Theoretical analysis of mixed *Plasmodium malariae* and *Plasmodium falciparum* infections with partial cross-immunity

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**ABSTRACT**

A deterministic model for assessing the dynamics of mixed species malaria infections in a human population is presented to investigate the effects of dual infection with *Plasmodium malariae* and *Plasmodium falciparum*. Qualitative analysis of the model including positivity and boundedness is performed. In addition to the disease free equilibrium, we show that there exists a boundary equilibrium corresponding to each species. The isolation reproductive number of each species is computed as well as the reproductive number of the full model. Conditions for global stability of the disease free equilibrium as well as local stability of the boundary equilibria are derived. The model has an interior equilibrium which exists if at least one of the isolation reproductive numbers is greater than unity. Among the interesting dynamical behaviours of the model, the phenomenon of backward bifurcation where a stable boundary equilibrium coexists with a stable interior equilibrium, for a certain range of the associated invasion reproductive number less than unity is observed. Results from analysis of the model show that, when cross-immunity between the two species is weak, there is a high probability of coexistence of the two species and when cross-immunity is strong, competitive exclusion is high. Further, an increase in the reproductive number of species *i* increases the stability of its boundary equilibrium and its ability to invade an equilibrium of species *j*. Numerical simulations support our analytical conclusions and illustrate possible behaviour scenarios of the model.

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1. Introduction

Malaria is the world’s most prevalent vector borne disease and it still remains among the most devastating diseases occurring in the world. It represents 10% of Africa’s overall disease burden (World Malaria Report, 2005). Children under five years of age are particularly vulnerable to *Plasmodium falciparum* infection. There were 881,000 [610,000–1,212,000] estimated malaria deaths in 2006, of which 91% were in Africa and 85% were of children under the age of five (World Malaria Report, 2008). The symptoms and epidemiological manifestations from this micro-organism are highly variable and geographically determined by a balanced interplay of the parasite with human host and vector. Despite persistent control efforts set up since the end of the fifties, the emergence of resistance of the parasite to drugs and of the mosquito vector to insecticides, combined with the difficulties in implementing and maintaining effective control schemes have led to a resurgence of the disease in many parts of the world (Hayton and Su, 2008; Faulde et al., 2007). In addition, despite over a century of research, much of the biology of malaria parasites and how they interact with their human host and with each other remains to be discovered (Mayxay et al., 2004).

Among the numerous *Plasmodium* species that infect reptiles, birds and mammals, four of them are human specific: *P. falciparum*, *Plasmodium vivax*, *Plasmodium malariae* and *Plasmodium ovale*. *P. falciparum* is the most virulent agent responsible for 200–300 million infections and 1–3 million deaths annually, mainly in Africa (Volkman et al., 2001). Mixed-species infections are frequently observed, and almost all combinations of species have been found within human populations and individuals (Mason et al., 1999). Mixed-species malaria infections are often not recognized or underestimated (Mayxay et al., 2004). *P. falciparum* and *P. malariae* are malaria species that occur endemically in many parts of sub-Saharan Africa (Bousema et al., 2006, of which 91% were in Africa and 85% were of children under the age of five (World Malaria Report, 2005). Children under five years of age are particularly vulnerable to *Plasmodium falciparum* infection. There were 881,000 [610,000–1,212,000] estimated malaria deaths in 2006, of which 91% were in Africa and 85% were of children under the age of five (World Malaria Report, 2008). The symptoms and epidemiological manifestations from this micro-organism are highly variable and geographically determined by a balanced interplay of the parasite with human host and vector. Despite persistent control efforts set up since the end of the fifties, the emergence of resistance of the parasite to drugs and of the mosquito vector to insecticides, combined with the difficulties in implementing and maintaining effective control schemes have led to a resurgence of the disease in many parts of the world (Hayton and Su, 2008; Faulde et al., 2007). In addition, despite over a century of research, much of the biology of malaria parasites and how they interact with their human host and with each other remains to be discovered (Mayxay et al., 2004).

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2008). The co-occurrence of *P. falciparum* and *P. malariae* is often higher than would be expected on the basis of their individual parasite prevalence, and one parasite species may influence the infection dynamics of the other (Arez et al., 2003). Experimental studies indicated that different parasite species seem to interact, affecting mortality, pathology and infection dynamics (Richie, 1988; Collins and Jeffery, 1999).

At least seven species of *Anopheles* have been shown to carry more than one species of human *Plasmodium* in the field (McKenzie and Bossert, 1999) and all four malaria species of humans can be carried by *Anopheles gambiae* (Fonèville et al., 1992). Even though numerous articles are published every year about the parasite and the disease (Ollomo et al., 2009), a few mathematical studies have been devoted to analysing the effects of mixed infections within a host (Mason and McKenzie, 1999; Mason et al., 1999) by considering the blood-stage population dynamics of a dual infection with *P. malariae* and *P. falciparum* and *P. vivax* and *P. falciparum*. To the best of our knowledge, there are no mathematical models developed up to date for fully assessing the impact of mixed malaria infections in a human population.

Interaction between different human *Plasmodium* species when simultaneously infecting the same host (vertebrate or vector) also may have an effect on the dynamics of transmission of each species, but such studies are scarce. In this work, we explore the dynamics of dual malaria infections with *P. falciparum* and *P. malariae* in a naïve human population by incorporating immunity raised by one species, or stage of parasite which also acts against the other species or stage (Richie, 1988). A comprehensive qualitative assessment of the population-level implications of the dual infection with the two species in a community is carried out. The paper is organized as follows. In the following section, we formulate a deterministic mathematical model for mixed species malaria infections, which incorporates the key epidemiological and biological features of malaria infection. In Section 3, we analyse the model by computing the reproductive numbers of the two species in isolation, invasion reproductive numbers and determining stability of the boundary equilibria. Conditions for existence of an interior equilibrium and its local stability are established in this section. Numerical simulations follow in Section 4 and finally, in Section 5, we summarize and discuss the results of the study.

