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ORIGINAL ARTICLE

Mathematical Study of the Role of Gametocytes and an Imperfect Vaccine on Malaria Transmission Dynamics

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Abstract A mathematical model is developed to assess the role of gametocytes (the infectious sexual stage of the malaria parasite) in malaria transmission dynamics in a community. The model is rigorously analysed to gain insights into its dynamical features. It is shown that, in the absence of disease-induced mortality, the model has a globally-asymptotically stable disease-free equilibrium whenever a certain epidemiological threshold, known as the *basic reproduction number* (denoted by $\mathcal{R}_0$), is less than unity. Further, it has a unique endemic equilibrium if $\mathcal{R}_0 > 1$. The model is extended to incorporate an imperfect vaccine with some assumed therapeutic characteristics. Theoretical analyses of the model with vaccination show that an imperfect malaria vaccine could have negative or positive impact (in reducing disease burden) depending on whether or not a certain threshold (denoted by ∇) is less than unity. Numerical simulations of the vaccination model show that such an imperfect anti-malaria vaccine (with a modest efficacy and coverage rate) can lead to effective disease control if the reproduction threshold (denoted by $\mathcal{R}_{\text{vac}}$) of the disease is reasonably small. On the other hand, the disease cannot be effectively controlled using such a vaccine if $\mathcal{R}_{\text{vac}}$ is high. Finally, it is shown that the average number of days spent in the class of infectious individuals with higher level of gametocyte is critically important to the malaria burden in the community.

Keywords Malaria · Gametocyte · Vaccine · Equilibria · Stability

1. Introduction

Despite the concerted effort aimed at eradicating malaria globally, the disease continues to be a major cause of morbidity and mortality in the tropical and sub-tropical regions of the world, with some parts of Africa being the most affected (Marsh, 1998).

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Malaria accounts for 300 million cases and over a million fatalities globally every year (World Health Organization Expert Committee on Malaria, 2003), and such burden is expected to significantly increase due to changes in climatic conditions (notably changes in temperature and rainfall) in malaria-endemic regions (Lindsay and Martens, 1998; Zhou et al., 2004). Malaria infection is caused by the protozoan *Plasmodium*, and transmitted to humans by *Anopheles* mosquitoes (after taking a blood meal from humans). Four species of the parasite (*P. falciparum*, *P. vivax*, *P. ovale*, and *P. malarie*) infect humans. These species differ in geographical distribution, microscopic appearance, and clinical features (potential of infection, potential for severe disease, and ability to cause relapses). Of the four species, *P. falciparum* is the most virulent, and potentially lethal to humans.

Numerous mathematical and statistical modeling work has been carried out to gain insights into the transmission dynamics of malaria, dating back to the pioneering work of Sir Ronald Ross (1911) (see, for instance, Chiyaka et al., 2007a, 2007b; Chitnis et al., 2006; Diebner et al., 2000; McQueen and McKenzie, 2004; Ngwa and Shu, 2000). However, these models tend not to explicitly incorporate the role of the infectious sexual stage of the parasite, known as *gametocytes*, in the transmission process. Gametocytes are known to be essential for the transmission of malaria parasite (Drakeley et al., 2006; Schneider et al., 2007; Teboh-Ewungkem et al., 2009) and are vital to the maintenance of the malaria transmission cycle. Such transmission also depends on the maturation of the gametocyte and the size of the blood meal taken.

The malaria parasite life-cycle involves two hosts, namely mosquitoes and humans. Gametocytes are responsible for the transmission of malaria to the mosquito vector. They are produced in humans, where they remain in an arrested cell development state until ingested by a feeding female anopheles mosquito. Male (micro-) gametes released in the insect's midgut fertilize activated female (macro-) gametes (Baton and Ranford-Cartwright, 2005). This leads to the development of different stages of the parasite in the mosquito and ultimately results in the formation of *sporozoites* in the mosquito's salivary glands that render the mosquito infectious to humans. These *sporozoites* are released to the blood stream of the human host when an infectious mosquito takes a blood meal from the host. The *sporozoites* are then carried by blood into the victim's liver, where they invade liver cells, transform and mature into *shizonts,* and then rupture to release *merozoites*. These released *merozoites* invade and infect red blood cells immediately or die after about 30 minutes. The *merozoites* that invade red blood cells then enlarge and turn into immature asexual ring forms—*trophozoites*. Some of these ring stage *trophozoites* will either mature into *schizonts*, which will eventually rupture releasing more *merozoites*, or differentiate into the sexual erythrocytic stages—the gametocytes, which can then be picked up by a female mosquito, after a blood meal. When the sexual stage gametocytes are present in the human blood stream, the human is said to be infectious. The progressive cycles of parasites multiplication and rupture of red blood cells are responsible for the disease symptoms which may include shivering, bouts of fever, anaemia, pain in the joints, and headache in the infected individual.

A number of studies (clinical/statistical/experimental) have shown a positive correlation between gametocyte density in a host and the proportion of mosquitoes that become infectious after feeding on that host (Bilker et al., 1997; Collins and Jeffery, 2003; McKenzie et al., 2002; Talman et al., 2004). Very few mathematical studies (Hoshen et al., 2000; McKenzie and Bossert, 1998; McKenzie et al., 2005; Teboh-Ewungkem et al., 2009) have

been carried out to assess the impact of gametocytes and their density on the parasite dynamics in a host, in a vector, and in human populations. Koella and Anita (1995), and Hellreigel (1992) modeled the within host parasite dynamics and their interaction with the human immune response. Although the aforementioned studies have given some insights into the role of gametocytes on the transmission dynamics and control of malaria, they all considered within-host dynamics (not population-level dynamics), and did not include the use of an imperfect anti-malaria vaccine. The purpose of the current study is to design, and rigorously analyse, a population-level model for assessing the role of gametocyte density on malaria transmission dynamics in the presence of an imperfect malaria vaccine.

Although there is currently no effective anti-malaria vaccine available for use in humans (Saul, 2007; Vekemans and Ballou, 2008), a number of candidate vaccines are under development and/or undergoing various stages of clinical trials (see, for instance, Dubovsky, 2001; Genton and Reed, 2007; MVI, 2007; Mikolajczak et al., 2007; Saul, 2007; Udhayakumar, 1998; Vekemans and Ballou, 2008; Wang et al., 1998). For the most part, some of these vaccines are designed to target the liver stages (pre-erythrocytic stages) of the parasite to reduce the chances of a human being infected (Dubovsky, 2001; Mikolajczak et al., 2007; Saul, 2007; Vekemans and Ballou, 2008), while others are designed to target the asexual blood stages (erythrocytic stage) of the parasite, to reduce disease severity and risk of death during infection) (Dubovsky, 2001; Genton and Reed, 2007; Saul, 2007; Vekemans and Ballou, 2008). In addition, there are other vaccines that are designed to target the sexual stages of the parasite to prevent its transmission to a mosquito vector and ultimately to another human (Dubovsky, 2001; Saul, 2007; Vekemans and Ballou, 2008). However, as noted by Vekemans et al. (2008), an ideal vaccine should be cheap, extremely safe, induce life long immunity, be active against all types of *the plasmodiun falciparum* parasite, and result in a substantial interruption of the malaria life cycle *via* vaccine-induced responses. Unfortunately, this remains a daunting and elusive task. Consequently, the current strategies for malaria vaccine development are focused on achieving more modest goals of reducing the risk of infection and reducing the transformation of the sexual staged gametocytes to gametes in the mosquito (Vekemans and Ballou, 2008). In fact, efforts for vaccine development against the pre-erythrocytic and the erythrocytic stages have focused on strategies aiming at a 50% or more efficacy rate (Vekemans and Ballou, 2008), which are considered as a sizeable scale implementation by many public-health officials (Moorthy et al., 2007; Vekemans and Ballou, 2008). Thus, it is instructive to design models for assessing the potential impact of a future anti-malaria vaccine. Such a vaccine is expected to be imperfect and may possess some important therapeutic characteristics such as, blocking infection (at some efficacy level), reducing transmissibility in breakthrough infection, slowing onset of symptoms, slowing mortality rate and accelerating the rate of acquisition of infection-acquired immunity. This study will offer a qualitative assessment of a malaria transmission model in the presence of a vaccine against the pre-erythrocytic and the erythrocytic stages of the parasite with the aforementioned characteristics.

The paper is organized as follows. A basic, continuous-time, deterministic model for the transmission dynamics of malaria is formulated in Section 2, and rigorously analysed in Section 3. The model is extended to include an imperfect anti-malaria vaccine in Section 4. Numerical simulations are reported in Section 5.

2. Formulation of basic model

The (basic) malaria model to be developed will take the form of a non-linear deterministic (continuous-time) system of differential equations. In the formulation, only populations involved in disease transmission are considered; these include the adult female mosquito and humans of all ages and sexes. Transmission occurs only between the host (humans) and the female vector (mosquito) populations. The model sub-divides the total human population at time t, denoted by $N_h(t)$, into a number of mutually-exclusive compartments namely, susceptible (S_h; people who have not contracted the disease), exposed (E_h; people who are incubating the disease but are not yet infectious), infectious (I_h; people with gametocytes in their blood which can be picked up by a vector on contact) and the temporarily-immune class (M_h; those who do not immediately join the susceptible class upon recovery). The infectious class ($I_h(t)$) is sub-divided into two sub-classes of individuals with lower (I_{1h}) and higher (I_{2h}) gametocyte level, respectively, where infectious individuals with higher gametocyte level are assumed to be more infectious than those with lower gametocyte level (Macdonaldy, 1950; Talman et al., 2004). Gametocyte density tends to follow the asexual density (sometimes with a time lag) with the ratio of gametocytes to asexual stages in *plasmodium falciparum* less than 1:10 (Carter and Graves, 1988; McKenzie et al., 2005; Talman et al., 2004); with even lower ratios (1:156) (Day et al., 1998). Hence, all infectious individuals are assumed to start in the low infectious class I_{1h}), with then transitions between the two infectious classes (the low (I_{1h}) and the high (I_{2h})) and ending in the low class before becoming temporarily immune. Hence, the total human population at time t is given by

$$N_h(t) = S_h(t) + E_h(t) + I_{1h}(t) + I_{2h}(t) + M_h(t).$$

Similarly, the total female vector population at time t, denoted by $N_v(t)$, is sub-divided into susceptible vectors (S_v; mosquitoes that have not contracted the parasite), exposed (E_v; mosquitoes with the parasite in their gut), and infectious (I_v; mosquitoes with parasites (sporozoites) in their salivary glands that can be transmitted to humans on contact) classes, so that

$$N_v(t) = S_v(t) + E_v(t) + I_v(t).$$

The population of susceptible humans at time t ($S_h(t)$) is increased by the recruitment of humans, by birth or immigration (at a rate Π_h), and by the loss of natural immunity in temporarily-immune individuals (at a rate r_h). This population is diminished by natural death (at a rate μ_h) and infection, which can be acquired following effective contact with an infectious female mosquito at a rate λ_v, where by Garba et al. (2008)

$$\lambda_v = \frac{C_{vh} I_v}{N_h}.$$

The parameter C_{vh} is the effective contact rate of vectors. It is defined as the product of the biting rate of mosquitoes and the probability of transmission per bite (from an infectious mosquito to a susceptible human). Putting all these together gives the following equation for the rate of change of the susceptible human population:

$$\frac{dS_h}{dt} = \Pi_h + r_h M_h - \lambda_v S_h - \mu_h S_h. \tag{1}$$

The population of exposed humans is generated by the infection of susceptible individuals (at the rate λ_v). It is reduced by the development of the parasite in the human which may lead to disease symptoms (at a rate σ_h) and natural death (at the rate μ_h). Thus,

$$\frac{dE_h}{dt} = \lambda_v S_h - \sigma_h E_h - \mu_h E_h. \tag{2}$$

During the life cycle of the malaria parasite in a human, a merozoite generated from schizogonic development within an erythrocyte has one of two potential fates after escaping its original host cell and infecting a new erythrocyte host cell:

(1) The merozoite may become a trophozoite and repeat the cycle of schizogony and merozoite production, or
(2) After transforming into a trophozoite, the parasite may alternatively undergo gametocytogenesis, generating either a male or female gametocyte within the host erythrocyte (Talman et al., 2004).

