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Optimal control analysis of a malaria disease transmission model that includes treatment and vaccination with waning immunity

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ABSTRACT

We derive and analyse a deterministic model for the transmission of malaria disease with mass action form of infection. Firstly, we calculate the basic reproduction number, R_0, and investigate the existence and stability of equilibria. The system is found to exhibit backward bifurcation. The implication of this occurrence is that the classical epidemiological requirement for effective eradication of malaria, $R_0 < 1$, is no longer sufficient, even though necessary. Secondly, by using optimal control theory we derive the conditions under which it is optimal to eradicate the disease and examine the impact of a possible combined vaccination and treatment strategy on the disease transmission. When eradication is impossible, we derive the necessary conditions for optimal control of the disease using Pontryagin's Maximum Principle. The results obtained from the numerical simulations of the model show that a possible vaccination combined with effective treatment regime would reduce the spread of the disease appreciably.

1. Introduction

The ability of malaria to still increase mortality and morbidity continues to inflict major public health and socioeconomic burdens in developing countries (Chiyaka et al., 2008). Around 200 million persons are at constant risk of infection globally (Marsh, 1998), with some parts of Africa being the worst affected, where most victims are children and women. World Health Organization (WHO) revealed that malaria kills at least one million people annually in sub-Saharan Africa (WHO, 2003) with the potential to significantly increase in response to climate change and Human Immunodeficiency Virus (HIV) (Lindsay and Martens, 1998). Malaria is transmitted to humans when they are bitten by an infected female Anopheles mosquito. Few days after the bites, clinical symptoms such as pain, fever, sweats develop. Mosquitoes acquire infection from infected human after a blood meal. Although malaria being a life-threatening disease, it is preventable and curable when the infected individual seek treatment early. Existing methods for controlling the disease include insecticides, treated bednets, drugs for disease prevention and treatment. These interventions led to a substantial reduction in morbidity and mortality in many areas. However, malaria still persists as a major public health problem and the disease burden may rise again. This is due to the costs of interventions, availability of treatment and its adverse effects and also to the increasing rate of parasite drug-resistance and mosquito insecticide-resistance. All these call for the development of an effective and cost-effective malaria vaccine. Many vaccine candidates such as SPf66, CSP, NYVAC-Pf7, [NANP]19-5.1 and RTS,S were developed and have undergone field trials. RTS,S is the most clinically advanced vaccine candidate, used in combination with different adjuvant systems, this vaccine provides protection for young children and infants against infection and clinical disease caused by *Plasmodium falciparum* in malaria-endemic areas (Alonso et al., 2004, 2005; see also Sacarlal et al., 2008, 2009; Aponte et al., 2007; Bejon et al., 2008; Abdulla et al., 2008; Polhemus et al., 2009; Owusu-Agyei et al., 2009; Bojang et al., 2001, 2009). In 2009, a Phase III trial on infants and young children was carried out in seven African countries to confirm its efficacy and safety. This is expected to be submitted to regulatory authorities in 2012 and hence could possibly be available for targeted use among young children between 5 and 17 months old by 2013.

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Mathematical modelling is useful in analysing the diseases dynamics (Mushayabasa et al., 2011), outcomes and cost-effectiveness of some interventions. A number of mathematical models have been proposed to study the transmission dynamics of malaria. Some of these studies focused on eradication of the disease, by targeting mosquitoes as a strategy for controlling the disease (Ashrafi and Gumel, 2008; Chiyaka et al., 2008; Mukandavire et al., 2009; Nakul et al., 2006), others studied the effect of vaccination on the dynamics of the disease (Vásquez Pinzón et al., 2003; Maire et al., 2006). Besides, studies have also confirmed that eradicating the disease by eliminating mosquitoes (as a control strategy) has been an unsuccessful approach (Sachs, 2002); hence, there is need to consider optimal control in the mathematical modelling of malaria to curtail the spread of the disease rather than eradication.

There have been applications of optimal control methods to epidemiological models, but most of these studies focused on HIV and TB diseases dynamics. The authors in Adams et al. (2004), Denis et al. (1997), Karrakchou et al. (2006), and Kirschner et al. (1997) studied the optimal chemotherapy treatment in controlling the virus reproduction in an HIV patient. In Goldman and Lightwood (2002), Gupta and Rink (1973), Wickwire (1975), and Sethi (1978), optimal control was used to minimize the costs of both diseases and treatment. In Cesar (2006) and Sethi and Staats (1978) the authors used optimal control to investigate the best strategy for educational campaigns during the outbreak of an epidemic and at the same time minimizing the number of infective humans. The authors in Kar and Batabyal (2011) also used Optimal control to study a nonlinear mathematical SIR epidemic model with a vaccination program. Other applications of optimal control include modelling of Leukemia (Ainseba and Benosman, in press; Nanda et al., 2007).