### 2. Model formulation

The human population is divided into four classes which are proportion of susceptible $x(t)$, proportion infected with *P. falciparum* $y_f(t)$, proportion infected with *P. malariae* $y_m(t)$ and the proportion with mixed infections $y_{fm}(t)$. It is assumed that the mosquito dynamics operate on a much faster time scale than the human dynamics, therefore the mosquito population is considered to be at equilibrium with respect to changes in the human population. This allows its dynamics to be collapsed into the inoculation rate $h_i$, $i = f, m$. The derivation of this rate will not be carried out here as it was done elsewhere (Koella, 1991; Laxminarayan, 2004). Let the total infective population be $y = y_f + y_m + y_{fm}$. The inoculation rate for *P. falciparum* infections is given by

$$h_f = Ac^2 \beta_f^f \rho_f \epsilon_f \tau_f \frac{y_f}{\mu_f + \gamma_f + \beta_f^f \epsilon_f \tau_f},$$

and the inoculation rate for *P. malariae* infections is given by

$$h_m = Ac^2 \beta_m \rho_m \epsilon_m \tau_m \frac{y_m}{\mu_m + \gamma_m + \beta_m \epsilon_m \tau_m}.$$  

where $c$ is the biting rate, $\beta_i^j$ ($i = f, m$) is the probability that a bite by an infectious mosquito results in transmission of the parasites to the susceptible human, $\beta_i^j$ ($i = f, m$) is the probability that a bite results in transmission of the parasites to a susceptible mosquito (Chiyaka et al., 2007), $A$ is the mosquito density (number of mosquitoes per human), $\tau_f$ is the incubation period of parasites in the mosquito, $\mu_m$ is the natural mortality rate of mosquitoes and $\gamma_f$ is an excess death rate due to the presence of parasites in the bodies of mosquitoes. A field study carried out showed that the malaria parasite, *P. falciparum*, alters the blood-feeding behaviour of its mosquito vector, *A. gambiae* s.l. In two ways. First, mosquitoes infected with sporozoites, took up larger blood meals than uninfected mosquitoes and second, mosquitoes harbouring sporozoites were more likely to bite several people per night thus increasing the probability of dying during feeding (Koella et al., 1998). This effect was also considered elsewhere (Chiyaka et al., 2008a).

Susceptible humans become infected with *P. falciparum* or *P. malariae* at the inoculation rates $h_f$ or $h_m$, respectively. Infected individuals either recover from infection at a rate $\nu_i, i = f, m$ to become susceptible again. Individuals infected with *P. falciparum* parasites can be coinfected with *P. malariae* parasites at a rate $\sigma_m h_m$, and those infected with *P. malariae* can be coinfected with *P. falciparum* parasites at a rate $\sigma_m h_f$ and enter the coinfected class $y_{fm}$. The parameter $\sigma_m$ is a “cross-immunity coefficient”, the relative effectiveness of immune effectors raised by *P. falciparum*, when acting on *P. malariae* and $\sigma_m$ is a “cross-immunity coefficient”, the relative effectiveness of immune effectors raised by *P. malariae*, when acting on *P. falciparum* (Mason et al., 1999).

The coinfected population recovers from *P. malariae* infections at a rate $\nu_m y_{fm}$ and recover from *P. falciparum* infections at a rate $\nu_f y_f$. The factors $\nu_f$ and $\nu_m$ model the relative change in recovery rates of *P. malariae* infections and *P. falciparum* infections, respectively, of a dually infected individual. Deaths occur at a rate $\delta$ (i.e. the life-expectancy is $1/\delta$) and are not affected by disease status. Deaths are balanced by births into the susceptible class, so that the population size remains constant. The flow diagram for model system (3) is shown in Fig. 1. The aforementioned assumptions lead to the following system of differential equations which describes the dynamics of *P. malariae* and *P. falciparum* mixed infections in a population:

$$\frac{dx}{dt} = \delta - \delta x + (h_f + h_m)x + r_f y_f + r_m y_{fm},$$

$$\frac{dy_f}{dt} = h_f x - \sigma_m h_m y_f + \nu_m y_{fm} - (r_f + \delta) y_f,$$

$$\frac{dy_m}{dt} = h_m x - \sigma_m h_f y_f + \nu_f y_{fm} - (r_m + \delta) y_m,$$

$$\frac{dy_{fm}}{dt} = \sigma_m h_m y_f + \sigma_m h_f y_f - (\nu_f y_{fm} + \nu_m y_{fm} + \delta y_{fm}).$$  

(3)

We assume that all parameters are positive and the initial conditions of model system (3) are given as

$$x(0) > 0, \quad y_f(0) \geq 0, \quad y_m(0) \geq 0, \quad y_{fm} \geq 0.$$

(4)

### 2.1. Basic properties

System (3) will be analysed in a domain $D \subset \mathbb{R}^4$:

$$D = \{ (x, y_f, y_m, y_{fm}) \in \mathbb{R}^4 : \begin{cases} x > 0, \\ y_f \geq 0, \\ y_m \geq 0, \\ y_{fm} \geq 0, \\ x + y_f + y_m + y_{fm} = 1 \end{cases} \}.$$  

(5)
3. Model analysis

3.1. Basic reproductive number

The basic reproductive number is defined as the number of secondary infections produced by a primary infection in a population that is totally susceptible. The dynamical behaviour of the disease is governed by this threshold. The disease free equilibrium of system (3) is given by

\[ \varepsilon_0 = (\delta^0, y_f^0, y_m^0, y_{fm}^0) = (1, 0, 0, 0). \]

Following the method of the next generation approach (van den Driessche and Watmough, 2002), the spectral radius of the next generation matrix for model (3) can easily be shown to be

\[ \rho(FV^{-1}) = R_0 = \max \left\{ \frac{A_2 \beta_h \beta_m e^{\gamma_0} \gamma_0 \gamma}{(\gamma_f + \delta)(\gamma_m + \delta)} \right\} = \max \{ R_f, R_m \}, \]

where \( R_f \) is the reproductive number due to \( P. falciparum \) infections and \( R_m \) is the reproductive number due to \( P. malariae \) infections. The reproductive number \( R_i, i = f, m \) is also referred to as the isolation reproductive number (Nuno et al., 2005) and is the average number of secondary infections generated by the simultaneous introduction of both species in a fully susceptible population. It determines the independent capacity of each species to invade.

