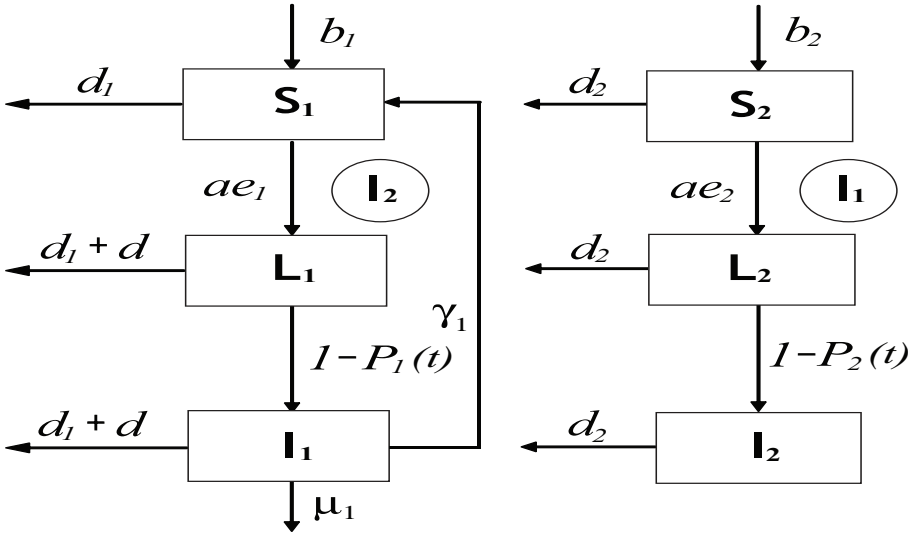

FIGURE 1. The transmission diagram of the host-vector SLIS model

Here, the integrals are in the Riemann-Stieltjes sense. This SLIS model can be visually illustrated by the diagram in Figure 1.

Since the emphasis of this paper is the impact of latencies, we will follow the existing models in [16, 17, 18, 19, 20] to assume constant total populations for both human beings and female vector mosquitoes, i.e., $N(t) = N$ and $M(t) = M$ both are constants. This can be achieved by, for example, assuming that

(A1) Disease related deaths can be ignored (i.e., setting $d = 0$);
(A2) The natural birth rates balance the natural death rates for both host and vector (i.e., $b_1 = d_1$ and $b_2 = d_2$).

There may be other situations that can lead to constant populations, (e.g., a compensation to the disease caused deaths by immigration for human host). However for simplicity of discussion, we simply assume (A1) and (A2) in the rest of the paper. We point out that in many situations, $N(t)$ and $M(t)$ vary only slightly, and this also constitute a good scenario for approximating $N(t)$ and $M(t)$ by constants. With these assumptions, one only needs to work on four out of the six variables. We choose S_1, I_1, S_2 and I_2 for which the governing differential equations are derived as below.

Differentiating the L_1 and L_2 equations (in the sense of Riemann-Stieltjes integral) leads to

$$\begin{cases} L_1'(t) = ae_1 I_2(t)\frac{S_1(t)}{N} + \int_0^t ae_1 I_2(\xi)\frac{S_1(\xi)}{N} e^{-d_1(t-\xi)} D_t P_1(t-\xi)\,\mathrm{d}\xi - d_1 L_1(t), \\ L_2'(t) = ae_2 S_2(t)\frac{I_1(t)}{N} + \int_0^t ae_2 S_2(\xi)\frac{I_1(\xi)}{N} e^{-d_2(t-\xi)} D_t P_2(t-\xi)\,\mathrm{d}\xi - d_2 L_2(t). \end{cases} \tag{7}$$

Here and hereafter, D_t means the derivative with respect to variable t. In the L_1 equation above, each term has its own biological meaning: the first term is the rate of new infections, the second term accounts for the rate at which the infected individuals move to the infectious class from the exposed class, and the third term is due to natural death. The terms in the L_2 equations are explained in the same

way. Passing to the I_1 and I_2 equations and keeping the S_1 and S_2 equations (6) lead to the following reduced system

$$\begin{cases} \frac{\mathrm{d}S_1}{\mathrm{d}t} = d_1 N - ae_1 I_2(t)\frac{S_1(t)}{N} + \gamma_1 I_1(t) - d_1 S_1(t), \\ \frac{\mathrm{d}I_1}{\mathrm{d}t} = -\int_0^t ae_1 I_2(\xi)\frac{S_1(\xi)}{N} e^{-d_1(t-\xi)} D_t P_1(t-\xi)\,\mathrm{d}\xi - (d_1+\gamma_1) I_1(t), \\ \frac{\mathrm{d}S_2}{\mathrm{d}t} = d_2 M - ae_2 S_2(t)\frac{I_1(t)}{N} - d_2 S_2, \\ \frac{dI_2}{dt} = -\int_0^t ae_2 S_2(\xi)\frac{I_1(\xi)}{N} e^{-d_2(t-\xi)} D_t P_2(t-\xi)\,\mathrm{d}\xi - d_2 I_2(t) \end{cases} \tag{8}$$

Rescaling (8) by

$$\begin{cases} \frac{S_1(t)}{N} \to S_1(t), \quad \frac{L_1(t)}{N} \to L_1(t), \quad \frac{I_1(t)}{N} \to I_1(t), \\ \frac{S_2(t)}{M} \to S_2(t), \quad \frac{L_2(t)}{M} \to L_2(t), \quad \frac{I_2(t)}{M} \to I_2(t) \end{cases}$$

gives

$$\begin{cases} \frac{\mathrm{d}S_1}{\mathrm{d}t} = d_1 - ae_1 m I_2(t) S_1(t) + \gamma_1 I_1(t) - d_1 S_1(t), \\ \frac{\mathrm{d}I_1}{\mathrm{d}t} = -\int_0^t ae_1 m I_2(\xi) S_1(\xi) e^{-d_1(t-\xi)} D_t P_1(t-\xi)\,\mathrm{d}\xi - (d_1+\gamma_1) I_1(t), \\ \frac{\mathrm{d}S_2}{\mathrm{d}t} = d_2 - ae_2 S_2(t) I_1(t) - d_2 S_2, \\ \frac{\mathrm{d}I_2}{\mathrm{d}t} = -\int_0^t ae_2 S_2(\xi) I_1(\xi) e^{-d_2(t-\xi)} D_t P_2(t-\xi)\,\mathrm{d}\xi - d_2 I_2(t) \end{cases} \tag{9}$$

with the following obvious constraints:

$$S_1(t) + L_1(t) + I_1(t) = 1, \quad S_2(t) + L_2(t) + I_2(t) = 1, \tag{10}$$

where $m = \frac{M}{N}$ represents the average mosquito number per person.

3. **Mathmatical analysis of the model.** By the theory for integro-differential equations in [15], one knows that for any given initial values $S_i(0) \geq 0$ and $I_i(0) \geq 0$, $i = 1, 2$, system (9) has a unique solution with $(S_1(t), I_1(t), S_2(t), I_2(t))$ satisfying the initial conditions. From the biological significance, we only need to consider system (9) in the set

$$\Omega := \{(S_1, I_1, S_2, I_2) \in R^4 : S_1 > 0,\ I_1 \geq 0,\ S_1 + I_1 \leq 1,\ S_2 > 0,\ I_2 \geq 0,\ S_2 + I_2 \leq 1.\}.$$

Indeed, one can easily show that the set Ω is positively invariant in the sense stated in the following lemma.

