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Mathematical modelling of the impact of vaccination on malaria epidemiology

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Abstract. This paper presents a mathematical model for human malaria transmission caused by *Plasmodium falciparum* which incorporates the effects of pre-erythrocytic vaccine on the transmission dynamics of the disease. This model is extended to incorporate the effects of erythrocytic and transmission blocking vaccines. Analysis of the reproductive number for the extended model $R_\phi(\gamma, \theta_{1,2}, \epsilon)$, shows that effectiveness of the vaccine depends critically on its efficacy, infection blocking, disease modification, transmission blocking, proportion vaccinated and duration of its effectiveness. The minimum vaccination rate required to eradicate malaria depends on its endemicity in each region. We deduce that pre-erythrocytic vaccine works faster than transmission blocking vaccine in reducing the number of infectious humans. In our analysis, we were able to quantify the effectiveness of combining two or more subunits over using only one subunit. Our analysis shows that a vaccine that reduces the infectious period of an infected human always reduces the number of secondary infections. Numerical simulations are also performed to compare the general behaviour of the models.

AMS Subject Classifications: 92D30, 34D05

Keywords: Malaria; Reproductive number; Efficacy; Numerical simulations

1. Introduction

Malaria, caused by a protozoan parasite *Plasmodium falciparum*, is transmitted to humans by the bite of an infected and infectious female mosquito of the genus *Anopheles*. It remains one of the major causes of morbidity and mortality [45]. Malaria is

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most common in the tropical regions especially Africa [43]. There are estimated 300-500 million clinical cases and there are between 1-1.5 million malaria related deaths annually [9, 61]. Though preventable and curable, controlling malaria has become more and more challenging as the malaria parasite becomes resistant to prophylactic drugs [28, 37, 53] and as the mosquito that transmits the parasite develops resistance to insecticides [33]. Although child mortality in Africa has declined in recent years, malaria's share of that mortality has increased because of the spread of drug resistance of the parasite, the breakdown of health services in many affected areas, the interaction of the disease with human immunodeficiency virus (HIV) infection, and possibly the effects of climate change [27]. Traditional means of controlling malaria may save many lives, but they alone cannot adequately prevent the misery and deaths this devastating disease causes. Nor can they alone erase the enormous impact of malaria on local and national economic development [24].

Malaria control efforts include attempts to develop effective vaccines, eradicate mosquito vectors and develop new drugs [50]. Historically, vaccines have been one of the most cost effective and easily administered means of controlling infectious diseases, yet no licensed vaccines exist for malaria. The first report of human protection from malaria by vaccination was made in 1973 [12]. History on malaria vaccination attempts is documented [46]. Accumulating basic and clinical research suggests that effective vaccines for malaria can be developed and could significantly reduce morbidity and mortality and potentially reduce spread of infection [10, 11, 20, 23, 46, 49, 59]. The progress is slowed down by the parasite's intricate life cycle which has distinct developmental stages in both the host and the vector. A vaccine effective in killing one stage may not inhibit the growth of the other [21]. The stages involved in the movement of the parasite between host and vector are well documented [5, 25, 46, 56, 62]. The human immune response to *Plasmodium falciparum* is also well documented [25, 51, 57].

Malaria vaccines should be designed to protect people from disease and death, boosting the immune system to combat parasites. But unless a malaria vaccine leads to the death of every single parasite, the ones that survive could continue to circulate in a vaccinated population. An optimum vaccine should then have the ability to elicit protective immunity that blocks infection as well as prevent pathology and interrupt transmission of parasites. The most effective vaccine should be comprised of subunits from different parasite stages. These subunits are as follows:

- Pre-erythrocytic vaccine protects against the infectious form injected by the anopheles mosquito (sporozoite) by inhibiting invasion of liver cells [35, 46, 64] and /or inhibit parasite development in the liver [46]. This is done by first targeting the parasite during the short time span that the sporozoites are in the bloodstream. Production of protective antibodies that will block and neutralize sporozoites from invading liver cells should be induced by the sporozoite vaccine. Secondly, sporozoites can be targeted once they are inside the liver cells, through induction of cytotoxic T-lymphocytes (CTLs) that will destroy sporozoite infected liver cells.
- Erythrocytic (blood stage) vaccine prevents merozoites from infecting red blood

cells and when inside the red blood cells antibodies can be directed towards malaria antigens that are expressed on the surface of red blood cells to inhibit parasite multiplication in the red blood cells or destroying infected cells, thus preventing (or diminishing) severe disease during blood infection [34].

- Transmission blocking (sexual stage) vaccine interrupts the cycle of transmission by inhibiting further development of parasites once they-along with antibodies produced in response are ingested by the mosquito. This vaccine does not prevent the disease in an infected host but is important in reducing the spread of malaria to new hosts.

Since 1911 different aspects of modelling malaria have been investigated [54]. Modelling acquired immunity to malaria has been proposed and discussed [19]. Some further work on this aspect has been conducted [4, 6]. Some models on the transmission dynamics of malaria have been written and discussed (see [18, 30, 48, 55] and references cited therein). Some have included environmental effects [42, 56, 62, 63], evolution of immunity [38] and spread of resistance to drugs [37].

Although modelling vaccination in other epidemic diseases has been done [3, 26, 41, 44], for malaria vaccination, a few analytic studies of stage-specific malaria vaccines have been done mathematically [2, 16, 32]. In [2], they assumed that the pre-erythrocytic vaccine completely blocks infection so none of the vaccinated humans become infected as long as the vaccine does not wear off. They also considered the transmission blocking vaccine to block transmission to mosquitoes. They assumed a vaccination strategy that immunizes a fraction of infants before the age of infection. Struchner *et al.* [60] built upon the model of Dietz *et al.* [19] and considered natural immunity that can wane with time but its duration and effectiveness is prolonged by boosting from natural infection. On this model they considered the effects of stage specific vaccines independently [32]. They considered a constant population and did not include disease induced death rate. de Zoysa [16] also basing his model on that of Dietz *et al.* [19] developed it to account for transmission blocking immunity in an endemic area. Vaccine-induced immunity is assumed to be lost if not boosted within four months. These models [2, 16, 32] have also been reviewed [31]. The following aspects considered in our model differentiate it from those that have been done: we considered a variable population, vaccination is done throughout the susceptible population, the three subunits of malaria vaccine have been combined to determine their overall effect, we considered disease induced death rate and have been able to get critical vaccination rates for the different vaccines if considered singly and/or combined. We did not consider acquired natural immunity. This makes our model more suitable for describing the situation in non endemic populations. In formulating our model we consider the dynamics of malaria infection including both human and mosquito populations [1, 62, 48, 47]. The uninfected class of humans is divided into two groups which are susceptibles which are not vaccinated and vaccinated groups. We assume that if the pre-erythrocytic vaccine is less than completely effective, then even a few sporozoites that emerge from the liver cause the host to suffer clinical malaria [52]. For the extended model in addition to two classes of susceptibles, we consider two classes of the infectious humans which are those that have been vaccinated and those

that have not.

The rest of the paper is organised as follows: In section 2 we formulate the pre-erythrocytic vaccination model, and show that the solutions to the model are always positive and bounded. In section 3 we deduce the reproductive number for the model without vaccination, R_0 and derive the reproductive number of the pre-erythrocytic vaccination model, $R_\phi(\gamma)$. We analyse the local and global stability of the disease free equilibrium when $R_\phi(\gamma) < 1$ and show that at least an endemic equilibrium exists when $R_\phi(\gamma) > 1$. We extend the model, in section 4, to incorporate the effects of erythrocytic and transmission blocking vaccines. The reproductive number for the extended model $R_\phi(\gamma, \theta_{1,2}, \epsilon)$ is deduced. Analysis of the reproductive numbers is performed in section 5. We deduce conditions necessary to slow down the spread of the disease. Numerical simulations to determine the general behaviour of the models and sensitivity analysis are performed in section 6. A brief discussion and concluding remarks round up the paper in section 7.

2. Pre-erythrocytic vaccination model

We begin by formulating a deterministic model of malaria transmission dynamics with pre-erythrocytic vaccination. The model divides the human population into four classes: susceptibles who are not vaccinated $S_h(t)$, vaccinated $V_h(t)$, exposed (those who are infected but not yet infectious) $E_h(t)$ and infectious $I_h(t)$ (individuals with sexual forms of the parasite (gametocytes)). The mosquito population is divided into three classes: susceptibles $S_m(t)$, exposed (those infected but not infectious) $E_m(t)$ and infectious (mosquitoes with sporozoites in their salivary glands) $I_m(t)$. We assume that humans are born into the susceptible class at a rate $\Lambda_h > 0$. These individuals are vaccinated at a constant rate $\phi > 0$ and enter the vaccinated class. The vaccine also wears off at a constant rate $\sigma > 0$. The susceptible humans are infected with the parasite by mosquitoes with a transmission probability $\beta_h > 0$ from an infected mosquito to a susceptible human. $c > 0$ is the biting rate of mosquitoes. The infectious humans can recover and return to the susceptible class (with no immunity) at a constant rate $r_h > 0$ (recovery rate) and die from the disease at a rate $\alpha_h > 0$. All individual humans, whatever their status are subject to a natural death, at a rate $\mu_h > 0$. It is assumed that if the pre-erythrocytic vaccine is less than 100% effective then the vaccinated individuals can also be infected with the parasite. It is assumed that if an individual in the $V_h(t)$ class is infected then that individual becomes infectious. This is because any successful transition of even a few parasites to the blood stages (due to a leaky pre-erythrocytic vaccine) will result in an infection that carries the potential for clinical malaria at the expected threshold [52]. The parameter $(1-\gamma)$ can be interpreted as a factor by which pre-erythrocytic vaccination reduces transmission of the parasite from an infected mosquito to a vaccinated human. $0 < \gamma < 1$, $\gamma = 1$ means that the vaccine is completely effective (i.e. all the parasites are cleared before or during their development in the liver) while $\gamma = 0$ means the vaccine is utterly ineffective. Effect of vaccination is assumed to disappear after an infection, that is there is no recovery to the V_h class. $\tau_h > 0$ is the average time from

initial infection, that is when an infected mosquito injects sporozoites into the host to the appearance of gametocytes in the blood.

For the mosquito population *Anopheles* mosquitoes enter the susceptible class $S_m(t)$, at a rate $\Lambda_m > 0$. The probability of transmission from an infected human to a susceptible mosquito is $\beta_m > 0$ and both susceptible and infected mosquitoes die naturally at a rate $\mu_m > 0$. $\tau_m > 0$ is the average time from initial infection of the mosquito, that is when it takes gametocytes during a blood meal to the appearance of sporozoites in its salivary glands.