From Theorem 2 of van den Driessche and Watmough (2002), the following result follows.

**Theorem 2.** The disease free equilibrium \( \varepsilon_0 \) of the model system (3) is locally asymptotically stable if \( R_0 < 1 \) and unstable otherwise.

**Theorem 3.** If \( R_f < 1 \) and \( R_m < 1 \), then \( \varepsilon_0 \) is the only equilibrium and it is globally asymptotically stable in \( D \).

**Proof.** Let \( L = y_f + y_m + y_{fm} \), \( g_f = A_2 \beta_h \beta_m e^{\gamma_0} \gamma_0 \gamma \) and \( g_m = A_2 \beta_h \beta_m e^{\gamma_0} \gamma_0 \gamma \), then

\[ L' = h_j x (\gamma_f + \delta)y_f + h_m x (\gamma_m + \delta)y_m = y_f \left( \frac{g_f x}{(\mu_f + \delta) (1 - x)} \right) + y_m \left( \frac{g_m x}{(\mu_m + \delta) (1 - x)} \right) \]

If \( R_f \leq 1 \) and \( R_m \leq 1 \), then

\[ -\delta y_f \leq y_f \left( \gamma_f + \delta \right) \leq 0. \]

**3.2. Boundary equilibria and invasion reproductive numbers**

The reproductive number for models with multiple strains is usually the maximum of the reproductive numbers for the two (or more strains) in isolation. The reproductive number in this case describes the initial dynamics of an infected introduced into a completely susceptible population. However, multiple strain models pose multiple endemic equilibria and there is a threshold number connected with the ability of one strain to invade and eliminate another. Therefore, dominance of one strain in that population is determined not just by its ability to invade a completely susceptible population but also by its ability to invade an established population of the other strain (Martcheva et al., 2007). In this context, this reproductive number is the expected number of secondary infections produced by one infected...
individual with one species of human malaria parasites, introduced into a population where the other species is at equilibrium.

To compute the invasion reproductive numbers, we need to find the boundary equilibria of the model system (3). The boundary equilibrium with *P. falciparum* infections only is given by

\[
\mathcal{E}_f = (x_f, y_f, z_f, y_m) = \left( \begin{array}{c} \gamma_f + 1 \\ \gamma_f (R_f - 1) \\ \gamma_f (R_f - 1) \\ 0, 0 \end{array} \right),
\]

and the boundary equilibrium with *P. malariae* infections only is

\[
\mathcal{E}_m = (x_m, y_m, z_m, y_m) = \left( \begin{array}{c} \gamma_m + 1 \\ \gamma_m (R_m - 1) \\ \gamma_m (R_m - 1) \\ 0, 0 \end{array} \right),
\]

where \( \gamma_f = (\mu_f + \alpha_f)/(\beta_f c) \) and \( \gamma_m = (\mu_m + \alpha_m)/(\beta_m c) \). The reproductive number associated with *P. falciparum* equilibrium is obtained by linearizing system (3) about \( \mathcal{E}_f \). The corresponding matrices \( F \) and \( V \) are computed by considering \( y_m \) and \( y_m \) to be disease-free variables and \( x_f \) and \( y_f \) to be non-disease variables. The spectral radius of \( FV^{-1} \) given by

\[
\rho_F = \frac{R_f (1 + \gamma_f^*) (\delta + \beta_f d_f) (\sigma_m (R_f - 1) + a_d (1 + \gamma_f))}{((R_f - 1) (m + 1) + \gamma_f (R_f - 1) (\sigma_f (R_f - 1) + a_d (1 + \gamma_f)))},
\]

where \( \eta_f = \gamma_f (\delta + \beta_f d_f) / (\sigma_m (R_f - 1) + a_d (1 + \gamma_f)) \) and \( \sigma_m = \epsilon_f \) is defined as the reproductive number for *P. malariae* near the *P. falciparum* equilibrium. This reproductive number is defined as the invasion reproductive number of *P. malariae* and it measures the ability of *P. malariae* to invade a population where *P. falciparum* infections are already present and at equilibrium.

Following the same procedure, linearizing system (3) about \( \mathcal{E}_m \), the reproductive number for *P. falciparum* near the *P. malariae* equilibrium is

\[
\rho_F = \frac{R_m (1 + \gamma_m^*) (\delta + \beta_m d_m) (\sigma_m (R_m - 1) + a_d (1 + \gamma_m))}{((R_m - 1) (m + 1) + \gamma_m (R_m - 1) (\sigma_m (R_m - 1) + a_d (1 + \gamma_m)))},
\]

where \( \gamma_m = (\delta + \beta_m d_m) / (\sigma_m (R_m - 1) + a_d (1 + \gamma_m)) \) and it determines the ability of *P. falciparum* to invade a population where *P. malariae* infections are already present and at equilibrium. It is defined as the invasion reproductive number of *P. falciparum*.

By evaluating the Jacobian matrices of system (3) at \( \mathcal{E}_f \) and \( \mathcal{E}_m \) and studying the eigenvalues of the respective matrices, we obtain the results of stability of the boundary equilibria which are summarized in Theorem 4.