Very little has been done in the area of applying optimal control theory to study and analyse the dynamics of malaria. Recently, optimal control was applied to study the impact of chemo-therapy on malaria disease with infective immigrants (Makinde and Okosun, 2011), while Blayneh et al. (2009) studied the effects of prevention and treatment on malaria, using an SEIR model. It was also used in a malaria model with genetically modified mosquitoes but without human population (Rafikov et al., 2009).

In this paper we consider an SEIR malaria model that includes both human and vector populations and incorporates treatment and vaccination measures. The aim is to gain some insights into the best intervention for minimizing the transmission of malaria disease within the population and to explore the impacts of various intervention scenarios, namely, vaccination and treatment. We analyse the stability and bifurcation of the model, then we incorporate into the model appropriate cost functions in order to study and determine the possible impacts of these strategies in controlling the disease. We further carried out detailed qualitative optimal control analysis of the resulting model and derive the conditions under which it is optimal to eradicate rather than control the disease. In the case when eradication is impossible, we give the necessary conditions for optimal control of the disease using Pontryagin's Maximum Principle, in order to determine optimal strategies for controlling the spread of the disease.

The organization of the paper is as follows, in Section 2, we derive a model consisting of ordinary differential equations that describes the interactions between humans and mosquitoes populations and the underlying assumptions. Section 3 is devoted to the mathematical analysis of the malaria model. In Section 4, we derive the conditions under which it will be optimal to eradicate rather than to control the disease. Furthermore, we use Pontryagin's Maximum Principle to find the necessary conditions for the optimal control of the disease when eradication is impossible. In Section 5 the simulation results are shown to illustrate the effect of vaccination and treatment. Our conclusions are discussed in Section 6.

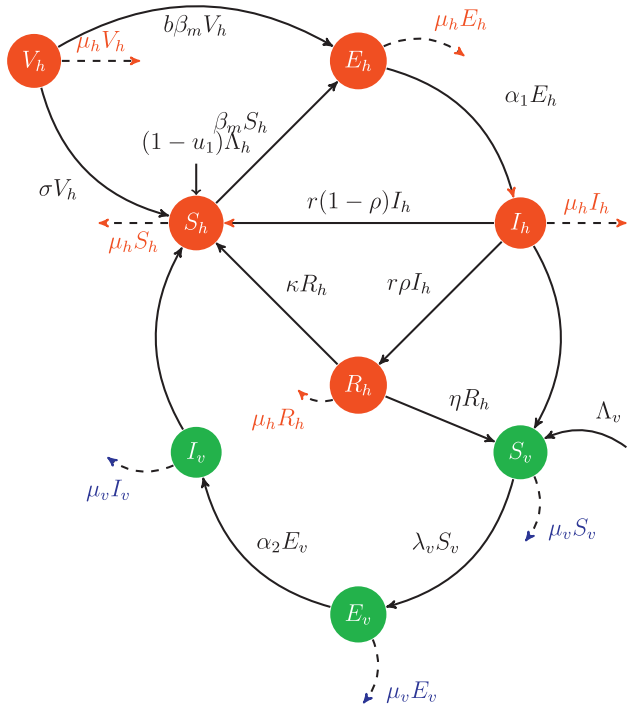

Fig. 1. Flow diagram for malaria disease transmission. For symbols, see text.

2. Model Formulation

The model sub-divides the total human population, denoted by N_h, into sub-populations of susceptible individuals (S_h), those exposed to malaria parasite (E_h), individuals with malaria symptoms (I_h), recovered human (R_h) and vaccinated individuals V_h. So that $N_h = S_h + E_h + I_h + R_h + V_h$.

The total vector (mosquito) population, denoted by N_v, is subdivided into susceptible mosquitoes (S_v), mosquitoes exposed to the malaria parasite (E_v) and infectious mosquitoes (I_v). Thus, $N_v(t) = S_v + E_v + I_v$ (Fig. 1).