The total variable population sizes of humans and mosquitoes are

$$N_h(t) = S_h(t) + V_h(t) + E_h(t) + I_h(t), \quad N_m(t) = S_m(t) + E_m(t) + I_m(t). \tag{2.1}$$

The disease is assumed to have been in the population for at least a time $\tau = \max\{\tau_h, \tau_m\}$. The equations for the model take the following forms for $t > \tau$.

$$\begin{aligned}
\frac{dS_h(t)}{dt} &= \Lambda_h - \mu_h S_h(t) + r_h I_h(t) - \beta_h c I_m(t)\frac{S_h(t)}{N_h(t)} - \phi S_h(t) + \sigma V_h(t),\\
\frac{dV_h(t)}{dt} &= \phi S_h(t) - \mu_h V_h(t) - \beta_h c(1-\gamma) I_m(t)\frac{V_h(t)}{N_h(t)} - \sigma V_h(t),\\
E_h(t) &= \int_{t-\tau_h}^{t} \beta_h c I_m(u)\frac{S_h(u) + (1-\gamma)V_h(u)}{N_h(u)} e^{-\mu_h(t-u)}du,\\
\frac{dI_h(t)}{dt} &= \beta_h c I_m(t-\tau_h)\frac{S_h(t-\tau_h) + (1-\gamma)V_h(t-\tau_h)}{N_h(t-\tau_h)} e^{-\mu_h\tau_h}\\
&\quad -(r_h + \alpha_h + \mu_h) I_h(t),\\
\frac{dS_m(t)}{dt} &= \Lambda_m - \beta_m c S_m(t)\frac{I_h(t)}{N_h(t)} - \mu_m S_m(t),\\
E_m(t) &= \int_{t-\tau_m}^{t} \beta_m c S_m(u)\frac{I_h(u)}{N_h(u)} e^{-\mu_m(t-u)}du,\\
\frac{dI_m(t)}{dt} &= \beta_m c S_m(t-\tau_m)\frac{I_h(t-\tau_m)}{N_h(t-\tau_m)} e^{-\mu_m\tau_m} - \mu_m I_m(t).
\end{aligned} \tag{2.2}$$

System of equations (2.2) hold for new time $t > 0$ if time is shifted by τ time units with given nonnegative initial conditions on $[-\tau, 0]$. To analyse the model (2.2), we find an equivalent delay differential equation system so that standard theorems may be applied. Differentiating the third and sixth equations in (2.2), we get

$$\begin{aligned}
\frac{dE_h(t)}{dt} &= \zeta_h I_m(t)\frac{S_h(t) + (1-\gamma)V_h(t)}{N_h(t)} - \zeta_h I_m(t-\tau_h)e^{-\mu_h\tau_h} \times\\
&\quad \frac{S_h(t-\tau_h) + (1-\gamma)V_h(t-\tau_h)}{N_h(t-\tau_h)} - \mu_h E_h(t),\\
\frac{dE_m(t)}{dt} &= \zeta_m S_m(t)\frac{I_h(t)}{N_h(t)} - \zeta_m S_m(t-\tau_m)\frac{I_h(t-\tau_m)}{N_h(t-\tau_m)} e^{-\mu_m\tau_m} - \mu_m E_m(t).
\end{aligned} \tag{2.3}$$

where $\zeta_h = \beta_h c$ and $\zeta_m = \beta_m c$. From (2.1), we deduce that the rates of change of the

total population of humans and the total population of mosquitoes are given as

$$\frac{dN_h(t)}{dt} = \Lambda_h - \mu_h N_h(t) - \alpha_h I_h(t), \quad \frac{dN_m(t)}{dt} = \Lambda_m - \mu_m N_m(t). \tag{2.4}$$

We know that $E_h(t) = N_h(t) - S_h(t) - V_h(t) - I_h(t)$ and $E_m(t) = N_m(t) - S_m(t) - I_m(t)$. Throughout this paper we will analyse the equivalent system to (2.2) which is

$$\begin{aligned}
\frac{dS_h(t)}{dt} &= \Lambda_h - \mu_h S_h(t) + r_h I_h(t) - \zeta_h I_m(t)\frac{S_h(t)}{N_h(t)} - \phi S_h(t) + \sigma V_h(t),\\
\frac{dV_h(t)}{dt} &= \phi S_h(t) - \mu_h V_h(t) - \zeta_h(1-\gamma) I_m(t)\frac{V_h(t)}{N_h(t)} - \sigma V_h(t),\\
\frac{dI_h(t)}{dt} &= \zeta_h I_m(t-\tau_h)\frac{S_h(t-\tau_h) + (1-\gamma)V_h(t-\tau_h)}{N_h(t-\tau_h)} e^{-\mu_h \tau_h}\\
&\quad -(r_h + \alpha_h + \mu_h) I_h(t),\\
\frac{dN_h(t)}{dt} &= \Lambda_h - \mu_h N_h(t) - \alpha_h I_h(t),\\
\frac{dS_m(t)}{dt} &= \Lambda_m - \zeta_m S_m(t)\frac{I_h(t)}{N_h(t)} - \mu_m S_m(t),\\
\frac{dI_m(t)}{dt} &= \zeta_m S_m(t-\tau_m)\frac{I_h(t-\tau_m)}{N_h(t-\tau_m)} e^{-\mu_m \tau_m} - \mu_m I_m(t),\\
\frac{dN_m(t)}{dt} &= \Lambda_m - \mu_m N_m(t).
\end{aligned} \tag{2.5}$$

Let us define the regions

$$\begin{aligned}
\Omega_+ &= \{S_h, V_h, I_h, N_h, S_m, I_m, N_m \,|\, S_h \geq 0, V_h \geq 0, I_h \geq 0, S_m \geq 0, I_m \geq 0,\\
&\quad N_h \geq S_h + V_h + I_h, N_h > 0, N_m \geq S_m + I_m, N_m > 0\}\\
\Omega &= \{S_h \geq 0, V_h \geq 0, I_h \geq 0, N_h \geq S_h + V_h + I_h, \Lambda_h/\mu_h \geq N_h \geq \Lambda_h/(\mu_h + \alpha_h),\\
&\quad S_m \geq 0, I_m \geq 0, N_m \geq S_m + I_m, \Lambda_m/\mu_m \geq N_m > 0\},
\end{aligned}$$

and let the initial conditions of the model system (2.5) be given as

$$\begin{aligned}
S_h(t+\theta) &= \varphi_1, \quad V_h(t+\theta) = \varphi_2, \quad I_h(t+\theta) = \varphi_3, \quad N_h(t+\theta) = \varphi_4,\\
S_m(t+\theta) &= \varphi_5, \quad I_m(t+\theta) = \varphi_6, \quad N_m(t+\theta) = \varphi_7, \quad \text{for } (-\tau \leq \theta \leq 0),
\end{aligned} \tag{2.6}$$

where $t \geq 0$, $\tau = \max(\tau_h, \tau_m)$, $\varphi = (\varphi_1, \varphi_2, \varphi_3, \varphi_4, \varphi_5, \varphi_6, \varphi_7)^T \in C$ such that $\varphi_i \geq 0$ and $\varphi_i(0) > 0$ for $i = 1, 2, \ldots 7$, with $N_h(t) > 0$ and $N_m(t) > 0$ on this interval. C denotes the Banach space $C([-\tau, 0], \mathbb{R}^7)$ of continuous functions mapping the interval $[-\tau, 0]$ into $\mathbb{R}^7$.

We show in Appendix A that the solutions

$$(S_h(t), V_h(t), I_h(t), N_h(t), S_m(t), I_m(t), N_m(t))$$

of model (2.5) remain positive for all time $t > 0$.

3. Reproductive numbers, equilibria and stability

3.1. Reproductive number

The reproductive number is usually defined as the expected number of secondary cases produced in a population of susceptibles by a single infected individual during his/her entire period of infectiousness, and mathematically as the dominant eigenvalue of a positive linear operator [17]. For a population with a proportion of vaccinated susceptibles the threshold quantity R_ϕ, is known as the vaccinated reproductive number [7]. In this context, it measures the expected number of new secondary cases produced from a single infected individual in a population where anti-malaria vaccines are used as a control measure. We will denote the reproductive number when pre-erythrocytic vaccine is administered as $R_\phi(\gamma)$. We write the reproductive number with ϕ and γ to highlight the effect of vaccination and pre-erythrocytic vaccine efficacy respectively.

We will denote the reproductive number for the model without vaccination as R_0. It can easily be shown that

$$R_0 = \frac{\zeta_h \zeta_m \Lambda_m \mu_h e^{-(\mu_h \tau_h + \mu_m \tau_m)}}{\mu_m^2 \Lambda_h (r_h + \alpha_h + \mu_h)}. \tag{3.1}$$

It can be shown that model (2.5) has a disease free equilibrium (DFE) denoted by E^0 and

$$\begin{aligned} E^0 &= (S_h^0, V_h^0, I_h^0, N_h^0, S_m^0, I_m^0, N_m^0), \\ &= \left(\frac{\Lambda_h(\mu_h + \sigma)}{\mu_h(\mu_h + \sigma + \phi)}, \frac{\Lambda_h \phi}{\mu_h(\mu_h + \sigma + \phi)}, 0, \frac{\Lambda_h}{\mu_h}, \frac{\Lambda_m}{\mu_m}, 0, \frac{\Lambda_m}{\mu_m} \right). \end{aligned} \tag{3.2}$$

To find the reproductive number we introduce an infectious human or mosquito into a population which is at a disease free equilibrium state as follows: Suppose a single newly infectious mosquito is introduced into a population at disease free equilibrium, where a proportion of susceptibles have been vaccinated with pre-erythrocytic vaccine. This mosquito still present in the population at time t with a probability of surviving its infectious period $e^{-\mu_m t}$, infects humans (susceptibles and vaccinated) at a rate $\zeta_h \dfrac{S_h^0 + (1-\gamma)V_h^0}{N_h^0}$. These humans become infectious at time $t \geq \tau_h$ with probability $e^{-\mu_h \tau_h}$. Hence the expected number of humans who become infectious due to this mosquito during its entire period of infectiousness is

$$\int_0^\infty \zeta_h \frac{S_h^0 + (1-\gamma)V_h^0}{N_h^0} e^{-\mu_h \tau_h} e^{-\mu_m t} dt = \frac{\zeta_h e^{-\mu_h \tau_h}(\mu_h + \sigma + (1-\gamma)\phi)}{\mu_m(\mu_h + \sigma + \phi)} = R_{\phi_{mh}}(\gamma). \tag{3.3}$$

Suppose a newly infectious human is introduced into a population at disease free equilibrium. This human still present in the population at time t with a probability of surviving his/her infectious period $e^{-(r_h + \alpha_h + \mu_h)t}$, infects mosquitoes at a rate $\zeta_m \dfrac{S_m^0}{N_h^0}$. These mosquitoes become infectious at time $t \geq \tau_m$ with a probability $e^{-\mu_m \tau_m}$. Hence

the expected number of mosquitoes which become infectious due to this human during his/her entire period of infectiousness is

$$\int_0^\infty \zeta_m \frac{S_m^0}{N_h^0} e^{-\mu_m \tau_m} e^{-(r_h+\alpha_h+\mu_h)t} dt = \frac{\mu_h \Lambda_m \zeta_m e^{-\mu_m \tau_m}}{\mu_m \Lambda_h (r_h+\alpha_h+\mu_h)} = R_{\phi_{hm}}(\gamma). \tag{3.4}$$

$R_{\phi_{mh}}(\gamma)$ and $R_{\phi_{hm}}(\gamma)$ are the disease reproductive numbers from mosquitoes to humans and from humans to mosquitoes respectively in a population where pre-erythrocytic vaccine is used as a control strategy. The product

$$\begin{aligned} R_{\phi_{mh}}(\gamma) R_{\phi_{hm}}(\gamma) = R_\phi(\gamma) &= \frac{\zeta_h \zeta_m \Lambda_m \mu_h e^{-\mu_h \tau_h} e^{-\mu_m \tau_m} (\mu_h + \sigma + (1-\gamma)\phi)}{\mu_m^2 \Lambda_h (r_h+\alpha_h+\mu_h)(\mu_h+\sigma+\phi)} \\ &= R_0 \frac{\mu_h + \sigma + (1-\gamma)\phi}{\mu_h + \sigma + \phi}, \end{aligned} \tag{3.5}$$

gives the total reproductive number from host to host or from vector to vector.