Lemma 3.1. *If $(S_1(0), I_1(0), S_2(0), I_2(0)) \in \Omega$ satisfies $S_1(0) + I_1(0) = 1$ and $S_2(0) + I_2(0) = 1$, then system (9) has a unique solution $(S_1(t), I_1(t), S_2(t), I_2(t))$ satisfying the initial conditions, which remains in Ω for all $t \geq 0$. Moreover, if $I_1(0) + I_2(0) > 0$, then $I_1(t) > 0$ and $I_2(t) > 0$ for $t > 0$.*

The proof of this Lemma is by a quite standard argument, namely, by using the variation-of-constant formula to individual equations as well as by way of contradiction, which is similar to that of Lemma 2.1 in [25]. We omit it to save space.

Let

$$\hat{P}_i := \lim_{t\to\infty} \int_0^t e^{-d_i u} P_i(u)\,\mathrm{d}u, \quad i = 1, 2.$$

Clearly, $\hat{P}_1$ (resp. $\hat{P}_2$) is the average time that an infected human being (resp. female mosquito) remains in the latent class before becoming infectious or dying (see [25]). By the properties of $P_i(u)$, one knows that

$$0 < \hat{P}_i < \lim_{t\to\infty} \int_0^t e^{-d_i u}\, \mathrm{d}u = 1/d_i, i = 1, 2.$$

Actually, $\hat{P}_1 d_1$ (resp. $\hat{P}_2 d_2$) is the probability that an infected host (resp. mosquito) will die during the latent period. Hence, Q_1 (resp. Q_2) represents the proportion of the exposed hosts (resp. vectors) that could survive the latent period, where

$$\begin{aligned} Q_i &:= -\lim_{t\to\infty} \textstyle\int_0^t e^{-d_i(t-\xi)} D_t P_i(t-\xi)\, \mathrm{d}\xi \\ &= 1 - d_i \hat{P}_i \in (0, 1), \quad i = 1, 2. \end{aligned}$$

Using Q_i, $i = 1, 2$, the basic reproduction number for the model (9) can then be defined as

$$\mathcal{R}_0 = m \frac{ae_1}{\gamma_1 + d_1} \cdot Q_1 \cdot \frac{ae_2}{d_2} \cdot Q_2, \tag{11}$$

accounting for the average number of secondary infections that a single infectious human being (female mosquito), once introduced into fully susceptible populations of mosquitoes and humans, is expected to cause to the humans (female mosquitoes) during the infection period. Here, due to the transmission nature of this vector-host disease, $\mathcal{R}_0$ consists of two parts: $m\frac{ae_1}{\gamma_1+d_1}\cdot Q_1$ accounts for how many new infectious mosquitoes an infectious human being can result in during his infection period and $\frac{ae_2}{d_2} \cdot Q_2$ explains how many new infectious human beings an infectious mosquito can lead to during its infection period.

Model system (9) has a disease free equilibrium E_0, given by $E_0 = (1, 0, 1, 0)$. In terms of the biological meaning of the basic reproduction number, $\mathcal{R}_0 = 1$ should be a threshold value for the stability/instability of E_0 for the model (9), as is confirmed in the following Theorem.

Theorem 3.2. *If $\mathcal{R}_0 < 1$, then E_0 is globally asymptotically stable in Ω; if $\mathcal{R}_0 > 1$, then E_0 becomes unstable.*

Proof of Theorem 3.2. The linearization of (9) at E_0 is

$$X'(t) = AX(t) + \int_0^t C(t-\xi)X(\xi)d\xi, \tag{12}$$

where

$$A = \begin{pmatrix} -d_1 & \gamma_1 & 0 & -ae_1 m \\ 0 & -(d_1+\gamma_1) & 0 & 0 \\ 0 & -ae_2 & -d_2 & 0 \\ 0 & 0 & 0 & -d_2 \end{pmatrix},$$

$$C(t) = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -ae_1 m e^{-d_1 t} D_t P_1(t) \\ 0 & 0 & 0 & 0 \\ 0 & -ae_2 e^{-d_2 t} D_t P_2(t) & 0 & 0 \end{pmatrix}.$$

Denote by $\bar{X}(z)$ the Laplace transform of $X(t)$. Applying the Laplace transform to (12) yields

$$[z\, I_d - A - \bar{C}(z)]\bar{X}(z) = X(0),$$

where I_d is the 4×4 identity matrix and $\bar{C}(z)$ is the Laplace transform of $C(t)$, i.e.,

$$\bar{C}(z)=\begin{pmatrix} 0 & 0 & 0 & 0\\ 0 & 0 & 0 & -B_1(z)\\ 0 & 0 & 0 & 0\\ 0 & -B_2(z) & 0 & 0\end{pmatrix},$$

with

$$\begin{aligned} B_1(z) &= \lim_{t\to\infty}\int_0^t ae_1me^{-(d_1+z)(t-\xi)}D_tP_1(t-\xi)\,\mathrm{d}\xi\\ &= \int_0^\infty ae_1me^{-(d_1+z)\xi}D_\xi P_1(\xi)\,\mathrm{d}\xi,\\ B_2(z) &= \lim_{t\to\infty}\int_0^t ae_2e^{-(d_2+z)(t-\xi)}D_tP_2(t-\xi)\,\mathrm{d}\xi=\int_0^\infty ae_2e^{-(d_2+z)\xi}D_\xi P_2(\xi)\,\mathrm{d}\xi. \end{aligned}$$

Thus, the stability of E_0 is determined by the roots of the characteristic equation $\mathbf{det}[z\,I_d-A-\bar{C}(z)]=0$, that is,

$$\mathbf{det}\begin{pmatrix} z+d_1 & -\gamma_1 & 0 & ae_1m\\ 0 & z+d_1+\gamma_1 & 0 & B_1(z)\\ 0 & ae_2 & z+d_2 & 0\\ 0 & B_2(z) & 0 & z+d_2\end{pmatrix}=0.$$

Expanding the determinant leads to

$$(z+d_1)(z+d_2)h(z)=0, \tag{13}$$

where

$$h(z)=(z+d_2)(z+\gamma_1+d_1)-B_1(z)B_2(z). \tag{14}$$

Since $z=-d_1$ and $z=-d_2$ are two negative real roots of (13), the stability of E_0 is fully determined by the roots of $h(z)=0$, which is equivalent to

$$z^2+(d_1+\gamma_1+d_2)z+d_2(d_1+\gamma_1)=B_1(z)B_2(z). \tag{15}$$

Assume that $\mathcal{R}_0<1$. Then

$$\begin{aligned} &\left|z^2+(d_1+\gamma_1+d_2)z+d_2(d_1+\gamma_1)\right|^2=|B_1(z)B_2(z)|^2\\ &\le (a^2e_1e_2mQ_1Q_2)^2=[d_2(\gamma_1+d_1)\mathcal{R}_0]^2\\ &<[d_2(\gamma_1+d_1)]^2. \end{aligned} \tag{16}$$

Let $z=x+iy$. If $x\ge 0$, then we have

$$\begin{aligned} &\left|z^2+(d_1+\gamma_1+d_2)z+d_2(d_1+\gamma_1)\right|^2\\ =\;&\left|x^2-y^2+(d_1+\gamma_1+d_2)x+d_2(d_1+\gamma_1)+i[2xy+(d_1+\gamma_1+d_2)y]\right|^2\\ \ge\;& y^4+y^2[2x^2+2x(d_1+\gamma_1+d_2)+d_1^2+\gamma_1^2+d_2^2+2d_1\gamma_1]+[d_2(d_1+\gamma_1)]^2\\ \ge\;&[d_2(d_1+\gamma_1)]^2, \end{aligned} \tag{17}$$

which contradicts (16). Therefore, the real part x must be negative, implying that E_0 is locally asymptotically stable if $\mathcal{R}_0<1$.

