

## CAN MULTIPLE MALARIA SPECIES CO-PERSIST?\*

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**Abstract.** There are several species of malaria protozoa spreading in different geographic regions. On the other hand, the world becomes more highly connected by travel than ever before. This raises a natural concern of possible epidemics caused by multiple species of malaria parasites in one region. In this study, we use mathematical models to explore such a possibility. First, we propose a model to govern the within-host dynamics of two species. Analysis of this model practically excludes the possibility of co-persistence (or superinfection) of the two species in one host. Then we move on to set up another model to describe the dynamics of disease transmission between human and mosquito populations without the co-infection class (using the results in section 2). By analyzing this model, we find that epidemics involving both species in a single region are possible.

**Key words.** malaria, strains, within-host level, between-host level, basic reproduction number, stability, persistence, compound matrix

**AMS subject classifications.** 34D05, 34D20, 34D23, 92B05, 92D30, 92D25

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**1. Introduction.** Malaria is widespread and the most prevalent infectious disease in the world. It causes millions of infections every year, 90% of which are either children under age five or pregnant women. Since the 1980s, this disease has been claimed to have been eradicated in many developed countries, such as the United States, Canada, and some European countries. Although mortality rates associated with malaria infection have been reduced from more than a million to an estimated 700,000–881,000 per year, according to the latest report from the *Roll Back Malaria* partnership of the World Health Organization [33], the disease still remains endemic in most tropical and subtropical areas (about 108 countries) and is associated with the poverty in these regions.

The malaria pathogen consists of members of eukaryotic protists of the genus *Plasmodium*. Humans, reptiles, birds, and various mammals are potential hosts for more than 100 species of plasmodium. Among these there are five major species that have been reported to cause significant numbers of malaria infections in humans. They are *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, and *P. knowlesi*. These protozoa are transferred from mosquito salivary glands to human bloodstream via mosquito bites; hence malaria is a mosquito-borne disease. Due to their different ring forms, malaria parasites have different characteristics during the infection process. For example, *P. falciparum* infections have the highest disease-induced mortality rate, and this protozoan is responsible for 90% of malaria-induced deaths. Because *P. falciparum* is highly parasitic in red blood cells (Rbcs) of all ages (other species are restricted to Rbcs at particular stages of development), it can therefore cause high rates of parasitaemia [30]. The species *P. vivax* has a wider range for its survival temperature.

Tracing back to ten thousand years ago, *P. falciparum* was originally from West Africa, while *P. vivax* co-evolved with nonhuman primates, i.e., Asian macaques,

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and was originally found in Asian and Central West Africa independently [5, 22]. Currently, the geographical distribution of *Plasmodium* infections is as follows. Nearly 85% of cases in Africa are caused by *P. falciparum*, and the remaining cases are caused by the other strains. *P. vivax* has the widest geographical distribution, existing in most countries in Asia, Central and South America, and the Middle East, where 70–90% of malaria infections are caused by this species, and the rest are mainly due to *P. falciparum* [2, 24]. *P. malariae* causes sporadic infections in Africa, parts of India, the western Pacific, and South America, whereas *P. ovale* is restricted to tropical Africa, New Guinea, and the Philippines [2]. *P. knowlesi* has been reported in Southeast Asian countries such as Malaysia, Thailand, Vietnam, Myanmar, and the Philippines [6, 9, 23, 25, 29]. In some regions, more than one malaria species has been found, and this raises a natural concern: can such a co-existence of multiple malaria species persist in a single region?

This concern has been debated by researchers since the first case of co-existence was reported. Maitland, Williams, and Newbold [19] argued that newly transmitted *P. falciparum* infections were suppressing patient infections (either new or latent) with *P. vivax*. Mayxay et al. [21] found that on the Thai-Burma border, pregnant women whose first attack of malaria during pregnancy was caused by *P. vivax* had a significantly lower risk of developing *P. falciparum* infections later in the pregnancy. Moreover, statistical analysis by McKenzie and Bossert [20] showed that the number of mixed infections was not significant compared with that of single-infection cases for *P. falciparum* and *P. vivax*. On the other hand, based on the data they collected, McKenzie and Bossert [20] claimed that at the level of human populations, four malaria species had been established in the populations in Madagascar and New Guinea.

In this paper, we address the concern of co-existence of multiple species by using mathematical models. For simplicity, we consider only two species, but we believe that the approach can be applied to the situation with more than two species. Another justification for choosing two species is the fact that the two major species, *P. falciparum* and *P. vivax*, contribute 90% of malaria infections in most areas. In section 2, we propose a model represented by a system of ordinary differential equations (ODEs) to describe the life cycle of malaria parasites at the erythrocytic phase. The dynamics of the model predicts that generically co-infection by two species within a host cannot persist. In section 3, we model malaria transmission at the human and mosquito population level. We first propose another ODE model for a single-species case containing the recovered class for humans and then extend this model to a two-species version in a natural way. Notice that the cross-immunity between species is complicated; e.g., there is no obvious cross-immunity between *P. falciparum* and *P. vivax* infections [14]. Hence, we need to incorporate extra terms into the two-species model to reflect this fact. For both one-species and two-species models, we address well-posedness, identify the basic reproduction numbers, and show the threshold role these numbers play. Moreover, we explore the long term dynamics including the stability of various equilibria and persistence of the model systems. Our results show that although two species of malaria parasites cannot co-persist within a single host, two species can persist in a single region at the population level. We conclude the paper with section 4, where we summarize the main results and discuss the biological implications as well as some possible future works. Some numerical simulation results are also given to support our conclusion on persistence at the population level.

**2. Within-host level.** The life cycle of malaria parasites inside human bodies consists of two phases: an exoerythrocytic and an erythrocytic phase. The exoery-

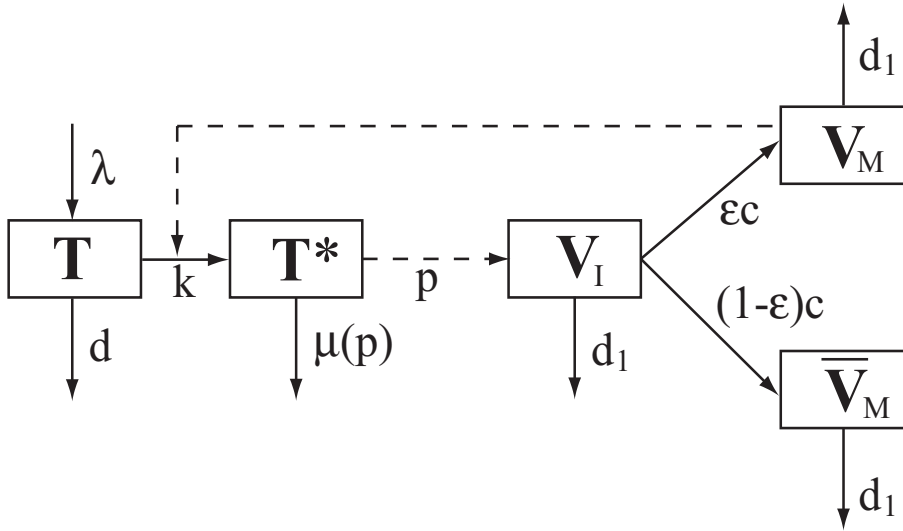


FIG. 1. *One-species case.*

throcytic phase involves infection of the hepatic system (liver). After an effective bite, a mosquito injects sporozoites, which rapidly attach to and enter the liver cells through the bloodstream. An asymptomatic period follows, during which parasites mature and multiply asexually within the liver cells, forming hepatic schizonts (see, e.g., [30]). Once hepatic schizonts rupture the liver cells, they release merozoites back into the bloodstream. After entering the erythrocytic phase, the free merozoites penetrate Rbcs, where they develop into ring forms and undergo sexual or asexual maturation. Sexual maturation produces male and female gametocytes, and sexually propagates infectious gametocytes that wait to be drawn into the gut of female mosquitoes. Asexual maturation forms schizonts, which invade healthy Rbcs and repeat the cycle again and again, causing the well-recognized pattern of cyclical fevers in humans.

From the above description, the developmental process of malaria parasites within a host can be illustrated by the diagram in Figure 1. Here  $T$ ,  $T^*$ ,  $V_I$ ,  $V_M$ , and  $\bar{V}_M$  represent the populations of healthy Rbcs, infected Rbcs, immature merozoites, asexually mature merozoites, and sexually mature gametocytes, respectively. It is assumed that (i) healthy Rbcs are recruited at a constant rate  $\lambda$ ; (ii) uninfected target cells die at rate  $d$ ; (iii) parasites at all phases die at a rate  $d_1$ ; (iv) asexually mature merozoites infect healthy Rbcs according to a mass-action law with constant rate  $k$ ; (v) infected Rbcs then produce immature merozoites at rate  $p$  and are killed (ruptured) at rate  $\mu(p)$  associated with the production rate; and finally, (vi) a proportion  $\epsilon c$  of immature merozoites remains asexual and keep searching for healthy Rbcs, whereas the rest mature sexually in the bloodstream.