3.2. Local and global stability of the disease free equilibrium

To determine the local stability of the disease free state we first rewrite the infectious compartments as integral equations and we will use the method of Kribbs-Zaleta [40]. From system of equations (2.5) the equations for the infectious classes can be written as

$$\begin{aligned} I_h(t) &= \int_{-\infty}^{t+\tau_h} \zeta_h I_m(s-\tau_h) \frac{S_h(s-\tau_h) + (1-\gamma) V_h(s-\tau_h)}{N_h(s-\tau_h)} e^{-\mu_h \tau_h} \times \\ &\quad e^{-(r_h+\alpha_h+\mu_h)(t-(s-\tau_h))} ds, \\ I_m(t) &= \int_{-\infty}^{t+\tau_m} \zeta_m S_m(s-\tau_m) \frac{I_h(s-\tau_m)}{N_h(s-\tau_m)} e^{-\mu_m \tau_m} e^{-\mu_m (t-(s-\tau_m))} ds. \end{aligned} \tag{3.6}$$

First, we consider the integral equation of $I_h(t)$. Let $\psi_0 = r_h + \alpha_h + \mu_h$, $S_h(t) = S_h^* + s_h(t)$, $S_m(t) = S_m^* + s_m(t)$, $I_h(t) = I_h^* + i_h(t)$, $I_m(t) = I_m^* + i_m(t)$ and $N_h(t) = N_h^* + n_h(t)$. Allowing constant and quadratic terms to drop out, we have

$$\begin{aligned} i_h(t) &= \zeta_h e^{-\mu_h \tau_h} \int_{-\infty}^{t+\tau_h} \left(\frac{I_m^* [s_h(s-\tau_h) + (1-\gamma) v_h(s-\tau_h)]}{N_h^*} \right. \\ &\qquad \left. + \frac{i_m(s-\tau_h)[S_h^* + (1-\gamma) V_h^*]}{N_h^*} \right) e^{-\psi_0 (t-(s-\tau_h))} ds. \end{aligned}$$

Substituting $x = t - (s - \tau_h)$ and noting that at E^0, $I_m^* = 0$ and $\frac{S_h^* + (1-\gamma)V_h^*}{N_h^*} = \frac{\mu_h + \sigma + (1-\gamma)\phi}{\mu_h + \sigma + \phi}$, this reduces to

$$i_h(t) - \zeta_h e^{-\mu_h \tau_h} \frac{\mu_h + \sigma + (1-\gamma)\phi}{\mu_h + \sigma + \phi} \int_0^\infty i_m(t-x) e^{-\psi_0 x} dx = 0.$$

The roots of a characteristic equation describe the rate of exponential growth of the linearised system. Since we are looking for these roots, we assume temporarily that $i_m(t)$ has the form of an exponential function: $k_{i_m}e^{\lambda t}$, so that λ is our root. Substituting this function into the integral, we get

$$i_h(t) - \zeta_h e^{-\mu_h \tau_h} \frac{\mu_h + \sigma + (1-\gamma)\phi}{\mu_h + \sigma + \phi} \int_0^\infty k_{i_m} e^{\lambda t} e^{-\lambda x} e^{-\psi_0 x} dx = 0. \tag{3.7}$$

Pulling $k_{i_m}e^{\lambda t}$ outside the integral and if we undo the substitution, we get

$$(\psi_0 + \lambda) i_h(t) - \zeta_h e^{-\mu_h \tau_h} \frac{\mu_h + \sigma + (1-\gamma)\phi}{\mu_h + \sigma + \phi} i_m(t) = 0. \tag{3.8}$$

Repeating the same process on the equation for $I_m(t)$, we get

$$(\mu_m + \lambda) i_m(t) - \zeta_m e^{-\mu_m \tau_m} \frac{\Lambda_m \mu_h}{\mu_m \Lambda_h} i_h(t) = 0. \tag{3.9}$$

These equations in $i_m(t)$ and $i_h(t)$, give us a characteristic equation of the form $det(J_2 - \lambda I_{2\times 2}) = 0$, where $I_{2\times 2}$ is a 2×2 identity matrix and J_2 is a 2×2 matrix

$$J_2 = \begin{pmatrix} -\psi_0 & \zeta_h e^{-\mu_h \tau_h} \frac{\mu_h + \sigma + (1-\gamma)\phi}{\mu_h + \sigma + \phi} \\ \zeta_m e^{-\mu_m \tau_m} \frac{\Lambda_m \mu_h}{\mu_m \Lambda_h} & -\mu_m \end{pmatrix}. \tag{3.10}$$

The characteristic equation simplifies to

$$\lambda^2 + (\psi_0 + \mu_m)\lambda + \psi_0 \mu_m (1 - R_\phi(\gamma)) = 0.$$

Using the *Routh-Hurwitz* stability criterion, we conclude that the disease free equilibrium is stable if $R_\phi(\gamma) < 1$, and unstable otherwise. Thus we have the following theorem:

Theorem 3.1. *The disease free equilibrium, E^0 of model* (2.5) *is locally asymptotically stable if $R_\phi(\gamma) < 1$ and unstable if $R_\phi(\gamma) > 1$.*

The disease free equilibrium state E^0 is also globally asymptotically stable as in Lemma 3.1 and the proof is in Appendix B.

Lemma 3.1. *For the system* (2.5)*, the disease free equilibrium is globally asymptotically stable if $R_\phi(\gamma) < 1$.*

3.3. Existence of endemic equilibrium

Endemic equilibrium of the model (2.5) corresponds to the case where the disease may persist in the population, that is when $I_h, I_m \neq 0$. Since the expression for the endemic equilibrium is too long to be clearly expressed in closed form, we shall show its existence based on some conditions on the model parameters. To do this, let $(S_h^*, V_h^*, I_h^*, N_h^*, S_m^*, I_m^*, N_m^*)$ be an endemic equilibrium in the interior of Ω and

equate the right hand side of (2.5) to zero except the third equation. Expressing S_h^*, V_h^*, N_h^*, S_m^*, I_m^* and N_m^* in terms of I_h^* we get

$$\begin{aligned}
S_h^*(I_h^*) &= \frac{(\Lambda_h + r_h I_h^*)(\psi_5(\mu_h+\sigma)+(1-\gamma)\psi_6 I_h^*)\psi_5}{(\psi_5(\mu_h+\sigma)+(1-\gamma)\psi_6 I_h^*)(\psi_5(\mu_h+\phi)+\psi_6 I_h^*)-\phi\sigma\psi_5^2},\\
V_h^*(I_h^*) &= \frac{(\Lambda_h + r_h I_h^*)\phi\psi_5^2}{(\psi_5(\mu_h+\sigma)+(1-\gamma)\psi_6 I_h^*)(\psi_5(\mu_h+\phi)+\psi_6 I_h^*)-\phi\sigma\psi_5^2},\\
N_h^*(I_h^*) &= \frac{\Lambda_h-\alpha_h I_h^*}{\mu_h},\\
S_m^*(I_h^*) &= \frac{\Lambda_m(\Lambda_h-\alpha_h I_h^*)}{\mu_m\Lambda_h+(\mu_h\zeta_m-\alpha_h\mu_m)I_h^*},\\
I_m^*(I_h^*) &= \frac{\mu_h\Lambda_m\zeta_m e^{-\mu_m\tau_m}I_h^*}{\mu_m(\mu_m\Lambda_h+(\mu_h\zeta_m-\alpha_h\mu_m)I_h^*)},\\
N_m^*(I_h^*) &= \frac{\Lambda_m}{\mu_m},
\end{aligned} \tag{3.11}$$

where $\psi_5 = \mu_m(\Lambda_h-\alpha_h I_h^*)(\mu_m\Lambda_h+(\mu_h\zeta_m-\alpha_h\mu_m)I_h^*)$ and $\psi_6 = \mu_h^2\Lambda_m\zeta_h\zeta_m e^{-\mu_m\tau_m}$.

Substituting (3.11) in the third equation of (2.5) results in the following equation in I_h^*.

$$\zeta_h I_m^*\frac{S_h^*+(1-\gamma)V_h^*}{N_h^*}e^{-\mu_h\tau_h}-(r_h+\alpha_h+\mu_h)I_h^*=0. \tag{3.12}$$

Expanding (3.12), we get an equation in terms of I_h^* which is

$$I_h^*(B_4 I_h^{*4}+B_3 I_h^{*3}+B_2 I_h^{*2}+B_1 I_h^*+B_0)=0, \tag{3.13}$$

where the coefficients $\{B_4,\ldots,B_0\}$ are as shown in Appendix C.

Clearly $I_h^*=0$ is a solution which gives the disease free equilibrium (3.2). We can also see that B_4 is negative and the sign of B_0 coincides with that of $(R_\phi(\gamma)-1)$. If $R_\phi(\gamma)>1$, $B_0>1$. In a similar manner to [48], we show that there is at least an endemic equilibria when $R_\phi(\gamma)>1$. By using Descartes' Rule of Sign as stated in [39], when $R_\phi(\gamma)>1$ there is at least one sign change in the sequence of coefficients $\{B_4,\ldots,B_0\}$ hence there exists at least a positive real root of (2.5) which is not $I_h^*=0$.

The above results on the existence of the endemic equilibria of model (2.5) can be summarized in the following lemma:

Lemma 3.2. *The vaccination model* (2.5) *always has a disease free equilibrium* $E^0=\left(\frac{\Lambda_h(\mu_h+\sigma)}{\mu_h(\mu_h+\sigma+\phi)},\frac{\Lambda_h\phi}{\mu_h(\mu_h+\sigma+\phi)},0,\frac{\Lambda_h}{\mu_h},\frac{\Lambda_m}{\mu_m},0,\frac{\Lambda_m}{\mu_m}\right)$ *and at least one endemic equilibrium when* $R_\phi(\gamma)>1$.

4. Model extension

We extend the pre-erythrocytic vaccination model to include in addition to pre-erythrocytic vaccine, blood stage (erythrocytic) vaccine and transmission blocking

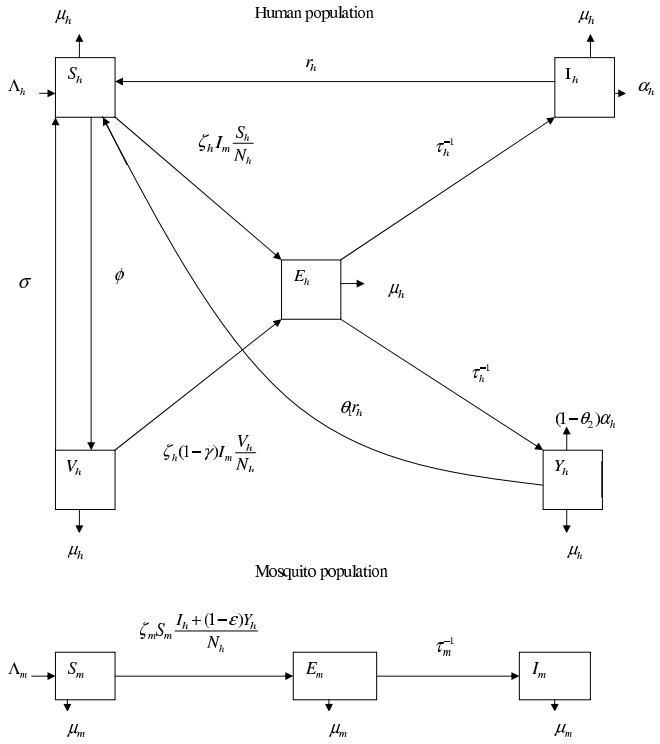

Figure 1: The schematic diagram of malaria transmission between human and mosquito populations when pre-erythrocytic, erythrocytic and transmission blocking vaccines are administered.