Next, assume that $\mathcal{R}_0>1$. To show that E_0 is unstable, it suffices to show that $h(z)=0$ admits a positive real root. Considering $z=x>0$ and let

$$T(x)=x^2+(d_1+\gamma_1+d_2)x+d_2(d_1+\gamma_1),\quad B(x)=B_1(x)B_2(z). \tag{18}$$

Note that $T(x)$ is increasing in $x\ge 0$ and

$$T(0)=d_2(\gamma_1+d_1)\ \text{ and }\ T(\infty)=\infty.$$

On the other side,

$$\begin{aligned} B(x) &= \left(\lim_{t\to\infty}\int_0^t ae_1me^{-(d_1+x)(t-\xi)}D_tP_1(t-\xi)\,\mathrm{d}\xi\right)\times \\ &\quad \left(\lim_{t\to\infty}\int_0^t ae_2e^{-(d_2+x)(t-\xi)}D_tP_2(t-\xi)\,\mathrm{d}\xi\right) \\ &= \lim_{t\to\infty}\int_0^t\int_0^t a^2e_1e_2me^{-(d_1+x)(t-\xi)-(d_2+x)(t-\eta)}D_tP_1(t-\xi)\,D_tP_2(t-\eta) \\ &\quad \mathrm{d}\xi\,\mathrm{d}\eta \end{aligned}$$

is decreasing for $x > 0$, and $B(0) = a^2e_1e_2mQ_1Q_2$. Now $\mathcal{R}_0 > 1$ is equivalent to $T(0) < B(0)$ which implies that the equation $T(x) = B(x)$ has a positive real root, that is, $h(z) = 0$ has a positive real root. Therefore, E_0 is unstable if $\mathcal{R}_0 > 1$.

Next, we show that E_0 is also globally attractive when $\mathcal{R}_0 < 1$. To this end, we use the notations

$$x^\infty = \limsup_{t\to\infty} x(t) \quad \text{and} \quad x_\infty = \liminf_{t\to\infty} x(t)$$

for a function defined for all large t. Let $(S_1(t), I_1(t), S_2(t), I_2(t))$ be a solution of (9) in Ω. By Lemma 3.1, we know that $S_1^\infty, I_1^\infty, S_2^\infty$ and I_2^∞ all exist and satisfy $0 \le S_1^\infty \le 1, 0 \le I_1^\infty \le 1, 0 \le S_2^\infty \le 1$ and $0 \le I_2^\infty \le 1$. By the Fluctuation Lemma [11], there is a sequence t_n with $t_n \to \infty$ as $n \to \infty$ such that

$$I_1(t_n) \to I_1^\infty, \quad \text{and} \quad I_1'(t_n) \to 0 \quad \text{as} \quad n \to \infty. \tag{19}$$

Rewrite the differential equation for $I_1(t)$ in (9) as

$$I_1'(t) + (\gamma_1 + d_1)I_1(t) = -\int_0^t ae_1mS_1(\xi)I_2(\xi)e^{-d_1(t-\xi)}D_tP_1(t-\xi)\,\mathrm{d}\xi. \tag{20}$$

Evaluating this equation at $t = t_n$ and letting $n \to \infty$ on both sides of the resulting equation, we obtain

$$(\gamma_1 + d_1)I_1^\infty \le \limsup_{n\to\infty}\left(-\int_0^{t_n} ae_1mS_1(\xi)I_2(\xi)e^{-d_1(t_n-\xi)}D_tP_1(t_n-\xi)\,\mathrm{d}\xi\right). \tag{21}$$

By the Lebesgue - Fatou Lemma (see [23], P468), it follows that

$$(\gamma_1 + d_1)I_1^\infty \le ae_1mS_1^\infty I_2^\infty Q_1. \tag{22}$$

Similarly, we can establish the following:

$$d_2I_2^\infty \le ae_2S_2^\infty I_1^\infty Q_2. \tag{23}$$

The two inequalities (22) and (23) imply that either I_1^∞ and I_2^∞ are both positive or both zero. We show that the former is impossible if $\mathcal{R}_0 < 1$. Otherwise, (22) and (23) would yield

$$(\gamma_1 + d_1) \le \frac{a^2e_1e_2mS_1^\infty S_2^\infty Q_1Q_2}{d_2}, \tag{24}$$

which equivalents to

$$\frac{1}{\mathcal{R}_0} \le S_1^\infty S_2^\infty.$$

This would lead to $1 < S_1^\infty S_2^\infty$ under $\mathcal{R}_0 < 1$, a contradiction to "$S_1^\infty \le 1$ and $S_2^\infty \le 1$". Therefore, $I_1^\infty = 0$ and $I_2^\infty = 0$, implying

$$I_1(t) \to 0, \;\; I_2(t) \to 0 \;\; \text{as} \;\; t \to \infty. \tag{25}$$

Applying (25) and the theory of asymptotically autonomous systems (see, e.g., [4]) to the $S_i(t)$ equations in (9), we conclude that

$$S_1(t) \to 1 \text{ and } S_2(t) \to 1 \text{ as } \quad t \to \infty. \tag{26}$$

Thus, E_0 is globally attractive, and hence, globally asymptotically stable in Ω provided that $\mathcal{R}_0 < 1$. The proof of the theorem is completed. □

When $\mathcal{R}_0 > 1$, for general functions $P_1(t)$ and $P_2(t)$, the dynamics of model (9) is difficult to determine. For example, even the important concept of endemic equilibrium remains a problem: for some choices of $P_1(t)$ and $P_2(t)$, model (9) may allow an endemic equilibrium while for others choices, it may not support an endemic equilibrium. To proceed further, we consider two special cases of $P_1(t)$ and $P_2(t)$, for which we are able to obtain some further information about the dynamics of (9).

3.1. **Special Case I—An ODE system.** In this section, we adopt $P_i(t) = e^{-\varepsilon_i t}, i = 1, 2$ where ε_1 and ε_2 are positive constants. This means that the probabilities of infected hosts and vector remaining in the latent classes follow negatively exponentially distributions with mean exposed times being $1/\varepsilon_1$ and $1/\varepsilon_2$ respectively. In this case, model (9) reduces to the following system of ordinary differential equations:

$$\begin{cases} \frac{\mathrm{d}S_1(t)}{\mathrm{d}t} = -ae_1 m S_1(t) I_2(t) + d_1 + \gamma_1 I_1(t) - d_1 S_1(t) \\ \frac{\mathrm{d}I_1(t)}{\mathrm{d}t} = \varepsilon_1 \left[1 - I_1(t) - S_1(t)\right] - (d_1 + \gamma_1) I_1(t), \\ \frac{\mathrm{d}S_2(t)}{\mathrm{d}t} = -ae_2 S_2 I_1(t) + d_2 - d_2 S_2(t), \\ \frac{\mathrm{d}I_2(t)}{\mathrm{d}t} = \varepsilon_2 \left[1 - I_2(t) - S_2(t)\right] - d_2 I_2(t). \end{cases} \tag{27}$$

The two survival factors Q_1 and Q_2 are now given by $Q_i = \frac{\varepsilon_i}{\varepsilon_i + d_i}, i = 1, 2$, and accordingly, the basic reproduction number becomes

$$\mathcal{R}_0 = \frac{ae_1 m}{\gamma_1 + d_1} \cdot \frac{ae_2}{d_2} \cdot \frac{\varepsilon_1}{\varepsilon_1 + d_1} \cdot \frac{\varepsilon_2}{\varepsilon_2 + d_2}. \tag{28}$$