Translating the diagram into differential equations, we obtain the following model system:

$$(2.1) \quad \begin{cases} \dot{T}(t) = \lambda - dT - kV_M T, \\ \dot{T}^*(t) = kV_M T - \mu(p)T^*, \\ \dot{V}_I(t) = pT^* - d_1V_I - cV_I, \\ \dot{V}_M(t) = \epsilon_1 cV_I - d_1V_M, \\ \dot{\bar{V}}_M(t) = (1 - \epsilon_1)cV_I - d_1\bar{V}_M. \end{cases}$$

Clearly, the last equation in system (2.1) is decoupled from the others. Hence, we need to consider only the following reduced system:

$$(2.2) \quad \begin{cases} \dot{T}(t) = \lambda - dT - kV_M T, \\ \dot{T}^*(t) = kV_M T - \mu(p)T^*, \\ \dot{V}_I(t) = pT^* - d_1V_I - cV_I, \\ \dot{V}_M(t) = \epsilon_1cV_I - d_1V_M. \end{cases}$$

When a host is infected by two different species of malaria parasites, the dynamics of the Rbcs and the parasites of the two species within the host can be described by the following system of ODEs, which is a very straightforward expansion of the one-species model (2.2):

$$(2.3) \quad \begin{cases} \dot{T}(t) = \lambda - dT - k_1V_{M1}T - k_2V_{M2}T, \\ \dot{T}_1^*(t) = k_1V_{M1}T - \mu(p_1)T_1^*, \\ \dot{T}_2^*(t) = k_2V_{M2}T - \mu(p_2)T_2^*, \\ \dot{V}_{I1}(t) = p_1T_1^* - d_1V_{I1} - c_1V_{I1}, \\ \dot{V}_{I2}(t) = p_2T_2^* - d_2V_{I2} - c_2V_{I2}, \\ \dot{V}_{M1}(t) = \epsilon_1c_1V_{I1} - d_1V_{M1}, \\ \dot{V}_{M2}(t) = \epsilon_2c_2V_{I2} - d_2V_{M2}. \end{cases}$$

Here the meanings of all variables and parameters are similar to those in system (2.2) and self-explanatory, with the integer subscripts 1 and 2, denoting species 1 and 2, respectively. Similarly, the model system (2.3) is demonstrated by the diagram in Figure 2.

The form of the model system (2.3) is a special case of a more general system studied in [13], where  $n$  strains and  $k$  development stages are considered. Hence, we can use the results in [13] to obtain the dynamics of system (2.2). To this end, we introduce the following two quantities:

$$\mathcal{R}_i = \frac{\lambda k_i \epsilon_i c_i p_i}{d d_i \mu(p_i)(d_i + c_i)}, \quad i = 1, 2.$$

Each of them is the respective basic reproduction number for the corresponding parasite species in the absence of the other species. Then,  $\mathcal{R}_0 = \max(\mathcal{R}_1, \mathcal{R}_2)$  gives the full basic reproduction number for model (2.3) (see [13]). Applying Theorem 3.1 in [13] to (2.3), we conclude that the dynamics of model (2.3) can be described by the following theorem, where for an equilibrium  $E$ ,  $W^s(E)$  denotes the stable manifold of  $E$ .

**THEOREM 2.1.** *For (2.3), the following hold:*

- (i) *If  $\mathcal{R}_0 \leq 1$ , then the infection free equilibrium (IFE)  $E_0 = (\lambda/d, 0, 0, 0, 0, 0, 0)$  is globally asymptotically stable in  $\mathbb{R}_+^7$ .*
- (ii) *If  $\mathcal{R}_0 > 1$ , then  $E_0$  becomes unstable. In this case, there are the following possibilities:*
  - (ii)-1 *If  $\mathcal{R}_1 > 1$  and  $\mathcal{R}_2 < 1$ , then in addition to the IFE, there is the species-1 endemic equilibrium  $E_1$ , which is globally asymptotically stable in  $\mathbb{R}_+^7 \setminus W^s(E_0)$ .*

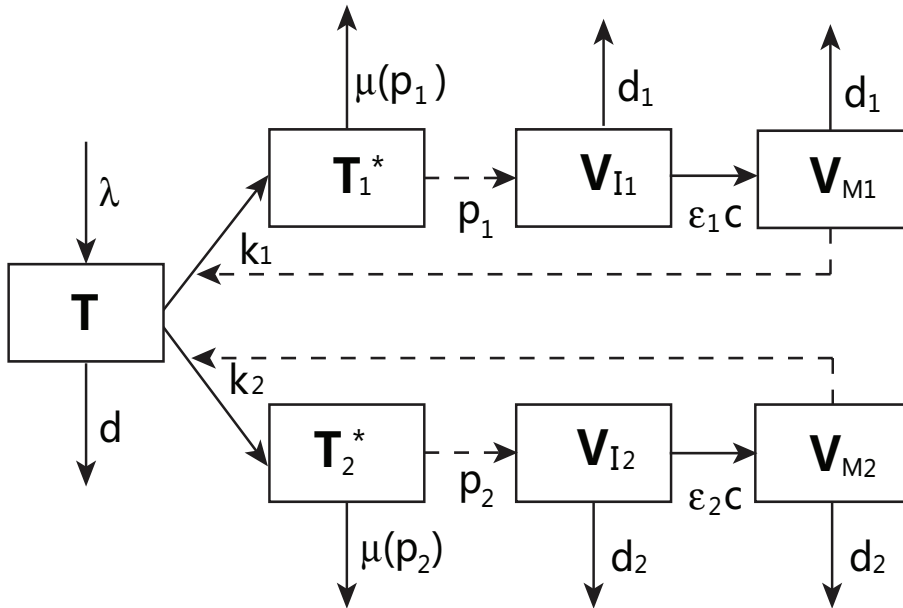


FIG. 2. Two-species case.

- (ii)-2 If  $\mathcal{R}_2 > 1$  and  $\mathcal{R}_1 < 1$ , then in addition to the IFE, there is the species-2 endemic equilibrium  $E_2$ , which is globally asymptotically stable in  $\mathbb{R}_+^7 \setminus W^s(E_0)$ .
- (ii)-3 If both  $\mathcal{R}_1 > 1$  and  $\mathcal{R}_2 > 1$ , but  $\mathcal{R}_1 > \mathcal{R}_2$ , then in addition to the IFE, there are the species-1 endemic equilibrium  $E_1$  and species-2 endemic equilibrium  $E_2$ , but  $E_2$  is unstable and  $E_1$  is globally asymptotically stable in  $\mathbb{R}_+^7 \setminus \{W^s(E_0) \cup W^s(E_2)\}$ .
- (ii)-4 If both  $\mathcal{R}_1 > 1$  and  $\mathcal{R}_2 > 1$ , but  $\mathcal{R}_2 > \mathcal{R}_1$ , then in addition to the IFE, there are the species-1 endemic equilibrium  $E_1$  and species-2 endemic equilibrium  $E_2$ , but  $E_1$  is unstable and  $E_2$  is globally asymptotically stable in  $\mathbb{R}_+^7 \setminus \{W^s(E_0) \cup W^s(E_1)\}$ .

Theorem 2.1 shows that both species of the malaria parasites will die out (when  $\mathcal{R}_0 \leq 1$ ), or competitive exclusion generically holds when  $\mathcal{R}_0 > 1$ —“generically” in the sense of  $\mathcal{R}_1 \neq \mathcal{R}_2$ . In [13], no results were obtained for the case when there are more than one species that have the same species-specific reproduction number. Turning to the two-species case, this corresponds to the case  $\mathcal{R}_1 = \mathcal{R}_2 > 1$ . Some tedious but straightforward calculations show that in such a critical situation, in addition to  $E_0$ ,  $E_1$ , and  $E_2$ , there will be infinitely many co-existence equilibria (positive equilibria with all components positive). Indeed, if we let

$$F(x) = \mu(p_2)k_2\epsilon_2c_2(d_2^2 + c_2^2)x + d\mu(p_2)d_2(d_2 + c_2) - \lambda k_2\epsilon_2c_2p_2,$$

then

$$E_3(x) = \left( \frac{\mu(p_2)d_2(d_2 + c_2)}{k_2\epsilon_2c_2p_2}, \frac{F(x)}{k_2\epsilon_2c_2p_2\mu(p_1)}, \frac{(d_2 + c_2)x}{p_2}, \frac{p_1F(x)}{k_2\epsilon_2c_2p_2\mu(p_1)(d_1 + c_1)}, \right. \\ \left. x, \frac{F(x)}{k_1\mu(p_2)d_2(d_2 + c_2)}, \frac{\epsilon_2c_2x}{d_2} \right)$$

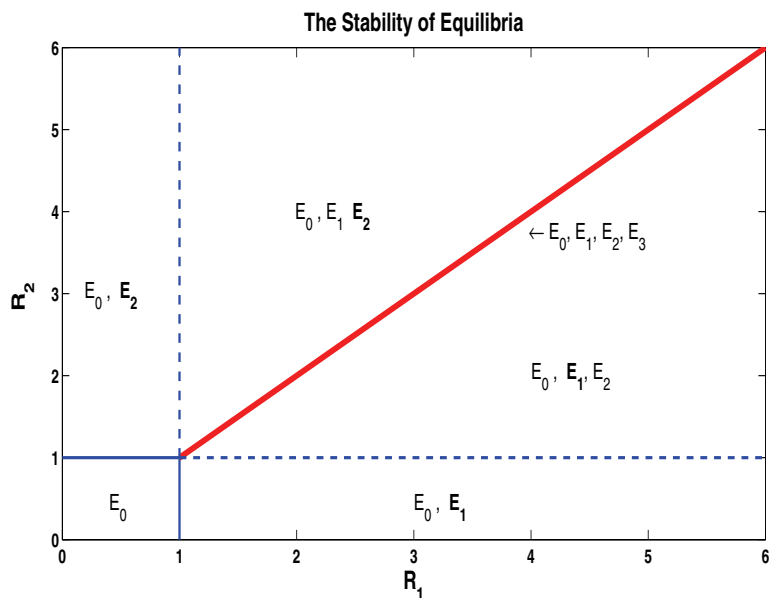


FIG. 3. Summary of equilibria and their stability: Only those in bold are stable. On the solid segment on the diagonal line, infinitely many co-existence equilibria exist, represented by  $E_3$ .

is an equilibrium for all  $x \in (0, \infty)$ . This and the results in Theorem 2.1 are visualized in Figure 3, where the equilibria shown by the bold font are the stable ones.

Although the global dynamics of system (2.3) are unknown when  $\mathcal{R}_1 = \mathcal{R}_2 > 1$ , we conjecture that the asymptotic behavior of a solution depends on the initial data. Since  $\mathcal{R}_1$  and  $\mathcal{R}_2$  contain more than ten model parameters, the equation  $\mathcal{R}_1 = \mathcal{R}_2 > 1$  is indeed a very sensitive condition and is unlikely to hold in reality. Therefore, we conclude that generically, two species of the malaria parasites cannot co-persist within a single host. This suggests that when modeling the spread of malaria at the population level, we can exclude the class of hosts that carry two species of the malaria parasites.

**3. Between-host level.** In this section, we explore the spread of two species of the malaria parasites between the human and mosquito populations. To this end, we need a basic model for a single species and then to extend it to a model for two species, as we did for the within-host level in the previous section.