Gametocytogenesis occurs in five stages and represents the initiation of the sexual phase of the parasite's life cycle, with gametocytaemia (the presence of gametocytes in the periphery) arising 7–15 days after the initial sexual wave and peak gametocytemia occurring between 16–28 days after the initial asexual blood forms (Day et al., 1998; Eichner et al., 2001; Talman et al., 2004). Therefore, increased gametocyte density and load, might be the result of length of infection (Talman et al., 2004) or also other immune factors that regulate the merozoite cyclic cycle of producing gametocytes or more merozoites. Hence, the assumption that all infectious individuals start at some low gametocyte level from this first initial wave with the possibility of achieving an increase in gametocyte load with subsequent waves, especially if untreated due to the delay of symptoms or financial constraints or some other reason. In fact, Dunyo et al. (2006), in their trials on asymptomatic groups of patients of adults and children infected with *plasmodium falciparum*, found that gametocyte load was highest in the placebo group, and substantially lower in the groups treated with sulfadoxine-pyrimethamine or sulfadoxine-pyrimethamine and artesunate. Hence, over the course of the infection, with no treatment, some members can have this higher gametocyte load.

Therefore, the population of infectious humans with lower level of gametocytes (I_{1h}) is generated by the development of the parasite (gametocytes) in exposed individuals (at the rate σ_h) as well as by individuals in the higher gametocyte class (I_{2h}) who revert to lower gametocyte level (at a rate α_1). Furthermore, this population is diminished by the development of higher gametocyte level (at a rate α_2), the development of temporal immunity (which can be acquired naturally, at a rate τ_h), by natural death (at the rate μ_h), and by disease-induced death (at a rate δ_1). Thus,

$$\frac{dI_{1h}}{dt} = \sigma_h E_h + \alpha_1 I_{2h} - \alpha_2 I_{1h} - \tau_h I_{1h} - \mu_h I_{1h} - \delta_1 I_{1h}. \tag{3}$$

Similarly, the population of infectious humans with higher level of gametocytes (I_{2h}) is generated by individuals in the lower gametocyte class (I_{1h}) who develop higher gametocyte level (at the rate α_2). Individuals in the I_{2h} class can also (naturally) drop to lower level of gametocytes (at the rate α_1). Furthermore, this population is diminished by

natural death (at the rate μ_h) and disease-induced death (at a rate δ_2). Hence,

$$\frac{dI_{2h}}{dt} = \alpha_2 I_{1h} - \alpha_1 I_{2h} - \mu_h I_{2h} - \delta_2 I_{2h}. \tag{4}$$

The population of temporarily-immune individuals is generated by the acquisition of temporal immunity by infectious individuals in the I_{1h} class (at the rate τ_h) and diminished by the complete loss of temporal immunity (at the rate r_h) and natural death (at the rate μ_h), so that

$$\frac{dM_h}{dt} = \tau_h I_{1h} - r_h M_h - \mu_h M_h. \tag{5}$$

In other words, it is assumed that individuals with lower level of gametocytes can acquire temporal immunity, and such immunity can be completely lost (so that immune individuals move to the susceptible class, $S_h(t)$, at the rate r_h).

Susceptible vectors are generated at a rate Π_v and lost by natural death (at a rate μ_v), or by infection, which can be acquired when susceptible mosquitoes take a blood meal from infectious humans (at a rate λ_h), where

$$\lambda_h = \frac{C_{hv}(I_{1h} + \omega I_{2h})}{N_h},$$

with $\omega > 1$ accounting for the assumed higher infectiousness of individuals in the higher gametocyte class (I_{2h}) in comparison to those in the lower gametocyte class (I_{1h}). The parameter C_{hv} is the effective contact rate of humans, and is defined as the product of the average number of mosquito bites received by humans and the probability of transmission (from an infectious human to a susceptible mosquito). Thus,

$$\frac{dS_v}{dt} = \Pi_v - \lambda_h S_v - \mu_v S_v. \tag{6}$$

Exposed vectors are generated following the infection of susceptible vectors (at the rate λ_h), and diminished due to the development of the parasite (*sporozoites*) in the mosquito (at a rate σ_v) and natural death (at the rate μ_v), so that

$$\frac{dE_v}{dt} = \lambda_h S_v - \sigma_v E_v - \mu_v E_v. \tag{7}$$

Finally, infectious vectors are generated following the development and generation of the parasite (*sporozoites*) in the exposed mosquitoes salivary glands (at the rate σ_v) and reduced by natural death (at the rate μ_v). It is assumed that infectious vectors remain in this class until they die (at the rate μ_v). This gives

$$\frac{dI_v}{dt} = \sigma_v E_v - \mu_v I_v. \tag{8}$$

Thus, the basic gametocyte model for the transmission dynamics of malaria is given by the following system of differential equations:

$$
\begin{aligned}
\frac{dS_h}{dt} &= \Pi_h + r_h M_h - \lambda_v S_h - \mu_h S_h,\\
\frac{dE_h}{dt} &= \lambda_v S_h - \sigma_h E_h - \mu_h E_h,\\
\frac{dI_{1h}}{dt} &= \sigma_h E_h + \alpha_1 I_{2h} - \alpha_2 I_{1h} - \tau_h I_{1h} - \mu_h I_{1h} - \delta_1 I_{1h},\\
\frac{dI_{2h}}{dt} &= \alpha_2 I_{1h} - \alpha_1 I_{2h} - \mu_h I_{2h} - \delta_2 I_{2h},\\
\frac{dM_h}{dt} &= \tau_h I_{1h} - r_h M_h - \mu_h M_h,\\
\frac{dS_v}{dt} &= \Pi_v - \lambda_h S_v - \mu_v S_v,\\
\frac{dE_v}{dt} &= \lambda_h S_v - \sigma_v E_v - \mu_v E_v,\\
\frac{dI_v}{dt} &= \sigma_v E_v - \mu_v I_v.
\end{aligned}
\tag{9}
$$

The basic model (9) is an extension of some standard models for vector-borne diseases, such as those in Chiyaka et al. (2007a, 2007b), Chitnis et al. (2006), Diebner et al. (2000), Garba et al. (2008), McQueen and McKenzie (2004), Ngwa and Shu (2000), by

(i) incorporating the role of gametocytes in malaria transmission dynamics (by way of including compartments for individuals with lower (I_{1h}) and higher (I_{2h}) gametocyte levels, as well as the back-and-forth transitions between these compartments);
(ii) including the dynamics of temporarily-immune individuals (adding the fact that such individuals can lose their immunity and return to the susceptible class).

Furthermore, the model (9) will be extended in Section 4 to include an imperfect anti-malaria vaccine with various (assumed) therapeutic benefits. In addition to the extensions of some earlier models, this study contributes to the literature by offering rigorous qualitative analysis of the resulting models.

3. Mathematical analysis of the basic model

In this section, the basic model (9) will be qualitatively analysed to gain insights into its dynamical features (particularly, to determine associated epidemiological thresholds which govern the persistence or elimination of malaria in a given-human population). To make the mathematical analysis of this section more tractable, we will consider the case where the disease-induced death is negligible (so that, $\delta_1 = \delta_2 = 0$). This will make epidemiological sense if the population being considered is in the developed nations, since data from the World Health Organization suggests that malaria-induced mortality in such nations is rather small (Pan American Health Organization, 2007). However, this assumption will be relaxed in Section 4.1 and also in the numerical simulations section (where scenarios for endemic regions, $\delta_1 \neq 0$ and $\delta_2 \neq 0$, are considered).

Consequently, adding the first five equations of the model (9), with $\delta_1 = \delta_2 = 0$, gives $\frac{dN_h}{dt} = \Pi_h - \mu_h N_h$, so that $N_h(t) \to \frac{\Pi_h}{\mu_h}$ as $t \to \infty$. Thus, $\frac{\Pi_h}{\mu_h}$ is an upper bound of $N_h(t)$ provided that $N_h(0) \leq \frac{\Pi_h}{\mu_h}$. Further, if $N_h(0) > \frac{\Pi_h}{\mu_h}$, then $N_h(t)$ will decrease to this level. Similar calculation for the vector equations shows that $N_v \to \frac{\Pi_v}{\mu_v}$ as $t \to \infty$. Hence, the following feasible region:

$$\Omega = \left\{ (S_h, E_h, I_{1h}, I_{2h}, M_h, S_v, E_v, I_v) \in \mathbb{R}_+^8 : N_h \leq \frac{\Pi_h}{\mu_h} = N_h^*,\ N_v \leq \frac{\Pi_v}{\mu_v} = N_v^* \right\}$$

is positively-invariant. For $\delta_1 = \delta_2 = 0$, the susceptible human (S_h) and vector (S_v) populations can be expressed (at steady-state) as $S_h = N_h^* - E_h - I_{1h} - I_{2h} - M_h$ and $S_v = N_v^* - E_v - I_v$, respectively. Thus, it is sufficient to study the limiting case of (9), given by

$$\begin{aligned}
\frac{dE_h}{dt} &= \lambda_{v1}\left(N_h^* - E_h - I_{1h} - I_{2h} - M_h\right) - \sigma_h E_h - \mu_h E_h,\\
\frac{dI_{1h}}{dt} &= \sigma_h E_h + \alpha_1 I_{2h} - \alpha_2 I_{1h} - \tau_h I_{1h} - \mu_h I_{1h},\\
\frac{dI_{2h}}{dt} &= \alpha_2 I_{1h} - \alpha_1 I_{2h} - \mu_h I_{2h},\\
\frac{dM_h}{dt} &= \tau_h I_{1h} - r_h M_h - \mu_h M_h,\\
\frac{dE_v}{dt} &= \lambda_{h1}\left(N_v^* - E_v - I_v\right) - \sigma_v E_v - \mu_v E_v,\\
\frac{dI_v}{dt} &= \sigma_v E_v - \mu_v I_v,
\end{aligned} \tag{10}$$

in the region,

$$\Omega_1 = \left\{ (E_h, I_{1h}, I_{2h}, M_h, E_v, I_v) \in \mathbb{R}_+^6 : E_h + I_{1h} + I_{2h} + M_h \leq N_h^*,\ E_v + I_v \leq N_v^* \right\},$$

where,

$$\lambda_{v1} = \frac{C_{vh} I_v}{N_h^*} \quad \text{and} \quad \lambda_{h1} = \frac{C_{hv}(I_{1h} + \omega I_{2h})}{N_h^*}.$$

Thus, unlike the basic model (9), which uses a standard incidence formulation, the limiting model (10) is a mass action model (see Sharomi et al., 2007 for detailed discussion on the two forms of the incidence functions).