The model is given by the following system of ordinary differential equations:

$$\begin{aligned}
\frac{dS}{h} &= (1-u_1(t))\Lambda_h + \kappa R_h - \beta_m S_h + \sigma V_h - \mu_h S_h \\
&\quad + (\theta + \tau u_2(t))(1-\rho)I_h \\
\frac{dE}{h} &= \beta_m S_h + b\beta_m V_h - (\alpha_1 + \mu_h)E_h \\
\frac{dI}{h} &= \alpha_1 E_h - (\theta + \tau u_2(t) + \psi + \mu_h)I_h \\
\frac{dR}{h} &= (\theta + \tau u_2(t))\rho I_h - (\kappa + \mu_h)R_h \\
\frac{dV}{h} &= u_1(t)\Lambda_h - (\mu_h + \sigma)V_h - b\beta_m V_h \\
\frac{dS}{v} &= \Lambda_v - \lambda_v S_v - \mu_v S_v \\
\frac{dE}{v} &= \lambda_v S_v - (\alpha_2 + \mu_v)E_v \\
\frac{dI}{v} &= \alpha_2 E_v - \mu_v I_v.
\end{aligned} \tag{1}$$

Susceptible individuals are recruited at a rate Λ_h, where a proportion $u_1 \in [0, 1]$ of them is successfully vaccinated at birth. Susceptible individuals acquire malaria through contact with infectious mosquitoes at a rate β_m. Due to waning effect, some vaccinated individuals will move to the exposed class at a rate

$b\beta_m$, where $(1-b)\in[0,1]$ is the efficacy of vaccine or they loose their immunity completely and move to the susceptible class at a rate σ. Exposed individuals move to the infectious class at a rate α_1. Individuals with malaria are treated under control, at a rate $\tau u_2(t)$, θ are individuals who recovered spontaneously. A proportion of them, ρ, moves to the recovered class with temporary immunity and the other proportion moves to the susceptible class. Non treated infected individuals die at a rate ψ. Recovered individual loose immunity at a rate κ and become susceptible again. The term μ_h is the natural death rate.

Susceptible mosquitoes (S_v) are generated at a rate Λ_v and acquire malaria through contacts with infected humans at a rate λ_v. Mosquitoes are assumed to suffer death due to natural causes and various control measures (insecticides, destruction of mosquitoes breeding sites, etc.) at a rate μ_v. Newly infected mosquitoes move to the exposed class (E_v), and later progress to the class of symptomatic mosquitoes (I_v) at a rate α_2. We also consider two forms of infection for mosquitoes.

The interactions between humans and mosquitoes have been modeled using the mass action law (see Ashrafi and Gumel, 2008; Dietz et al., 1974; Yang, 2000, 2001; Isao et al., 2004; Li, 2008; Koella and Anita, 2003; Blayneh et al., 2009; Makinde and Okosun, 2011) and standard incidence law (see Gumel and Song, 2008; Chiyaka et al., 2008, 2009; Nakul et al., 2006, 2008; Garba et al., 2008; Mukandavire et al., 2009; Tumwiine et al., 2008).

Here $\beta_m=\beta\epsilon\phi I_v$ and $\lambda_v=\lambda\epsilon\phi(\eta R_h+I_h)$, where β is the transmission probability per bite, ϵ is the per capita biting rate of mosquitoes and ϕ is the contact rate of vector per human per unit time. The terms λ and η are the probability for a vector to get infected by an infectious human and modification parameter, respectively.

3. Mathematical Analysis of the Malaria Model

3.1. Positivity and Boundedness of Solutions

For the malaria transmission model (1) to be epidemiologically meaningful, it is important to prove that all solutions with non-negative initial data will remain non-negative for all time.

Theorem 1. *If $S_h(0)$, $E_h(0)$, $I_h(0)$, $R_h(0)$, $V_h(0)$, $S_v(0)$, $E_v(0)$, $I_v(0)$ are non negative, then so are $S_h(t)$, $E_h(t)$, $I_h(t)$, $R_h(t)$, $V_h(t)$, $S_v(t)$, $E_v(t)$ and $I_v(t)$ for all time $t>0$. Moreover,*

$$\limsup_{t\to\infty} N_h(t)\le\frac{\Lambda}{h}\quad\text{and}\quad\limsup_{t\to\infty} N_v(t)\le\frac{\Lambda}{v}. \tag{2}$$

Furthermore, if $N_h(0)\le\Lambda_h/\mu_h$, then $N_h(t)\le\Lambda_h/\mu_h$, and if $N_v(0)\le\Lambda_v/\mu_v$, then $N_v(t)\le\Lambda_v/\mu_v$.