**Theorem 4.** The boundary equilibria \( \mathcal{E}_f \) is locally asymptotically stable whenever \( R_f > 1 \) and \( R_m < \sqrt{f(R_f)} \) and boundary equilibria \( \mathcal{E}_m \) is locally stable whenever \( R_m > 1 \) and \( R_f < \sqrt{g(R_m)} \), where

\[
F(\mathcal{R}_f) = \frac{((R_f - 1) (m + 1) + \gamma_f (R_f - 1) (\sigma_f (R_f - 1) + a_d (1 + \gamma_f)))}{(1 + \gamma_f (\delta + \beta_f d_f) / (\sigma_m (R_f - 1) + a_d (1 + \gamma_f)))},
\]

\[
g(\mathcal{R}_m) = \frac{((R_m - 1) (m + 1) + \gamma_m (R_m - 1) (\sigma_m (R_m - 1) + a_d (1 + \gamma_m)))}{(1 + \gamma_m (\delta + \beta_m d_m) / (\sigma_m (R_m - 1) + a_d (1 + \gamma_m)))}.
\]

The condition \( R_m < \sqrt{f(R_f)} \) is equivalent to \( R_m^* < 1 \) while the condition \( R_f < \sqrt{g(R_m)} \) is equivalent to the condition \( R_f^* < 1 \). In the case of full immunity (\( \sigma_m = \sigma_m = 0 \)) and when \( \beta_f = \beta_m \) then \( \mathcal{E}_f \) is locally stable if \( R_f^* > 1 \) and \( R_f > R_m \) and \( \mathcal{E}_m \) is locally stable if \( R_m^* > 1 \) and \( R_m > R_f \).

### 3.3. Interior equilibrium

We will follow closely the method from Velasco-Hernandez (1994) to show that there exists an interior endemic equilibrium, that is, an equilibrium point with positive densities of both *P. falciparum* and *P. malariae* infections. The interior equilibrium will be denoted by \( \mathcal{E}_I = (x_f^*, y_f^*, y_m^*, y_m^*) \). To determine the existence of the endemic equilibrium point, we begin by defining the inoculation rates

\[
h_f(t) = \frac{g_f(y_f(t))}{(\mu_f + \alpha_f + \beta_f c (1-x(t)))}, \quad h_m(t) = \frac{g_m(y_m(t))}{(\mu_m + \alpha_m + \beta_m c (1-x(t)))}.
\]

for *P. falciparum* and *P. malariae* infections, respectively, where

\[
g_f = \frac{\mu_f c}{\beta_f c}, \quad g_m = \frac{\mu_m c}{\beta_m c}.
\]

It follows from (3) that the associated expressions for the population densities at equilibrium are

\[
x^* = \delta + r_f y_f^* + r_m y_m^*, \quad y_f^* = \frac{v_f y_f^* + v_m y_m^*}{v_f + v_m}, \quad y_m^* = \frac{v_m y_m^* + v_m y_m^*}{v_m + v_m}, \quad y_m^* = \frac{\sigma_m h_m^* y_f^* + \sigma_m h_m^* y_m^*}{a_3},
\]

where

\[
\begin{align*}
&v_1 = \sigma_m h_m^* + (r_f + \delta) - \frac{r_f h_f^*}{\delta + h_f^* + h_m^*} a_1, \quad v_2 = \frac{r_m h_f^*}{\delta + h_f^* + h_m^*} a_2, \\
&v_3 = \frac{\delta h_f^*}{\delta + h_f^* + h_m^*}, \quad v_4 = \frac{\delta h_f^*}{\delta + h_f^* + h_m^*}, \quad v_5 = \frac{\delta h_f^*}{\delta + h_f^* + h_m^*}, \quad v_6 = \frac{\delta h_f^*}{\delta + h_f^* + h_m^*}.
\end{align*}
\]

Substituting expressions (15) into expressions for \( h_f \) and \( h_m \) in (14) we obtain

\[
\begin{align*}
&h_f^* = \frac{g_f y_f^*}{(\mu_f + \alpha_f + \beta_f c (1-x^*)}, \\
&h_m^* = \frac{g_m y_m^*}{(\mu_m + \alpha_m + \beta_m c (1-x^*)}.
\end{align*}
\]

at the equilibrium point. Let \( \pi_f(h_f, h_m) \) and \( \pi_m(h_f, h_m) \) be the right hand sides of the two equations in (16), respectively. To find the equilibria of (3) we need to determine the fixed points of the equation

\[
\pi_f(h_f, h_m) = \pi_m(h_f, h_m).
\]

It is clear that the inoculation rate is zero at the disease free equilibrium, therefore \( \pi(0,0) \) also vanishes and hence \( h_f = h_m = 0 \) is a fixed point of \( \pi(0,0) \) corresponding to the disease equilibria \( \mathcal{E}_0 \) of (3). The Jacobian of \( \pi \) evaluated at \( h_f = h_m = 0 \) gives

\[
D\pi(0,0) = \begin{pmatrix} R_f & 0 \\ 0 & R_m \end{pmatrix}.
\]

We note that \( R_0 = \max(R_f, R_m) \) and we have already shown that when \( R_f < 1 \) and \( R_m < 1 \), the disease free is globally asymptotically stable. If \( R_0 > 1 \), the parasites may spread in the population. The task now is to show that \( H \) has a non-zero fixed point corresponding to the interior endemic equilibrium of (3) thus there exists at least a solution \((h_f^*, h_m^*) \in \mathbb{R}^+ \times \mathbb{R}^+ \) satisfying the expressions in (16). For fixed \( h_m > 0 \), we consider the real-valued
function $\pi_L^h(h_z) = \pi_f(h_z, h_m)$. We can see that $\pi_L^h(0) \geq 0$ and $\lim_{h_z \to -\infty} \pi_L^h(h_z) = \frac{g_0(\varepsilon_1 \rho_1 + \delta)}{(\mu_2 + \varepsilon_1 + \rho_1)(h_z + \sigma_f h_m)} < \infty$.