3.1. Disease-free equilibrium (DFE)

The limiting system (10) has a DFE given by

$$\mathcal{E}_1 = \left(E_h^*, I_{1h}^*, I_{2h}^*, M_h^*, E_v^*, I_v^*\right) = (0, 0, 0, 0, 0, 0). \tag{11}$$

The linear stability of $\mathcal{E}_1$ can be studied using the *next generation operator* technique in van den Driessche and Watmough (2002). The associated non-negative matrix, F_1, for

the new infection terms, and the non-singular M-matrix, Q_1, for the remaining transfer terms, are given, respectively, by

$$F_1 = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & C_{vh} \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \frac{C_{hv}N_v^*}{N_h^*} & \frac{C_{hv}\omega N_v^*}{N_h^*} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

$$Q_1 = \begin{pmatrix} k_1 & 0 & 0 & 0 & 0 & 0 \\ -\sigma_h & k_2 & -\alpha_1 & 0 & 0 & 0 \\ 0 & -\alpha_2 & k_3 & 0 & 0 & 0 \\ 0 & -\tau_h & 0 & k_4 & 0 & 0 \\ 0 & 0 & 0 & 0 & k_5 & 0 \\ 0 & 0 & 0 & 0 & -\sigma_v & \mu_v \end{pmatrix},$$

with, $k_1 = \sigma_h + \mu_h$, $k_2 = \alpha_2 + \tau_h + \mu_h$, $k_3 = \alpha_1 + \mu_h$, $k_4 = \mu_h + r_h$ and $k_5 = \mu_v + \sigma_v$. The associated *basic reproduction number*, denoted by $\mathcal{R}_0$, is then given by $\mathcal{R}_0 = \rho(F_1 Q_1^{-1})$, where ρ is the spectral radius of $F_1 Q_1^{-1}$. It follows that

$$\mathcal{R}_0 = \sqrt{\frac{N_v^* C_{hv} C_{vh} \sigma_h \sigma_v (\omega\alpha_2 + k_3)}{N_h^* k_1 k_5 \mu_v (k_2 k_3 - \alpha_1\alpha_2)}},$$

with, $k_2k_3 - \alpha_1\alpha_2 = k_2\mu_h + \alpha_1(\tau_h + \mu_h) > 0$. Thus, by Theorem 2 of van den Driessche and Watmough (2002), the following result is established.

Lemma 1. *The DFE, $\mathcal{E}_1$, of the system* (10), *given by* (11), *is locally-asymptotically stable* (*LAS*) *if* $\mathcal{R}_0 < 1$, *and unstable if* $\mathcal{R}_0 > 1$.

The threshold quantity, $\mathcal{R}_0$, measures the average number of secondary cases generated by a single infected individual (or vector) in a completely susceptible vector (or human) population (Anderson and May, 1990; Hethcote, 2000). It is a geometric mean. The above result implies that a small influx of infected individuals (or vector) would not generate large outbreaks if $\mathcal{R}_0 < 1$, and the disease will persist (be endemic) in the population if $\mathcal{R}_0 > 1$. However, in order for disease elimination to be independent of the initial sizes of the sub-populations of the model when $\mathcal{R}_0 < 1$, a global stability property must be established for the DFE when $\mathcal{R}_0 < 1$. This is explored below.

3.2. Global stability of the DFE of model (10)

We claim the following.

Theorem 1. *The DFE, $\mathcal{E}_1$, of the limiting model (10), is globally-asymptotically stable (GAS) in Ω_1 if $\mathcal{R}_0 \leq 1$.*

Proof: Consider the Lyapunov function

$$\mathcal{F} = f_1 E_h + f_2 I_{1h} + f_3 I_{2h} + f_4 E_v + f_5 I_v,$$

where

$$\begin{aligned} f_1 &= C_{hv} N_v^* \sigma_h \sigma_v (\omega\alpha_2 + k_3), \qquad f_2 = C_{hv} N_v^* \sigma_v k_1 (\omega\alpha_2 + k_3), \\ f_3 &= C_{hv} N_v^* \sigma_v k_1 (\omega k_2 + \alpha_1), \qquad f_4 = \mathcal{R}_0 \sigma_v k_1 N_h^* (k_2 k_3 - \alpha_1\alpha_2), \quad \text{and} \\ f_5 &= \mathcal{R}_0 N_h^* k_1 k_5 (k_2 k_3 - \alpha_1\alpha_2), \end{aligned}$$

with Lyapunov derivative given by (where a dot represents differentiation with respect to t)

$$\begin{aligned} \dot{\mathcal{F}} &= f_1 \dot{E}_h + f_2 \dot{I}_{1h} + f_3 \dot{I}_{2h} + f_4 \dot{E}_v + f_5 \dot{I}_v \\ &= f_1 \big[\lambda_{v1}\big(N_h^* - E_h - I_{1h} - I_{2h} - M_h\big) - k_1 E_h\big] + f_2[\sigma_h E_h + \alpha_1 I_{2h} - k_2 I_{1h}] \\ &\quad + f_3[\alpha_2 I_{1h} - k_3 I_{2h}] + f_4\big[\lambda_{h1}\big(N_v^* - E_v - I_v\big) - k_5 E_v\big] + f_5[\sigma_v E_v - \mu_v I_v] \\ &= I_{1h}\big[C_{hv} N_v^* \sigma_v k_1 (k_2 k_3 - \alpha_1\alpha_2)(\mathcal{R}_0 - 1)\big] \\ &\quad + I_{2h}\big[C_{hv} N_v^* \omega \sigma_v k_1 (k_2 k_3 - \alpha_1\alpha_2)(\mathcal{R}_0 - 1)\big] \\ &\quad + I_v\big[N_h^* \mu_v k_1 k_5 \mathcal{R}_0 (k_2 k_3 - \alpha_1\alpha_2)(\mathcal{R}_0 - 1)\big] \\ &\quad - f_1\left[\frac{C_{vh} I_v}{N_h^*}(E_h + I_{1h} + I_{2h} + M_h)\right] \\ &\quad - f_4\left[\frac{C_{hv}(I_{1h} + \omega I_{2h})}{N_h^*}(E_v + I_v)\right] \\ &= k_1 (k_2 k_3 - \alpha_1\alpha_2)\big[C_{hv} N_v^* \sigma_v (I_{1h} + \omega I_{2h}) + I_v N_h^* \mu_v k_5 \mathcal{R}_0\big](\mathcal{R}_0 - 1) \\ &\quad - f_1\left[\frac{C_{vh} I_v}{N_h^*}(E_h + I_{1h} + I_{2h} + M_h)\right] - f_4\left[\frac{C_{hv}(I_{1h} + \omega I_{2h})}{N_h^*}(E_v + I_v)\right]. \end{aligned}$$

Thus, $\dot{\mathcal{F}} \leq 0$ if $\mathcal{R}_0 \leq 1$ with $\dot{\mathcal{F}} = 0$ if and only if $E_h = I_{1h} = I_{2h} = M_h = E_v = I_v = 0$. It follows, from the Lasalle invariance principle (LaSalle, 1976) that $E_h \to 0$, $I_{1h} \to 0$, $I_{2h} \to 0$, $M_h \to 0$, $E_v \to 0$ and $I_v \to 0$ as $t \to \infty$ (i.e., the disease dies out). Thus, $(E_h, I_{1h}, I_{2h}, M_h, I_v, E_v) \to (0, 0, 0, 0, 0, 0)$ as $t \to \infty$. Further, since Ω_1 is positively-invariant, it follows that the DFE, $\mathcal{E}_1$, is GAS in Ω_1 for all non-negative initial conditions of the state variables of the model if $\mathcal{R}_0 \leq 1$. □

The epidemiological implication of Theorem 1 is that the disease will be eliminated from the population if $\mathcal{R}_0 \leq 1$ (regardless of the size of the initial outbreak). In other words, the classical epidemiological requirement of $\mathcal{R}_0 \leq 1$ is necessary and sufficient for disease elimination. Thus, any public health intervention mechanism that can bring

$\mathcal{R}_0$ to a value less than unity will lead to the elimination of malaria from the population under consideration. It is worth mentioning that if the assumption $\delta_1 = \delta_2 = 0$ (needed in the formulation of the limiting model (10)) is relaxed, the model (9) can exhibit dynamics different from what has been shown above, such as the presence of the phenomenon of backward bifurcation (see, for instance, Sharomi et al., 2007 and the references therein), where a stable DFE co-exits with a stable endemic equilibrium when $\mathcal{R}_0 < 1$ (Mukandavire et al. (2008) showed backward bifurcation in a basic model for malaria transmission without gametocyte dynamics; Garba et al. (2008) established the presence of this phenomenon in a study of dengue transmission dynamics, another vector-borne disease).