When $\mathcal{R}_0 > 1$, in addition to the disease free equilibrium E_0 which is unstable, (27) also admits an endemic equilibrium $E^* = (S_1^*, I_1^*, S_2^*, I_2^*)$, where

$$S_1^* = \frac{C_0}{C_1}, \quad I_1^* = \frac{\epsilon_1 d_2 (\mathcal{R}_0 - 1)}{C_1} \quad S_2^* = C_2, \quad I_2^* = \frac{\mathcal{R}_0 - 1}{C_3}, \tag{29}$$

where

$$\begin{aligned} C_0 &= d_2 d_1 + d_2 \gamma_1 + d_2 \epsilon_1 + \epsilon_1 a e_2, \\ C_1 &= \tfrac{\epsilon_1 a e_2}{(d_1+\epsilon_1)(d_1+\gamma_1)(\epsilon_2+d_2)} (\epsilon_1\epsilon_2\gamma_1 + \epsilon_1\epsilon_2 d_1 + \epsilon_2 d_1^2 + \epsilon_2\gamma_1 d_1 + \epsilon_1\gamma_1 d_2 \\ &\quad + \epsilon_2 d_1 d_2 + d_1^2 d_2 + \gamma_1 d_1 d_2 + \epsilon_1\epsilon_2 e_1 a m + \epsilon_2 d_1 e_1 a m + \epsilon_2\gamma_1 e_1 a m), \\ C_2 &= \tfrac{d_2}{\epsilon_2 e_1 a m (d_1 d_2 + \gamma_1 d_2 + \epsilon_1 d_2 + \epsilon_1 e_2 a)} \left(\epsilon_1\epsilon_2\gamma_1 + \epsilon_1\epsilon_2 d_1 + \epsilon_2 d_1^2 + \epsilon_2\gamma_1 d_1 \right. \\ &\quad \left. + \epsilon_1\gamma_1 d_2 + \epsilon_1 d_1 d_2 + d_1^2 d_2 + \gamma_1 d_1 d_2 + \epsilon_1\epsilon_2 e_1 a m + \epsilon_2 d_1 e_1 a m + \epsilon_2\gamma_1 e_1 a m\right), \\ C_3 &= \tfrac{a m e_1}{\epsilon_1 d_2 (d_1+\epsilon_1)(d_1+\gamma_1)(\epsilon_2+d_2)} (\epsilon_2 d_1 d_2 + d_1 d_2^2 + \gamma_1 d_2^2 + \epsilon_2\gamma_1 d_2 \\ &\quad \epsilon_1 d_2 a e_2 + \epsilon_1\epsilon_2 d_2 + \epsilon_1 d_2^2 + \epsilon_1\epsilon_2 a e_2) \end{aligned}$$

are all positive constants. The following theorem shows that if $\gamma_1 = 0$, the global dynamics of system (27) is completely determined in terms of $\mathcal{R}_0$, which acts as a threshold in the global sense.

Theorem 3.3. *Consider (27). If $\mathcal{R}_0 > 1$, then the endemic equilibrium E^* is globally asymptotically stable among all positive solutions in Ω, provided that $\gamma_1 = 0$.*

Proof of Theorem 3.3. To prove the global stability of E^*, we consider the full model system associated with (27) by adding the latent classes:

$$\begin{cases} S_1'(t) = -\beta_{12} I_2(t) S_1(t) + d_1 + \gamma_1 I_1(t) - d_1 S_1(t), \\ L_1'(t) = \beta_{12} I_2(t) S_1(t) - (\varepsilon_1 + d_1) L_1(t), \\ I_1'(t) = \varepsilon_1 L_1(t) - (d_1 + \gamma_1) I_1(t), \\ S_2'(t) = -\beta_{21} S_2(t) I_1(t) + d_2 - d_2 S_2(t), \\ L_2'(t) = \beta_{21} S_2(t) I_1(t) - (d_2 + \varepsilon_2) L_2(t), \\ I_2'(t) = \varepsilon_2 L_2(t) - d_2 I_2(t), \end{cases} \tag{30}$$

where, for the convenience of notation, we have introduced the new parameters $\beta_{12} = ae_1 m$ and $\beta_{21} = ae_2$. We will employ a Lyapunov function similar to those used in recent works [12, 13, 7, 8]. To this end, we set $v_1 = \beta_{21} S_2^* I_1^*$ and $v_2 = \beta_{12} S_1^* I_2^*$ and let

$$\begin{aligned} V(t) \quad &= v_1 (S_1 - S_1^* - S_1^* \ln \tfrac{S_1}{S_1^*} + L_1 - L_1^* - L_1^* \ln \tfrac{L_1}{L_1^*}) \\ &\quad + v_2 (S_2 - S_2^* - S_2^* \ln \tfrac{S_2}{S_2^*} + L_2 - L_2^* - L_2^* \ln \tfrac{L_2}{L_2^*}) \\ &\quad + v_1 \tfrac{\varepsilon_1 + d_1}{\varepsilon_1} \left(I_1 - I_1^* - I_1^* \ln \tfrac{I_1}{I_1^*} \right) + v_2 \tfrac{\varepsilon_2 + d_2}{\varepsilon_2} \left(I_2 - I_2^* - I_2^* \ln \tfrac{I_2}{I_2^*} \right) \end{aligned} \tag{31}$$

where S_i^* and I_i^*, $i = 1, 2$, are given in (29), and $L_1^* = (d_1 + \gamma_1) I_1^* / \varepsilon_1$ and $L_2^* = d_2 I_2^* / \varepsilon_2$ or equivalently, $L_i^* = 1 - S_i^* - I_i^*$, $i = 1, 2$. Differentiating $V(t)$ along any

positive solution of (30) gives

$$\begin{aligned}
V'(t) &= v_1\left[\left(1-\tfrac{S_1^*}{S_1}\right)S_1'+\left(1-\tfrac{L_1^*}{L_1}\right)L_1'\right]+v_2\left[\left(1-\tfrac{S_2^*}{S_2}\right)S_2'+\left(1-\tfrac{L_2^*}{L_2}\right)L_2'\right]\\
&\quad +v_1\tfrac{\varepsilon_1+d_1}{\varepsilon_1}\left(1-\tfrac{I_1^*}{I_1}\right)I_1'+v_2\tfrac{\varepsilon_2+d_2}{\varepsilon_2}\left(1-\tfrac{I_2^*}{I_2}\right)I_2'\\
&= v_1\Big\{d_1S_1^*\left(2-\tfrac{S_1}{S_1^*}-\tfrac{S_1^*}{S_1}\right)+\beta_{12}S_1^*I_2+[2\beta_{12}S_1^*I_2^*-\gamma_1I_1^*+\gamma_1I_1\\
&\quad -\beta_{12}I_2^*\tfrac{(S_1^*)^2}{S_1}+\gamma_1I_1^*\tfrac{S_1^*}{S_1}-\gamma_1I_1\tfrac{S_1^*}{S_1}-\beta_{12}I_2S_1\tfrac{L_1^*}{L_1}-(\varepsilon_1+d_1)L_1\Big]\\
&\quad +\tfrac{\varepsilon_1+d_1}{\varepsilon_1}\left[\varepsilon_1L_1-(d_1+\gamma_1)I_1-\varepsilon_1L_1\tfrac{I_1^*}{I_1}+(d_1+\gamma_1)I_1^*\right]\Big\}\\
&\quad +v_2\Big\{d_2S_2^*\left(2-\tfrac{S_2}{S_2^*}-\tfrac{S_2^*}{S_2}\right)+\beta_{21}S_2^*I_1+\Big[2\beta_{21}S_2^*I_1-\beta_{21}I_1^*\tfrac{(S_2^*)^2}{S_2}\\
&\quad -\beta_{21}S_2I_1\tfrac{L_2^*}{L_2}-(\varepsilon_2+d_2)L_2\Big]+\tfrac{\varepsilon_2+d_2}{\varepsilon_2}\left[\varepsilon_2L_2-d_2I_2-\varepsilon_2L_2\tfrac{I_2^*}{I_2}+d_2I_2^*\right]\Big\}\\
&= v_1d_1S_1^*\left(2-\tfrac{S_1}{S_1^*}-\tfrac{S_1^*}{S_1}\right)+v_2d_2S_2^*\left(2-\tfrac{S_2}{S_2^*}-\tfrac{S_2^*}{S_2}\right)\\
&\quad +v_1\left[\beta_{12}S_1^*I_2-\tfrac{(\varepsilon_1+d_1)(d_1+\gamma_1)}{\varepsilon_1}I_1\right]+v_2\left[\beta_{21}S_2^*I_1-\tfrac{d_2(\varepsilon_2+d_2)}{\varepsilon_2}I_2\right]\\
&\quad +v_1\left[3\beta_{12}S_1^*I_2^*-\beta_{12}I_2^*\tfrac{(S_1^*)^2}{S_1}-\beta_{12}I_2S_1\tfrac{L_1^*}{L_1}-\beta_{12}S_1^*I_2^*\tfrac{L_1}{L_1^*}\tfrac{I_1^*}{I_1}\right]\\
&\quad +v_1\gamma_1\left(I_1-I_1^*+I_1^*\tfrac{S_1^*}{S_1}-I_1\tfrac{S_1^*}{S_1}\right)\\
&\quad +v_2\left[3\beta_{21}S_2^*I_1^*-\beta_{21}I_1^*\tfrac{(S_2^*)^2}{S_2}-\beta_{21}S_2I_1\tfrac{L_2^*}{L_2}-\beta_{21}S_2^*I_1^*\tfrac{L_2}{L_2^*}\tfrac{I_2^*}{I_2}\right].
\end{aligned}$$