**3.1. A single-species model.** For a single species, we propose the following model, which is a modification of the classic Ross–Macdonald model:

$$(3.1) \quad \begin{cases} S'_H = b_H N_H - d_H S_H - ac_1 \frac{S_H}{N_H} I_M + \beta R_H, \\ I'_H = ac_1 \frac{S_H}{N_H} I_M - d_H I_H - \gamma I_H, \\ R'_H = \gamma I_H - d_H R_H - \beta R_H, \\ S'_M = b_M N_M - d_M S_M - ac_2 S_M \frac{I_H}{N_H}, \\ I'_M = ac_2 S_M \frac{I_H}{N_H} - d_M I_M. \end{cases}$$

Here, the host population is divided into three classes: susceptible ( $S_H$ ), infectious ( $I_H$ ), and recovered ( $R_H$ ), with  $N_H = S_H + I_H + R_H$  being the total host population; the mosquito population is divided into two classes: susceptible ( $S_M$ ) and infectious ( $I_M$ ), with  $N_M = S_M + I_M$  being the total mosquito population. Our emphasis in this work is the interaction of two species; thus we ignore the latency to avoid further complication.

The model parameters are explained as follows:

- $b_H$  and  $b_M$  are the birth rates of humans and mosquitoes (for humans, “birth” is in a general sense including other recruitments besides natural birth), and  $d_H$  and  $d_M$  are the death rates of humans and mosquitoes.
- $a$  is the biting rate,  $c_1$  is the probability that a bite by an infectious mosquito of a susceptible human being will cause infection, and  $c_2$  is the probability that a bite by a susceptible mosquito of an infectious human being will cause infection.
- $\gamma$  is the combined recovery rate, including the natural recovery and the recovery due to treatments.
- The temporary immunity of the recovered hosts follows a negative exponential distribution  $e^{-\beta t}$ ; hence recovered hosts return to the susceptible class at rate  $\beta$ .

It is known that malaria does not cause deaths to mosquitoes. We assume  $b_M = d_M$  so that the mosquitoes population remains a constant. Yet, malaria does cause deaths to humans. Indeed, in some regions such as sub-Saharan Africa, malaria is one of the major causes of mortality due to infectious disease. Here, to make the model more mathematically tractable, we also assume that disease-caused deaths can be balanced by the excessive general births including the natural birth rate (which is higher in those less developed regions) and other recruitment, so that the total population of the humans also remains constant. This is achieved by assuming  $b_H = d_H$  in (3.1). This allows us to replace the term  $R_H$  by  $N_H - S_H - I_H$  and the term  $S_M$  by  $N_M - I_M$  to reduce the system. Rescaling the system by  $\frac{S_H}{N_H} \rightarrow S_H, \frac{I_H}{N_H} \rightarrow I_H,$  and  $\frac{I_M}{N_M} \rightarrow I_M$  leads to

$$(3.2) \quad \begin{cases} S'_H = d_H - d_H S_H - ac_1 m S_H I_M + \beta(1 - S_H - I_H), \\ I'_H = ac_1 m S_H I_M - d_H I_H - \gamma I_H, \\ I'_M = ac_2(1 - I_M)I_H - d_M I_M, \end{cases}$$

where  $m = N_M/N_H$ . It is clear that the set

$$(3.3) \quad \{0 \leq S_H \leq 1, 0 \leq I_H \leq 1, 0 \leq I_M \leq 1\}$$

is positively invariant for system (3.2). Thus, model (3.2) (and hence (3.1)) is well-posed.

Obviously, system (3.2) admits the disease free equilibrium (DFE)  $E_0 = (1, 0, 0)$ . Linearizing system (3.2) at  $E_0$  leads to the following linear system:

$$(3.4) \quad \begin{cases} S'_H = -(d_H + \beta)S_H - \beta I_H - ac_1 m I_M, \\ I'_H = -(d_H + \gamma)I_H + ac_1 m I_M, \\ I'_M = ac_2 I_H - d_M I_M, \end{cases}$$

from which we can obtain the next generation matrix  $FV^{-1}$ , where

$$F = \begin{pmatrix} 0 & ac_1 \\ ac_2 m & 0 \end{pmatrix}, \quad V = \begin{pmatrix} (d_H + \gamma) & 0 \\ 0 & d_M \end{pmatrix}.$$

By the next generation method [28], the basic reproduction number of the model (3.2) is given as the spectral radius of  $FV^{-1}$ :

$$(3.5) \quad \mathcal{R}_0 = r(FV^{-1}) = \sqrt{\frac{a^2 c_1 c_2 m}{d_M(d_H + \gamma)}}.$$

The stability of  $E_0$  is fully determined by  $\mathcal{R}_0$ , as is confirmed in the following theorem.

**THEOREM 3.1.** *The DFE  $E_0$  is globally asymptotically stable if  $\mathcal{R}_0 < 1$ , and it is unstable when  $\mathcal{R}_0 > 1$ .*

*Proof.* The local asymptotic stability of  $E_0$  when  $\mathcal{R}_0 < 1$  and the instability of  $E_0$  when  $\mathcal{R}_0 > 1$  follow directly from Theorem 2 in [28]. We need only to show the global attractiveness of  $E_0$  when  $\mathcal{R}_0 < 1$ . Applying (3.3) to the  $I'_H$  and  $I'_M$  equations in (3.2), we see that they have the following as an upper comparison system:

$$(3.6) \quad \begin{cases} I'_H = ac_1 m I_M - (d_H + \gamma) I_H, \\ I'_M = ac_2 I_H - d_M I_M, \end{cases}$$

which has the matrix representation  $I'(t) = (F - V)I(t)$ , where  $I = (I_H, I_M)$ . Clearly, system (3.6) consists of the  $I'_H$  and  $I'_M$  equations in (3.4). Note that  $\mathcal{R}_0 = r(FV^{-1}) < 1$  if and only if  $\sigma(F - V) < 0$ , where  $\sigma(F - V)$  is the stability modulus of the matrix  $F - V$ ; that is,

$$\sigma(F - V) = \max\{Re(\lambda) : \lambda \text{ is an eigenvalue of } F - V\}.$$

Since system (3.6) is linear, the local stability of the trivial solution implies its global stability; that is, every solution of system (3.6) approaches the trivial solution. On the other hand, since system (3.6) is cooperative, by the comparison theorem (see, e.g., Theorem 1.1, p. 78, in [26]), for every solution of (3.2) satisfying system (3.3) its  $I_H$  and  $I_M$  components will be bounded from above by the solution of system (3.6) that has the same initial values, and thus, they will approach zero as well. Now, applying the theory of asymptotically autonomous systems (see, e.g., [3]) to the  $S_H$  equation in (3.2), we conclude that  $S_H(t) \rightarrow 1$  as  $t \rightarrow \infty$ . This implies that  $E_0$  is indeed globally attractive if  $\mathcal{R}_0 < 1$ , and this completes the proof.  $\square$

*Remark 3.1.* Here in this section, we follow [28] in using the spectral radius of the next generation matrix to define the respective basic reproduction numbers. Some researchers use the so-called survival function to define the basic reproduction; see, e.g., [11]. 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” [11]. For our model (3.2), the basic reproduction number obtained by the survival function approach does not carry the square root. However, since the critical value for this threshold parameter is 1, mathematically there will be no difference. For detailed discussion on this topic, we refer readers to [7, 8, 11, 28].

When  $\mathcal{R}_0 > 1$ , by explicitly solving the algebraic system for equilibria of system (3.2), we find that system (3.2) has a unique endemic equilibrium  $E^* = (S_H^*, I_H^*, I_M^*)$ ,



where

(3.7)

$$\begin{aligned}
 S_H^* &= \frac{N_H (d_H + \gamma) (d_M d_H + d_M \gamma + \beta d_M + d_H a c_2 + \beta a c_2)}{a c_2 O}, \\
 I_H^* &= \frac{N_H d_M (d_H + \gamma) (d_H + \beta) (R_0 - 1)}{a c_2 O}, \\
 I_M^* &= \frac{N_H d_M (d_H + \gamma) (d_H + \beta) (R_0 - 1)}{d_M d_H + d_M \gamma + \beta d_M + d_H a c_2 + \beta a c_2}, \\
 O &= a c_1 N_M d_H + a c_1 N_M \gamma + \beta N_H d_H + \beta N_H \gamma + d_H^2 N_H + d_H N_H \gamma + \beta a c_1 N_M,
 \end{aligned}$$

which are obviously positive. By tedious calculations, one can also show that  $S_H^*, I_H^*, I_M^* < 1$ , but this is also a result of the restriction  $S_H^* + I_H^* + R_H^* = 1$  and  $S_M^* + S_H^* = 1$ . Moreover, we can show that if  $\mathcal{R}_0 > 1$ , then the  $I_H$  and  $I_M$  components of solutions of (3.2) are uniformly strongly persistent in the sense stated in the following theorem.

**PROPOSITION 3.1.** *Assume that  $\mathcal{R}_0 > 1$ . Then  $I_H$  and  $I_M$  are uniformly persistent in the sense that there exists an  $\eta > 0$  such that for every solution of system (3.2) with  $I_H(0) > 0$  and  $I_M(0) > 0$ ,*

$$\liminf_{t \rightarrow \infty} I_H(t) \geq \eta, \quad \liminf_{t \rightarrow \infty} I_M(t) \geq \eta.$$

*Proof.* The proof is almost a duplicate of that of Theorem 3.5 in [31], and hence it is omitted here in order to save space.  $\square$

Let

$$\Gamma := \{x(t) = (S_H, I_H, I_M) \in \mathbb{R}_+^3 : S_H + I_H \leq 1, I_M \leq 1\},$$

and denote the interior of  $\Gamma$  by  $\Gamma_0$ . The following theorem gives sufficient conditions that ensure the global stability of  $E^*$  in  $\Gamma_0$ , and it will be used in describing the dynamics of a two-strain model naturally extended from (3.2).