vaccine. For pre-erythrocytic and blood stage vaccine approaches see [23, 46]. For blood stage effects of the vaccine, the host still gets malaria, but severity and lethality of the disease is reduced. This effect is modelled by parameters $\theta_1 \geq 1$ and $\theta_2, (0 < \theta_2 < 1)$, where θ_1 is the rate at which the recovery rate is increased and $(1 - \theta_2)$ is the rate at which the disease related death rate α_h is reduced due to the effects of vaccine on blood stages of the parasite. Transmission blocking vaccine will not prevent the host from getting malaria, nor will it lessen the symptoms of the disease. It is designed to evoke human antibodies that derail parasite development within the mosquito [21]. These will thus block the transmission of malaria from spreading to new hosts. This effect is represented by a parameter ϵ where $0 < \epsilon < 1$. $\epsilon = 1$ means that the vaccine is completely effective in blocking transmission. Thus for a mosquito that feeds on an infected vaccinated human, the gametocytes are killed in the human or are taken by a feeding mosquito but their development is hindered. $\epsilon = 0$ means that the vaccine is useless in blocking transmission. In this case it is necessary to divide the infectious class into two groups, the infectious class without

vaccination $I_h(t)$ and the infectious vaccinated class $Y_h(t)$. The extended model then becomes

$$\begin{aligned}
\frac{dS_h(t)}{dt} &= \Lambda_h - \mu_h S_h(t) + r_h I_h(t) + \theta_1 r_h Y_h(t) - \zeta_h I_m(t)\frac{S_h(t)}{N_h(t)} - \phi S_h(t) + \sigma V_h(t),\\
\frac{dV_h(t)}{dt} &= \phi S_h(t) - \mu_h V_h(t) - \zeta_h(1-\gamma) I_m(t)\frac{V_h(t)}{N_h(t)} - \sigma V_h(t),\\
\frac{dI_h(t)}{dt} &= \zeta_h I_m(t-\tau_h)\frac{S_h(t-\tau_h)}{N_h(t-\tau_h)}e^{-\mu_h\tau_h} - (r_h + \alpha_h + \mu_h) I_h(t),\\
\frac{dY_h(t)}{dt} &= \zeta_h(1-\gamma) I_m(t-\tau_h)\frac{V_h(t-\tau_h)}{N_h(t-\tau_h)}e^{-\mu_h\tau_h} - (\theta_1 r_h + (1-\theta_2)\alpha_h + \mu_h) Y_h(t),\\
\frac{dN_h(t)}{dt} &= \Lambda_h - \mu_h N_h(t) - \alpha_h I_h(t) - (1-\theta_2)\alpha_h Y_h(t),\\
\frac{dS_m(t)}{dt} &= \Lambda_m - \zeta_m S_m(t)\frac{I_h(t) + (1-\epsilon) Y_h(t)}{N_h(t)} - \mu_m S_m(t),\\
\frac{dI_m(t)}{dt} &= \zeta_m S_m(t-\tau_m)\frac{I_h(t-\tau_m) + (1-\epsilon) Y_h(t-\tau_m)}{N_h(t-\tau_m)}e^{-\mu_m\tau_m} - \mu_m I_m(t),\\
\frac{dN_m(t)}{dt} &= \Lambda_m - \mu_m N_m(t). \qquad (4.1)
\end{aligned}$$

The disease free equilibrium of system (4.1) is

$$E_0 = (S_{h*}, V_{h*}, I_{h*}, Y_{h*}, N_{h*}, S_{m*}, I_{m*}, N_{m*}), \qquad (4.2)$$

where $I_{h*} = Y_{h*} = I_{m*} = 0$ and $S_{h*} = S_h^0$, $V_{h*} = V_h^0$, $N_{h*} = N_h^0$, $S_{m*} = S_m^0$ and $N_{m*} = N_m^0$ as given in (3.2).

We note that when a vaccine with the three subunits has been administered into a population the transmission rate from a mosquito to a vaccinated human is reduced if $0 < \gamma < 1$, the transmission rate from a vaccinated infectious human to a susceptible mosquito is reduced if $0 < \epsilon < 1$ and the infectious period of that human may either increase or decrease. Therefore the reproductive number from human to human or from mosquito to mosquito should be the sum of the reproductive numbers from the proportion vaccinated and the proportion not vaccinated. Using the same approach as in section 3 we derive the reproductive number for the extended model (4.1).

We can show that the expected number of mosquitoes which become infectious due to a single vaccinated infectious human during his/her entire period of infectiousness is

$$\begin{aligned}
&\int_0^\infty \zeta_m(1-\epsilon)\frac{S_{m*}}{N_{h*}}e^{-\mu_m\tau_m}e^{-(\theta_1 r_h + (1-\theta_2)\alpha_h + \mu_h)t}dt\\
&\qquad = \frac{\zeta_m\Lambda_m\mu_h(1-\epsilon)e^{-\mu_m\tau_m}}{\mu_m\Lambda_h(\theta_1 r_h + (1-\theta_2)\alpha_h + \mu_h)} = R_{\phi_{hm}}(\gamma, \theta_{1,2}, \epsilon). \qquad (4.3)
\end{aligned}$$

The expected number of vaccinated humans who become infectious due to an infec-

tious mosquito during its entire period of infectiousness is

$$\int_0^\infty \zeta_h(1-\gamma)\frac{V_{h*}}{N_{h*}}e^{-\mu_h\tau_h}e^{-\mu_m t}dt = \frac{\zeta_h(1-\gamma)e^{-\mu_h\tau_h}\phi}{\mu_m(\mu_h+\sigma+\phi)} = R_{\phi_{mh}}(\gamma,\theta_{1,2},\epsilon). \tag{4.4}$$

Similarly the expected number of mosquitoes which become infectious due to a single infectious human (who is not vaccinated) during his/her entire period of infectiousness is

$$\int_0^\infty \zeta_m\frac{S_{m*}}{N_{h*}}e^{-\mu_m\tau_m}e^{-(r_h+\alpha_h+\mu_h)t}dt = \frac{\zeta_m\mu_h\Lambda_m e^{-\mu_m\tau_m}}{\mu_m\Lambda_h(r_h+\alpha_h+\mu_h)} = R_{hm} \tag{4.5}$$

and the expected number of humans who are not vaccinated who become infectious due to a single infectious mosquito during its period of infectiousness is

$$\int_0^\infty \zeta_h\frac{S_{h*}}{N_{h*}}e^{-\mu_h\tau_h}e^{-\mu_m t}dt = \frac{\zeta_h e^{-\mu_h\tau_h}(\mu_h+\sigma)}{\mu_m(\mu_h+\sigma+\phi)} = R_{mh}. \tag{4.6}$$

$R_{\phi_{hm}}(\gamma,\theta_{1,2},\epsilon)R_{\phi_{mh}}(\gamma,\theta_{1,2},\epsilon)$ is the reproductive number for the proportion vaccinated and $R_{hm}R_{mh}$ is the reproductive number for the proportion not vaccinated, hence for the entire population the reproductive number from human to human or from mosquito to mosquito for model (4.1), $R_\phi(\gamma,\theta_{1,2},\epsilon)$ is

$$\begin{aligned} R_\phi(\gamma,\theta_{1,2},\epsilon) &= R_{\phi_{hm}}(\gamma,\theta_{1,2},\epsilon)R_{\phi_{mh}}(\gamma,\theta_{1,2},\epsilon) + R_{hm}R_{mh} \\ &= \frac{\zeta_h\zeta_m\Lambda_h\mu_h e^{-\mu_h\tau_h}e^{-\mu_m\tau_m}\phi(1-\gamma)(1-\epsilon)}{\mu_m^2\Lambda_h(\theta_1 r_h+(1-\theta_2)\alpha_h+\mu_h)(\mu_h+\sigma+\phi)} \\ &\quad + \frac{\zeta_h\zeta_m\Lambda_h\mu_h e^{-\mu_h\tau_h}e^{-\mu_m\tau_m}(\mu_h+\sigma)}{\mu_m^2\Lambda_h(r_h+\alpha_h+\mu_h)(\mu_h+\sigma+\phi)} \\ &= \frac{R_0}{\mu_h+\sigma+\phi}\left(\mu_h+\sigma+\phi\frac{(1-\gamma)(1-\epsilon)(r_h+\alpha_h+\mu_h)}{\theta_1 r_h+(1-\theta_2)\alpha_h+\mu_h}\right). \end{aligned} \tag{4.7}$$

This is the reproductive number in a population where the three subunits of malaria vaccine have been administered.

We can show that E_0 is locally asymptotically stable when $R_\phi(\gamma,\theta_{1,2},\epsilon)<1$ by linearising the system at the disease free equilibrium as was done for the previous model.

The explicit form of the endemic equilibrium is too cumbersome to be written down here, therefore we will only investigate the existence of an endemic equilibrium. Expressing the endemic equilibrium of model (4.1) as
$(S_h^{**},V_h^{**},I_h^{**},Y_h^{**},N_h^{**},S_m^{**},I_m^{**},N_m^{**})$, let

$$\eta_m = \frac{I_m^{**}}{N_h^{**}} \quad \text{and} \quad \eta_h = \frac{I_h^{**}+(1-\epsilon)Y_h^{**}}{N_h^{**}}. \tag{4.8}$$

Substituting η_m and η_h in (4.1), we get

$$\begin{aligned}
S_h^{**} &= -\frac{\Lambda_h\varphi_0\kappa_2\varphi_7}{\varphi_7\eta_m\kappa_2 r_h\zeta_h e^{-\mu_h\tau_h}+\varphi_0(\theta_1 r_h\phi(1-\gamma)\eta_m\zeta_h e^{-\mu_h\tau_h}+\phi\kappa_2\sigma)-\varphi_0\varphi_7\varphi_8\kappa_2},\\
V_h^{**} &= \phi\frac{S_h^{**}}{\varphi_7},\\
I_h^{**} &= \frac{\eta_m\zeta_h e^{-\mu_h\tau_h}S_h^{**}}{\varphi_0},\\
Y_h^{**} &= \frac{\zeta_h(1-\gamma)\eta_m e^{-\mu_h\tau_h}V_h^{**}}{\kappa_2},\\
N_h^{**} &= \frac{\Lambda_h-\alpha_h(I_h^{**}+(1-\theta_2)Y_h^{**})}{\mu_h},\\
S_m^{**} &= \frac{\Lambda_m}{\mu_m+\eta_h\zeta_m},\\
I_m^{**} &= \frac{\eta_h\zeta_m e^{-\mu_m\tau_m}S_m^{**}}{\mu_m},\\
N_m^{**} &= \frac{\Lambda_m}{\mu_m}.
\end{aligned} \tag{4.9}$$

where $\varphi_7=\mu_h+\sigma+\zeta_h(1-\gamma)\eta_m$, $\varphi_8=\mu_h+\phi+\zeta_h\eta_m$. Expressing η_h in terms of η_m and substituting (4.9) in the third equation of (4.1) and equating to zero we get the following equation

$$\kappa_{10}\eta_m((\gamma-1)\zeta_h\eta_m-(\mu_h+\sigma))(A_4\eta_m^4+A_3\eta_m^3+A_2\eta_m^2+A_1\eta_m+A_0)=0, \tag{4.10}$$

where $A_i, i=1,\ldots,4$ and $\kappa_i, i=1,\ldots,10$ are given in Appendix D. Analysing (4.10), we see that one of the solutions is $\eta_m=0$ since $\kappa_{10}\neq 0$. This root corresponds to the disease free equilibrium state. The second root is $\eta_m=\frac{(\mu_h+\sigma)}{\zeta_h(\gamma-1)}$. This root is negative since $0<\gamma<1$. We investigate the possibility of a positive equilibrium from the remaining polynomial $(A_4\eta_m^4+A_3\eta_m^3+A_2\eta_m^2+A_1\eta_m+A_0)$. We note that A_4 is always positive and the sign of A_0 coincides with that of $(1-R_\phi(\gamma,\theta_{1,2},\epsilon))$. By using Descartes' Rule of Signs, we note that there is at least one sign change in the sequence of coefficients $\{A_4,\ldots,A_0\}$ when $R_\phi(\gamma,\theta_{1,2},\epsilon)>1$ hence the model (4.1) has at least a positive root. These results can be summarised in the following lemma:

Lemma 4.1. *The vaccination model* (4.1) *with three subunits of malaria vaccine always has a disease free equilibrium state and at least an endemic equilibrium that exists when* $R_\phi(\gamma,\theta_{1,2},\epsilon)>1$.