3.3. Existence of endemic equilibria

To find the conditions for the existence of the endemic equilibria of the model (9) (that is, equilibria of the model (9) for which the disease is endemic in the population), denoted by

$$\mathcal{E}_2 = \left(S_h^{**}, E_h^{**}, I_{1h}^{**}, I_{2h}^{**}, M_h^{**}, S_v^{**}, E_v^{**}, I_v^{**}\right),$$

the equations in the model (9) are solved in terms of the associated forces of infection at steady-state, namely

$$\lambda_v^{**} = C_{vh}\frac{I_v^{**}}{N_h^{**}} \quad \text{and} \quad \lambda_h^{**} = C_{hv}\frac{I_{1h}^{**} + \omega I_{2h}^{**}}{N_h^{**}}. \tag{12}$$

Setting the right-hand side of the equations in (9) to zero gives (in terms of $S_h^{**} > 0$)

$$\begin{aligned} E_h^{**} &= \frac{\lambda_v^{**} S_h^{**}}{k_1}, \qquad I_{1h}^{**} = A_1\lambda_v^{**} S_h^{**}, \qquad I_{2h}^{**} = B_1\lambda_v^{**} S_h^{**}, \qquad M_h^{**} = C_1\lambda_v^{**} S_h^{**}, \\ S_v^{**} &= \frac{\Pi_v}{\lambda_h^{**} + \mu_v}, \qquad E_v^{**} = \frac{\lambda_h^{**} S_v^{**}}{k_5}, \qquad I_v^{**} = \frac{\sigma_v\lambda_h^{**} S_v^{**}}{\mu_v k_5}, \end{aligned} \tag{13}$$

with,

$$A_1 = \frac{\sigma_h k_3}{k_1(k_2k_3 - \alpha_1\alpha_2)}, \qquad B_1 = \frac{\alpha_2\sigma_h}{k_1(k_2k_3 - \alpha_1\alpha_2)}, \qquad C_1 = \frac{\tau_h A_1}{k_4}.$$

Using (13) in (12), and simplifying, it follows that the endemic equilibria of the model system (9) satisfy the following polynomial,

$$a_2\left(\lambda_v^{**}\right)^2 + a_1\lambda_v^{**} + a_0 = 0, \quad \mathcal{R}_{\text{vac}} \tag{14}$$

where,

$$\begin{aligned} a_2 &= S_h^{**}\mu_v k_5\left[C_{hv}k_1(A_1 + \omega B_1) + \mu_v(1 + B_1k_1 + A_1k_1 + C_1k_1)\right] \\ &\quad \times (1 + B_1k_1 + A_1k_1 + C_1k_1), \\ a_1 &= S_h^{**}\mu_v k_5 k_1\left[C_{hv}k_1(A_1 + \omega B_1) + 2\mu_v(1 + B_1k_1 + A_1k_1 + C_1k_1)\right], \\ a_0 &= S_h^{**}k_1^2\mu_v^2 k_5\left(1 - \mathcal{R}_0^2\right). \end{aligned}$$

It is worth noting that the coefficients a_1 and a_2 are always positive. The coefficient a_0 is positive (negative) if $\mathcal{R}_0$ is less than (greater than) unity. Thus, all the coefficients of the quadratic (14) are positive when $\mathcal{R}_0 < 1$ (hence, the model has no positive real root in this case). For the case $\mathcal{R}_0 > 1$, the coefficient $a_0 < 0$, so that the model has one positive real root in this case (the components of this endemic equilibrium can be obtained by substituting the positive root of (14) into the expressions in (13)). Finally, when $\mathcal{R}_0 = 1$, the coefficient a_0 is zero, and Eq. (14) reduces to $\lambda_v^{**}(a_2\lambda_v^{**} + a_1) = 0$, with solutions $\lambda_v^{**} = 0$ (corresponding to the DFE, $\mathcal{E}_1$) and $\lambda_v^{**} = -\frac{a_1}{a_2} < 0$ (which is biologically meaningless). Thus, the model has no positive equilibrium when $\mathcal{R}_0 = 1$. These results are summarized below (note that the same result can be established if the reduced model (10) is analysed).

Lemma 2. *The model* (9) *has one positive* (*endemic*) *equilibrium whenever* $\mathcal{R}_0 > 1$, *and no positive equilibrium otherwise.*

Hence, the above mathematical analyses show that the basic malaria model (9) has a globally-asymptotically stable disease-free equilibrium whenever $\mathcal{R}_0 \leq 1$, and a unique endemic equilibrium if $\mathcal{R}_0 > 1$. In other words, the disease will be eliminated from the community if $\mathcal{R}_0 \leq 1$, and would persist otherwise.

4. Extended model with vaccination

The basic model (9) is now extended to incorporate an imperfect malaria vaccine. To do so, the following new variables are introduced for the populations of vaccinated individuals (V_h), exposed vaccinated individuals (E_{vh}) and infectious vaccinated individuals with lower (J_{1h}) and higher (J_{2h}) gametocyte level. Susceptible individuals are vaccinated at a rate ξ_h (so that the class of vaccinated individuals is increased at a rate ξ_h) and diminished due to vaccine waning (at a rate κ_h; vaccinated individuals when vaccine wane are moved to the susceptible class, S_h) and natural death (at the rate μ_h). Furthermore, since the vaccine is assumed to be imperfect, vaccinated individuals can acquire breakthrough infection at a reduced rate $(1-\epsilon)\lambda_v$, where $0 < \epsilon < 1$ represents the vaccine efficacy. Thus, the rate of change of the population of vaccinated individuals is given by

$$\frac{dV_h}{dt} = \xi_h S_h - (1-\epsilon)\lambda_v V_h - \kappa_h V_h - \mu_h V_h.$$

Although there may not be definitive clinical basis in support of the following assumptions, it seems reasonable to assume that a future anti-malaria vaccine would offer the following (therapeutic) benefits to vaccinated individuals who acquire breakthrough infection:

(i) slow development of symptoms;
(ii) reduce mortality rate; and
(iii) accelerate rate of development of temporal immunity.

The population of exposed vaccinated individuals is increased by breakthrough infection (at the rate $(1-\epsilon)\lambda_v$) and diminished by the development of clinical symptoms at a

rate $\theta_1\sigma_h$, where $0 < \theta_1 < 1$ is a modification parameter accounting for the assumed reduction in the rate at which exposed vaccinated individuals develop clinical symptoms of malaria in relation to exposed unvaccinated humans. This population is further diminished by natural death (at the rate μ_h). Thus,

$$\frac{dE_{vh}}{dt} = (1-\epsilon)\lambda_v V_h - \theta_1\sigma_h E_{vh} - \mu_h E_{vh}.$$

Infectious vaccinated individuals with lower gametocyte level (J_{1h}) are generated by the development of clinical symptoms by the exposed vaccinated individuals (at the rate $\theta_1\sigma_h$) and by the progression to lower gametocyte level of infectious vaccinated individuals with higher gametocytes (at the rate α_1). This population is diminished by progression to higher gametocyte class (at the rate α_2), acquisition of immunity (at a rate $\theta_2\tau_h$, where, $\theta_2 > 1$ accounts for the assumed increase in the rate of acquisition of immunity for vaccinated infected individuals in the J_{1h} class in comparison to unvaccinated infected individuals in the I_{1h} class), natural death (at the rate μ_h) and disease-induced death (at a rate $\theta_3\delta_1$, where $0 < \theta_3 < 1$ models the assumed reduction in the mortality rate of vaccinated infectious individuals in comparison to unvaccinated infectious individuals). It is assumed that the vaccine does not alter the back-and-forth transition between the two gametocyte levels in breakthrough infections (i.e., the rates α_1 and α_2 are retained, as in the basic model (9)). Thus, the equation for the rate of change of the population of vaccinated infectious individuals with lower gametocyte level is given by

$$\frac{dJ_{1h}}{dt} = \theta_1\sigma_h E_{vh} + \alpha_1 J_{2h} - \alpha_2 J_{1h} - \theta_2\tau_h J_{1h} - \mu_h J_{1h} - \theta_3\delta_1 J_{1h}.$$

Similarly, infectious vaccinated individuals with higher gametocyte level (J_{2h}) are generated by the progression to higher gametocyte level of infectious vaccinated individuals with lower gametocytes (at the rate α_2). The population J_{2h} is decreased by progression to the lower gametocyte level (at the rate α_1), natural death (at the rate μ_h) and disease-induced death (at the reduced rate $\theta_3\delta_2$). Hence,

$$\frac{dJ_{2h}}{dt} = \alpha_2 J_{1h} - \alpha_1 J_{2h} - \mu_h J_{2h} - \theta_3\delta_2 J_{2h}.$$

Owing to the incorporation of an imperfect vaccine in the model, the rate at which mosquitoes acquire infection from humans is re-defined as

$$\lambda_h^v = C_{hv}\frac{I_{1h} + \omega I_{2h} + \psi(J_{1h} + \omega J_{2h})}{N_h},$$

where, as before, $\omega > 1$ accounts for the assumed higher infectiousness of individuals in the higher gametocyte classes (I_{2h} and J_{2h}) in comparison to those in the lower gametocyte classes (I_{1h} and J_{1h}), respectively. Further, the modification parameter $0 < \psi < 1$ models the assumed vaccine-induced reduction in infectiousness of vaccinated infectious individuals compared to unvaccinated infectious individuals (in the I_{1h} and I_{2h} classes). Finally, the total human population at time t is now given by (note that the vector population is as in the basic model (9)).

$$N_h(t) = S_h(t) + V_h(t) + E_{uh}(t) + E_{vh}(t) + I_{1h}(t) + I_{2h}(t) + J_{1h}(t) + J_{2h}(t) + M_h(t).$$

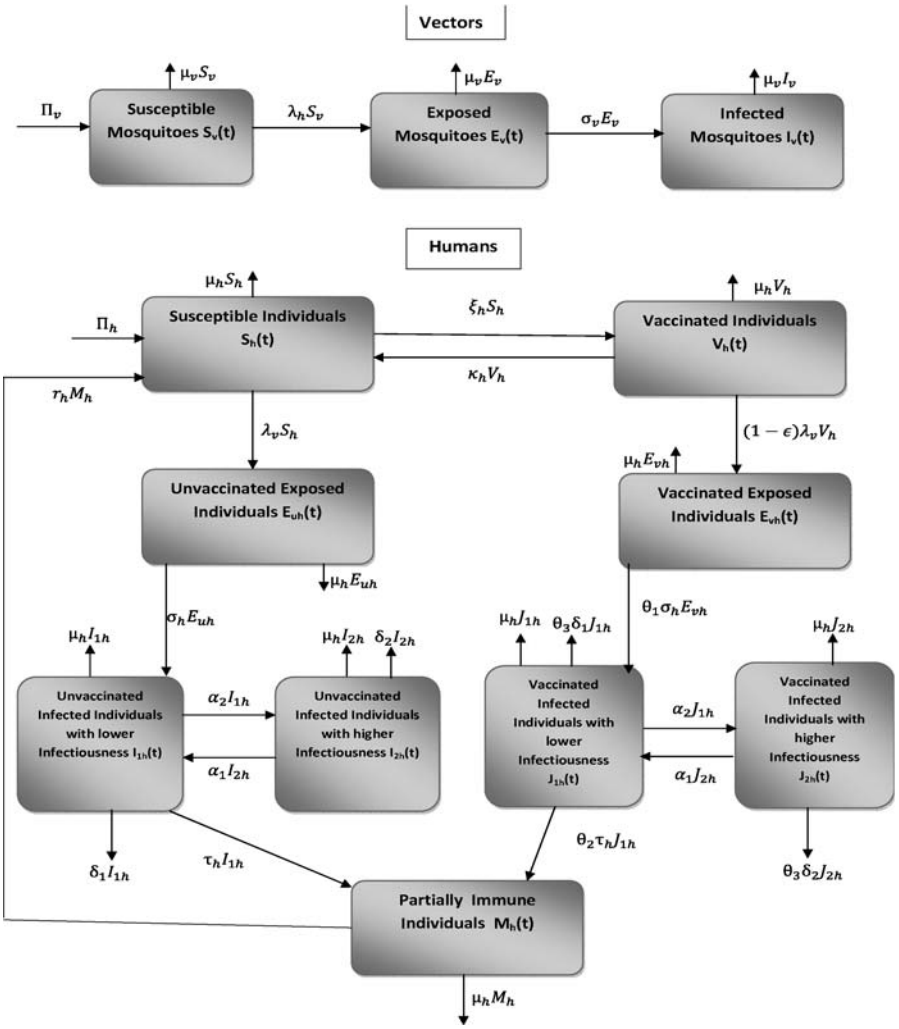

Fig. 1 Schematic diagram of the vaccination model (15).