**THEOREM 3.2.** *Assume that  $R_0 > 1$ . Then the unique endemic equilibrium  $E^*$  of system (3.2) is globally stable in  $\Gamma_0$ , provided that*

$$(3.8) \quad d_H + d_M - \max(-\beta, \beta - \gamma) > 0.$$

*Proof.* We will apply the main theorem in [15] to prove the global asymptotic stability of the unique endemic equilibrium  $E^*$ . To this end, we need to verify the so-called Bendixson criteria,  $\bar{q} < 0$ , where the definition of  $\bar{q}$  will be given later as we proceed. For the reader’s convenience, we will adopt the same notation and terminology as used in [15]. The theory has also been applied to some other disease models to prove the global asymptotic stability of the unique endemic equation (see, e.g., [16])

First, applying the comparison method to the  $S_H$  equation in system (3.2), we can easily show that  $S_H$  is also uniformly persistent. This together with Proposition 3.1 leads to the uniform persistence of system (3.2) in the bounded set  $\Gamma$ , which implies the existence of a compact  $K \subset \Gamma_0$  that is absorbing with respect to system (3.2) in  $\Gamma$ . Namely, for every compact set  $K_0 \subset \Gamma_0$ , we have  $x(t, K_0) \subset K$  for sufficiently large  $t$ , where  $x(t, x_0)$  represents the solution of (3.2) with the initial condition  $x_0 \in K$  (see, e.g., [1]).

The Jacobian matrix  $J$  of model system (3.2) associated with a general solution  $x(t) = (S_H(t), I_H(t), I_M(t))$  is

$$J = \begin{pmatrix} -d_H - ac_1mI_M - \beta & -\beta & -ac_1mS_H \\ ac_1mI_M & -d_H - \gamma & ac_1mS_H \\ 0 & ac_2(1 - I_M) & -ac_2I_H - d_M \end{pmatrix},$$

and its second additive compound matrix (see [16] for the definition; also refer to the appendix of [16] for detailed calculations) can be calculated as

$$\begin{pmatrix} -2d_H - ac_1mI_M - \beta - \gamma & ac_1mS_H & ac_1mS_H \\ ac_2(1 - I_M) & Q & -\beta \\ 0 & ac_1mI_M & -d_H - d_M - ac_2I_H - \gamma \end{pmatrix},$$

where  $Q = -d_H - d_M - \beta - ac_1mI_M - ac_2I_H$ .

Let  $A(x) = \text{diag}(1, I_H/I_M, I_H/I_M)$ . Then  $A$  is  $C^1$  and nonsingular in  $\Gamma_0$ . Let  $f = (f_1, f_2, f_3)$  denote the vector field of system (3.2). Then,

$$A_f A = \text{diag} \left( 0, \frac{I_M}{I_H} \left( \frac{I_H}{I_M} \right)_f, \frac{I_M}{I_H} \left( \frac{I_H}{I_M} \right)_f \right),$$

where  $A_f$  is the matrix resulting from replacing each of the entries of  $A$  by its directional derivative along  $f$ . Here for a scalar function  $g = g(S_H, I_H, I_M)$ , its directional derivative along  $f$  is

$$g_f = \left( \frac{\partial g}{\partial S_H}, \frac{\partial g}{\partial I_H}, \frac{\partial g}{\partial I_M} \right) \cdot f = \frac{\partial g}{\partial S_H} f_1 + \frac{\partial g}{\partial I_H} f_2 + \frac{\partial g}{\partial I_M} f_3.$$

Following [16], we construct the matrix  $B = (B_{ij})_{3 \times 3}$  in terms of

$$\begin{aligned} B_{11} &= -2d_H - ac_1mI_M - \beta - \gamma, \\ B_{12} &= \left( ac_1mS_H \frac{I_M}{I_H}, ac_1mS_H \frac{I_M}{I_H} \right), \\ B_{21} &= \left( ac_2(1 - I_M) \frac{I_H}{I_M}, 0 \right)^T, \\ B_{22} &= \begin{pmatrix} b_{11} & -\beta \\ ac_1mI_M & b_{22} \end{pmatrix}, \\ b_{11} &= \frac{I_M}{I_H} \left( \frac{I_H}{I_M} \right)_f - d_H - d_M - \beta - ac_1mI_M - ac_2I_H, \\ b_{22} &= \frac{I_M}{I_H} \left( \frac{I_H}{I_M} \right)_f - d_H - d_M - \gamma - ac_2I_H. \end{aligned}$$

We select the vector norm in  $R^3$  to be

$$\|(u, v, w)\|_0 = \sup \{|u|, |v| + |w|\}$$

and let  $\kappa_0$  denote the Lozinskiĭ measure induced by this vector norm (for the definition see, e.g., [17]). By [18], the following estimate holds:

$$(3.9) \quad \kappa_0(B) \leq \sup \{g_1, g_2\},$$

where

$$(3.10) \quad g_1 = B_{11} + \|B_{12}\|_r = -2d_H - ac_1mI_M - \beta - \gamma + \frac{ac_1mS_H I_M}{I_H}$$

and

$$(3.11) \quad g_2 = \kappa_1(B_{22}) + \|B_{21}\|_l = \frac{I_M}{I_H} \left( \frac{I_H}{I_M} \right)_f - d_H - d_M - ac_2I_H \\ + \max\{-\beta, \beta - \gamma\} + \frac{ac_1(1 - I_M)I_H}{I_M}.$$

Here,  $\|(u, v)\|_r = \max\{|u|, |v|\}$ ,  $\|(u, v)^T\|_l = |u| + |v|$ , and  $\kappa_1$  is the Lozinskii measure with respect to the  $l_1$  norm in  $\mathbb{R}^2$ . Thus,  $\kappa_1(B_{22})$  is calculated by the following procedure: add the absolute value of the off-diagonal elements to the diagonal one in each column of  $B_{22}$ , then take the maximum of the two sums [4].

From (3.2), we find

$$(3.12) \quad \frac{I_M}{I_H} \left( \frac{I_H}{I_M} \right)_f = \frac{I'_H}{I_H} - \frac{I'_M}{I_M}$$

and

$$(3.13) \quad \frac{ac_1mS_H I_M}{I_H} = \frac{I'_H}{I_H} + d_H + \gamma,$$

$$(3.14) \quad \frac{ac_2(1 - I_M)I_H}{I_M} = \frac{I'_M}{I_M} - d_M I_M.$$

The uniform persistence of the solution in Proposition 3.1 ensures that there are  $\eta > 0$  and  $T_0 > 0$ , for any solution of (3.2), regardless of the initial condition in  $K$  (the absorbing set), satisfying

$$(3.15) \quad I_H(t) > \eta, \quad I_M(t) > \eta \quad \text{for } t > T_0.$$

Substituting equalities (3.12)–(3.14) into (3.10)–(3.11) and making use of inequalities (3.15), we obtain

$$(3.16) \quad g_1 = -2d_H - ac_1mI_M - \beta - \gamma + \frac{ac_1mS_H I_M}{I_H} \\ \leq -2d_H - ac_1m\eta - \beta - \gamma + \frac{I'_H}{I_H} + d_H + \gamma \\ \leq \frac{I'_H}{I_H} - (d_H + \beta) \quad \text{for } t > T_0$$

and

$$(3.17) \quad g_2 = \frac{I'_H}{I_H} - \frac{I'_M}{I_M} - d_H - d_M + \max\{-\beta, \beta - \gamma\} - ac_2I_H + \frac{ac_2(1 - I_M)I_H}{I_M} \\ = \frac{I'_H}{I_H} - d_M I_M - d_H - d_M + \max\{-\beta, \beta - \gamma\} - ac_2I_H \\ \leq \frac{I'_H}{I_H} - d_H \eta - d_M - d_M + \max\{-\beta, \beta - \gamma\} - ac_2\eta \\ \leq \frac{I'_H}{I_H} - (d_H + d_M - \max\{-\beta, \beta - \gamma\}) \quad \text{for } t > T_0.$$

Let  $\delta_1 = d_H + \beta$  and  $\delta_2 = d_H + d_M - \max\{-\beta, \beta - \gamma\}$ , and set  $\delta = \min\{\delta_1, \delta_2\}$ . Then under the condition (3.8),  $\delta > 0$  and

$$\kappa_0(B) \leq \frac{I'_H}{I_H} - \delta \quad \text{for } t > T_0.$$

Thus, along each solution  $(S_H, I_H, I_M)$  of (3.2) such that  $(S_H(0), I_H(0), I_M(0)) \in K$  and for  $t > T_0$ , we get

$$\frac{1}{t} \int_0^t \kappa_0(B(s)) \, ds \leq \frac{1}{t} \int_0^T \kappa_0(B(s)) \, ds + \frac{1}{t} \log \frac{I_H(t)}{I_H(T)} - \delta \frac{t-T}{t} \rightarrow -\delta < 0 \quad \text{as } t \rightarrow \infty.$$

Therefore, we have

$$\bar{q} := \limsup_{t \rightarrow \infty} \sup_{x_0 \in \Gamma_0} \frac{1}{t} \kappa_0(B(s, x_0)) \, ds \leq \frac{-\delta}{2},$$

which verifies the Bendixson criterion. By Theorems 2.3 and 3.1 in [15], we conclude that  $E^*$  is globally asymptotically stable in  $\Gamma_0$ , and the proof is completed.  $\square$

*Remark 3.2.* Relation (3.8) can be guaranteed by some more explicit conditions. For example, each of the following is such a condition:

- (C1)  $\beta < \frac{\gamma}{2}$ ;
- (C2)  $\frac{\gamma}{2} \leq \beta < d_H + d_M + \gamma$ .

*Remark 3.3.* Translating the results in Theorems 3.1 and 3.2 for (3.2) to (3.1), parallel conclusions can be drawn for system (3.1) in  $\mathbb{R}_+^4$  space in a straightforward way by adding the component  $S_m = 1 - I_m$ .