5. Analysis of the reproductive numbers

A disease threshold quantity is a measure of the relative strength of the disease transmission versus dilution on infectives. R_0, $R_\phi(\gamma)$, $R_\phi(\theta_{1,2})$, $R_\phi(\epsilon)$ and $R_\phi(\gamma,\theta_{1,2},\epsilon)$,

denote the reproductive numbers of the model without vaccination, with pre-erythrocytic vaccine, with blood stage vaccine, with transmission blocking vaccine and a combination of all the three vaccine subunits respectively. We state the expressions for the different reproductive numbers for different combinations of the vaccines here:

$$\begin{aligned}
R_0 &= \frac{\zeta_h\zeta_m\Lambda_m\mu_h e^{-\mu_h\tau_h}e^{-\mu_m\tau_m}}{\mu_m^2\Lambda_h(r_h+\alpha_h+\mu_h)},\\
R_\phi(\gamma) &= \frac{R_0}{\mu_h+\sigma+\phi}(\mu_h+\sigma+(1-\gamma)\phi),\\
R_\phi(\theta_{1,2}) &= \frac{R_0}{\mu_h+\sigma+\phi}\left(\mu_h+\sigma+\phi\frac{r_h+\alpha_h+\mu_h}{\theta_1 r_h+(1-\theta_2)\alpha_h+\mu_h}\right),\\
R_\phi(\epsilon) &= \frac{R_0}{\mu_h+\sigma+\phi}(\mu_h+\sigma+(1-\epsilon)\phi),\\
R_\phi(\gamma,\theta_{1,2}) &= \frac{R_0}{\mu_h+\sigma+\phi}\left(\mu_h+\sigma+(1-\gamma)\phi\frac{r_h+\alpha_h+\mu_h}{\theta_1 r_h+(1-\theta_2)\alpha_h+\mu_h}\right),\\
R_\phi(\theta_{1,2},\epsilon) &= \frac{R_0}{\mu_h+\sigma+\phi}\left(\mu_h+\sigma+(1-\epsilon)\phi\frac{r_h+\alpha_h+\mu_h}{\theta_1 r_h+(1-\theta_2)\alpha_h+\mu_h}\right),\\
R_\phi(\gamma,\epsilon) &= \frac{R_0}{\mu_h+\sigma+\phi}(\mu_h+\sigma+(1-\gamma)(1-\epsilon)\phi),\\
R_\phi(\gamma,\theta_{1,2},\epsilon) &= \frac{R_0}{\mu_h+\sigma+\phi}\left(\mu_h+\sigma+(1-\gamma)(1-\epsilon)\phi\frac{r_h+\alpha_h+\mu_h}{\theta_1 r_h+(1-\theta_2)\alpha_h+\mu_h}\right).
\end{aligned} \tag{5.1}$$

By comparing the three reproductive numbers $R_\phi(\gamma)$, $R_\phi(\theta_{1,2})$ and $R_\phi(\epsilon)$, we see that the most effective vaccine is the one with the smallest factor among the three factors

$$(1-\gamma), \quad \frac{r_h+\alpha_h+\mu_h}{\theta_1 r_h+(1-\theta_2)\alpha_h+\mu_h}, \text{ and } (1-\epsilon)$$

which correspond to pre-erythrocytic vaccine, erythrocytic vaccine and transmission blocking vaccine respectively. In this section we determine the necessary conditions for slowing down the rate of disease progression to endemic levels and which reduce the effective reproductive number to levels below one. The effective reproductive number, $R_\phi(\gamma,\theta_{1,2},\epsilon)$ given in (4.7) is characterised by (i) γ the efficacy of pre-erythrocytic vaccine, (ii) ϵ efficacy of transmission blocking vaccine, (iii) θ_1 the degree of increase in recovery rate of infected vaccinated humans and (iv) θ_2 the degree of reduction in the disease induced mortality rate of an infected vaccinated human. The factor $\frac{r_h+\alpha_h+\mu_h}{\theta_1 r_h+(1-\theta_2)\alpha_h+\mu_h}$ is the ratio of infectious period of infectious vaccinated humans Y_h to the infectious period of infectious humans I_h.

To find the effects of pre-erythrocytic vaccine in protecting individuals who are vaccinated with all three subunits of the vaccine, we find the following limits

$$\lim_{\gamma\to 1}R_\phi(\gamma)=\lim_{\epsilon\to 1}R_\phi(\epsilon)=\lim_{\theta_1\to\infty,\theta_2\to 1}R_\phi(\theta_{1,2})=\frac{\mu_h+\sigma}{\mu_h+\sigma+\phi}R_0,$$

and secondly find $\lim_{\gamma\to 1} R_\phi(\gamma,\theta_{1,2},\epsilon)$. Therefore for a perfect vaccine (pre-erythrocytic, erythrocytic and transmission blocking), the only source of infection will be the susceptibles who are not vaccinated.

The disease does not spread to endemic levels if $R_0 < 1$, and in such a case vaccination might not be necessary. If $R_0 > 1$, vaccination is needed to slow down the disease or to bring the disease to eradication, and for this we find a critical vaccination rate ϕ^c, for which this is possible.

We will analyse the effects of the three subunits of malaria vaccine independently. For the pre-erthrocytic vaccine, we see that the condition $R_0 - R_\phi > 0$ is satisfied following an approach by Hsu-Schimt [36]. We first find the difference between R_0 and $R_\phi(\gamma)$

$$R_0 - R_\phi(\gamma) = R_0\left(1 - \frac{\mu_h + \sigma + (1-\gamma)\phi}{\mu_h + \sigma + \phi}\right) > 0. \tag{5.2}$$

Since the difference is positive then pre-erythrocytic vaccination is always helpful for reducing the basic reproductive number R_0. Positivity of the difference does not guarantee the eventual eradication of the epidemic, so we require a stronger condition $R_\phi(\gamma) < 1$. So secondly, we differentiate $R_\phi(\gamma)$ with respect to ϕ and get

$$\frac{dR_\phi(\gamma)}{d\phi} = \frac{-\gamma(\mu_h+\sigma)}{(\mu_h+\sigma+\phi)^2}R_0 < 0. \tag{5.3}$$

The condition above is necessary to slow down the progression of the disease. We now determine ϕ^c_γ, the critical pre-erythrocytic vaccination rate which reduces the reproductive number $R_\phi(\gamma)$ below one. This critical value is

$$\phi^c_\gamma = \frac{(\mu_h+\sigma)(R_0-1)}{1+R_0(\gamma-1)}. \tag{5.4}$$

It exists for $R_0 > 1 > R_0(1-\gamma)$. For eventual eradication of the disease with pre-erythrocytic vaccination as a control strategy the vaccination rate $\phi > \phi^c_\gamma$.

Repeating the same process for erythrocytic vaccine we see that $R_0 - R_\phi(\theta_{1,2}) > 0$. $dR_\phi(\theta_{1,2})/d\phi < 0$ if $\dfrac{r_h+\alpha_h+\mu_h}{\theta_1 r_h + (1-\theta_2)\alpha_h + \mu_h} < 1$ and the critical erythrocytic vaccination rate is

$$\phi^c_{\theta_{1,2}} = \frac{(\mu_h+\sigma)(\theta_1 r_h + (1-\theta_2)\alpha_h + \mu_h)(R_0-1)}{(\theta_1 r_h + (1-\theta_2)\alpha_h + \mu_h) - (r_h+\alpha_h+\mu_h)R_0}. \tag{5.5}$$

$\phi^c_{\theta_{1,2}}$ exists for $R_0 > 1 > \frac{r_h+\alpha_h+\mu_h}{\theta_1 r_h+(1-\theta_2)\alpha_h+\mu_h}R_0$.

For transmission blocking vaccine $R_0 - R_\phi(\epsilon) > 0$, $dR_\phi(\epsilon)/d\phi < 0$ and the critical transmission blocking vaccination rate

$$\phi^c_\epsilon = \frac{(\mu_h+\sigma)(R_0-1)}{1+R_0(\epsilon-1)}. \tag{5.6}$$

For the model with all the vaccine subunits the critical vaccination rate $\phi^c_{\gamma,\theta_{1,2},\epsilon}$ is given as

$$\phi^c_{\gamma,\theta_{1,2},\epsilon} = \frac{(\mu_h+\sigma)(\theta_1 r_h + (1-\theta_2)\alpha_h + \mu_h)(R_0-1)}{(\theta_1 r_h + (1-\theta_2)\alpha_h + \mu_h) - (\gamma-1)(\epsilon-1)(r_h+\alpha_h+\mu_h)R_0}, \tag{5.7}$$

which exists for

$$R_0 > 1 > (\gamma - 1)(\epsilon - 1)\frac{r_h + \alpha_h + \mu_h}{\theta_1 r_h + (1-\theta_2)\alpha_h + \mu_h}R_0. \tag{5.8}$$

A vaccination rate $\phi > \phi^c_{\gamma,\theta_{1,2},\epsilon}$ is likely to bring the disease to eradication.

If a vaccine is introduced into a population then the number of secondary infections will decrease if $R_\phi(\gamma, \theta_{1,2}, \epsilon) < R_0$ (i.e if the population reproductive number after introducing a vaccine is less than the current reproductive number). The condition $R_\phi(\gamma, \theta_{1,2}, \epsilon) < R_0$ reduces to

$$\frac{1/(\theta_1 r_h + (1-\theta_2)\alpha_h + \mu_h)}{1/(r_h + \alpha_h + \mu_h)} < \frac{1}{(1-\gamma)(1-\epsilon)}. \tag{5.9}$$

For a human who is successfully vaccinated, the erythrocytic vaccine will increase the recovery rate r_h by a factor θ_1 and/or reduce disease induced death rate by a factor $(1 - \theta_2)$. It then follows that the total duration of the infectious period $1/(\theta_1 r_h + (1-\theta_2)\alpha_h + \mu_h)$ of a vaccinated infectious human will either increase or decrease as compared to the infectious period $1/(r_h + \alpha_h + \mu_h)$ of an infectious non vaccinated human.

From the condition in (5.9), we deduce that a combination of the three subunits will result in a decrease in the number of secondary infections if the ratio of the infectious period of the vaccinated humans to the infectious period of a non vaccinated humans is less than the inverse of the product of $(1 - \gamma)$ and $(1 - \epsilon)$ which are the factors by which transmission rate is reduced from mosquitoes to humans and from humans to mosquitoes respectively. For example, for a 20% efficacious pre-erythrocytic vaccine and a 30% efficacious erythrocytic vaccine, there will be a decrease in the number of secondary infections if the period of infectiousness of a vaccinated human is increased by up to 1.7857 times the infectious period of a non vaccinated human. An erythrocytic vaccine which reduces the period of infectiousness will always lead to a decrease in the number of secondary infections.

Table 1 shows numerical values used for calculations in Table 2 and Table 3 unless stated and these numerical values are also used for numerical simulations in the following section.