The third and fourth terms on the right side of last equality cancel out:

$$\begin{aligned}
&v_1\left[\beta_{12}S_1^*I_2-\tfrac{(d_1+\varepsilon_1)(d_1+\gamma_1)}{\varepsilon_1}I_1\right]+v_2\left[\beta_{21}S_2^*I_1-\tfrac{d_2(\varepsilon_2+d_2)}{\varepsilon_2}I_2\right]\\
&=v_1v_2\left[\tfrac{I_2}{I_2^*}-\tfrac{I_1}{I_1^*}\right]+v_2v_1\left[\tfrac{I_1}{I_1^*}-\tfrac{I_2}{I_2^*}\right]=0
\end{aligned}$$

The sum of the fifth and seventh terms can be rewritten as

$$v_1v_2\left(6-\frac{S_1^*}{S_1}-\frac{S_1}{S_1^*}\frac{I_2}{I_2^*}\frac{L_1^*}{L_1}-\frac{S_2^*}{S_2}-\frac{S_2}{S_2^*}\frac{I_1}{I_1^*}\frac{L_2^*}{L_2}-\frac{L_1}{L_1^*}\frac{I_1^*}{I_1}-\frac{L_2}{L_2^*}\frac{I_2^*}{I_2}\right).$$

The sixth term vanishes since $\gamma_1=0$ is assumed. Thus, $V'(t)$ can be simplified as

$$\begin{aligned}
V'(t) &= v_1d_1S_1^*\left(2-\tfrac{S_1}{S_1^*}-\tfrac{S_1^*}{S_1}\right)+v_2d_2S_2^*\left(2-\tfrac{S_2}{S_2^*}-\tfrac{S_2^*}{S_2}\right)\\
&\quad +v_1v_2\left(6-\tfrac{S_1^*}{S_1}-\tfrac{S_1}{S_1^*}\tfrac{I_2}{I_2^*}\tfrac{L_1^*}{L_1}-\tfrac{S_2^*}{S_2}-\tfrac{S_2}{S_2^*}\tfrac{I_1}{I_1^*}\tfrac{L_2^*}{L_2}-\tfrac{L_1}{L_1^*}\tfrac{I_1^*}{I_1}-\tfrac{L_2}{L_2^*}\tfrac{I_2^*}{I_2}\right).
\end{aligned}\tag{32}$$

By the relation of arithmetic mean and geometric mean, we conclude that $V'(t) \le 0$ with the equality holding if and only if

$$\frac{S_1}{S_1^*} = \frac{L_1}{L_1^*} = \frac{I_1}{I_1^*} = \frac{S_2}{S_2^*} = \frac{L_2}{L_2^*} = \frac{I_2}{I_2^*} = 1.$$

By the Lyapunov-LaSalle Theorem, $\hat{E}^*$ is globally asymptotically stable for (30). Back to (27), we conclude that E^* is globally asymptotically stable for (27) among all positive solutions in Ω, completing the proof. □

3.2. **Special Case II—A DDE system.** Consider step functions for $P_1(t)$ and $P_2(t)$:

$$P_1(t) = \begin{cases} 1, & t \le \tau_1, \\ 0, & t > \tau_1. \end{cases} \quad \text{and} \quad P_2(t) = \begin{cases} 1, & t \le \tau_2, \\ 0, & t > \tau_2. \end{cases} \tag{33}$$

where $\tau_1 \ge 0$ and $\tau_2 \ge 0$ are constants. Although the latent period differs from individual to individual, choosing τ_1 and τ_2 as the respective average latencies for infected humans and infected female mosquitoes would make the above $P_1(t)$ and $P_2(t)$ reasonable approximations for the real situation.

With this pair of $P_1(t)$ and $P_2(t)$, the long term (e.g., for $t \ge \max\{\tau_1, \tau_2\}$) disease dynamics are governed by the following system of delay differential equations derived from (9):

$$\begin{cases} \frac{\mathrm{d}S_1(t)}{\mathrm{d}t} = -ae_1 m S_1(t) I_2(t) + d_1 - d_1 S_1(t) + \gamma_1 I_1(t), \\ \frac{\mathrm{d}I_1(t)}{\mathrm{d}t} = ae_1 m e^{-d_1\tau_1} S_1(t-\tau_1) I_2(t-\tau_1) - d_1 I_1(t) - \gamma_1 I_1(t), \\ \frac{\mathrm{d}S_2(t)}{\mathrm{d}t} = -ae_2 S_2(t) I_1(t) + d_2 - d_2 S_2(t), \\ \frac{\mathrm{d}I_2(t)}{\mathrm{d}t} = ae_2 e^{-d_2\tau_2} S_2(t-\tau_2) I_1(t-\tau_2) - d_2 I_2(t), \end{cases} \tag{34}$$

with

$$\begin{aligned} L_1'(t) &= ae_1 m S_1(t) I_2(t) - ae_1 m e^{-d_1\tau_1} S_1(t-\tau_1) I_2(t-\tau_1) - d_1 L_1(t), \\ L_2'(t) &= ae_2 S_2(t) I_1(t) - ae_2 e^{-d_2\tau_2} S_2(t-\tau_2) I_1(t-\tau_2) - d_2 L_2(t). \end{aligned} \tag{35}$$

Accordingly, Q_i can be calculated as $Q_i = e^{-d_i\tau_i}$, $i = 1, 2$, resulting in the following explicit formula for the basic reproduction number:

$$\mathcal{R}_0 = \frac{ae_1 m}{(d_1+\gamma_1)} \frac{ae_2}{d_2} e^{-d_1\tau_1} e^{-d_2\tau_2}. \tag{36}$$

For (34), when $\mathcal{R}_0 > 1$, the components of the unique endemic equilibrium $E^* = (S_1^*, I_1^*, S_2^*, I_2^*)$ can be more explicitly expressed by

$$S_1^* = \frac{(d_1+\gamma_1)D_1}{ae^{-d_1\tau_1}e_2 D_2}, \quad I_1^* = \frac{d_1(R_0-1)}{ae_2(d_1+\gamma_1)d_2 D_2},$$

$$S_2^* = \frac{d_2 D_2}{ae_1 m e^{-d2\tau_2} D_1}, \quad I_2^* = \frac{d_1(R_0-1)}{ae_1 m(d_1+\gamma_1)d_2 D_1},$$

where

$$\begin{aligned} D_1 &= \gamma_1 d_2(1 - e^{-d_1\tau_1}) + d_1 ae_2 e^{-d_1\tau_1} + d_1 d_2, \\ D_2 &= ae_1 m\gamma_1 e^{-d_2\tau_2}(1 - e^{-d_1\tau_1}) + ae_1 m e^{-d_2\tau_2} d_1 + d_1\gamma_1 + d_1^2. \end{aligned}$$

Theorem 3.2 has confirmed that the disease free equilibrium $E_0 = (1, 0, 1, 0)$ is globally asymptotically stable if $\mathcal{R}_0 < 1$ and it is unstable when $\mathcal{R}_0 > 1$. In the rest of this section, we explore the dynamics of (34) when $\mathcal{R}_0 > 1$.