The proof is omitted for simplicity. The feasible region for system (1) is therefore given by

$$\mathcal{D}=h\mathcal{D}\times v\mathcal{D}\subset\mathbb{R}^5_+\times\mathbb{R}^3_+ \tag{3}$$

where

$$h\mathcal{D}=\left\{(S_h,E_h,I_h,R_h,V_h)\in\mathbb{R}^5_+ : S_h+E_h+I_h+R_h+V_h\le\frac{\Lambda}{h}\right\}, \tag{4}$$

and

$$v\mathcal{D}=\left\{(S_v,E_v,I_v)\in\mathbb{R}^3_+ : S_v+E_v+I_v\le\frac{\Lambda}{v}\right\}. \tag{5}$$

$\mathcal{D}$ is positively invariant.

3.2. Steady States, Stability and Bifurcation

The disease-free equilibrium (DFE) of the malaria model (1) exists only when u_1 and u_2 are constant, it is given by

$$0\mathcal{E}=\left(\frac{\Lambda_h(\sigma+\mu_h-u_1\mu_h)}{(\sigma+\mu_h)\mu_h},0,0,0,\frac{u_1\Lambda_h}{\sigma+\mu_h},\frac{\Lambda}{v},0,0\right). \tag{6}$$

The basic reproduction number of the vaccination and treatment policy (1), R_0, is calculated by using the next generation matrix (Van den Driessche and Watmough, 2002). It is given by

$$R_0=\sqrt{\frac{\alpha_1\alpha_2\lambda\beta\Lambda_h\Lambda_v\epsilon^2\phi^2(\kappa+\eta r\rho+\mu_h)}{\mu_h\mu_v^2(\alpha_1+\mu_h)(\alpha_2+\mu_v)(\mu_h+\kappa)(\mu_h+\psi+r)}\left(1-\frac{u_1(1-b)\mu_h}{\mu_h+\sigma}\right)}, \tag{7}$$

where $r=\theta+u_2\tau$. It is clear that vaccination results into a reduction in R_0 by $u_1(1-b)\mu_h/\mu_h+\sigma$ which is the product of the coverage rate of vaccine, u_1, by the protective effect of the vaccine, $1-b$, divided by the odds ratio of loosing immunity $(\mu_h+\sigma)/\mu_h$.

The square root in (7) agrees with the findings of Lord et al. (1996) as the biological requirement in the human-vector host system for the parasite to pass through two types of individuals to complete its life cycle.

Further, using Theorem 2 in Van den Driessche and Watmough (2002), the following result is established.

Proposition 1. *The DFE of the vaccination model (1), is locally asymptotically stable if $R_0<1$, and unstable if $R_0>1$.*

Next we calculate the endemic steady states. Solving system (1) at the equilibrium we obtain $\beta^*_m=0$ (which corresponds to the DFE) or

$$A\beta^{*2}_m+B\beta^*_m+C=0 \tag{8}$$

where

$$\begin{aligned}A&=b[\alpha_1\Lambda_h\epsilon\lambda\phi(\kappa+\mu_h+\eta r\rho)+\mu_v(\alpha_1\\&\quad+\mu_h)(\mu_h+\kappa)(\mu_h+\psi)+r\mu_h\mu_v(\mu_h+\kappa+\alpha_1\rho)]\\B&=M(K-R_0^2)\\C&=\mu_h\mu_v(\mu_h+\sigma)(\alpha_1+\mu_h)(\mu_h+\kappa)(\mu_h+\psi+r)(1-R_0^2)\end{aligned} \tag{9}$$

where

$$\begin{aligned}M&=\mu_h\mu_v^2(\kappa+\mu_h)(r+\psi+\mu_h)(\alpha_1+\mu_h)(\alpha_2+\mu_v)\\K&=\frac{b\beta(\epsilon\phi)^2\alpha_1\alpha_2\Lambda_h\Lambda_v(\kappa+r\eta\rho+\mu_h)}{\mu_h\mu_v^2(\kappa+\mu_h)(r+\psi+\mu_h)(\alpha_1+\mu_h)(\alpha_2+\mu_v)}\end{aligned} \tag{10}$$

Note that the coefficient A is always positive and C (resp. B) is positive if R_0 is less than 1 (resp $\sqrt{K}$), respectively.