Thus, considering the above descriptions together with the basic model (9), the extended vaccination model for the transmission dynamics of malaria is given by the following system of differential equations (a schematic diagram of the model is depicted in Fig. 1; the associated variables and parameters of the model are described in Table 1).

$$\frac{dS_h}{dt} = \Pi_h + r_h M_h + \kappa_h V_h - \lambda_v S_h - \xi_h S_h - \mu_h S_h,$$
$$\frac{dV_h}{dt} = \xi_h S_h - (1-\epsilon)\lambda_v V_h - \kappa_h V_h - \mu_h V_h,$$

Table 1 Description of variables and parameters of the vaccination model (15)

Variables	Description		
$S_h(t)$	Susceptible individuals		
$V_h(t)$	Vaccinated individuals		
$E_{uh}(t)$	Unvaccinated exposed individuals		
$E_{vh}(t)$	Vaccinated exposed individuals		
$I_{1h}(t)$	Infected individuals with lower gametocyte level		
$I_{2h}(t)$	Infected individuals with higher gametocyte level		
$J_{1h}(t)$	Infected vaccinated individuals with lower gametocyte level		
$J_{2h}(t)$	Infected vaccinated individuals with higher gametocyte level		
$M_h(t)$	Temporarily-immune individuals		
$S_v(t)$	Susceptible mosquitoes		
$E_v(t)$	Exposed mosquitoes		
$I_v(t)$	Infectious mosquitoes		
Parameters	Description	Baseline values	Ref[a]
Π_h	Recruitment rate of humans	$[10^5$–$10^6]$ per year	Central Intelligence Agency, 2008
Π_v	Recruitment rate of vectors	$10^4 \times 365$ per year	Teboh-Ewungkem, 2009
μ_h	Natural death rate of host	$\frac{1}{55} \in [\frac{1}{45}, \frac{1}{60}]$ per year	Central Intelligence Agency, 2008
μ_v	Natural death rate of vector	$[\frac{365}{28}, \frac{365}{21}]$ per year	Center for Disease Control and Prevention, 2007
C_{hv}	Contact rate from host to vector	Variable	
C_{vh}	Contact rate from vector to host	Variable	

Table 1 (*Continued*)

Parameters	Description	Baseline values	Ref[a]
κ_h	Waning rate of vaccine	0.3	
ξ_h	Vaccination rate	0.7	
ϵ	Efficacy of vaccine	0.6	
σ_h	Progression rate to symptoms development for the host	$\frac{365}{14}$ per year	Mehlhorn, 2001
σ_v	Progression rate to symptoms development for the vector	$\frac{365}{12}$ per year	Anderson and May, 1990; Carter and Graves, 1988; Sinden, 1984
r_h	Rate of loss of immunity	$\frac{365}{68.5}$ per year	Ngwa and Shu, 2000
τ_h	Rate of development of temporal immunity for individuals with lower gametocyte level	Variable	
α_1, α_2	Transition rates between I_{2h} and I_{1h} classes	Variable	
ω	Modification parameter for increased infectiousness of individuals in higher gametocyte class	20	Tchuinkam et al., 1993
ψ	Modification parameter for reduced infectiousness of vaccinated individuals	0.7	
$\theta_1, \theta_2, \theta_3$	Modification parameters for infectiousness of vaccinated individuals	0.7, 1.2, 0.5, respectively	
δ_1	Disease-induced death rate for infectious individuals in the lower gametocyte class	$[0–4.1\times10^{-4}]\times365$ per year	Chitnis et al., 2008; Ngwa and Shu, 2000; Teboh-Ewungkem, 2009
δ_2	Disease-induced death rate for infectious individuals in the higher gametocyte class	$[0–4.1\times10^{-4}]\times365$ per year	Chitnis et al., 2008; Ngwa and Shu, 2000; Teboh-Ewungkem, 2009

[a]For most of the parameters not related to vaccination, we used values from available published literature some of which are shown above. The remaining variable parameter values will be feasible parameters carefully chosen in line with the literature on transmission intensity, mosquito behaviors, their biting rates and the number of bites a given mosquito can take (Chitnis et al., 2008; Vittor et al., 2006). For the vaccination model, we used what we thought are "realistically feasible" values (since such data does not exist, in the absence of a vaccine).

$$
\begin{aligned}
\frac{dE_{uh}}{dt} &= \lambda_v S_h - \sigma_h E_{uh} - \mu_h E_{uh},\\
\frac{dE_{vh}}{dt} &= (1-\epsilon)\lambda_v V_h - \theta_1\sigma_h E_{vh} - \mu_h E_{vh},\\
\frac{dI_{1h}}{dt} &= \sigma_h E_{uh} + \alpha_1 I_{2h} - \alpha_2 I_{1h} - \tau_h I_{1h} - \mu_h I_{1h} - \delta_1 I_{1h},\\
\frac{dI_{2h}}{dt} &= \alpha_2 I_{1h} - \alpha_1 I_{2h} - \mu_h I_{2h} - \delta_2 I_{2h},\\
\frac{dJ_{1h}}{dt} &= \theta_1\sigma_h E_{vh} + \alpha_1 J_{2h} - \alpha_2 J_{1h} - \theta_2\tau_h J_{1h} - \mu_h J_{1h} - \theta_3\delta_1 J_{1h},\\
\frac{dJ_{2h}}{dt} &= \alpha_2 J_{1h} - \alpha_1 J_{2h} - \mu_h J_{2h} - \theta_3\delta_2 J_{2h},\\
\frac{dM_h}{dt} &= \tau_h I_{1h} + \theta_2\tau_h J_{1h} - r_h M_h - \mu_h M_h,\\
\frac{dS_v}{dt} &= \Pi_v - \lambda_h^v S_v - \mu_v S_v,\\
\frac{dE_v}{dt} &= \lambda_h^v S_v - \sigma_v E_v - \mu_v E_v,\\
\frac{dI_v}{dt} &= \sigma_v E_v - \mu_v I_v.
\end{aligned}
\tag{15}
$$

The model (15) is an extension of the vaccination model for dengue disease, presented in Garba et al. (2008), and for malaria, presented in Chiyaka et al. (2007a), by including the aforementioned vaccine (therapeutic) characteristics (this entails adding compartments J_{2h} and J_{1h}) as well as the roles of gametocytes and partial-immunity in malaria transmission dynamics.

4.1. Mathematical analysis of the vaccination model

Using similar approach as in Section 3, the following region:

$$
\Omega_2 = \left\{ (S_h, V_h, E_{uh}, E_{vh}, I_{1h}, I_{2h}, J_{1h}, J_{2h}, M_h, S_v, E_v, I_v) \in \mathbb{R}_+^{12} : N_h \le \frac{\Pi_h}{\mu_h} = N_h^*, \right.
$$
$$
\left. N_v \le \frac{\Pi_v}{\mu_v} = N_v^* \right\}
$$

can be shown to be positively-invariant. It should be stated that, in this section, unlike in Section 3, the analysis of the model (15) will be carried out for the case $\delta_1 \neq 0$ and $\delta_2 \neq 0$.

4.1.1. Disease-free equilibrium

The DFE of the vaccination model (15) is given by

$$
\begin{aligned}
\mathcal{E}_3 &= \left(S_h^*, V_h^*, E_{uh}^*, E_{vh}^*, I_{1h}^*, I_{2h}^*, J_{1h}^*, J_{2h}^*, M_h^*, S_v^*, E_v^*, I_v^*\right)\\
&= \left[\frac{\Pi_h m_2}{\mu_h(m_2+\xi_h)}, \frac{\Pi_h \xi_h}{\mu_h(m_2+\xi_h)}, 0, 0, 0, 0, 0, 0, 0, \frac{\Pi_v}{\mu_v}, 0, 0\right],
\end{aligned}
\tag{16}
$$

where, $m_2 = \mu_h + \kappa_h$. The associated next generation matrices (F_2 and Q_2) are given by

$$F_2 = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{C_{vh}S_h^*}{N_h^*} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{(1-\epsilon)C_{vh}V_h^*}{N_h^*} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{C_{hv}S_v^*}{N_h^*} & \frac{C_{hv}\omega S_v^*}{N_h^*} & \frac{C_{hv}\psi S_v^*}{N_h^*} & \frac{C_{hv}\omega\psi S_v^*}{N_h^*} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

$$Q_2 = \begin{pmatrix} m_3 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & m_4 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -\sigma_h & 0 & m_5 & -\alpha_1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\alpha_2 & m_6 & 0 & 0 & 0 & 0 & 0 \\ 0 & -\theta_1\sigma_h & 0 & 0 & m_7 & -\alpha_1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\alpha_2 & m_8 & 0 & 0 & 0 \\ 0 & 0 & -\tau_h & 0 & -\theta_2\tau_h & 0 & m_9 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & m_{10} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\sigma_v & \mu_v \end{pmatrix},$$

where,

$$\begin{aligned} &m_3 = \sigma_h + \mu_h, \qquad m_4 = \theta_1\sigma_h + \mu_h, \qquad m_5 = \alpha_2 + \tau_h + \mu_h + \delta_1, \\ &m_6 = \alpha_1 + \mu_h + \delta_2, \qquad m_7 = \alpha_2 + \theta_2\tau_h + \mu_h + \theta_3\delta_1, \\ &m_8 = \alpha_1 + \mu_h + \theta_3\delta_2, \qquad m_9 = r_h + \mu_h \quad \text{and} \quad m_{10} = \mu_v + \sigma_v. \end{aligned} \tag{17}$$

It follows that the *vaccination reproduction number* for the model (15), denoted by $\mathcal{R}_{\text{vac}}$, is given by

$$\mathcal{R}_{\text{vac}} = \rho\big(F_2 Q_2^{-1}\big) = \sqrt{\frac{C_{hv}C_{vh}S_v^*\sigma_h\sigma_v(A_2 + B_2)}{(N_h^*)^2 m_3 m_4 m_{10}\mu_v(m_5 m_6 - \alpha_1\alpha_2)(m_7 m_8 - \alpha_1\alpha_2)}},$$

with

$$m_5m_6 - \alpha_1\alpha_2 = \alpha_1(\tau_h + \mu_h) + m_5\mu_h > 0,$$
$$m_7m_8 - \alpha_1\alpha_2 = \alpha_1(\theta_2\tau_h + \mu_h) + m_7\mu_h > 0,$$

and

$$A_2 = S_h^* m_4(m_7m_8 - \alpha_1\alpha_2)(\omega\alpha_2 + m_6),$$
$$B_2 = V_h^*(1-\epsilon)\psi\theta_1 m_3(m_5m_6 - \alpha_1\alpha_2)(\omega\alpha_2 + m_8).$$

Thus, by Theorem 2 of van den Driessche and Watmough (2002), the following result is established.