For the DDE model system (34), the phase space is $X = C([-\tau_1, 0], R^2) \times C([-\tau_2, 0], R^2))$. The fundamental theory for such a DDE system can be found in Hale [9]. For biological reasons, we consider the subset

$$X_+^1 = \{\Phi = (\phi_1, \phi_2, \phi_3, \phi_4) \in X : \left.\begin{array}{l} 0 \le \phi_1(\theta) \le 1,\ 0 \le \phi_2(\theta) \le 1 \ \text{ for, } \ \theta \in [-\tau_1, 0] \\ 0 \le \phi_3(\theta) \le 1,\ 0 \le \phi_4(\theta) \le 1 \ \text{ for, } \ \theta \in [-\tau_2, 0] \end{array}\right\}.$$

Let $X_+^0 = \{\Phi = (\phi_1, \phi_2, \phi_3, \phi_4) \in X_+^1 : \text{ either } \phi_2 \text{ or } \phi_4 \text{ is not identical to } 0\}$. Then for any $\Phi \in X_+^0$, the corresponding solution $(S_1(t), I_1(t), S_2(t), I_2(t))$ satisfies $0 < S_1(t) \le 1,\ 0 < I_1(t) \le 1,\ 0 < S_2(t) \le 1$ and $0 < I_2(t) \le 1$ for $t > 0$. We first show that if $R_0 > 1$, then the disease is weakly persistent in the sense stated in the following lemma.

Lemma 3.4. *Assume $R_0 > 1$. Then for any initial function $\Phi = (\phi_1, \phi_2, \phi_3, \phi_4) \in X_+^0$, the corresponding solution $(S_1(t), I_1(t), S_2(t), I_2(t))$ satisfies*

$$I_1^\infty > 0,\ I_2^\infty > 0,\ S_{1\infty} < 1,\ S_{2\infty} < 1.$$

Proof of Theorem 3.4. By way of contradiction, we assume that the statement is false. We first show that the following equalities would all hold:

$$\lim_{t\to\infty} I_1(t) = 0, \quad \lim_{t\to\infty} I_2(t) = 0, \quad \lim_{t\to\infty} S_1(t) = 1, \quad \lim_{t\to\infty} S_2(t) = 1. \tag{37}$$

Indeed, if $I_1^\infty = 0$, then $I_1(t) \to 0$ as $t \to \infty$. Applying the theory of asymptotically autonomous systems (see, e.g., [4]) to the S_2 and I_2 equations in (34), we conclude that $S_2(t) \to 1$ and $I_2(t) \to 0$, which further leads to, by the S_1 equation in (34), $S_1(t) \to 1$. Similarly, $I_1^\infty = 0$ also leads to (37). If $S_{1\infty} = 1$, then $S_1(t) \to 1$ as $t \to \infty$. By $0 \le I_1(t) = I - S_1(t) - L_1(t) \le 1 - S_1(t)$, we know that $I_1(t) \to 0$ which in turn implies $I_2(t) \to 0$ and $S_2(t) \to 1$ as $t \to \infty$. Similarly, $S_{2\infty} = 1$ also leads to (37).

Now, for any $\delta \in (0, 1)$, by (37), there is $T > 0$ such that

$$I_1(t, \phi_2) < \delta, \quad I_2(t, \phi_4) < \delta, \quad S_1(t, \phi_1) > 1 - \delta, \quad S_2(t, \phi_3) > 1 - \delta, \ \text{ for } \ t \ge T. \tag{38}$$

By (38) and the I_1 and I_2 equations in (34), we have

$$\left\{\begin{array}{l} \frac{\mathrm{d}I_1(t)}{\mathrm{d}t} \ge ae_1 m e^{-d_1\tau_1} I_2(t - \tau_1)(1 - \delta) - (d_1 + \gamma_1) I_1(t), \\ \\ \frac{\mathrm{d}I_2(t)}{\mathrm{d}t} \ge ae_2 e^{-d_2\tau_2} I_1(t - \tau_2)(1 - \delta) - d_2 I_2(t) \end{array}\right. \quad \text{for } \ t \ge T. \tag{39}$$

This suggests the following linear comparison system for $I_1(t)$ and $I_2(t)$:

$$\left\{\begin{array}{l} \frac{\mathrm{d}u_1(t)}{\mathrm{d}t} = ae_1 m e^{-d_1\tau_1} u_2(t - \tau_1)(1 - \delta) - (d_1 + \gamma_1) u_1(t), \\ \\ \frac{\mathrm{d}u_2(t)}{\mathrm{d}t} = ae_2 e^{-d_2\tau_2} u_1(t - \tau_2)(1 - \delta) - d_2 u_2(t). \end{array}\right. \tag{40}$$

Since (40) is monotone, the stability/instability of the trivial solution of (40) is the same as that of the linear system obtained by dropping the two delays in (40) (see, e.g. Smith [21]) which is determined by the following characteristic equation:

$$\lambda^2 + (d_1 + \gamma_1 + d_2)\lambda + (d_1 + \lambda_1) d_2 \left[1 - (1 - \delta)^2 \mathcal{R}_0\right] = 0. \tag{41}$$

Because $\mathcal{R}_0 > 1$, one can choose $\delta \in (0,1)$ sufficiently small so that $1-(1-\delta)^2\mathcal{R}_0 < 0$, and hence, (41) has a root with positive real part. This means that positive solutions of (41) are unbounded. On the other hand, the comparison theorem for delay differential equations (see, e.g., Smith [21]) implies that $I_1(t) \geq u_1(t)$ and $I_2(t) \geq u_2(t)$ where $(u_1(t), u_2(t))$ is the positive solution of (41) with the initial function (ϕ_2, ϕ_4) and hence is unbounded. This contradicts (37), and the contradiction completes the proof of the lemma. □

The following theorem claims that under $\mathcal{R}_0 > 1$, the disease is actually *uniformly strongly persistent*.

Theorem 3.5. *Assume that if $\mathcal{R}_0 > 1$. Then there exists an $\eta > 0$ such that for any initial function $\Phi = (\phi_1, \phi_2, \phi_3, \phi_4) \in X_+^0$, the corresponding solution $(S_1(t), I_1(t), S_2(t), I_2(t))$ satisfies*

(i) $\frac{d_1}{ae_1m+d_1} \leq S_{1\infty}$ *and* $\frac{d_2}{ae_2+d_2} \leq S_{2\infty}$;
(ii) $\eta \leq I_{1\infty}$ *and* $\eta \leq I_{2\infty}$.