Thus for every fixed $h_m > 0$, $\pi_L^h(h_z)$ is a bounded function. Since, in this case $R_0 > 1$ (needed for $S_0$ to be unstable), it can be shown after some calculations that $\pi_L^h(0) / h_z < 0$ and $\pi_L^h(h_z) / h_z < 0$. This implies that $\pi_L^h(h_z)$ is an increasing concave down function and has no change in convexity. Therefore, there is a unique $h_f^*$ such that $\pi_f(h_f^*, h_m) = h_f^*$. Substituting $h_f^*$ into the expression for $\pi_f(h_f^*, h_m)$ we get $\pi_f(h_f^*, h_m) = \pi_f^*$. We have established the following lemma:

**Lemma 1.** The model system (3) always has a disease free equilibrium which is globally asymptotically stable when both $R_j, R_m < 1$ and has an interior equilibrium which exists if at least one of the isolation reproductive numbers ($R_j > 1$ or $R_m > 1$) is greater than unity.

We will determine the local stability of the interior equilibrium $E^*$ using the centre manifold theorem described in Castillo-Chavez and Song (2004). The following changes are made to apply the theorem, $x = z_1$, $y_j = z_2$, $y_m = z_3$ and $y_m = z_4$ so that

$$h_j = z_1$$
$$h_m = z_2$$

Using the vector notation $Z = (z_1, z_2, z_3, z_4)^T$, model system (3) can be written in the form $dz/dt = W = (w_1, w_2, w_3, w_4)^T$ which is

$$w_1 = \delta - \delta z_1 - (h_j + h_m) z_1 + r_2 z_2 + r_m z_3,$$

$$w_2 = h_j z_1 - \sigma_f h_m z_2 - \varepsilon_1 r_m z_4 + (\delta - \delta) z_2,$$

$$w_3 = h_m z_1 - \sigma_m h_f z_2 + \varepsilon_2 r_f z_4 - (\delta - \delta) z_3,$$

$$w_4 = \sigma_f h_m z_2 + \sigma_m h_f z_2 + (\varepsilon_2 r_f + \varepsilon_1 r_m) z_3.$$

The Jacobian of system (19) at the $E_f$ boundary equilibrium is

$$J_{E_f} = \begin{pmatrix} -k_{11} & k_{12} & k_{13} & 0 \\ k_{12} & k_{22} & -k_{23} & \varepsilon_1 r_m \\ 0 & k_{32} & k_{33} & \varepsilon_2 r_f \\ 0 & 0 & k_{43} & -\alpha_3 \end{pmatrix},$$

where

$k_{11} = \frac{g_1(\mu_1 + \varepsilon_1 + \rho_1) z_2 + \delta}{p_2^2},$ $k_{12} = \delta - \delta - \frac{g_1 z_1}{p_2},$ $k_{13} = \varepsilon_1 r_m - \frac{g_1 z_1}{p_1},$

$k_{21} = \frac{g_1(\mu_1 + \varepsilon_1 + \rho_1) z_2 + \delta}{p_2^2},$ $k_{22} = -r_2 - \frac{g_1 z_2}{p_2},$ $k_{23} = \frac{g_m \sigma_m z_1 + \varepsilon_1 r_m}{p_1},$

$k_{33} = \frac{g_m \sigma_m z_1 + \varepsilon_1 r_m}{p_1}.$

where $p_1 = (\mu_1 + \varepsilon_1 + \rho_1) z_2,$ $p_2 = (\mu_1 + \varepsilon_1 + \rho_1) z_2$ and $\hat{z}_1, \hat{z}_2$ are the values of x and y at $E_f$ given in (9), respectively, from which it can be shown that $R_f^m = \frac{g_1(\varepsilon_1 r_m + \delta)}{\varepsilon_1}$.

where $q_1 = (1 + \gamma_j) R_m,$ $q_2 = e^2 r_f y_j^2 (R_f - 1),$ $q_3 = \alpha_j (1 + \gamma_j),$ $q_4 = (R_f - 1) \rho_m / p_1 + 1 + \gamma_j R_f,$ $q_5 = \hat{y} \sigma_f (R_f - 1) - q_3.$

Consider the case when $R_f^m = 1$. Further, suppose that $\sigma_m = \sigma_f$ is chosen as a bifurcation parameter, then solving for $\sigma_f$ gives $R_f^m = q_0 = \varepsilon_1 y_0 \sigma_f / (\varepsilon_1 q_2 + q_1)$. The right eigenvectors of $J_{E_f}(\sigma_f)$, that is $J_{E_f}$ evaluated at $\sigma_f = \sigma_f^m$ are given by $u = (u_1, u_2, u_3, u_4)^T$, $v = (v_1, v_2, v_2, v_2)^T$ where

$$u_1 = \frac{k_{11} k_{13} + k_{13} k_{12}}{k_{22} k_{11}} - \frac{k_{22} k_{13}}{k_{11}}, u_2 = \frac{k_{22} k_{13} - k_{13} k_{12}}{k_{11}}, u_3 = u_2 > 0, u_4 = \frac{v_1}{v_2},$$

$$v_1 = \frac{k_{23}}{k_{13}}, v_2 = v_3 = \frac{k_{23} - \varepsilon_1 r_m k_{33} - k_{13} k_{23}}{k_{33}}, v_4 = \frac{v_1}{v_2}.$$

The left eigenvector of $J_{E_f}(\sigma_f^m)$ is given by $v = (v_1, v_2, v_2, v_2)^T$ where $v_1 = k_{23}/k_{13}$ and $v_2 > 0, v_3 = (k_{23} - \varepsilon_1 r_m k_{33} - k_{13} k_{23})/k_{33}$, $v_4 = \varepsilon_1 r_m / v_2$.