Lemma 3. *The DFE, $\mathcal{E}_3$, of the vaccination model (15), given by (16), is LAS if $\mathcal{R}_{\text{vac}} < 1$, and unstable if $\mathcal{R}_{\text{vac}} > 1$.*

The threshold quantity, $\mathcal{R}_{\text{vac}}$, measures the average number of secondary cases generated by a single infected individual in a susceptible human population, where a fraction of the susceptible human population is vaccinated using an imperfect malaria vaccine.

4.1.2. Assessment of vaccine impact
In this section, the potential impact of the imperfect malaria vaccine is assessed by carrying out an uncertainty analysis on the vaccination threshold, $\mathcal{R}_{\text{vac}}$, as follows. The quantity $\mathcal{R}_{\text{vac}}$ is, first of all, expressed as a function of the fraction of susceptible individuals vaccinated at steady-state (given by $p = \frac{V_h^*}{N_h^*}$). That is,

$$\mathcal{R}_{\text{vac}} = \mathcal{R}_{\text{vac}}(p) = \sqrt{\frac{C_{hv}C_{vh}S_v^*\sigma_h\sigma_v(A_3 + B_3)}{(N_h^*)^2 m_3m_4m_{10}\mu_v(m_5m_6 - \alpha_1\alpha_2)(m_7m_8 - \alpha_1\alpha_2)}},$$

where

$$A_3 = N_h^*(1-p)m_4(m_7m_8 - \alpha_1\alpha_2)(\omega\alpha_2 + m_6),$$
$$B_3 = pN_h^*(1-\epsilon)\psi\theta_1 m_3(m_5m_6 - \alpha_1\alpha_2)(\omega\alpha_2 + m_8).$$

Differentiating $\mathcal{R}_{\text{vac}}$ partially with respect to p gives

$$\frac{\partial\mathcal{R}_{\text{vac}}}{\partial p} = -\frac{A_4(1-\nabla)}{2\mathcal{R}_{\text{vac}}}, \tag{18}$$

with

$$A_4 = \frac{C_{hv}C_{vh}S_v^*\sigma_h\sigma_v(\omega\alpha_2 + m_6)}{N_h^* m_3m_{10}\mu_v(m_5m_6 - \alpha_1\alpha_2)},$$

and

$$\nabla = \frac{(1-\epsilon)\psi\theta_1 m_3(m_5m_6 - \alpha_1\alpha_2)(\omega\alpha_2 + m_8)}{m_4(m_7m_8 - \alpha_1\alpha_2)(\omega\alpha_2 + m_6)}.$$

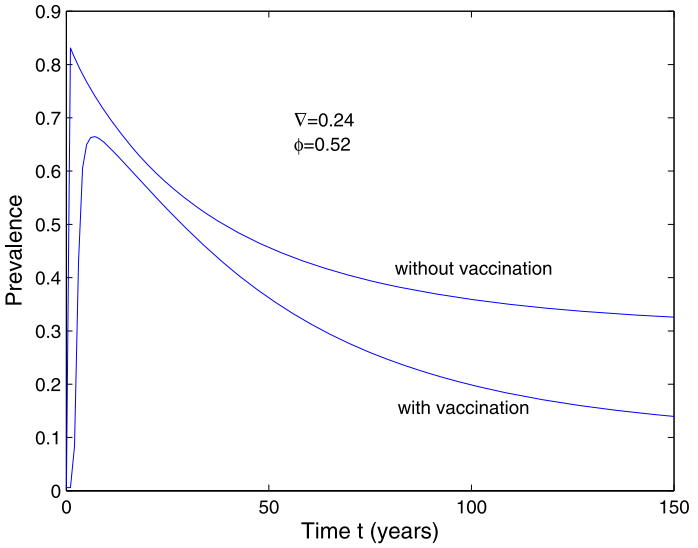

Fig. 2 Simulations of the vaccination model (15) showing disease prevalence as a function of time in the presence or absence of vaccination. Parameter values used are $C_{hv} = C_{vh} = 65$, $\alpha_1 = 0.5$, $\alpha_2 = 0.7$, $\tau_2 = 0.4$, $\delta_2 = 0.005$, $\delta_1 = 0.005$ and all other parameters as in Table 1 (so that, $\nabla = 0.24 < 1$, $\phi = 0.52 > 0$, $\mathcal{R}_{\text{vac}} = 1.20$, $\mathcal{R}_0 = 1.73$ and $\mathcal{R}_{0v} = 0.85$).

Since $A_4 > 0$ (and noting that $m_5 m_6 - \alpha_1\alpha_2 > 0$ and $m_7 m_8 - \alpha_1\alpha_2 > 0$ as shown in Section 4.1.1) and $\mathcal{R}_{\text{vac}} > 0$, it follows from (18) that $\frac{\partial \mathcal{R}_{\text{vac}}}{\partial p} < 0$ whenever $\nabla < 1$. That is, $\mathcal{R}_{\text{vac}}$ is a decreasing function of the vaccinated fraction, p, whenever $\nabla < 1$. Further, owing to the fact that a reduction in reproduction number implies reduction in disease burden (measured in terms of generation of new infections, disease-induced mortality, hospitalizations etc.), the above analyses show that an imperfect malaria vaccine will have a positive impact in reducing disease burden whenever $\nabla < 1$, and will not otherwise. Hence, the following lemma.

Lemma 4. *Consider the model* (15). *An imperfect malaria vaccine will have*:

(i) *a positive impact in reducing disease burden if* $\nabla < 1$;
(ii) *no impact in reducing disease burden if* $\nabla = 1$;
(iii) *detrimental impact* (*increase disease burden*) *if* $\nabla > 1$.

The above result is illustrated by simulating the vaccination model (15) using the parameters in Table 1 (unless otherwise stated in the associated figure caption). Figure 2 depicts the disease prevalence as a function of time. Figure 3 shows the case with $\nabla = 0.24 < 1$ (corresponding to a vaccine efficacy of 60%; i.e., $\epsilon = 0.6$), from which it is evident that the vaccine has a positive impact, since it reduces disease prevalence in comparison to the case when vaccination is not used.

In fact, a threshold value of the vaccine efficacy (denoted by ϵ_c) needed to ensure positive vaccine impact can be obtained by setting $\nabla = 1$ and solving for ϵ. Doing so

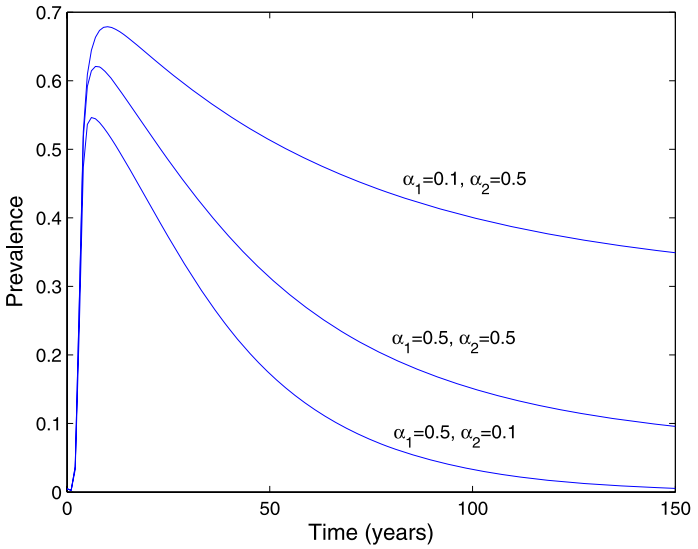

Fig. 3 Simulations of the vaccination model (15) assessing the impact of the back-and-forth transition between the infectious classes I_{1h} and I_{2h} with various values of α_1 and α_2. All other parameters are as given in Table 1.

gives

$$\epsilon_c = 1 - \frac{P_1}{P_2}, \tag{19}$$

where (note that $P_1 < P_2$ is needed to ensure $0 < \epsilon_c < 1$),

$$P_1 = m_4(m_7m_8 - \alpha_1\alpha_2)(\omega\alpha_2 + m_6),$$
$$P_2 = \psi\theta_1 m_3(m_5m_6 - \alpha_1\alpha_2)(\omega\alpha_2 + m_8).$$

Thus, we have the following result (in terms of vaccine efficacy)

Lemma 5. *An imperfect malaria vaccine will have*:

(i) *positive impact if* $\epsilon > \epsilon_c$;
(ii) *no impact if* $\epsilon = \epsilon_c$; *and*
(iii) *negative impact if* $\epsilon < \epsilon_c$.

Alternatively, the vaccine impact can be measured by re-writing $\mathcal{R}_{\text{vac}}$ as

$$\mathcal{R}^2_{\text{vac}} = \mathcal{R}^2_0\left[1 - \frac{\xi_h}{m_2 + \xi_h}\left(1 - \frac{\mathcal{R}^2_{0v}}{\mathcal{R}^2_0}\right)\right], \tag{20}$$

where

$$\mathcal{R}_0 = \sqrt{\frac{C_{hv}C_{vh}S_v^*\sigma_h\sigma_v(\omega\alpha_2 + m_6)}{N_h^* m_3 m_4 m_{10}\mu_v(m_5 m_6 - \alpha_1\alpha_2)}}, \tag{21}$$

is the basic reproduction number (defined in Section 3.1), and

$$\mathcal{R}_{0v} = \sqrt{\frac{C_{hv}C_{vh}S_v^*\sigma_h\sigma_v(1-\epsilon)\psi\theta_1(\omega\alpha_2 + m_8)}{N_h^* m_4 m_{10}\mu_v(m_7 m_8 - \alpha_1\alpha_2)}}, \tag{22}$$

is the reproduction number when every individual in the population is vaccinated. Using the notation in Blower et al. (2002), Elbasha and Gumel (2006), it follows from (20) that the *vaccination impact factor*, denoted by ϕ (with $0 < \phi < 1$), is given by

$$\phi = \frac{\xi_h}{m_2 + \xi_h}\left(1 - \frac{\mathcal{R}_{0v}^2}{\mathcal{R}_0^2}\right). \tag{23}$$

It should be noted from (23) that if $\mathcal{R}_{0v} < \mathcal{R}_0$, then the impact factor, ϕ, is positive; so that the vaccination program will reduce the basic reproduction number ($\mathcal{R}_0$) and, therefore, the vaccine will have positive impact (reduce disease burden) in this case. On the other hand, if $\mathcal{R}_{0v} > \mathcal{R}_0$, then $\phi < 0$; so that vaccination will have negative impact in the community. Finally, if $\phi = 0$, then $\mathcal{R}_{\text{vac}} = \mathcal{R}_0$; and the vaccine will have no impact in this case. Thus, we have the following theorem.