Proof of Theorem 3.5. Since $0 \leq I_1(t) \leq 1$ for $t \geq -\tau_2$ and $0 \leq I_2(t) \leq 1$ for all $t \geq -\tau_1$, the $S_1'(t)$ and $S_2'(t)$ equations in system (34) lead to

$$S_1'(t) \geq d_1 - ae_1mS_1(t) - d_1S_1(t) = d_1 - (ae_1m + d_1)S_1(t),$$

$$S_2'(t) \geq d_2 - ae_2S_2(t) - d_2S_2(t) = d_2 - (ae_2 + d_2)S_2(t).$$

By the standard comparison theorem (see, e.g., [21]), it follows that $S_1(t) \geq w_1(t)$, and $S_2(t) \geq w_2(t)$, where $(w_1(t), w_2(t))$ is the solution of

$$w_1'(t) = d_1 - ae_1mw_1(t) - d_1w_1(t),$$

$$w_2'(t) = d_2 - ae_2w_2(t) - d_2w_2(t).$$

with $w_1(0) \leq \phi_1(0)$, $w_2(0) \leq \phi_3(0)$. Thus,

$$S_{1\infty} \geq w_{1\infty} = \frac{d_1}{ae_1m + d_1}, \text{ and } S_{2\infty} \geq w_{2\infty} = \frac{d_2}{ae_2 + d_2}. \tag{42}$$

Next, applying the Fluctuation Lemma (see, e.g., [11]) to the $S_1'(t)$ and $S_2'(t)$ equations in system (34) gives

$$I_1^\infty \geq \frac{d_2 - d_2S_{2\infty}}{ae_2S_{2\infty}}, \quad I_2^\infty \geq \frac{d_1 - d_1S_{1\infty}}{ae_1mS_{1\infty}}. \tag{43}$$

By Lemma 3.4 and the inequalities in (43), we know that $\partial X_+^1 = X_+^1/X_+^0$ is a uniform *weak* repeller for X_+^0. Applying Theorem 1.4 of [24] to the solution semiflow $\mathbf{\Psi}(t, \Phi) = (S_1(t), I_1(t), S_2(t), I_2(t))$ of system (34) for $t \geq \max(\tau_1, \tau_2)$ with $\Phi \in X_+^0$, we conclude that ∂X_+^1 is also a uniform *strong* repeller for X_+^0, implying that the disease is uniformly strongly persistent. This means that there exists an $\eta > 0$ such that $I_{1\infty} \geq \eta$, $I_{2\infty} \geq \eta$, where η is independent of the initial function $\Phi \in X_+^0$. The proof is completed. □

The following theorem, parallel to Theorem 3.3 for (27), confirms the globally asymptotically stability of the endemic equilibrium E^* for (34) under the assumption $\gamma_1 = 0$.

Theorem 3.6. *Consider (34). Assume that $R_0 > 1$. Then the endemic equilibrium E^* is globally asymptotically stable in X_+^0, provided that $\gamma_1 = 0$.*

Proof of Theorem 3.6. We use a Lyapunov functional to prove the theorem. Let

$$\begin{aligned}
V &= ae_2e^{-d_2\tau_2}S_2^*I_1^*\left[e^{-d_1\tau_1}S_1^*\left(\frac{S_1}{S_1^*}-1-\ln\frac{S_1}{S_1^*}\right)+I_1^*\left(\frac{I_1}{I_1^*}-1-\ln\frac{I_1}{I_1^*}\right)\right]\\
&\quad +ae_1me^{-d_1\tau_1}S_1^*I_2^*\left[e^{-d_2\tau_2}S_2^*\left(\frac{S_2}{S_2^*}-1-\ln\frac{S_2}{S_2^*}\right)+I_2^*\left(\frac{I_2}{I_2^*}-1-\ln\frac{I_2}{I_2^*}\right)\right]\\
&\quad +ae_2e^{-d_2\tau_2}S_2^*I_1^*ae_1mS_1^*I_2^*e^{-d_1\tau_1}\times\\
&\quad \int_{-\tau_1}^{0}\left(\frac{S_1(t+s)I_2(t+s)}{S_1^*I_2^*}-1-\ln\frac{S_1(t+s)I_2(t+s)}{S_1^*I_2^*}\right)\mathrm{d}s\\
&\quad +ae_1me^{-d_1\tau_1}S_1^*I_2^*ae_2S_2^*I_1^*e^{-d_2\tau_2}\times\\
&\quad \int_{-\tau_2}^{0}\left(\frac{S_2(t+s)I_1(t+s)}{S_2^*I_1^*}-1-\ln\frac{S_2(t+s)I_1(t+s)}{S_2^*I_1^*}\right)\mathrm{d}s.
\end{aligned}$$

The derivative of V along the trajectory of (34) is

$$\begin{aligned}
V' &= ae_2S_2^*I_1^*e^{-d_2\tau_2}\left[d_1e^{-d_1\tau_1}S_1^*\left(2-\tfrac{S_1}{S_1^*}-\tfrac{S_1^*}{S_1}\right)\right.\\
&\quad +e^{-d_1\tau_1}\gamma_1\left(I_1-I_1^*+I_1^*\tfrac{S_1^*}{S_1}-I_1\tfrac{S_1^*}{S_1}\right)-(\gamma_1+d_1)I_1\\
&\quad +ae_1me^{-d_1\tau_1}I_2^*S_1^*+ae_1mI_2S_1^*e^{-d_1\tau_1}-ae_1me^{-d_1\tau_1}I_2^*\tfrac{(S_1^*)^2}{S_1}\\
&\quad -ae_1me^{-d_1\tau_1}I_2(t-\tau_1)S_1(t-\tau_1)\tfrac{I_1^*}{I_1}+ae_1me^{-d_1\tau_1}I_2^*S_1^*\\
&\quad \left.-ae_1me^{-d_1\tau_1}\ln\tfrac{I_2S_1}{I_2(t-\tau_1)S_1(t-\tau_1)}\right]\\
&\quad +ae_1mS_1^*I_2^*e^{-d_1\tau_1}\left[d_2S_2^*e^{-d_2\tau_2}\left(2-\tfrac{S_2}{S_2^*}-\tfrac{S_2^*}{S_2}\right)+2ae_2S_2^*I_1^*e^{-d_2\tau_2}\right.\\
&\quad +ae_2S_2^*I_1e^{-d_2\tau_2}-ae_2S_2^*I_1^*e^{-d_2\tau_2}\tfrac{S_2^*}{S_2}-d_2I_2-\\
&\quad ae_2e^{-d_2\tau_2}I_1(t-\tau_2)S_2(t-\tau_2)\tfrac{I_2^*}{I_2}\\
&\quad \left.-ae_2e^{-d_2\tau_2}\ln\tfrac{I_1S_2}{I_1(t-\tau_2)S_2(t-\tau_2)}\right].
\end{aligned}$$

Setting $c_1=ae_2I_1^*S_2^*e^{-d_2\tau_2}$ and $c_2=ae_1mI_2^*S_1^*e^{-d_1\tau_1}$, and reorganizing the above formula, we obtain

$$\begin{aligned}
V' =& c_1d_1e^{-d_1\tau_1}S_1^*\left(2-\frac{S_1}{S_1^*}-\frac{S_1^*}{S_1}\right)+c_2d_2e^{-d_2\tau_2}S_2^*\left(2-\frac{S_2}{S_2^*}-\frac{S_2^*}{S_2}\right)\\
&+c_1e^{-d_1\tau_1}\gamma_1\left(I_1-I_1^*+I_1^*\frac{S_1^*}{S_1}-I_1\frac{S_1^*}{S_1}\right)\\
&+\left(a^2e_1e_2me^{-d_1\tau_1-d_2\tau_2}I_1^*S_2^*I_2S_1^*-ae_1mI_2^*S_1^*e^{-d_1\tau_1}d_2I_2\right)
\end{aligned}$$

$$+\left[a^2e_1e_2me^{-d_1\tau_1-d_2\tau_2}I_1S_2^*I_2^*S_1^*-ae_2I_1^*S_2^*e^{-d_2\tau_2}(d_1+\gamma_1)I_1\right]$$

$$+c_1c_2\left[4-\frac{S_1^*}{S_1}-\frac{S_2^*}{S_2}-\frac{I_2(t-\tau_1)}{I_2^*}\frac{S_1(t-\tau_1)}{S_1^*}\frac{I_1^*}{I_1}\right.$$

$$\left.-\frac{I_1(t-\tau_2)}{I_1^*}\frac{S_2(t-\tau_2)}{S_2^*}\frac{I_2^*}{I_2}-\ln\frac{I_2S_1}{I_2(t-\tau_1)S_1(t-\tau_1)}-\ln\frac{I_1S_2}{I_1(t-\tau_2)S_2(t-\tau_2)}\right].$$