**3.2. A two-species model.** In this subsection, we consider the situation in which two species of malaria parasites have been brought into the same region. We would like to know if both species can persist in the region. We naturally wish to expand the one-species model (3.1) to this case by adding another set of variables corresponding to the second species. In other words, we will adopt all assumptions in subsection 3.1 leading to system (3.1), and accordingly propose the following two-species model:

$$(3.18) \quad \left\{ \begin{array}{l} S'_H = d_H N_H - d_H S_H - ae_{11} \frac{S_H}{N_H} I_{M1} - ae_{12} \frac{S_H}{N_H} I_{M2} + \beta_1 R_{H1} + \beta_2 R_{H2}, \\ I'_{H1} = ae_{11} \frac{S_H}{N_H} I_{M1} - d_H I_{H1} - \gamma_1 I_{H1} + ae_1 \frac{R_{H2}}{N_H} I_{M1}, \\ R'_{H1} = \gamma_1 I_{H1} - ae_2 \frac{R_{H1}}{N_H} I_{M2} - d_H R_{H1} - \beta_1 R_{H1}, \\ I'_{H2} = ae_{12} \frac{S_H}{N_H} I_{M2} - d_H I_{H2} - \gamma_2 I_{H2} + ae_2 \frac{R_{H1}}{N_H} I_{M2}, \\ R'_{H2} = \gamma_2 I_{H2} - ae_1 \frac{R_{H2}}{N_H} I_{M1} - d_H R_{H2} - \beta_2 R_{H2}, \\ S'_M = d_M N_M - d_M S_M - ae_{21} S_M \frac{I_{H1}}{N_H} - ae_{22} S_M \frac{I_{H2}}{N_H}, \\ I'_{M1} = ae_{21} S_M \frac{I_{H1}}{N_H} - d_M I_{M1}, \\ I'_{M2} = ae_{22} S_M \frac{I_{H2}}{N_H} - d_M I_{M2}. \end{array} \right.$$

Here, all variables and parameters are self-explanatory and are as in (3.1), but some have integer subscripts that distinguish species 1 and species 2, except for the last term in the  $I'_{H1}$  and  $I'_{H2}$  equations. These two new terms are the result of the complication of cross-immunity between two species. Indeed, immunization studies in [12, 14] on the Ras proteins of *P. vivax* and *P. falciparum* performed with human volunteers did not seem to support cross-immunity, meaning that individuals who have recovered from infection by one species do not gain extra protection from the other species. Another study [10] conducted in Southeast Asia actually showed that the incidence of *P. vivax* infection after treatment of *P. falciparum* infection is substantially greater than what would be expected on the basis of entomological inoculation rates, and this motivates us to use a probability parameter  $e_1$  different from  $e_{11}$ , and  $e_2$  different from  $e_{12}$ . Clearly,  $e_1 = 0 = e_2$  corresponds to the situation of complete cross-immunity, and in this case the model is of a competitive nature. However, when  $e_1 > 0$  and  $e_2 > 0$ , the model demonstrates not only *competitive* but also *cooperative* interactions between the two species.

This model can be graphically illustrated by the diagram in Figure 4.

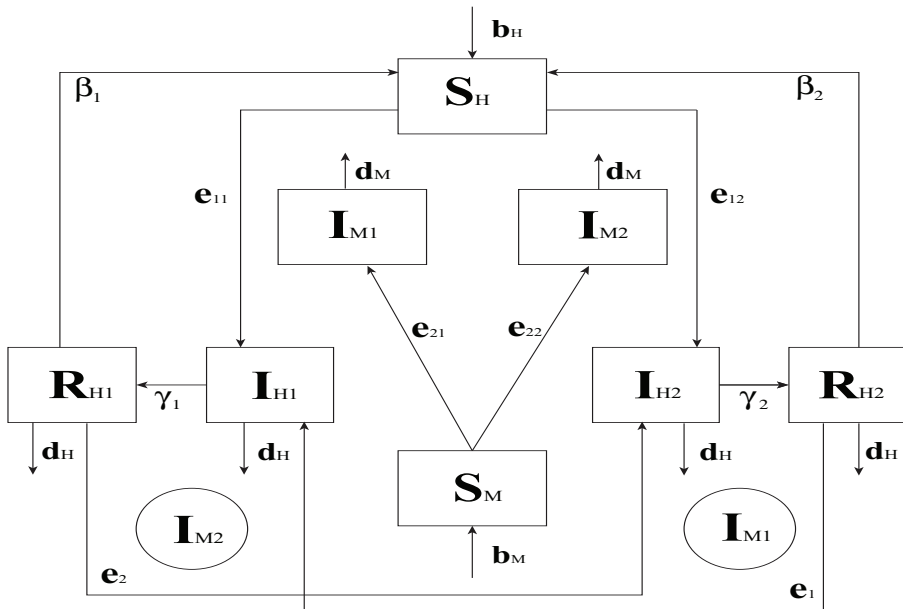


FIG. 4. Two-species case at population level.

We still denote by  $N_H$  the total population of human beings, and by  $N_M$  the total population of the female mosquitoes. Addition still gives  $S'_H + I'_{H1} + R'_{H1} + I'_{H2} + R'_{H2} = b_H N_H - d_H N_H = 0$  and  $S'_M + I'_{M1} + I'_{M2} = b_H N_M - d_H N_M = 0$ ; that is,  $N_H$  and  $N_M$  remain constants. As usual, we rescale the variables in system (3.18) by

$$\frac{S_H}{N_H} \rightarrow S_H, \quad \frac{I_{Hi}}{N_H} \rightarrow I_{Hi}, \quad \frac{R_{Hi}}{N_H} \rightarrow R_{Hi}, \quad i = 1, 2,$$

and

$$\frac{S_M}{N_M} \rightarrow S_M, \quad \frac{I_{Mi}}{N_M} \rightarrow I_{Mi}, \quad i = 1, 2,$$

yielding

$$(3.19) \quad \begin{cases} S'_H = d_H - d_H S_H - ae_{11}mS_H I_{M1} - ae_{12}mS_H I_{M2} + \beta_1 R_{H1} + \beta_2 R_{H2}, \\ I'_{H1} = ae_{11}mS_H I_{M1} - d_H I_{H1} - \gamma_1 I_{H1} + ae_1 m R_{H2} I_{M1}, \\ R'_{H1} = \gamma_1 I_{H1} - ae_2 m R_{H1} I_{M2} - d_H R_{H1} - \beta_1 R_{H1}, \\ I'_{H2} = ae_{12}mS_H I_{M2} - d_H I_{H2} - \gamma_2 I_{H2} + ae_2 m R_{H1} I_{M2}, \\ R'_{H2} = \gamma_2 I_{H2} - ae_1 m R_{H2} I_{M1} - d_H R_{H2} - \beta_2 R_{H2}, \\ S'_M = d_M - d_M S_M - ae_{21}S_M I_{H1} - ae_{22}S_M I_{H2}, \\ I'_{M1} = ae_{21}S_M I_{H1} - d_M I_{M1}, \\ I'_{M2} = ae_{22}S_M I_{H2} - d_M I_{M2}, \end{cases}$$

where  $m = N_M/N_H$ .

From the biological meanings of all variables in system (3.19), we need only to consider system (3.19) within the set

$$X = \left\{ \begin{aligned} &(S_H, I_{H1}, R_{H1}, I_{H2}, R_{H2}, S_M, I_{M1}, I_{M2}) \in \mathbb{R}^8 : \\ &0 \leq S_H, S_M I_{H1}, R_{H1}, I_{H2}, R_{H2}, I_{M1}, I_{M2} \leq 1, \\ &S_H + I_{H1} + R_{H1} + I_{H2} + R_{H2} = 1, S_M + I_{M1} + I_{M2} = 1. \end{aligned} \right\}$$

By the standard argument on invariance of semiflows (see, e.g., Chapter 5 in Smith [26]), we can easily show that the set  $X$  is positively invariant for system (3.19). This justifies that the model (3.19) is well-posed and is thus biologically meaningful. In the rest of this paper, we will discuss the long term dynamics of (3.19) in  $X$ .

**3.3. A two-species model—Disease free equilibrium and basic reproduction number.** The model (3.19) has a DFE given by  $\bar{E}_0 = (1, 0, 0, 0, 0, 1, 0, 0)$ . Here in this section, we will add a bar to the notation for the equilibria and basic reproduction numbers to distinguish the two-species case from the one-species case in subsection 3.1.

To explore the possibilities of other equilibria, we define

$$\bar{\mathcal{R}}_i = \sqrt{\frac{a^2 e_{1i} e_{2i} m}{d_M (d_H + \gamma_i)}}, \quad i = 1, 2.$$

Clearly,  $\bar{\mathcal{R}}_i$  is the  $i$ -species basic reproduction number for the malaria parasite in the absence of species  $j$  ( $j \neq i$ ). Therefore, by the results in subsection 3.1, we know that if  $\bar{\mathcal{R}}_1 > 1$ , then there is the species-1 endemic equilibrium

$$\bar{E}_1^* = (S_{H1}^*, I_{H1}^*, R_{H1}^*, 0, 0, S_{M1}^*, I_{M1}^*, 0),$$

where  $S_{H1}^*, I_{H1}^*, S_M^*$ , and  $I_{M1}^*$  are all positive constants given by formulas similar to (3.7), but with those species-specific parameters associated with species 1, and  $R_{H1}^* = 1 - S_{H1}^* - I_{H1}^*$ . Similarly, when  $\bar{\mathcal{R}}_2 > 1$ , there is the species-2 endemic equilibrium

$$\bar{E}_2^* = (S_{H2}^*, 0, 0, I_{H2}^*, R_{H2}^*, 0, S_{M2}^*, I_{M12}^*),$$

with  $R_{H2}^* = 1 - S_{H2}^* - I_{H2}^*$ .