The centre manifold theory can be used to analyse the dynamics of (19), with $\sigma_m = \sigma_f^m$, since it has at least one non-hyperbolic equilibrium point. Using Theorem 4.1 in Castillo-Chavez and Song (2004), we compute a and b. Let $w_k$ be the kth component of w, then

$$a = \sum_{j=1}^{n} v_k u_j \frac{\partial^2 W_k}{\partial z_j^2}$$

and $b = \sum_{k=1}^{n} v_k u_k \frac{\partial^2 W_k}{\partial z_k^2}.$

For the system (19), the associated non-zero partial derivatives of the right hand side functions $W_i$ are given by

$$\frac{\partial^2 f_1}{\partial z_1^2} = \frac{g_1 \left( \frac{\partial^2 z_1}{\partial z_1^2} \right)}{p_1^2} \left( 1 - \frac{\partial^2 z_1}{\partial z_2^2} \right),$$

$$\frac{\partial^2 f_1}{\partial z_2^2} = \frac{g_1 \left( \frac{\partial^2 z_1}{\partial z_2^2} \right)}{p_2^2} \left( 1 - \frac{\partial^2 z_1}{\partial z_2^2} \right),$$

$$\frac{\partial^2 f_2}{\partial z_1^2} = \frac{g_1 \left( \frac{\partial^2 z_2}{\partial z_1^2} \right)}{p_1^2} \left( 1 - \frac{\partial^2 z_2}{\partial z_2^2} \right),$$

$$\frac{\partial^2 f_2}{\partial z_2^2} = \frac{g_1 \left( \frac{\partial^2 z_2}{\partial z_2^2} \right)}{p_2^2} \left( 1 - \frac{\partial^2 z_2}{\partial z_2^2} \right).$$
and

\[ \frac{\partial^2 f_2}{\partial z_3 \partial \sigma_{fm}} = \frac{g_{m} \dot{z}_2}{p_1} \quad \text{and} \quad \frac{\partial^2 f_4}{\partial z_3 \partial \sigma_{fm}} = \frac{\partial^2 f_2}{\partial z_3 \partial \sigma_{fm}}. \]

After some algebraic manipulations, it follows from the computations of \(a\) and \(b\) that

\[ a = \sum_{k=1}^{n} v_k u_j \frac{\partial^2 w_k}{\partial z_2 \partial z_j}(\xi_j) > 0 \quad \text{and} \quad b = \sum_{k=1}^{n} v_k u_j \frac{\partial^2 w_k}{\partial z_2 \partial \sigma_{fm}}(\xi_j) > 0. \]

Therefore it follows from Theorem 4.1 of Castillo-Chavez and Song (2004) that model system (3) will undergo a backward bifurcation at \( R_m^l = 1 \) (or \( R_m^l = 1 \) if \( \varepsilon_m^* \) is used).

### 3.4. Bifurcations

The definitions of \( F(R_f) \) and \( G(R_m) \) in (13) imply that \( F(1) = G(1) = 1 \). For large values of \( R_f \), the function \( F(R_f) \) is approximately linear in \( R_f \) with a slope that is greater than one and \( G(R_m) \) is approximately linear in \( R_m \) for large values of \( R_m \) with a slope greater than one. This gives a picture of the graphs for the two functions when considering stability. A summary of the stability results for the \( P. falciparum \) infections and \( P. malariae \) infections is stated in Theorem 4. The characterization of the stability regions for \( P. falciparum \) and \( P. malariae \) can be determined by the functions \( F(R_f) \) and \( G(R_m) \) in (13). As the coefficients of cross-immunity are varied, changes in the regions of stability for either a single or both species can be illustrated. There is a value of \( \sigma_{fm} \) which is

\[ \dot{\sigma}_{fm} = \frac{a_i(1 + \gamma_j) + \eta_j \sigma_{mf} R_f}{\varepsilon_2 R_f^2 \gamma_j^2}, \]

at which

\[ F(R_f) = \frac{\partial F(R_f, \sigma_{fm})}{\partial \sigma_{fm}} \bigg|_{\sigma_{fm}} = 0. \]

When \( R_f > 1 \), we have

- \( F(R_f) > 0 \), \( F(R_f) > 1 \) if \( \sigma_{fm} < \dot{\sigma}_{fm} \),
- \( F(R_f) < 0 \), \( F(R_f) < 1 \) if \( \sigma_{fm} > \dot{\sigma}_{fm} \),
- \( F(R_f) = 0 \), \( F(R_f) = 1 \) if \( \sigma_{fm} = \dot{\sigma}_{fm} \).

Corresponding results can be obtained for \( P. malariae \) infections for the value of \( \sigma_{mf} \) by interchanging the subscripts \( f \) and \( m \). The graphs that show the variation of the reproductive numbers with different values of cross-immunity are shown in Fig. 2.

The region of stability of each species decreases as the level of cross-immunity of species \( i \) against species \( j \) decreases (approaching one), thus increasing the coexistence of the two species. This implies that when cross-immunity is weak, it is more likely to have coexistence. When cross-immunity is strong, the coexistence region decreases and competitive exclusion is high. Thus the species with a higher invasion reproductive number is more likely to become established.

The results from this section can be summarized in Lemma 2.

**Lemma 2.** Model system (3) has

(i) a disease free equilibrium \( \varepsilon_{i0} \), which always exists and is globally asymptotically stable if \( R_f < 1 \) and \( R_m < 1 \);

(ii) two boundary equilibria given as

(a) \( P. falciparum \) only equilibrium \( \varepsilon_{f1} \), which is locally asymptotically stable whenever \( R_f > 1 \) and \( R_m^l < 1 \);

(b) \( P. malariae \) only equilibrium \( \varepsilon_{m}^* \), which is locally asymptotically stable if \( R_m > 1 \) and \( R_m^m < 1 \);

(iii) an interior equilibrium \( \varepsilon^* \) which exists if at least one of the isolation reproductive numbers \( R_m^i, i = f, m \) is greater than one and is locally asymptotically stable if the corresponding invasion reproductive number \( R_f^i \) is greater than unity and for a certain range of associated invasion reproductive number less than unity.