From Table 2 we deduce that if the factors $(1 - \gamma)$, $(1 - \epsilon)$ and $\frac{r_h+\alpha_h+\mu_h}{\theta_1 r_h+(1-\theta_2)\alpha_h+\mu_h}$ have the same numerical value then the effectiveness of pre-erythrocytic, transmission blocking and erythrocytic vaccines is the same. If one subunit of the vaccine has a very high efficacy then combining it with another subunit of high efficacy gives a small difference in the percentage decrease in the reproductive number as compared to combining subunits of low efficacies. For example if $\gamma = 0.85$ then percentage decrease in R_0 is 73.86%, and combining pre-erythrocytic and transmission blocking vaccines where $\gamma = \epsilon = 0.85$ the percentage decrease in R_0 is 84.90%. The difference is only 11.04%. Whereas for low efficacy pre-erythrocytic vaccine, of $\gamma = 0.3$, then percentage decrease in R_0 is 25.97% and combining it with a low efficacy transmission blocking vaccine of $\epsilon = 0.3$ gives a percentage decrease of 44.32%. The difference is 18.35%.

Definition	Symbol	Value	Reference
Human birth rate	Λ_h	0.11 h d^{-1}	estimated
Vaccination rate	ϕ	0.06 h d^{-1}	estimated
Rate of loss of vaccine-induced immunity	σ	0.009 h d^{-1}	[8]
Transmission probability of infection to humans	β_h	0.5	[29]
Human biting rate	c	0.5 b d^{-1}	[19]
Human recovery rate	r_h	0.005 h d^{-1}	estimated
Disease induced death rate	α_h	0.0004 h d^{-1}	estimated
Natural death rate for humans	μ_h	0.000045 h d^{-1}	estimated
Efficacy of pre-erythrocytic vaccine	γ	0.34	estimated
Latent period for humans	τ_h	14 d	estimated
Factor which increases recovery rate	θ_1	4	estimated
Factor which decreases disease death rate	θ_2	0.06	estimated
Efficacy of transmission blocking vaccine	ϵ	0.85	estimated
Mosquito birth rate	Λ_m	6.0 m d^{-1}	estimated
Transmission probability of infection to mosquitoes	β_m	0.15	[29]
Natural death rate of mosquitoes	μ_m	0.05 m d^{-1}	[1]
Latent period for mosquitoes	τ_m	12 d	[1, 13, 15]

Table 1: Values of parameters used in the numerical simulations. The letters m, h, b, d stand for mosquitoes, humans, bites and day respectively.

From Table 3 we deduce that for different vaccine combinations the vaccination rate required is less than the vaccination rate when administering only one subunit. For example, we take a country like Zimbabwe with a population of about 11 634 663 people [65] and we assume demographic and disease parameters as shown in Table 1. Using Table 3, we deduce that if only one subunit of the vaccine is used, then to eradicate the disease the critical vaccination rate should be about 7.21×10^6 humans per day. For two combinations, the critical vaccination rate should be about 6.28×10^5 humans per day and for all three subunits the critical vaccination rate should be 5.58×10^5 humans per day. From this we conclude that for countries with high malaria endemicity, using one vaccine subunit may imply a high vaccination rate in order to eradicate malaria. Such a high vaccination rate may be unattainable in poor-resource settings.

Reproductive number	Efficacy	Numerical value of reproductive number	Percentage decrease in R_0
R_0	-	6.16	0
$R_\phi(\gamma)$	$\gamma = 0.85$	1.61	73.86
$R_\phi(\theta_{1,2})$	$\theta_1 = 7.2, \theta_2 = 0.06$	1.61	73.86
$R_\phi(\epsilon)$	$\epsilon = 0.85$	1.61	73.86
$R_\phi(\gamma, \theta_{1,2})$	$\gamma = 0.85, \theta_1 = 7.2,$		
	$\theta_2 = 0.06$	0.93	84.90
$R_\phi(\theta_{1,2}, \epsilon)$	$\theta_1 = 7.2, \theta_2 = 0.06,$		
	$\epsilon = 0.85$	0.93	84.90
$R_\phi(\gamma, \epsilon)$	$\gamma = \epsilon = 0.85$	0.93	84.90
$R_\phi(\gamma, \theta_{1,2}, \epsilon)$	$\gamma = 0.85, \theta_1 = 7.2,$		
	$\theta_2 = 0.06, \epsilon = 0.85$	0.82	86.61
$R_\phi(\epsilon)$	$\gamma = 0.3$	4.56	25.97
$R_\phi(\epsilon, \gamma)$	$\gamma = \epsilon = 0.3$	3.43	44.32

Table 2: Table that shows numerical values of reproductive numbers and % decreases in R_0 for the given vaccine efficacy.

Critical vaccination rate (CVR)	Efficacy	Numerical value of CVR	Percentage increase in $\phi^c_{\gamma,\theta_{1,2},\epsilon}$
$\phi^c_{\gamma,\theta_{1,2},\epsilon}$	$\gamma = \epsilon = 0.85,$		
	$\theta_1 = 7.2, \theta_2 = 0.06$	0.048	0
$\phi^c_\gamma = \phi^c_{\theta_{1,2}} = \phi^c_\epsilon$	$\gamma = 0.85, \theta_1 = 7.2,$		
	$\theta_2 = 0.06, \epsilon = 0.85$	0.62	1191.67
$\phi^c_{\gamma,\theta_{1,2}} = \phi^c_{\theta_{1,2},\epsilon} = \phi^c_{\gamma,\epsilon}$	$\gamma = 0.85, \theta_1 = 7.2,$		
	$\theta_2 = 0.06, \epsilon = 0.85$	0.054	12.50

Table 3: Values of critical vaccination rates with the corresponding vaccine efficacy and their percentage increases from the critical vaccinate rate $\phi^c_{\gamma,\theta_{1,2},\epsilon}$, of model (4.1).

6. Numerical simulations and sensitivity analysis

To study the time course of the infection, we numerically integrate equations in system (2.5) and equations in system (4.1). Programs were written in C^{++} programming language, using the fourth order Runge Kutta method. The parameters used are shown in Table 1 unless stated.

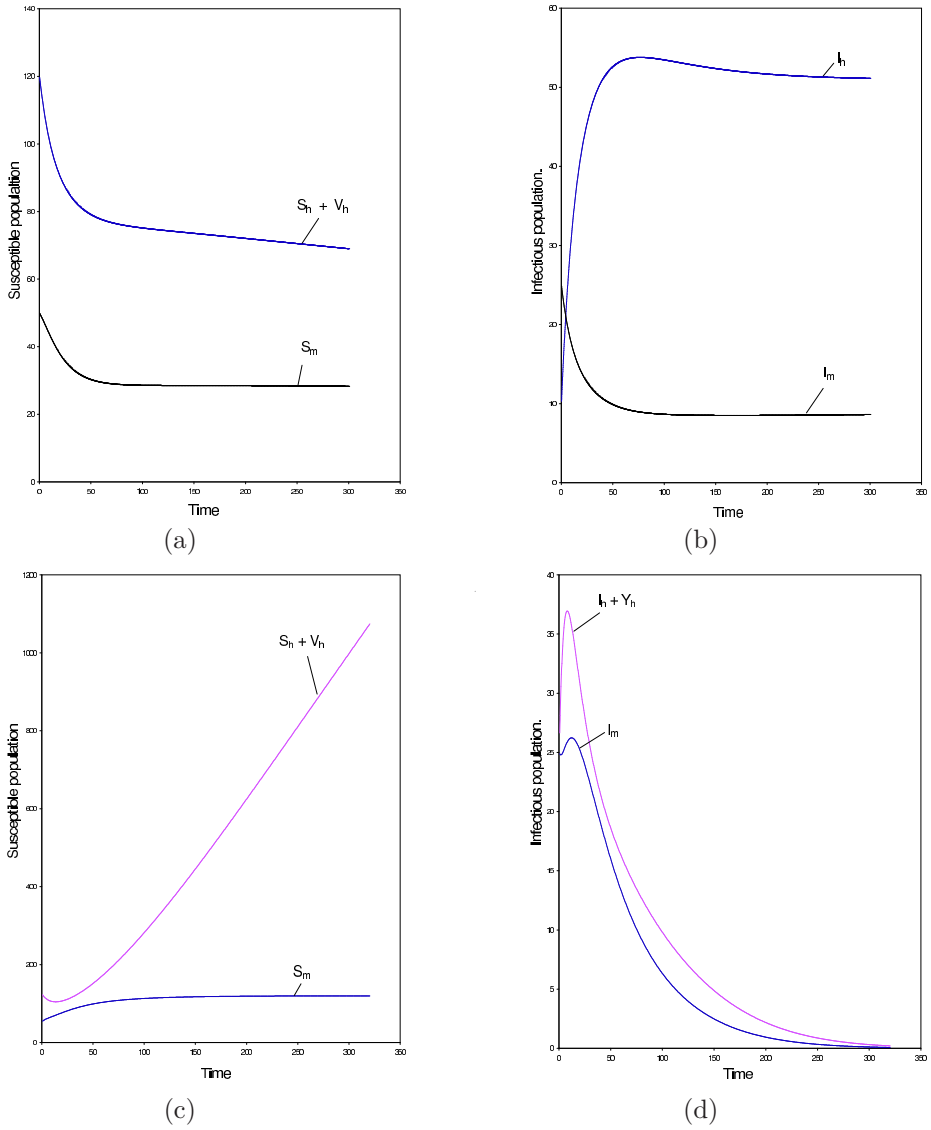

Figure 2: Graphs that show the behaviour of the model with pre-erythrocytic vaccine only and the model with all three subunits of the vaccine. The dynamics of (a) susceptible and vaccinated classes of model (2.5), (b) susceptible and vaccinated classes of model (4.1), (c) infectious classes of model (2.5) and (d) infectious classes of model (4.1).

Figure 2 shows the behaviour of models (2.5) and (4.1). The initial conditions for these models are $S_h(0) = 100$, $V_h(0) = 20$, $I_h(0) = 10$, $Y_h(0) = 15$, $N_h(0) = 150$, $S_m(0) = 50$ and $I_m(0) = 25$. Time is measured in days. The fixed parameters used

are as shown in Table 1. Figures 2(a) and 2(b) are for model (2.5) while Figures 2(c) and 2(d) are for model (4.1). For pre-erythrocytic vaccination model the susceptibles decrease to endemic levels while the infectious class for the human and mosquito populations also reach endemic levels for the same model. For model (4.1), the susceptible classes increase to values corresponding to those for the disease free state. For the human population $S_h + V_h \to \Lambda_h/\mu_h \approx 2444$ and for mosquito population $S_m \to \Lambda_m/\mu_m \approx 120$ while the infectious classes go to zero. This shows that in a population with a pre-erythrocytic vaccination that has failed to control the disease then introducing a vaccine with all subunits reduces the disease to disease free state.

In Figure 3, the initial conditions are $S_h(0) = 100$, $V_h(0) = 20$, $I_h(0) = 10$, $Y_h(0) = 15$, $N_h(0) = 150$, $S_m(0) = 50$, and $I_m(0) = 25$. Time is measured in steps of 0.1 so for all graphs in Figure 3 time is multiplied by 10^{-1}. Figure 3(a) shows the effects of varying γ in the absence of erythrocytic and transmission blocking vaccines. γ is varied from 0.2 to 0.8 in steps of 0.2. The values of parameters are as shown in Table 1 except that $\epsilon = 0.0$, $\theta_1 = 1.0$ and $\theta_2 = 0.0$. Figure 3(b) shows the effects of varying ϵ in the absence of pre-erythrocytic and transmission blocking vaccines. ϵ is varied from 0.2 to 0.8 in steps of 0.2. All the other parameters are as shown in Table 1 except that $\gamma = 0.0$, $\theta_1 = 1.0$ and $\theta_2 = 0.0$. These graphs show that increasing γ and increasing ϵ decrease the number of infectious populations. When increasing γ, the minimum time taken is about 60 days and when increasing ϵ it takes about 80 days to bring the infectious humans to zero. This shows that using pre-erythrocytic vaccine works faster than using transmission blocking vaccine in reducing the number of infectious humans although their long term effects are the same.