Linearizing system (3.19) at  $\bar{E}_0$  leads to

$$(3.20) \quad \begin{cases} S'_H = -d_H S_H - ae_{11}mI_{M1} - ae_{12}mI_{M2} + \beta_1 R_{H1} + \beta_2 R_{H2}, \\ I'_{H1} = ae_{11}mI_{M1} - (d_H + \gamma_1)I_{H1}, \\ R'_{H1} = \gamma_1 I_{H1} - (d_H + \beta_1)R_{H1}, \\ I'_{H2} = ae_{12}mI_{M2} - (d_H + \gamma_2)I_{H2}, \\ R'_{H2} = \gamma_2 I_{H2} - (d_H + \beta_2)R_{H2}, \\ S'_M = -d_M S_M - ae_{21}I_{H1} - ae_{22}I_{H2}, \\ I'_{M1} = ae_{21}I_{H1} - d_M I_{M1}, \\ I'_{M2} = ae_{22}I_{H2} - d_M I_{M2}. \end{cases}$$

Note that in system (3.20) the four equations for  $I'_{H1}$ ,  $I'_{H2}$ ,  $I'_{M1}$ , and  $I'_{M2}$  are decoupled from the other four equations, forming the following subsystem:

$$(3.21) \quad \begin{cases} I'_{H1} = ae_{11}mI_{M1} - d_H I_{H1} - \gamma_1 I_{H1}, \\ I'_{M1} = ae_{21}I_{H1} - d_M I_{M1}, \\ I'_{H2} = ae_{12}mI_{M2} - d_H I_{H2} - \gamma_2 I_{H2}, \\ I'_{M2} = ae_{22}I_{H2} - d_M I_{M2}. \end{cases}$$

Let  $\bar{I} = (I_{H1}, I_{M1}, I_{H2}, I_{M2})$ . Note that we have switched the order of  $I_{M1}$  and  $I_{H2}$  in  $\bar{I}$ . Obviously, system (3.21) can be represented by the matrix form

$$(3.22) \quad \bar{I}'(t) = (\bar{F} - \bar{V})\bar{I}(t),$$

where  $\bar{F}$  is the new infection matrix given by

$$\bar{F} = \begin{pmatrix} 0 & ae_{11}m & 0 & 0 \\ ae_{21} & 0 & 0 & 0 \\ 0 & 0 & 0 & ae_{12}m \\ 0 & 0 & ae_{22} & 0 \end{pmatrix}$$

and

$$\bar{V} = \begin{pmatrix} (d_H + \gamma_1) & 0 & 0 & 0 \\ 0 & d_M & 0 & 0 \\ 0 & 0 & (d_H + \gamma_2) & 0 \\ 0 & 0 & 0 & d_M \end{pmatrix}.$$

Following [28], the next generation matrix for the model (3.19) is then given by

$$\bar{F}\bar{V}^{-1} = \begin{pmatrix} 0 & ae_{11}m/d_M & 0 & 0 \\ ae_{21}/(d_H + \gamma_1) & 0 & 0 & 0 \\ 0 & 0 & 0 & ae_{12}m/d_M \\ 0 & 0 & ae_{22}/(d_H + \gamma_2) & 0 \end{pmatrix},$$

and the basic reproduction number is the spectral radius of this matrix:

$$(3.23) \quad \bar{\mathcal{R}}_0 = r(\bar{F}\bar{V}^{-1}) = \max \left\{ \sqrt{\frac{a^2 e_{11} e_{21} m}{d_M (d_H + \gamma_1)}}, \sqrt{\frac{a^2 e_{12} e_{22} m}{d_M (d_H + \gamma_2)}} \right\} = \max\{\bar{\mathcal{R}}_1, \bar{\mathcal{R}}_2\}.$$

The following theorem is a direct result of Theorem 2 in [28], which confirms that the stability of the DFE is fully determined by  $\bar{\mathcal{R}}_0$ .

**THEOREM 3.3.** *If  $\bar{\mathcal{R}}_0 < 1$ , then the DFE is asymptotically stable. If  $\bar{\mathcal{R}}_0 > 1$ , it is unstable.*

**3.4. A two-species model—Disease persistence.** When  $\bar{\mathcal{R}}_0 > 1$ , at least one of the two individual basic reproduction numbers  $\bar{\mathcal{R}}_1$  and  $\bar{\mathcal{R}}_2$  is larger than 1. If  $\bar{\mathcal{R}}_1 > 1$ , we have seen in the above subsection that  $\bar{E}_1^* = (S_{H1}^*, I_{H1}^*, R_{H1}^*, 0, 0, S_{M1}^*, I_{M1}^*, 0)$  exists. We introduce the quantity

$$\bar{\mathcal{R}}_{21} = \frac{a^2 e_{12} e_{22} m S_{H1}^* S_{M1}^* + a^2 e_{22} e_2 m S_{M1}^* R_{H1}^*}{d_M (d_H + \gamma_2)},$$

which measures the number of secondary infections by species 2, assuming that species 1 is settled at  $\bar{E}_1^*$ . We may call  $\bar{\mathcal{R}}_{21}$  the species 1-mediated basic reproduction number for species 2. Symmetrically, if  $\bar{\mathcal{R}}_2 > 1$ , then  $\bar{E}_2^* = (S_{H2}^*, 0, 0, I_{H2}^*, R_{H1}^*, 0, S_{M2}^*, I_{M2}^*)$  exists, and we can define the species 2-mediated basic reproduction number for species 1 by

$$\bar{\mathcal{R}}_{12} = \frac{a^2 e_{11} e_{21} m S_{H2}^* S_{M2}^* + a^2 e_{21} e_1 m S_{M2}^* R_{H2}^*}{d_M (d_H + \gamma_1)}.$$

We point out that the cooperative effects between the two species due to the lack of cross-immunity are also reflected in the formulas for  $\bar{\mathcal{R}}_{21}$  and  $\bar{\mathcal{R}}_{12}$  through the parameters  $e_1$  and  $e_2$ .

The following theorem provides some information on the disease dynamics under  $\bar{\mathcal{R}}_0 > 1$ .

**THEOREM 3.4.** *Assume that  $\bar{\mathcal{R}}_0 > 1$ .*

- (i) *In the case  $\bar{\mathcal{R}}_1 > 1$ : if  $\bar{\mathcal{R}}_{21} > 1$ , then  $\bar{E}_1^*$  is unstable; if  $\bar{\mathcal{R}}_{21} < 1$ , then  $\bar{E}_1^*$  is asymptotically stable, provided that*

$$(3.24) \quad d_H + d_M - \max(-\beta_1, \beta_1 - \gamma_1) > 0.$$

- (ii) *In the case  $\bar{\mathcal{R}}_2 > 1$ : if  $\bar{\mathcal{R}}_{12} > 1$ , then  $\bar{E}_2^*$  is unstable; if  $\bar{\mathcal{R}}_{12} < 1$ , then  $\bar{E}_2^*$  is asymptotically stable, provided that*

$$(3.25) \quad d_H + d_M - \max(-\beta_2, \beta_2 - \gamma_2) > 0.$$

*Proof.* We give only the proof of (i), as the proof of (ii) is similar.

Linearizing system (3.19) at  $\bar{E}_1^*$  and expanding the determinant defining the characteristic equation, after some tedious calculations, the characteristic equation  $H_2(z) = 0$  is given by

$$(3.26) \quad H_2(z) = (z + d_M)(z + d_H)(z + \beta_2 + a e_{1n} I_{M1}^*) h_1(z) h_2(z),$$

where

$$h_1(z) = z^2 + (\gamma_1 + d_M + d_H)z + (d_M d_H + d_M \gamma_1 - a^2 e_{12} e_{22} m S_{H1}^* S_{M1}^* - a^2 e_{22} e_2 m S_{M1}^* R_{H1}^*),$$

$$h_2(z) = z^3 + Q_1 z^2 + Q_2 z + Q_3,$$



$$\begin{aligned}
 Q_1 &= ae_{21}I_{H1}^* + \gamma_1 + ae_{11}mI_{M1}^* + d_M + 2d_H + \beta_1, \\
 Q_2 &= \beta d_M + \gamma_1 d_M + ae_{11}mI_{M1}^* d_M + 2d_M d_H + a^2 e_{11} m I_{M1} e_{21} I_{H1}^* + \gamma_1 ae_{21} I_{H1}^* \\
 &\quad - a^2 e_{21} S_{M1}^* e_{11} m S_{H1}^* + ae_{11} m I_{M1}^* \gamma_1 + \beta_1 \gamma_1 + ae_{11} m I_{M1}^* \beta_1 + 2ae_{21} I_{H1}^* d_H \\
 &\quad + d_H \gamma_1 + ae_{11} m I_{M1}^* d_H + \beta_1 d_H + d_H^2 + ae_{21} I_{H1}^* \beta_1, \\
 Q_3 &= d_M \beta_1 \gamma_1 + ae_{21} I_{H1}^* d_H^2 + d_M ae_{11} m I_{M1}^* d_H + ae_{21} I_{H1}^* d_H \beta_1 + d_M d_H^2 \\
 &\quad + a^2 e_{11} m I_{M1}^* e_{21} I_{H1}^* d_H - \beta_1 a^2 e_{21} S_{M1}^* e_{11} m S_{H1}^* + a^2 e_{11} m I_{M1}^* \beta_1 e_{21} I_{H1}^* \\
 &\quad + a^2 e_{11} m I_{M1}^* \gamma_1 e_{21} I_{H1}^* + ae_{11} m I_{M1} \beta_1 d_M + d_M ae_{11} m I_{M1}^* \gamma_1 + d_M d_H \beta_1 \\
 &\quad + d_M d_H \gamma_1 + \beta_1 \gamma_1 ae_{21} I_{H1}^* + d_H \gamma_1 ae_{21} I_{H1}^* - d_H a^2 e_{21} S_{M1}^* e_{11} m S_{H1}^*,
 \end{aligned}$$

which are obtained by running *Maple*. Note that there is a difference in notation between  $h_2(z)$  and the characteristic equation of system (3.2) only at the endemic equilibrium  $E^*$ . Thus, by (3.24) and Theorem 3.2 combined with the Routh–Hurwitz criteria, we know that

$$(3.27) \quad Q_1 > 0, \quad Q_2 > 0, \quad Q_3 > 0, \quad Q_1 Q_2 - Q_3 > 0.$$

Inequality (3.27) in turn implies that all roots of  $h_2(z) = 0$  have negative real parts. Hence, the stability of  $\bar{E}_1^*$  is fully determined by the roots of  $h_1(z) = 0$ . It is easily seen that if  $\bar{\mathcal{R}}_{21} < 1$ , then the two roots of  $h_1(z) = 0$  have negative real parts, implying that  $\bar{E}_1^*$  is locally asymptotically stable; and if  $\bar{\mathcal{R}}_{21} > 1$ , then  $h_1(z) = 0$  has a positive real root, implying that  $\bar{E}_1^*$  is unstable. The proof is completed.  $\square$

Conditions (3.8), (3.24), and (3.25) can also be implied by some explicit conditions, similar to those in Remark 3.2.