The third term vanishes due to the assumption $\gamma_1 = 0$. Both the fourth and fifth terms are also zero by the equations for the equilibrium E^*. Now the sixth (last) term can be further rewritten as

$$c_1c_2\left[\left(1-\frac{S_1^*}{S_1}+\ln\frac{S_1^*}{S_1}\right)+\left(1-\frac{S_2^*}{S_2}+\ln\frac{S_2^*}{S_2}\right)+(1-x+\ln x)+(1-y+\ln y)\right],$$

where

$$x=\frac{I_2(t-\tau_1)}{I_2^*}\frac{S_1(t-\tau_1)}{S_1^*}\frac{I_1^*}{I_1},\quad y=\frac{I_1(t-\tau_2)}{I_1^*}\frac{S_2(t-\tau_2)}{S_2^*}\frac{I_2^*}{I_2}.$$

Thus,

$$\begin{aligned}V' &= c_1d_1e^{-d_1\tau_1}S_1^*\left(2-\frac{S_1}{S_1^*}-\frac{S_1^*}{S_1}\right)+c_2d_2S_2^*e^{-d_2\tau_2}\left(2-\frac{S_2}{S_2^*}-\frac{S_2^*}{S_2}\right)\\ &\quad +c_1c_2\left[\left(1-\frac{S_1^*}{S_1}+\ln\frac{S_1^*}{S_1}\right)+\left(1-\frac{S_2^*}{S_2}+\ln\frac{S_2^*}{S_2}\right)\right.\\ &\quad \left.+(1-x+\ln x)+(1-y+\ln y)\right]. \qquad (44)\end{aligned}$$

Now, by the relation between arithmetic and geometric means and the property of the function $g(u) = 1 - u + \ln u$, we conclude that $V' \le 0$ and $V' = 0$ if and only if (S_1, I_1, S_2, I_2) is at E^*. It follows from the Lyapunov-LaSelle Theorem for DDEs (see [9]) that E^* is globally asymptotically stable in X_+^0, completing the proof. □

4. **Conclusion and discussion.** In this paper, we have modified the classic Ross-Macdonald model for the disease dynamics of Malaria by incorporating latencies both in human beings and in the female mosquitoes. The novelty of our model is that we have introduced two general probability functions ($P_1(t)$ and $P_2(t)$) to reflect the fact that the latencies of the malaria parasite differ from individuals to individuals in both humans and mosquitoes. We have justified the well-posedness of the new model, identified the basic reproduction number $\mathcal{R}_0$ for the model and analyzed the dynamics of the model. We have shown, very naturally and as in most works on disease models, that when $\mathcal{R}_0 < 1$, the disease free equilibrium E_0 is globally asymptotically stable, meaning that the disease will eventually die out; and if $\mathcal{R}_0 > 1$, E_0 becomes unstable. When $\mathcal{R}_0 > 1$, the dynamics of the model become more difficult for general $P_1(t)$ and $P_2(t)$, and this forces us to consider some specific functions. When $P_1(t)$ and $P_2(t)$ are both exponential functions, the model reduces to a system of ordinary differential equations; when $P_1(t)$ and $P_2(t)$ are both step functions, the long term disease dynamics are governed by a system of delay differential equations. In both cases, we are able to show that when $\mathcal{R}_0 > 1$ then the disease will persist; moreover if there is no recovery ($\gamma_1 = 0$), then all admissible positive solutions will converge to the unique endemic equilibrium.

Our approach may provide a frame work for dynamics of other mosquito-borne diseases. Taking Dengue as an example, since this disease is caused by dengue *virus*

(unlike malaria protozoa), the recovered human beings will carry immunity and hence will not return to the susceptible class, implying $\gamma_1 = 0$ in the corresponding model. Therefore, our approach (actually results) can be easily applied to the corresponding model(s) for dengue disease.

From the formula of the basic reproduction number $\mathcal{R}_0$ for our model, we can see that it is indeed smaller than the one obtained by ignoring the latencies (i.e., setting $Q_1 = 1$ and $Q_2 = 1$). In other words, if the latencies are neglected in modelling the disease dynamics, the basic reproduction number will be over calculated, regardless of what forms of the latency probability functions $P_1(t)$ and $P_2(t)$ are adopted

We point out that there is a mathematical theory for disease model which defines the basic reproduction number as the spectral radius of the so called next generation operator. Here in this paper, our $\mathcal{R}_0$ is defined by the so called survival function (see,e.g.,[10]). The difference lies in that " the survival function gives the total number of infections in the same class produced by a single infective of that class, while the next generation operator gives the mean number of new infections per infective in any class per generation. Value corresponding to the latter definition thus depend on the number of infective classes in the infection cycle " [10]. Taking the the ODE model (27) as an example, using the next generation operator (matrix in this case) approach from [5, 26], the basic reproduction number for (27) is defined as

$$\mathcal{R}_0 = \sqrt{\frac{ae_1m}{\gamma_1 + d_1} \cdot \frac{ae_2}{d_2} \cdot \frac{\varepsilon_1}{\varepsilon_1 + d_1} \cdot \frac{\varepsilon_2}{\varepsilon_2 + d_1}}, \tag{45}$$

which is the square root of the formula in (28). Note that many researchers have used survival function scenario to define basic reproduction numbers for vector-borne diseases, see e.g., [2, 10, 20] and the references therein. Note that because the threshold value for the basic reproduction number is at 1, such a difference does not cause any mathematical problem in exploring the threshold property of vector-borne disease models. For a detailed discussion on this topic, we refer readers to [5, 6, 10, 26].

We conclude the paper by a remark that the way we have incorporated latencies in this paper may also help clarify the confusion for (1.3) mentioned in the introduction. Indeed, by adding $\tau_1 > 0$ and $\tau_2 > 0$ into the model, latent classes in both humans and mosquitoes are admitted and hence, the terms $1 - x(t - \tau_1)$ and $1 - y(t - \tau_2)$ should be replaced by $1 - l_1(t - \tau_1) - x(t - \tau_1)$ and $1 - l_2(t - \tau_2) - y(t - \tau_2)$ respectively, where $l_1(t)$ is the proportion of the latent human beings and $l_2(t)$ is the proportion of the latent mosquitoes with both satisfying equations corresponding to (35). Since $1 - x(t - \tau_1)$ is larger than $1 - l_1(t - \tau_1) - x(t - \tau_1)$ and $1 - y(t - \tau_2)$ is larger than $1 - l_2(t - \tau_2) - y(t - \tau_2)$, this may explain why the solutions of (1.3) with initial values from $[0, 1] \times [0, 1]$ may go beyond this region. When only considering a discrete latency in mosquitoes, a similar situation is also discussed in Aron and May [2].

Acknowledgments. The authors would like to thank the two anonymous referees for their comments which have led to an improvement in the presentation of the paper.

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Received February 07, 2012; revised August 21, 2012.

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