In Figure 3(c), the graphs labeled z_1 show the effect of varying ϵ in the presence of both pre-erythrocytic and erythrocytic vaccines. ϵ is varied from $0.4 - 0.8$ in steps of 0.2. θ_1 and θ_2 are as shown in Table 1 and $\gamma = 0.4$. The graphs labeled z_2 show the effect of varying γ in the presence of erythrocytic vaccine and transmission blocking vaccine. γ is varied from $0.4 - 0.8$ in steps of 0.2 and $\epsilon = 0.4$. The graphs show that when increasing the efficacy of transmission blocking vaccine in the presence of the other two subunits, it takes a longer time for the population of the infectious humans to be cleared than the time taken when increasing pre-erythrocytic vaccine with the other two subunits. This shows that a vaccine combination with a high efficacy pre-erythrocytic vaccine subunit can be used to clear an infection within a shorter time than a vaccine combination with a high efficacy transmission blocking vaccine. This result can also be deduced from the formulas of $R_{\phi_{hm}}(\gamma, \theta_{1,2}, \epsilon)$ and $R_{\phi_{mh}}(\gamma, \theta_{1,2}, \epsilon)$, where it can be noted that increasing ϵ reduces the expected number of mosquitoes which become infectious and increasing γ reduces the expected number of vaccinated humans who become infectious. This is always true if the erythrocytic vaccine reduces the infectious period of the vaccinated human as compared to the infectious period of a non vaccinated human.

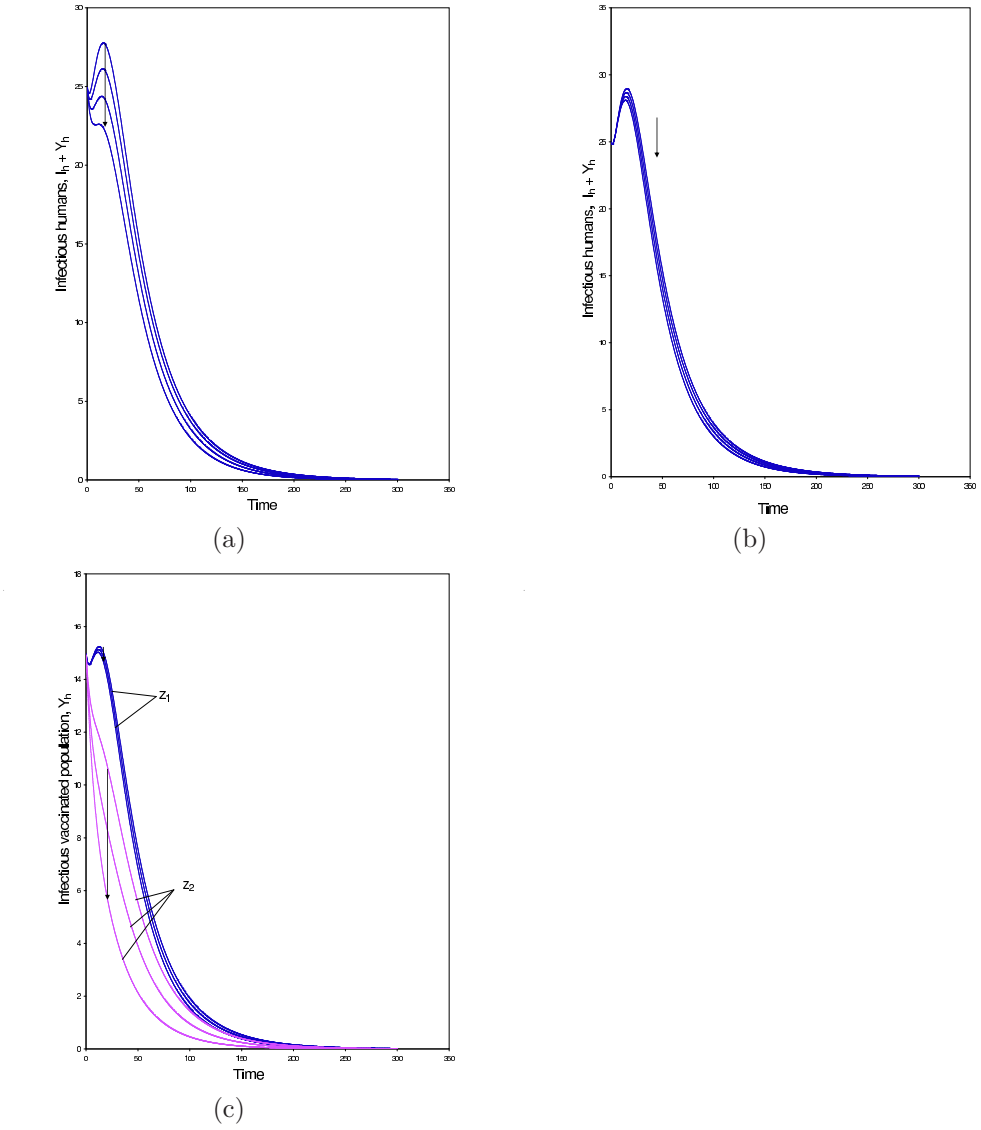

Figure 3: Graphs that show the behaviour infectious humans of model (4.1). In (a), γ is varied from $0.2-0.8$ in steps of 0.2 and is increasing in the direction of the arrow. $\epsilon = 0.0$, $\theta_1 = 1.0$ and $\theta_2 = 0.0$. (b) The graphs are obtained by varying ϵ in steps of 0.2 from $0.2 - 0.8$, and is increasing in the direction of the arrow. $\gamma = 0.0$, $\theta_1 = 1.0$ and $\theta_2 = 0.0$. (c) The graphs labelled z_1 are obtained by varying ϵ and those labeled z_2 are obtained by varying γ. These two parameters are varied from $0.4-0.8$ in steps of 0.2. The direction of the arrows shows direction of increase.

7. Summary and concluding remarks

In this paper we have presented and analysed two mathematical models for assessing the effects of pre-erythrocytic vaccination and the effects of a combination of the subunits of a malaria vaccine which are pre-erythrocytic, erythrocytic and transmission blocking vaccines in limiting the spread of malaria in a given community. We started off by briefly reviewing some literature on previous work and some insight into possible malaria vaccines and their effects. Though mathematical models in malaria are well established, the few studies that have been done were to assess the effects of each subunit on its own and not combining two or three subunits as was done in this paper. Our model is suitable for describing malaria disease transmission in nonendemic areas or populations visiting endemic areas, that is, populations without acquired immunity.

We formulated and analysed a mathematical model for monitoring the dynamics of susceptibles, vaccinated and infected classes in which only pre-erythrocytic vaccine is used as a control strategy. This model is then qualitatively analysed and conditions sufficient for existence and stability of its equilibria are derived. There is a threshold parameter $R_\phi(\gamma)$ and the disease can persist if $R_\phi(\gamma)$ exceeds one. The disease free equilibrium state always exists and is globally stable if $R_\phi(\gamma) < 1$. For $R_\phi(\gamma) > 1$, our analysis shows that there exists an endemic equilibrium.

The impact of a combination of pre-erythrocytic, erythrocytic and transmission blocking vaccines is then studied by extending the pre-erythrocytic vaccine model to incorporate the other two vaccines. We show using numerical simulations, using a reasonable set of parameters the general behaviour of the two models. The analysis shows that the introduction of a vaccine with all three subunits brings the disease to eradication levels if pre-erythrocytic vaccine fails.

General analysis of the model with all three subunits shows that the effects of combining the three subunits shows that a vaccination coverage that exceeds $\phi^c_{\gamma,\theta_{1,2},\epsilon}$ is likely to eradicate the disease. We also show that the number of secondary infections can be reduced if the ratio of the infectious period of the vaccinated human to the infectious period of a non vaccinated human is less than the inverse of the product of $(1-\gamma)$ and $(1-\epsilon)$ which are the factors by which transmission rate is reduced from mosquitoes and from humans respectively. We also deduce that regardless of the efficacy of pre-erythrocytic and erythrocytic vaccines, an erythrocytic vaccine which reduces the period of infectiousness will always reduce the number of secondary infections.

Our analysis on the effects of administering the vaccine subunits in combinations shows that using two or three combinations has a much higher percentage decrease in the reproductive number than when using only one vaccine. We also deduce that combining vaccines of very high efficacies and using one vaccine of high efficacy results in a small difference in the respective reproductive numbers as compared to combining two vaccines of low efficacy and one vaccine of low efficacy. This implies that given limited resources a vaccine of high efficacy can be used alone but when the efficacy is very low then combination vaccine is needed to greatly reduce number of secondary infections.

We also deduce that for non endemic areas, travellers and possibly the military, pre-erythrocytic vaccine with erythrocytic vaccine should be of interest. The inclusion of a transmission blocking would also prolong the useful life of vaccines against other stages by preventing the spread of parasites that become resistant to these vaccines.

Many factors are involved in the spread of malaria. One of which is the ratio of mosquitoes to humans. This ratio is one of the factors that determines, among other factors, like proximity of households to larval habitats [58], the biting rate of mosquitoes. The distribution of mosquitoes is an important factor in determining prevalence of *Plasmodium* infections in humans [43]. As there are many parameters involved in malaria transmission we note that this work was constrained by lack of reliable data or unavailability of data. As a result we used estimated values of some parameters. Our numerical results are therefore based on these parameters. Models considered in this study do not incorporate other important features in malaria transmission such as partial immunity and seasonal effects. A natural extension of this work is to include these features and to find reliable data.

Several candidate malaria vaccines are currently under development in different parts of the world. This study on vaccination effects in malaria endemicity provides useful tools for assessing the effectiveness and the impact different vaccines and a combination of them have on the affected population. It also highlights important parameters in assessing the usefulness of these vaccines. Vaccination can be a major step in protecting humans from suffering and death from malaria. Even though vaccination can be implemented, personal protection of the humans from mosquito bites should not be neglected. Compliance on malaria chemoprophylaxis should also be adopted.

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Appendix A

Lemma A.1. *The solutions* $(S_h(t), V_h(t), I_h(t), N_h(t), S_m(t), I_m(t), N_m(t))$ *of* (2.5) *remain positive for all time* $t > 0$. *Furthermore,*

$$\limsup_{t\to+\infty} N_h(t) \leq \frac{\Lambda_h}{\mu_h}, \qquad \limsup_{t\to+\infty} N_m(t) \leq \frac{\Lambda_m}{\mu_m}.$$

Proof. From the first equation of model system (2.5), we have

$$\frac{dS_h(t)}{dt} \geq -\left(\mu_h + \zeta_h \frac{I_m(t)}{N_h(t)} + \phi\right) S_h(t).$$

By direct integration we obtain

$$S_h(t) \geq \varphi_1(0) \exp\left\{ - \int_0^t \left(\mu_h + \phi + \zeta_h \frac{I_m(q)}{N_h(q)} \right) dq \right\} > 0$$

as long as $\int_0^t \frac{I_m(q)}{N_h(q)} dq < +\infty$. Clearly $S_h(t) > 0$ for all $t > 0$.
From the second equation of (2.5) we have

$$\frac{dV_h(t)}{dt} \geq -\left(\mu_h + \zeta_h(1-\gamma) I_m(t)/N_h(t) + \sigma\right) V_h(t).$$

On integration we get

$$V_h(t) \geq \varphi_2(0) \exp\left\{ - \int_0^t \left(\mu_h + \zeta_h(1-\gamma) I_m(q)/N_h(q) + \sigma\right) dq \right\} > 0.$$

We repeat the same argument on all the other equations of (2.5) and show that $I_h(t) > 0$, $N_h(t) > 0$, $S_m(t) > 0$, $I_m(t) > 0$ and $N_m(t) > 0$ for all time $t > 0$.