### 4. Numerical analysis

The model was analysed numerically using two approaches. The graphs for the invasion reproductive numbers and contour plots were determined and analysed using Mathematica 5.0 (Wolfram Research). To observe the dynamics of the model system (3) over time, we integrated the system of equations, using the fourth order Runge Kutta methods in the C++ programming language. For computer runs we set the initial densities of \( x, y_f, y_m \) and \( y_{mf} \) to 0.5, 0.3, 0.1 and 0.1, respectively. Time is in days and all the rates are per day. The fixed parameters used are shown in Table 1.

The plots in Fig. 3 show the relationship between the invasion reproductive numbers and the isolation reproductive numbers. They were obtained by varying the reproductive numbers \( R_f \) and \( R_m \). In Fig. 3(a) \( R_f \) was varied from 1 to 10 and \( R_m \) from 0 to 10, and in Fig. 3(b) \( R_f \) was varied from 0 to 10 and \( R_m \) from 1 to 10. As \( R_f \) increases \( R_m^l \) decreases and \( R_m^m \) increases and the opposite is true when \( R_m \) is increasing. Thus an increase in the reproductive number of species \( i \) increases the stability of its boundary equilibrium and increases its ability to invade an equilibrium of species \( j \).

The contour plots in Fig. 4 show the response of the equilibrium values of the infected \( y_f \) proportion. The plots were obtained by varying the induced death rate of mosquitoes and biting rate. From the plots, we deduce that an increase in biting rate increases the number of the infected population. The opposite effect is observed for increasing induced death rate. These two intervention strategies are the most common strategies used in malaria prevention and control. Their relative effectiveness were discussed in detail in another study (Chiyaka et al., 2008b).

The results from Fig. 5 show the existence of the four equilibria of model system (3). The graphs were obtained by varying the values \( \beta_f^i \) and \( \beta_m^i \). In Fig. 5(a), \( R_f = R_m = 0.82 \). The graphs show that when the respective reproductive numbers are all less than unity then the disease free equilibrium exists and it has been shown to be globally asymptotically stable for \( R_m < 1 \). For the existence of the \( P. malariae \) only equilibrium the values of the reproductive numbers are \( R_f = 1.20 \) and \( R_m = 1.67 \) with \( R_m^l = 1.41 \) and \( R_m^m = 0.75 \). Since \( R_m^m < 1 \) then, the equilibrium \( \varepsilon_{m}^* \) is stable and this condition is illustrated by the graphs in Fig. 5(b). Similarly for the existence of \( \varepsilon_{f1} \), \( R_m > 0.98 < 1 \) and \( R_f^l > 1.39 \) and the values of \( R_m = 2.00 > 1 \) and \( R_f^l > 2.41 > 1 \). The existence of the interior equilibrium where both \( P. falciparum \) and \( P. malariae \) infections are present is depicted in Fig. 5(d). In this figure \( R_m = 1.24 > 1 \) and \( R_f^l = 1.28 \) where the reproductive numbers are \( R_f = R_m = 2.81 \).

### 5. Summary and conclusions

We formulated and presented a mathematical model for analysing the effects of mixed \( P. falciparum \) and \( P. malariae \) infections with different values of cross-immunity for screening the effects of various malaria control strategies.
malaria infections in a human population where infection with one species confers some partial cross-immunity against infection with the other species. Though mathematical models for malaria infections are well established, no studies have been done on the dynamics of mixed malaria species in a population. Analysis of the model shows that there exists a domain where the model is epidemiologically and mathematically well-posed. The model is then qualitatively analysed for the existence and stability of its equilibria. The disease free equilibrium is globally asymptotically stable when \( R_{f01} \) and \( R_{m01} < 1 \). Results on stability of the boundary equilibria show that the \( P. falciparum \) only equilibrium is locally asymptotically stable. When parameter values are in region (i) \( A_1 \), only \( P. falciparum \) will be maintained, (ii) \( A_2 \), only \( P. malariae \) is maintained, (iii) \( A_3 \), both species will be maintained and (iv) \( A_4 \), none of the two species is maintained. The other parameter values are as shown in Table 1.

### Table 1

Table showing numerical values of parameters used in the simulations.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural death rate of humans</td>
<td>( \delta )</td>
<td>0.000042/day</td>
<td>Chiyaka et al. (2009)</td>
</tr>
<tr>
<td>Probability that a bite results in infection to humans</td>
<td>( b_f, b_m )</td>
<td>0.5, 0.5</td>
<td>Gu et al. (2003)</td>
</tr>
<tr>
<td>Probability that a bite results in transmission of parasites to mosquitoes</td>
<td>( b_f^m, b_m^m )</td>
<td>[0.4 - 1]</td>
<td>Laxminarayan (2004)</td>
</tr>
<tr>
<td>Biting rate</td>
<td>( c )</td>
<td>0.33/day</td>
<td>Koella and Antia (2003)</td>
</tr>
<tr>
<td>Number of female mosquitoes per human host</td>
<td>( m )</td>
<td>0.06</td>
<td>Estimate</td>
</tr>
<tr>
<td>Rate of recovery of infected humans</td>
<td>( \tau_f, \tau_m )</td>
<td>0.005, 0.006/day</td>
<td>Chiyaka et al. (2008a)</td>
</tr>
<tr>
<td>Enhancement factors for recovery</td>
<td>( \nu_f, \nu_m )</td>
<td>1.1, 1.2</td>
<td>Estimate</td>
</tr>
<tr>
<td>Cross-immunity coefficients</td>
<td>( \sigma_{f0}, \sigma_{mf} )</td>
<td>0.5, 0.5</td>
<td>Estimate</td>
</tr>
<tr>
<td>Incubation period of parasites in mosquitoes</td>
<td>( \tau_v )</td>
<td>12 days</td>
<td>Detinova (1962)</td>
</tr>
<tr>
<td>Mosquito mortality rate</td>
<td>( \mu_v )</td>
<td>0.04/day</td>
<td>Chiyaka et al. (2008a)</td>
</tr>
<tr>
<td>Induced mortality rate of mosquitoes</td>
<td>( \zeta_v )</td>
<td>0.01/day</td>
<td>Chiyaka et al. (2008a)</td>
</tr>
</tbody>
</table>