Theorem 2. *The use of an imperfect malaria vaccine will have*:

(i) *positive impact in the community if* $\phi > 0$ ($\mathcal{R}_{0v} < \mathcal{R}_0$);
(ii) *no impact if* $\phi = 0$ ($\mathcal{R}_{0v} = \mathcal{R}_0$); *and*
(iii) *negative impact in the community if* $\phi < 0$ ($\mathcal{R}_{0v} > \mathcal{R}_0$).

Figure 2 shows that when $\phi = 0.52 > 0$, the vaccine will have a positive impact.

In summary, the above analyses for the vaccination model provide a rigorous mathematical framework for assessing various vaccine characteristics aimed at determining optimal combinations (of these characteristics) that can lead to effective disease control. The lack of realistic vaccine-related parameter values (since no such vaccine is currently available) hampers our ability to provide a realistic quantitative estimate (based on realistic vaccine efficacy and coverage levels) of the impact of vaccination on disease control. Such an estimate can, of course, be made once such data becomes available. For now, our study only provides a qualitative assessment of the role of a future anti-malaria vaccine; suggesting that effective disease control is feasible using an imperfect malaria vaccine under certain conditions (notably, having high enough efficacy and coverage levels such that the threshold quantity ∇ is less than unity).

4.2. Global stability of the DFE for $\delta_1 = \delta_2 = 0$

Here, the global asymptotic stability property of the DFE ($\mathcal{E}_3$) of the model (15) will be explored for the case when $\delta_1 = \delta_2 = 0$. By setting $\delta_1 = \delta_2 = 0$ in the model (15), it follows

that $S_h = N_h^* - V_h - E_{uh} - E_{vh} - I_{1h} - I_{2h} - J_{1h} - J_{2h} - M_h$ and $S_v = N_v^* - E_v - I_v$ at steady-state. Further, the forces of infection, λ_v and λ_h^v, reduce to λ_{v1} (defined as before) and

$$\lambda_{h1}^v = C_{hv} \frac{I_{1h} + \omega I_{2h} + \psi(J_{1h} + \omega J_{2h})}{N_h^*},$$

respectively. Hence, the global stability of $\mathcal{E}_3$, can be established by considering the following limiting system (mass action equivalent) of the vaccination model (15):

$$\begin{aligned}
\frac{dV_h}{dt} &= \xi_h\big(N_h^* - V_h - E_{uh} - E_{vh} - I_{1h} - I_{2h} - J_{1h} - J_{2h} - M_h\big) \\
&\quad - (1-\epsilon)\lambda_{v1} V_h - \kappa_h V_h - \mu_h V_h, \\
\frac{dE_{uh}}{dt} &= \lambda_{v1}\big(N_h^* - V_h - E_{uh} - E_{vh} - I_{1h} - I_{2h} - J_{1h} - J_{2h} - M_h\big) \\
&\quad - \sigma_h E_{uh} - \mu_h E_{uh}, \\
\frac{dE_{vh}}{dt} &= (1-\epsilon)\lambda_{v1} V_h - \theta_1 \sigma_h E_{vh} - \mu_h E_{vh}, \\
\frac{dI_{1h}}{dt} &= \sigma_h E_{uh} + \alpha_1 I_{2h} - \alpha_2 I_{1h} - \tau_h I_{1h} - \mu_h I_{1h}, \\
\frac{dI_{2h}}{dt} &= \alpha_2 I_{1h} - \alpha_1 I_{2h} - \mu_h I_{2h}, \\
\frac{dJ_{1h}}{dt} &= \theta_1 \sigma_h E_{vh} + \alpha_1 J_{2h} - \alpha_2 J_{1h} - \theta_2 \tau_h J_{1h} - \mu_h J_{1h}, \\
\frac{dJ_{2h}}{dt} &= \alpha_2 J_{1h} - \alpha_1 J_{2h} - \mu_h J_{2h}, \\
\frac{dM_h}{dt} &= \tau_h I_{1h} + \theta_2 \tau_h J_{1h} - r_h M_h - \mu_h M_h, \\
\frac{dE_v}{dt} &= \lambda_{h1}^v\big(N_v^* - E_v - I_v\big) - \sigma_v E_v - \mu_v E_v, \\
\frac{dI_v}{dt} &= \sigma_v E_v - \mu_v I_v,
\end{aligned} \tag{24}$$

in the positively-invariant region,

$$\begin{aligned}
\Omega_3 = \big\{&(V_h, E_{uh}, E_{vh}, I_{1h}, I_{2h}, J_{1h}, J_{2h}, M_h, E_v, I_v) \in \mathbb{R}_+^{10} : \\
&V_h + E_{uh} + E_{vh} + I_{1h} + I_{2h} + J_{1h} + J_{2h} + M_h \le N_h^*,\ E_v + I_v \le N_v^*\big\}.
\end{aligned}$$

The associated reproduction number for the limiting model (24), denoted by $\mathcal{R}_{\text{vac}}^1$, is given by

$$\mathcal{R}_{\text{vac}}^1 = \rho\big(F_3 Q_2^{-1}\big) = \sqrt{\frac{C_{hv} C_{vh} N_v^* \sigma_h \sigma_v (A_5 + B_2)}{(N_h^*)^2 m_3 m_4 m_{10} \mu_v (m_5 m_6 - \alpha_1 \alpha_2)(m_7 m_8 - \alpha_1 \alpha_2)}}, \tag{25}$$

where, $m_3, m_4, m_5, m_6, m_7, m_8$ and m_{10} are as defined in (17) with $\delta_1 = \delta_2 = 0$ and the matrix Q_2 is also as defined before. The matrix F_3 is given by

$$F_3 = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & C_{vh} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{(1-\epsilon)C_{vh}V_h^*}{N_h^*} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{C_{hv}N_v^*}{N_h^*} & \frac{C_{hv}\omega N_v^*}{N_h^*} & \frac{C_{hv}\psi N_v^*}{N_h^*} & \frac{C_{hv}\psi\omega N_v^*}{N_h^*} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}.$$

In (25), $A_5 = N_h^* m_4(m_7 m_8 - \alpha_1\alpha_2)(\omega\alpha_2 + m_6) > 0$ and B_2 is as defined before. Thus, by Theorem 2 of van den Driessche and Watmough (2002), the following result is established.

Lemma 6. *The DFE, $\mathcal{E}_3$, of the limiting system (24), given by (16), is LAS if $\mathcal{R}_{\text{vac}}^1 < 1$, and unstable if $\mathcal{R}_{\text{vac}}^1 > 1$.*

Define the region,

$$\Omega_4 = \left\{(V_h, E_{uh}, E_{vh}, I_{1h}, I_{2h}, J_{1h}, J_{2h}, M_h, E_v, I_v) \in \Omega_3 : V_h \le V_h^*\right\}.$$

We claim the following result.

Theorem 3. *The DFE of the model (24), given by (16), is GAS in Ω_4 if $\mathcal{R}_{\text{vac}}^1 < 1$.*

Proof: We first need to prove that the set Ω_4 is positively-invariant and attracting, and then use a comparison theorem argument. It can be seen from the first equation of the limiting system (24) that

$$\begin{aligned} \frac{dV_h}{dt} &= \xi_h\left(N_h^* - V_h - E_{uh} - E_{vh} - I_{1h} - I_{2h} - J_{1h} - J_{2h} - M_h\right) \\ &\quad - (1-\epsilon)\lambda_{v1}V_h - (\kappa_h + \mu_h)V_h \\ &\le \xi_h N_h^* - (\kappa_h + \xi_h + \mu_h)V_h \\ &\le (\kappa_h + \xi_h + \mu_h)\left(\frac{\xi_h N_h^*}{\kappa_h + \xi_h + \mu_h} - V_h\right) = (\kappa_h + \xi_h + \mu_h)\left(V_h^* - V_h\right). \end{aligned}$$

Hence, $V_h(t) \leq V_h^* - (V_h^* - V_h(0))e^{-(\kappa_h+\xi_h+\mu_h)t}$. It follows that either $V_h(t)$ approaches V_h^* asymptotically or $V_h(t) \leq V_h^*$ in finite time (note that $dV_h/dt < 0$ if $V_h(t) > V_h^*$). Thus, the set Ω_4 is positively-invariant and attracting. Further, the equations for the infected components of (24) can be re-written as

$$\begin{pmatrix} \frac{dE_{uh}}{dt} \\ \frac{dE_{vh}}{dt} \\ \frac{dI_{1h}}{dt} \\ \frac{dI_{2h}}{dt} \\ \frac{dJ_{1h}}{dt} \\ \frac{dJ_{2h}}{dt} \\ \frac{dM_h}{dt} \\ \frac{dE_v}{dt} \\ \frac{dI_v}{dt} \end{pmatrix} = (F_3 - Q_2 - T) \begin{pmatrix} E_{uh} \\ E_{vh} \\ I_{1h} \\ I_{2h} \\ J_{1h} \\ J_{2h} \\ M_h \\ E_v \\ I_v \end{pmatrix},$$

where the matrices F_3 and Q_2 are as defined above, and the matrix T is given by

$$T = \begin{pmatrix} \lambda_{v1} & \lambda_{v1} & \lambda_{v1} & \lambda_{v1} & \lambda_{v1} & \lambda_{v1} & \lambda_{v1} & 0 & \frac{C_{vh}V_h}{N_h^*} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{(1-\epsilon)C_{vh}V_h^*}{N_h^*}(1 - \frac{V_h}{V_h^*}) \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \lambda_{h1}^v & \lambda_{h1}^v \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}.$$

Since $V_h \leq V_h^*$ (for all $t \geq 0$) in Ω_4, it follows that the matrix T is non-negative. Thus,

$$\begin{pmatrix} \frac{dE_{uh}}{dt} \\ \frac{dE_{vh}}{dt} \\ \frac{dI_{1h}}{dt} \\ \frac{dI_{2h}}{dt} \\ \frac{dJ_{1h}}{dt} \\ \frac{dJ_{2h}}{dt} \\ \frac{dM_h}{dt} \\ \frac{dE_v}{dt} \\ \frac{dI_v}{dt} \end{pmatrix} \leq (F_3 - Q_2) \begin{pmatrix} E_{uh} \\ E_{vh} \\ I_{1h} \\ I_{2h} \\ J_{1h} \\ J_{2h} \\ M_h \\ E_v \\ I_v \end{pmatrix}. \tag{26}$$

If $\mathcal{R}^1_{\text{vac}} < 1$, then $\rho(F_3 Q_2^{-1}) < 1$ (from the local stability result given in Lemma 5, which is equivalent to $F_3 - Q_2$ having all its eigenvalues in the left-half plane (van den Driessche and Watmough, 2002)). It follows that the linearized differential inequality system (26) is stable whenever $\mathcal{R}^1_{\text{vac}} < 1$. Consequently, by the comparison theorem (Lakshmikantham et al., 1989), it follows that $(E_{uh}, E_{vh}, I_{1h}, I_{2h}, J_{1h}, J_{2h}, M_h, E_v, I_v) \to (0, 0, 0, 0, 0, 0, 0, 0, 0, 0)$. Substituting $E_{uh} = E_{vh} = I_{1h} = I_{2h} = J_{1h} = J_{2h} = M_h = E_v = I_v = 0$ into the first equation of the model (24) gives $V_h(t) \to V_h^*$ as $t \to \infty$. Further, since Ω_4 is positively-invariant, it follows that the DFE, $\mathcal{E}_3$, is GAS in Ω_4 if $\mathcal{R}^1_{\text{vac}} < 1$. □

The epidemiological implication of the above result is that malaria will be eliminated from the community if the imperfect vaccine can lead to a situation where $\mathcal{R}_{\text{vac}}$ is less than unity. It should be mentioned that similar global stability result is established in Garba et al. (2008) for a vaccine model of dengue disease (using Lyapunov function theory and the LaSalle invariance principle). The vaccine model in Garba et al. (2008) did not incorporate the aforementioned therapeutic characteristics (as well as the roles of gametocytes and temporal immunity).