The next theorem gives conditions under which one species of the malaria parasites can persist in the host and vector populations.

**THEOREM 3.5.** *Suppose  $\bar{\mathcal{R}}_0 > 1$ .*

- (i) *If either (A1)  $\bar{\mathcal{R}}_1 > 1$  and  $\bar{\mathcal{R}}_2 < 1$ , or (B1)  $\bar{\mathcal{R}}_2 > 1$ ,  $\bar{\mathcal{R}}_{12} > 1$ , and condition (3.25) holds, then  $I_{H1}$  and  $I_{M1}$  are uniformly persistent in the sense that there is a positive constant  $\eta_1 > 0$  such that for every solution of system (3.19) with  $I_{H1}(0) > 0$  and  $I_{M1}(0) > 0$*

$$\liminf_{t \rightarrow \infty} I_{H1}(t) \geq \eta_1, \quad \liminf_{t \rightarrow \infty} I_{M1}(t) \geq \eta_1.$$

- (ii) *If either (A2)  $\bar{\mathcal{R}}_2 > 1$  and  $\bar{\mathcal{R}}_1 < 1$ , or (B2)  $\bar{\mathcal{R}}_1 > 1$ ,  $\bar{\mathcal{R}}_{21} > 1$ , and condition (3.24) holds, then  $I_{H2}$  and  $I_{M2}$  are uniformly persistent in the sense that there is a positive constant  $\eta_2 > 0$  such that for every solution of system (3.19) with  $I_{H2}(0) > 0$  and  $I_{M2}(0) > 0$*

$$\liminf_{t \rightarrow \infty} I_{H2}(t) \geq \eta_2, \quad \liminf_{t \rightarrow \infty} I_{M2}(t) \geq \eta_2.$$

*Proof.* We will show the proof only for case (i), as the proof for case (ii) is similar. Denote

$$\begin{aligned}
 X_0 &= \{(S_H, I_{H1}, R_{H1}, I_{H2}, R_{H2}, S_M, I_{M1}, I_{M2}) \in X : I_{H1} > 0 \text{ and } I_{M1} > 0\}, \\
 \partial X_0 &= X/X_0 = \{(S_H, I_{H1}, R_{H1}, I_{H2}, R_{H2}, S_M, I_{M1}, I_{M2}) \in X, I_{H1} = 0 \text{ or } I_{M1} = 0\}.
 \end{aligned}$$

By the form of system (3.19), it is easy to see that both  $X_0$  and  $X$  are positively invariant. Obviously,  $\partial X_0$  is relatively closed in  $X$ . The boundedness of the solution established in subsection 3.2 confirms that system (3.19) is a point dissipative system.

Set

$$M_\partial = \{x_0 \in X : \Phi(t)x_0 \in \partial X_0 \text{ for all } t \geq 0\},$$

and let

$$M_0 = \{(S_H, I_{H1}, R_{H1}, I_{H2}, R_{H2}, S_M, I_{M1}, I_{M2}) \in X : I_{H1} = 0 \text{ and } I_{M1} = 0\}.$$

We show that  $M_\partial = M_0$ . Clearly, we have  $M_\partial \supset M_0$ , so we need only to prove  $M_\partial \subset M_0$ . Suppose not; then there exists  $x_0$  such that  $x_0 \in M_\partial$  but  $x_0 \notin M_0$ . Then, either the second or the seventh component of  $x_0$  is positive. For the former, by the seventh equation in system (3.19),  $I_{M1}(t)$  is activated (nonzero) for  $t > 0$ , which in turn activates  $I_{H1}(t)$ , implying that  $x_0 \notin M_\partial$ , a contradiction. For the latter, by the second equation in system (3.19),  $I_{H1}(t)$  is activated for  $t > 0$ , which in turn activates  $I_{M1}(t)$ , implying that  $x_0 \notin M_\partial$ , also a contradiction. Thus, we have shown  $M_\partial = M_0$ .

Next, we show that for every solution in  $X_0$  the  $I_H$  and  $I_M$  components are weakly persistent in the sense that

$$(3.28) \quad \limsup_{t \rightarrow \infty} I_{H1}(t) > 0 \quad \text{and} \quad \limsup_{t \rightarrow \infty} I_{M1}(t) > 0.$$

For the sake of contradiction, we assume that inequalities (3.28) do not hold. Then either (P1)  $\lim_{t \rightarrow \infty} I_{H1}(t) = 0$  or (P2)  $\lim_{t \rightarrow \infty} I_{M1}(t) = 0$ . For (P1), applying the theory of asymptotically autonomous systems to the  $I'_M(t)$  equation, we conclude that (P2) also holds. Similarly, (P2) also implies (P1). Further applying the theory of asymptotically autonomous systems to the  $R_{H1}(t)$  equation, it follows that  $R_{H1}(t) \rightarrow 0$  as  $t \rightarrow \infty$ . Thus, either (P1) or (P2) leads to

$$(3.29) \quad \lim_{t \rightarrow \infty} I_{H1}(t) = 0, \quad \lim_{t \rightarrow \infty} I_{M1}(t) = 0, \quad \text{and} \quad \lim_{t \rightarrow \infty} R_{H1}(t) = 0.$$

Therefore, the  $S_H, I_{H2}, R_{H2}, S_M,$  and  $I_{M2}$  equations in system (3.19) have the following as the limiting system:

$$(3.30) \quad \begin{cases} S'_H = d_H - d_H S_H - ae_{12}mS_H I_{M2} + \beta_2 R_{H2}, \\ I'_{H2} = ae_{12}mS_H I_{M2} - d_H I_{H2} - \gamma_2 I_{H2}, \\ R'_{H2} = \gamma_2 I_{H2} - d_H R_{H2} - \beta_2 R_{H2}, \\ S'_M = d_M - d_M S_M - ae_{22}S_M I_{H2}, \\ I'_{M2} = ae_{22}S_M I_{H2} - d_M I_{M2}. \end{cases}$$

*Case (A1):*  $\bar{\mathcal{R}}_1 > 1$  and  $\bar{\mathcal{R}}_2 < 1$ . By Theorem 3.1,  $(1, 0, 0, 1, 0)$  is an equilibrium of system (3.30), and it is globally asymptotically stable if  $\bar{\mathcal{R}}_2 < 1$ . Therefore, for any  $\bar{\epsilon}_1 > 0$ , there exists  $\bar{T}_1 > 0$  such that

$$(3.31) \quad S_H(t) \geq 1 - \bar{\epsilon}_1, \quad S_M(t) \geq 1 - \bar{\epsilon}_1, \quad R_{H2}(t) \geq \bar{\epsilon}_1 \quad \text{for } t > \bar{T}_1.$$

Applying the inequalities in (3.31) to the  $I_{H1}$  and  $I_{M1}$  equations in the original system (3.19), we obtain

$$(3.32) \quad \begin{aligned} I'_{H1} &\geq ae_{11}m(1 - \bar{\epsilon}_1)I_{M1} - d_H I_{H1} - \gamma_1 I_{H1}, \\ I'_{M1} &\geq ae_{21}(1 - \bar{\epsilon}_1)I_{H1} - d_M I_{M1}, \end{aligned} \quad \text{for } t > \bar{T}_1.$$

This suggests the following linear comparison system for  $I_{H1}(t)$  and  $I_{M1}(t)$ :

$$(3.33) \quad \begin{cases} u'_1 = ae_{11}m(1 - \bar{\epsilon}_1)u_2 - (d_H + \gamma_1)u_1, \\ u'_2 = ae_{21}(1 - \bar{\epsilon}_1)u_1 - d_M u_2. \end{cases}$$

Because  $\bar{\mathcal{R}}_1 > 1$ , by continuity, we can choose  $\bar{\epsilon}_1$  sufficiently small so that

$$(3.34) \quad \frac{a^2 e_{11} e_{21} m (1 - \bar{\epsilon})^2}{d_M (d_H + \gamma_1)} > 1,$$

which implies that the stability modulus of system (3.33) is positive. Therefore the positive solutions of system (3.33) are unbounded. On the other hand, solutions of system (3.34) are unbounded, which implies, by the comparison theorem, unboundedness of  $(I_{H1}(t), I_{M1}(t))$ , a contradiction.

*Case (B1):*  $\bar{\mathcal{R}}_2 > 1$ ,  $\bar{\mathcal{R}}_{12} > 1$ , and condition (3.25) holds. Applying Theorem 3.2 to system (3.30) (under  $\bar{\mathcal{R}}_2 > 1$  and condition (3.25)), we have  $S_H(t) \rightarrow S_{H2}^*$ ,  $I_{H2}(t) \rightarrow I_{H2}^*$ ,  $R_{H2}(t) \rightarrow R_{H2}^*$ ,  $S_M(t) \rightarrow S_{M2}^*$ ,  $I_{M2}(t) \rightarrow I_{M2}^*$ . Hence, for any  $\bar{\epsilon}_2 > 0$ , there exists  $\bar{T}_2 > 0$  such that

$$(3.35) \quad S_H(t) \geq S_{H2}^* - \bar{\epsilon}_2, \quad S_M(t) \geq S_{M2}^* - \bar{\epsilon}_2, \quad R_{H2}(t) \geq R_{H2}^* - \bar{\epsilon}_2 \quad \text{for } t > \bar{T}_2.$$

Applying the inequalities in (3.35) to  $I_{H1}$  and  $I_{M1}$  in the original system (3.19), we obtain

$$(3.36) \quad \begin{aligned} I'_{H1} &\geq ae_{11}m(S_{H2}^* - \bar{\epsilon}_2)I_{M1} - d_H I_{H1} - \gamma_1 I_{H1} + ae_1m(R_{H2}^* - \bar{\epsilon}_2)I_{M1}, \\ I'_{M1} &\geq ae_{21}(S_{M2}^* - \bar{\epsilon}_2)I_{H1} - d_M I_{M1}, \end{aligned} \quad \text{for } t > \bar{T}_2.$$