**Fig. 2.** Bifurcation diagrams in the \((R_f, R_m)\)-plane for different values of \( \sigma_{f0} \) and \( \sigma_{mf} \) where in (a) \( \sigma_{f0} < \delta_{f0m} \), (b) \( \sigma_{mf} > \delta_{mf} \), (c) \( \delta_{f0m} < \gamma_i < \delta_{f0m} \) (d) \( \delta_{f0m} < \delta_{m0f} < \delta_{mf} \), where \( i, j = m, f \) (i \( \neq \) j). When parameter values are in region (i) \( A_1 \), only \( P. falciparum \) will be maintained, (ii) \( A_2 \), only \( P. malariae \) is maintained, (iii) \( A_3 \), both species will be maintained and (iv) \( A_4 \), none of the two species is maintained. The other parameter values are as shown in Table 1.
when $R_f > 1$ and $R_m^f < 1$ and the $P. malariae$ only equilibrium is locally asymptotically stable when $R_m > 1$ and $R_m^f < 1$. It was also noted that for a special case with $\sigma_{fo} = \sigma_{fm} = 0$ and $\beta_f = \beta_m$, the boundary equilibria for species $i$ becomes locally asymptotically stable when $R_i > 1$ and $R_i > R_f$. The model has an interior equilibrium (where both species are present) which exists when one of the isolation reproductive numbers is greater than unity.

The phenomenon of backward bifurcation, where a stable boundary equilibrium co-exists with a stable interior equilibrium for a certain range of associated corresponding invasion reproductive number less than unity is observed. This implies that there is a possibility of coexistence driven by cross-immunity even when one of the isolation reproductive number of one species is less than one. Thus, the region of stability of the coexistence equilibrium is increased. As cross-immunity decreases (approaches one), the region of stability of each species is reduced giving rise to an increase in the region of coexistence. Results also show that as cross-immunity of one species against the other becomes weak the chances of existence of both species is high and when cross-immunity becomes strong (approaching zero) then there is high probability of one species eliminating the other that is competitive exclusion is high. This might explain the dominance of $P. falciparum$ in some areas and the coexistence of the two species in others.

In the model analysis we deduced that there are some critical factors of cross-immunity which determine whether a species has greater chances of being eliminated or that the two species have increasing regions of coexistence. We know that $P. falciparum$ is the most virulent agent, if one is first infected with $P. malariae$, then later coinfected with $P. falciparum$ there may be a decrease in the severity of infection because of the immunity raised by the first infection. This therefore implies that if the cross-immunity is strong enough, then there might be a possibility of suppressing the more virulent $P. falciparum$ infections. This result echoes with other field studies where African children with mixed infections comprising $P. falciparum$ and $P. malariae$ and/or $P. ovale$ had fewer or no symptoms compared to those with single species infections in admission blood samples (Black, 1994; Alifrangis et al., 1999). It was also observed from a study of within-host dynamics (Mason et al., 1999) that an existing $P. malariae$ infection can reduce the peak parasitaemia of subsequent $P. falciparum$ superinfection by as much as 50%. On the other hand, if one is infected with $P. falciparum$ first and with $P. malariae$ later then, due to high parasitaemia of $P. falciparum$ and generation of strong immune responses (strong cross-immunity) $P. malariae$ can be suppressed and fail to flourish (competitive exclusion) due to immune responses generated against $P. falciparum$. This result was also found from analysis of blood stage dynamics of mixed $P. falciparum$ and $P. malariae$ infections (Mason et al., 1999) where it was concluded that $P. malariae$ cannot establish high parasitaemia or high prevalence in areas where it must infect patients already infected with $P. falciparum$.

From analysing neurosyphilis malaria therapy data, McKenzie et al. (2002) found that earlier and increased $P. falciparum$ gametocyte production was associated with prior or concurrent $P. malariae$ infection when compared with $P. falciparum$ single infections. This result agrees with studies carried out in Suba District of western Kenya (Bousema et al., 2008). It would be interesting to incorporate (in a future model) increased infectiousness of $P. falciparum$ in mixed species infections and investigate its effects in the dynamics of the model. Earlier gametocyte
Fig. 5. Graphs showing the population proportions for (a) disease free, (b) equilibrium for *P. malariae* infections only, (c) equilibrium for *P. falciparum* infections only and (d) interior equilibrium. The graphs are obtained by varying $\beta_f$ and $\beta_m$ and all other parameters used are from Table 1.
production could be beneficial to the malaria infected patient since parasites are diverted to non-pathogenic sexual stages faster in mixed infections but might also affect prevalence and infectivity of gametocytes giving a negative public health impact since higher densities of gametocytes in mixed species infections are likely to result in higher proportion of infected mosquitoes (Bousena et al., 2008). It may be necessary to assess the prevalence of genotypes and/or mixed-species infections before control measures are implemented (Marques et al., 2005) because for missed mixed infections, incorrect treatment could be given.

For mathematical tractability of the model we have made several assumptions. Therefore our results are based on the formulation of the model. A step towards quantitative predictions can be made by creating more complex epidemiological models by relaxing some of the assumptions made in the formulation of the model. However, the work carried out enables us to gain valuable insights into effects of mixed malaria infections in humans. A better understanding of the dynamics of transmission would provide further insights in planning and assessing the impact of current and future control strategies. Careful examination of methods used to detect these parasites and interpretation of individual- and population-based data are necessary to understand the influence of mixed Plasmodium species infections on malaria. This should ensure that deployment of future antimalarial vaccines and drugs will be conducted in a safe and timely manner. More detailed studies can be done taking into account a variable human population size that is by considering disease induced death in the human population.

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References