For the second part of the proof, we have for the total human and mosquito population

$$\frac{dN_h(t)}{dt} \leq \Lambda_h - \mu_h N_h(t), \quad \frac{dN_m(t)}{dt} \leq \Lambda_m - \mu_m N_m(t),$$

which implies that $S_h(t), V_h(t), I_h(t), S_m(t), I_m(t)$ is uniformly bounded. All solutions starting in Ω_+ approach, enter or stay in Ω. This completes the proof. □

Appendix B

Lemma B.2. *For the system* (2.5)*, the disease free equilibrium is globally asymptotically stable if* $R_\phi(\gamma) < 1$.

Proof. From the equation of $I_h(t)$ from system of equations in (3.6), we use the substitution $x = t - (s - \tau_h)$, take the lim sup of both sides of the equation and apply the fact that $\limsup \int f \leq \int \limsup f$ (see [40], Lemma 2) to get

$$\begin{aligned}
&\limsup_{t\to\infty} I_h(t) \\
&= \limsup_{t\to\infty} \int_0^\infty \zeta_h I_m(t-x) \frac{S_h(t-x) + (1-\gamma) V_h(t-x)}{N_h(t-x)} e^{-\mu_h \tau_h} e^{-\psi_0 x} dx, \\
&\leq \int_0^\infty \limsup_{t\to\infty} \frac{S_h(t-x) + (1-\gamma) V_h(t-x)}{N_h(t-x)} \zeta_h e^{-\mu_h \tau_h} \limsup_{t\to\infty} I_m(t-x) e^{-\psi_0 x} dx, \\
&\leq \limsup_{t\to\infty} \frac{S_h(t) + (1-\gamma) V_h(t)}{N_h(t)} \zeta_h e^{-\mu_h \tau_h} \limsup_{t\to\infty} I_m(t) \int_0^\infty e^{-\psi_0 x} dx, \\
&= \frac{\zeta_h e^{-\mu_h \tau_h}}{\psi_0} \frac{\mu_h + \sigma + (1-\gamma)\phi}{\mu_h + \sigma + \phi} \limsup_{t\to\infty} I_m(t), \qquad \text{(B.1)}
\end{aligned}$$

Using the same approach to the equation of $I_m(t)$ in (3.6), and using the substitution $x = t - (s - \tau_m)$ in the equation of $I_m(t)$ and taking lim sup of both sides we get

$$\limsup_{t\to\infty} I_m(t) \leq \frac{\zeta_m \Lambda_m \mu_h e^{-(\mu_m+\alpha_m)\tau_m}}{(\mu_m+\alpha_m)^2 \Lambda_h} \limsup_{t\to\infty} I_h(t). \tag{B.2}$$

Substituting $(B.2)$ into $(B.1)$, we obtain

$$\limsup_{t\to\infty} I_h \leq R_0 \frac{\mu_h+\sigma+(1-\gamma)\phi}{\mu_h+\sigma+\phi} \limsup_{t\to\infty} I_h(t) = R_\phi(\gamma) \limsup_{t\to\infty} I_h(t).$$

If $R_\phi(\gamma) < 1$, we have a strict inequality (and contradiction)

$$\limsup_{t\to\infty} I_h(t) < \limsup_{t\to\infty} I_h(t)$$

unless $\limsup_{t\to\infty} I_h(t) = 0$. If $\limsup_{t\to\infty} I_h(t) = 0$ it follows $\limsup_{t\to\infty} I_m(t) = 0$. Thus the disease free equilibrium is globally asymptotically stable if $R_\phi(\gamma) < 1$. □

Appendix C

$$\begin{aligned}
B_4 &= -\alpha_h^2 \mu_h \mu_m^2 \psi_0 (\mu_h \zeta_m - \alpha_h \mu_m)^2 (\mu_h + \sigma + \phi),\\
B_3 &= \alpha_h (\mu_h \zeta_m - \alpha_h \mu_m) \mu_h \mu_m \psi_0 ((1-\gamma)\psi_6 + 2\Lambda_h \mu_m (\mu_h + \sigma + \phi)(\mu_h \zeta_m - 2\alpha_h \mu_m))\\
&\quad + \alpha_h (\mu_h \zeta_m - \alpha_h \mu_m) \mu_m \psi_6 (\psi_0 - r_h e^{-\mu_h \tau_h}),\\
B_2 &= \mu_m \Lambda_h \psi_6 e^{-\mu_h \tau_h} (\mu_h + \sigma + (1-\gamma)\phi)(r_h(\mu_h \zeta_m - 2\alpha_h \mu_m) - \alpha_h(\mu_h \zeta_m - \alpha_h \mu_m))\\
&\quad + \mu_h \mu_m^2 \Lambda_h^2 \psi_0 (\alpha_h (\mu_h \zeta_m - \alpha_h \mu_m)(4\mu_h \zeta_m - 5\alpha_h \mu_m) - (\mu_h \zeta_m - \alpha_h \mu_m)^2),\\
B_1 &= \mu_m \Lambda_h^2 \psi_6 (\mu_h + \sigma + (1-\gamma)\phi)((\mu_m(r_h - \alpha_h) + (\mu_h \zeta_m - \alpha_h \mu_m))e^{-\mu_h \tau_h} - \psi_0)\\
&\quad + 2\mu_h \mu_m^3 \Lambda^3 \psi_0 (\mu_h + \sigma + \phi)(2\alpha_h \mu_m - \mu_h \zeta_m)\\
&\quad + \mu_h \Lambda_h (1-\gamma)\psi_6 (\psi_6/\mu_h - \mu_m^2 \Lambda_h \psi_0),\\
B_0 &= \mu_h \mu_m^4 \Lambda_h^4 \psi_0 (\mu_h + \sigma + \phi)(R_\phi(\gamma) - 1).
\end{aligned}$$

Appendix D

$$
\begin{aligned}
A_4 &= (\gamma-1)^2\kappa_8\mu_m\zeta_h^2(\kappa_8\mu_m-\kappa_2\zeta_h(\varphi_0\mu_m+\mu_h\zeta_m e^{-\mu_h\tau_h})\\
&\quad +\varphi_0\kappa_2^2(\varphi_0\mu_m+\mu_h\zeta_m e^{-\mu_h\tau_h})),\\
A_3 &= (2\mu_m(\varphi_0\kappa_9+\varphi_0\kappa_2\kappa_4\zeta_h-(\mu_h+\sigma)\kappa_8)+\kappa_7\mu_h\zeta_h\zeta_m e^{-\mu_h\tau_h})\times\\
&\quad (\kappa_8-\varphi_0\kappa_2\zeta_h)(\gamma-1)\Lambda_h\mu_m\zeta_h+(\gamma-1)^2\kappa_2\kappa_6\zeta_h^2\zeta_m(\kappa_1-\varphi_0\kappa_2\zeta_h)\\
&\quad +(\gamma-1)\zeta_h^2\zeta_m\Lambda_h\mu_h\mu_m e^{-\mu_h\tau_h}((\kappa_7\kappa_6-\varphi_0\kappa_2\kappa_9)+(\mu_h+\sigma)\kappa_2(2\kappa_8-\varphi_0\kappa_2\zeta_h)),\\
A_2 &= \varphi_0\Lambda_h\mu_m(\varphi_0\kappa_9\mu_m+\kappa_2\zeta_h^2(\varphi_0\kappa_4^2\mu_m-(\gamma-1)\kappa_0\mu_h^2e^{-\mu_h\tau_h}))\\
&\quad +\Lambda_h(\mu_h+\sigma)\kappa_8\mu_m^2((\mu_h+\sigma)\kappa_8-2\varphi_0\kappa_9)\\
&\quad -(\gamma-1)\kappa_1\kappa_6\zeta_h\zeta_m(\kappa_7+2(\mu_h+\sigma)\kappa_2)\\
&\quad +\varphi_0(\gamma-1)\kappa_2\kappa_6\zeta_h\zeta_m(\kappa_2\kappa_4\zeta_h+\kappa_3)+2\varphi_0\kappa_2\kappa_4\Lambda_h\mu_m^2\zeta_h(\varphi_0\kappa_9-(\mu_h+\sigma)\kappa_8)\\
&\quad +(\kappa_7+(\mu_h+\sigma)\kappa_2)(\varphi_0\kappa_2\zeta_h^2\zeta_m((\gamma-1)\kappa_6+\Lambda_h\kappa_4\mu_h\mu_m e^{-\mu_h\tau_h})\\
&\quad +(\varphi_0\kappa_9-(\mu_h+\sigma)\kappa_8)\varphi_0\kappa_2\kappa_6\Lambda_h\mu_h\mu_m\zeta_h e^{-\mu_h\tau_h}),\\
A_1 &= \kappa_6\zeta_m(\kappa_7+(\mu_h+\sigma)\kappa_2)((\mu_h+\sigma)\kappa_1-\varphi_0\kappa_2\kappa_4\zeta_h-\varphi_0\kappa_3)+\varphi_0\kappa_0\kappa_2^2\mu_h\zeta_h\zeta_m\times\\
&\quad ((\mu_h+\sigma)\Lambda_h\mu_h\mu_m e^{-\mu_h\tau_h}+(\gamma-1)\kappa_8)\\
&\quad +\varphi_0\kappa_0\kappa_2\Lambda_h\mu_h\mu_m(2\mu_m(\varphi_0\kappa_9-(\mu_h+\sigma)\kappa_8)+\zeta_h(2\varphi_0\kappa_2\kappa_4\mu_m+\kappa_7\mu_h e^{-\mu_h\tau_h})),\\
A_0 &= (\varphi_0\kappa_0\kappa_2\mu_h\mu_m)^2\Lambda_h(1-R_\phi(\gamma,\theta_{1,2},\epsilon)),
\end{aligned}
$$

where

$$
\begin{aligned}
\kappa_0 &= \mu_h+\sigma+\phi,\\
\kappa_1 &= \kappa_2 r_h\zeta_h e^{-\mu_h\tau_h},\\
\kappa_2 &= \theta_1 r_h+(1-\theta_2)\alpha_h+\mu_h,\\
\kappa_3 &= \phi(\gamma-1)\theta_1 r_h\zeta_h e^{-\mu_h\tau_h},\\
\kappa_4 &= \mu_h(2-\gamma)+\sigma+(1-\gamma)\phi,\\
\kappa_5 &= \theta_1 r_h+\alpha_h(1-\theta_2),\\
\kappa_6 &= \Lambda_m\mu_h^2\zeta_h e^{-\mu_h\tau_h}e^{-\mu_m\tau_m},\\
\kappa_7 &= \varphi_0(\epsilon-1)(\gamma-1)\phi,\\
\kappa_8 &= \kappa_2(r_h+\alpha_h)\zeta_h e^{-\mu_h\tau_h},\\
\kappa_9 &= \phi(\gamma-1)\kappa_5\zeta_h e^{-\mu_h\tau_h},\\
\kappa_{10} &= \varphi_0\Lambda_h\kappa_2\zeta_2 e^{-\mu_h\tau_h}.
\end{aligned}
$$

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