It can be shown, using the technique in Section 3.3, that the vaccination model (15) has a unique endemic equilibrium whenever $\mathcal{R}_{\text{vac}} > 1$.

5. Simulations of the vaccination model

Further simulations of the vaccination model (15), are performed with non-zero induced death rates, using reasonable set of parameter values that are in line with the literature on malaria transmission, transmission intensity, mosquito behaviors, the number of bites a given mosquito can make (Anderson and May, 1990; Carter and Graves, 1988; Center for Disease Control and Prevention, 2007; Central Intelligence Agency, 2008; Chitnis et al., 2008; Mehlhorn, 2001; Ngwa and Shu, 2000; Sinden, 1984; Vittor et al., 2006) as shown in Table 1 (unless otherwise stated), are carried out in this section. Since there are currently no effective anti-malaria vaccines, the vaccine-related parameters of the vaccination model (15) are assumed (making them as biologically feasible and realistic as possible). The impact of the back-and-forth transition between the infectious classes is monitored by depicting a plot of the prevalence as a function of time in Fig. 3. It follows from Fig. 3 that the number of infections is reduced if the transition rate from the higher (I_{2h}) to the lower (I_{1h}) gametocyte class (α_1) is less than the transition rate from the lower (I_{1h}) to the higher (I_{2h}) gametocyte class (α_2). That is, the number of cases is minimized if infectious individuals spend more time in the lower gametocyte class than in the higher gametocyte class. On the other hand, if the transition rate from I_{2h} to I_{1h} is higher than from I_{1h} to I_{2h}, the number of infections will increase. For instance, if the number of days spent before moving from the higher to the lower gametocytes level is 10 days (i.e., $\frac{1}{\alpha_1} = 10$) and the number of days spent before moving from the lower to the higher gametocytes level is 2 days (i.e., $\frac{1}{\alpha_2} = 2$), the peak prevalence is 68% (approximately). Similarly, if the number of days before moving from the higher to the lower gametocytes level is 2 days and the number of days before moving from the lower to the higher gametocytes level is 10 days, the peak prevalence reduces to 55% (Fig. 3).

The impact of the vaccination program is assessed by depicting contour plots of the reproduction number in the presence of vaccination ($\mathcal{R}_{\text{vac}}$) as a function of the vaccine

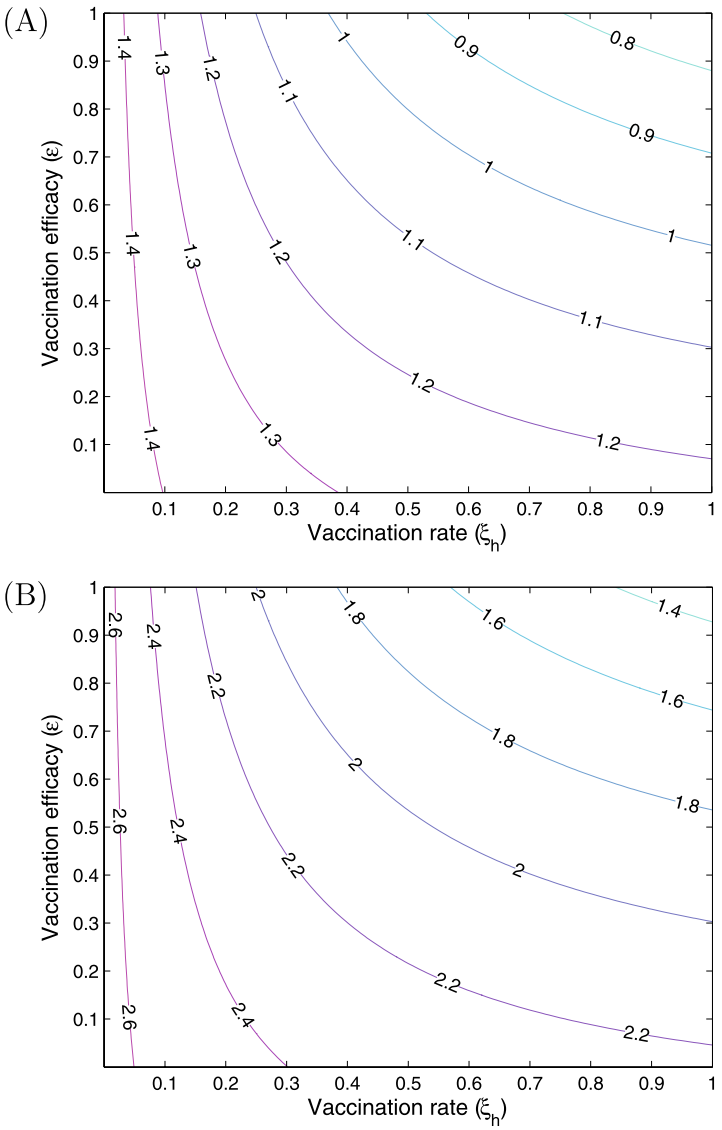

Fig. 4 Simulations of the vaccination model (15) showing contour plots of $\mathcal{R}_{\text{vac}}$ as a function of the vaccination coverage rate (ξ_h) and vaccine efficacy (ϵ) with: $\alpha_1 = 0.5$, $\alpha_2 = 0.7$, $\delta_2 = 0.005$, $\delta_1 = 0.005$, and $\tau_h = 0.4$. All other parameters as in Table 1. (A) $C_{hv} = C_{vh} = 52$ and $\mathcal{R}_0 = 1.41$. (B) $C_{hv} = C_{vh} = 100$ and $\mathcal{R}_0 = 2.71$.

efficacy (ϵ) and vaccination coverage rate (ξ_h) in Fig. 4. It is shown (Fig. 4A) that for relatively low values of the basic reproduction number ($\mathcal{R}_0$), such as $\mathcal{R}_0 = 1.41$, the use of an imperfect malaria vaccine with modest efficacy (e.g., 60%) and coverage (e.g., $\xi_h = 0.6$) can lead to disease elimination (since, such levels of efficacy and coverage rate will result

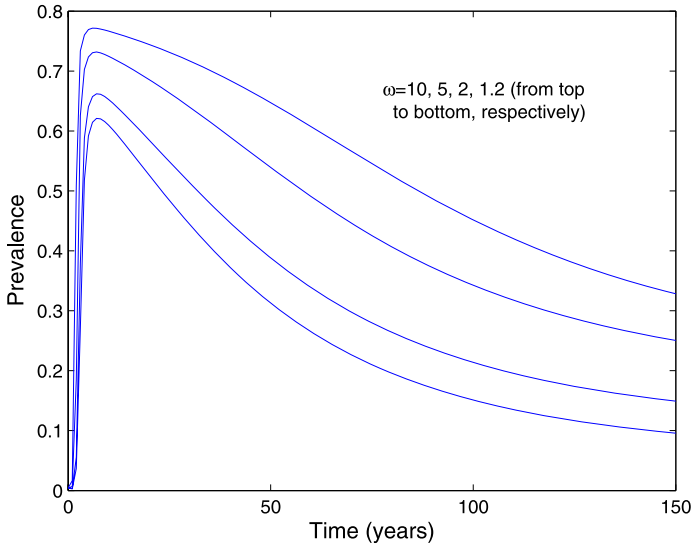

Fig. 5 Simulations of the vaccination model (15) assessing the impact of the relative infectiousness parameter (ω) with: $C_{hv} = C_{vh} = 65$, $\alpha_1 = 0.5$, $\alpha_2 = 0.7$, $\tau_h = 0.4$, $\delta_2 = 0.005$, and $\delta_1 = 0.005$. All other parameters as in Table 1.

in $\mathcal{R}_{\text{vac}} < 1$; which may lead to disease elimination). On the other hand, if the associated reproduction number is relatively high (e.g., $\mathcal{R}_0 = 2.71$), the use of a vaccination program alone would not result in disease elimination, since such a program would fail to make $\mathcal{R}_{\text{vac}} < 1$ (Fig. 4B). Therefore, in such a scenario (with high $\mathcal{R}_0$ value), the vaccination program must be complemented with other interventions (such as vector-reduction strategies and personal protection) to have a realistic chance of effectively controlling the disease spread.

Further simulations suggest that changes in the infectiousness parameter ω have somewhat marginal effect on the disease transmission dynamics (Fig. 5).

6. Conclusions

The paper presents a basic deterministic model of the transmission dynamics of malaria. The model allows for the assessment of the role of gametocytes density on disease spread. The basic model is extended to incorporate an imperfect vaccine, with some therapeutic characteristics. Rigorous mathematical analyses are carried out to gain insights into the qualitative dynamics of the two models. Some of the main mathematical and epidemiological findings of this study include the following:

(i) Both the basic model and the extended vaccination model, have globally-stable disease-free equilibrium whenever their associated reproduction threshold is less than unity and the associated disease-induced mortality is negligible. Further, each model has a unique endemic equilibrium whenever its reproduction threshold exceeds unity;

(ii) The disease can be controlled if the average number of days spent in the lower infectious gametocytes class (I_{1h}) before moving to the higher infectious gametocytes class (I_{2h}) is significantly higher than the time spent in the higher infectious gametocytes class (I_{2h}) before moving to the lower infectious gametocytes class (I_{1h}). The longer the time spent in the I_{2h} class the higher the disease burden;
(iii) Numerical simulations of the vaccination model show that an imperfect vaccine with a modest efficacy (such as 60%) and coverage rate can result in effective disease control (or elimination) if the associated basic reproduction number of the disease is reasonably small (such as, $\mathcal{R}_0 < 2$). However, such a vaccine would not be adequate to eliminate the disease if the basic reproduction number is large enough (e.g., $\mathcal{R}_0 > 2$);
(iv) An imperfect malaria vaccine could have positive, zero, or negative impact depending on whether or not a certain threshold, defined as ∇, is less than, equal to, or greater than unity (this result is also expressed in terms of a "vaccine impact" factor, ϕ).

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