This suggests the following linear comparison system for  $H_{H1}(t)$  and  $H_{M1}(t)$ :

$$(3.37) \quad \begin{cases} v'_1 = [ae_{11}m(S_{H2}^* - \bar{\epsilon}_2) + ae_1m(R_{H2}^* - \bar{\epsilon}_2)]v_2 - (d_H + \gamma_1)v_1, \\ v'_2 = ae_{21}(S_{M2}^* - \bar{\epsilon}_2)v_1 - d_M v_2. \end{cases}$$

Since  $\bar{\mathcal{R}}_{12} > 1$ , by continuity, we can choose  $\bar{\epsilon}_2$  sufficiently small so that

$$\begin{aligned} &\frac{[ae_{11}m(S_{H2}^* - \bar{\epsilon}_2) + ae_1m(R_{H2}^* - \bar{\epsilon}_2)]ae_{21}(S_{M2}^* - \bar{\epsilon}_2)}{d_M(d_H + \gamma_2)} \\ &= \frac{a^2 e_{11} e_{21} m (S_{H2}^* - \bar{\epsilon}_2) (S_{M2}^* - \bar{\epsilon}_2) + a^2 e_{21} e_1 m (S_{M2}^* - \bar{\epsilon}_2) (R_{H2}^* - \bar{\epsilon}_2)}{d_M(d_H + \gamma_2)} > 1. \end{aligned}$$

This implies that the characteristic equation of the linear system (3.37) has a positive real root, which means the positive solutions of (3.33) are unbounded. Similar to the proof of case (A1), this would further imply that  $(I_{H1}(t), I_{M1}(t))$  is unbounded, also a contradiction.

Combining the above, we have proved that (3.28) is valid. In the case of (A1),  $\bar{E}_0$  is the only equilibrium in  $M_0$ , and every forward orbit in  $M_0$  converges to  $\bar{E}_0$ . Note that (3.28) implies that  $\bar{E}_0$  is an isolated invariant set in  $X$ , and  $W^S(\bar{E}_0) \cap X_0$  is empty, where  $W^S(\bar{E}_0)$  means the stable manifold at  $\bar{E}_0$ . By [27, Theorem 4.6], we conclude that system (3.19) is uniformly persistent with respect to  $(X_0, \partial X_0)$ . Under condition (B1), there are only two equilibria  $\bar{E}_0$  and  $\bar{E}_2^*$  in  $M_0$ . From (3.28) and the fact that  $M_\partial = M_0$ , we know that these two equilibria are isolated in  $X$ ,

and  $W^S(\bar{E}_0) \cap X_0$  and  $W^S(\bar{E}_2^*) \cap X_0$  are empty, and so every forward orbit in  $M_0$  converges to either  $\bar{E}_0$  or  $\bar{E}_2^*$ . Moreover,  $\bar{E}_0$  and  $\bar{E}_2^*$  are acyclic in  $M_0$ . Again, by [27, Theorem 4.6], we conclude that system (3.19) is uniformly persistent with respect to  $(X_0, \partial X_0)$ . Therefore, under either (A1) or (B1),  $I_H$  and  $I_M$  are uniformly persistent, and the proof is completed.  $\square$

Combining (i) and (ii) in the above theorem, we have the following results on persistence of both species of the malaria parasites.

**THEOREM 3.6.** *Assume one of the following holds:*

- (i)  $\bar{\mathcal{R}}_1 > 1, \bar{\mathcal{R}}_2 < 1, \bar{\mathcal{R}}_{21} > 1$ , and condition (3.24) holds;
- (ii)  $\bar{\mathcal{R}}_2 > 1, \bar{\mathcal{R}}_1 < 1, \bar{\mathcal{R}}_{12} > 1$ , and condition (3.25) holds; and
- (iii)  $\bar{\mathcal{R}}_1 > 1, \bar{\mathcal{R}}_2 > 1, \bar{\mathcal{R}}_{12} > 1, \bar{\mathcal{R}}_{21} > 1$ , and conditions (3.24) and (3.25) hold.

*Then both species are uniformly persistent in the sense that there is a positive constant  $\bar{\eta}$  such that every solution  $(S_H, I_{H1}, R_{H1}, I_{H2}, R_{H2}, S_M, I_{M1}, I_{M2})$  with initial condition in  $\bar{X}_0$  satisfies*

$$\liminf_{t \rightarrow \infty} I_{Hi} \geq \eta, \quad \liminf_{t \rightarrow \infty} I_{Mi} \geq \eta, \quad i = 1, 2,$$

where  $\bar{X}_0 = \{(S_H, I_{H1}, R_{H1}, I_{H2}, R_{H2}, S_M, I_{M1}, I_{M2}) \mid 0 < S_H, S_M \leq 1, 0 \leq R_{H1}, R_{H2} < 1, 0 < I_{H1} < 1, 0 < I_{M1} < 1, 0 < I_{H2} < 1, 0 < I_{M2} < 1\}$ . Moreover, system (3.19) admits at least one positive equilibrium (co-existence equilibrium).

*Proof.* The uniform persistence of both species is a consequence of Theorem 3.5. The existence of a positive equilibrium follows from the co-existence theorem in [32].  $\square$

**4. Conclusion and discussion.** We have set up an ODE model (3.19) to describe the dynamics of disease transmission involving two species of malaria parasites in a well mixed human and mosquito environment. The model is a natural expansion of a one-species model (3.1), but with the fact of “no cross-immunity” incorporated. The model also makes use of the result from a within-host model (i.e., (2.3)) for two species which generically excludes persistence of both species within a single host. This allows us to ignore the co-infected class in our two-species model.

We have investigated the dynamics of both systems (3.1) and (3.19). More specifically, we have identified the basic reproduction numbers and showed their threshold role for both models by studying the stability of the equilibria and the persistence of the model systems. Our analysis of the two-species model (3.19) shows that two species of malaria parasites may both persist in a single region under certain circumstances reflected by the conditions in Theorem 3.6. These conditions are all expressed in terms of inequalities and, hence, are robust in terms of parameters. This is in contrast to the two-species model (2.3) at within-host level, for which competition exclusion holds unless an identity ( $\mathcal{R}_1 = \mathcal{R}_2$ ) holds. The persistence of both species claimed in Theorem 3.6 can be observed in numeric simulations; see, e.g., Figure 5. The co-persistence can be partially attributed to the cooperative effect in the model (3.19), which is due to the lack of cross-immunity. This is reflected in the conditions in Theorems 3.5 and 3.6. For example, in Theorem 3.5, either (A1) or (B1) can lead to the persistence of species 1. While (A1) accounts for the case that species 1 outcompetes species 2, (B1) provides a scenario that species 2 can not only survive by itself but also help species 1 survive. Among those inequalities,  $R_1 > 1$  and (3.24) ( $R_1 > 1$  and (3.25)) account for the intrinsic (or individual) survival capability of species 1 (species 2), while  $R_{ij} > 1$  explains the survival capability of strain  $i$  under the cooperation of strain  $j$  by providing species  $i$  with individuals recovered from infection by species  $j$ .

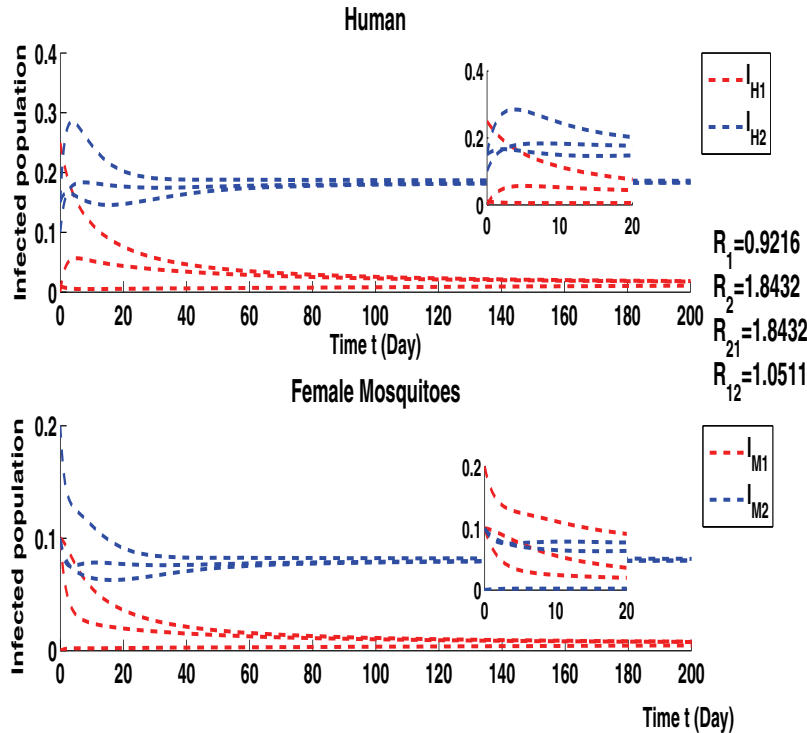


FIG. 5. Both species can persist at the population level. Simulations are done with the following parameter values and initial conditions:  $a = 0.5$ ,  $e_1 = 0.9$ ,  $e_2 = 0.5$ ,  $e_{11} = 0.4$ ,  $e_{21} = 0.2$ ,  $e_{12} = 0.5$ ,  $e_{22} = 0.5$ ,  $n = 7.25$ ,  $\gamma_1 = 0.3$ ,  $\gamma_2 = 0.21$ ,  $d_H = 0.001$ ,  $d_M = 0.2$ ,  $\beta_1 = 1/3$ ,  $\beta_2 = 1/6$ ;  $S_H = 0.6$ ,  $I_{H1} = 0.25$ ,  $R_{H1} = 0$ ,  $I_{H2} = 0.15$ ,  $R_{H2} = 0$ ,  $S_M = 0.8$ ,  $I_{M1} = 0.1$ ,  $I_{M2} = 0.1$ .

Under the conditions in Theorem 3.6, there is a positive equilibrium for (3.19). Unfortunately we are unable to study the stability of this positive equilibrium and the global dynamics of the model (3.19) under these conditions. We leave this as a possible future avenue of research.

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