We have the following results.

Proposition 2.

1. *If $K\ge1$ then system (1) exhibits a transcritical bifurcation.*
2. *If $K<1$ then system (1) exhibits a backward bifurcation.*

Proof.

1. For $K\ge1$ we obtain when $R_0>1$ that $C<0$. This implies that system (1) has a unique endemic steady state. If $R_0\le1$, then $C\ge0$ and $B\ge0$. In this case system (1) has no endemic steady states.
2. For $K<1$ we discuss the following cases:
   i. $R_0>1$, in this case $C<0$ and system (1) has a unique endemic steady state.
   ii. $R_0\le\sqrt{K}$, in this case both B and C are positive implying that system (1) has no endemic steady states.
   iii. $\sqrt{K}<R_0<1$, here $C>0$ and $B<0$ while the discriminant of (8), $\Delta(R_0):=B^2-4AC$, can be either positive or negative. We have $\Delta(1)=B^2>0$ and $\Delta(\sqrt{K})=-4AC<0$, then there exists

R_{0c} such that $\Delta(R_{0c})=0$, $\Delta(R_0)<0$ for $\sqrt{K} < R_0 < R_{0c}$ and $\Delta(R_0)>0$ for $R_{0c}<R_0$. This together with the signs of B and C imply that system (1) has no endemic steady states when $\sqrt{K} < R_0 < R_{0c}$, one endemic steady state when $R_0 = R_{0c}$ and two endemic steady states when $R_{0c} < R_0 < 1$.

□

Backward bifurcation has been studied for malaria disease by many authors (Ashrafi and Gumel, 2008; Zhixing et al., 2008; Doedel et al., 2002; Augas et al., 2008). The occurrence of such bifurcation suggests that eradication of malaria is achievable only when the (constant) controls are greater than a critical value less than one. Moreover, for the disease not to become endemic again, treatment/vaccination controls must be maintained at this level for all time. This is because the system will ultimately re-stabilize at its previous endemic steady state when treatment/vaccination is stopped. In the next section we proceed to study the optimal control and analysis of the model with time dependent controls.

4. Application of Optimal Control to the Malaria Model

From the previous section we conclude that eradication of the disease may be too costly when constant controls are considered as it requires treatment/vaccination at higher levels for all time. For eradication to be achievable in a finite time, we need to consider time dependent controls.

When the control is time dependent the disease free equilibrium no longer exists. We use an approach similar to the one in Barrett and Hoel (2007) which consists in applying the Pontryagin's Maximum Principle to determine the conditions under which eradication of the disease can be achieved in finite time. The analysis will be restricted to the model with mass-action force of infection only.

We seek to minimize the number of infective individuals and the cost of applying treatment and vaccination controls. The objective functional that we consider is given by

$$J = \min_{u_1,u_2} \int_0^t e^{-qt}(wI_v + mI_h + nu_1^2 + cu_2^2)dt \tag{11}$$

subject to differential Eq. (1).

Here wI_v and mI_h are the cost associated with a number I_v of infected mosquitoes and I_h of infected individuals, q is the discounted rate, nu_1^2 is the cost of vaccinating and cu_2^2 the cost of treatment, while T is the time period of the intervention. In line with Adams et al. (2004), Denis et al. (1997), Joshi et al. (2006), and Karrakchou et al. (2006), we choose a linear function for the cost on infection, wI_v, mI_h, and quadratic forms for the cost on the controls nu_1^2 and cu_1^2. We also assume that the weight factor c associated with control u_2 is greater than the one (n) associated with control u_1. This assumption is based on the facts that the cost associated with u_1 includes the cost of vaccination, educational campaign for public acceptance and administration, while the cost associated with u_2 will include that of antimalarial drugs, surveillance, drug management, clinical tests and hospitalization.

We seek an optimal control $u_1^\sharp, u_2^\sharp$ such that

$$J(u_1^\sharp, u_2^\sharp) = \min_{u_1,u_2\in\mathcal{U}} J(u_1, u_2) \tag{12}$$

where $\mathcal{U} = \{u : u \text{ismeasurableand} 0 \le u(t) \le 1 \text{for} t \in [0, t_f]\}$ is the control set.

The necessary conditions that an optimal control must satisfy come from the Pontryagin's Maximum Principle (Pontryagin et al., 1962). This principle converts (1)–(12) into a problem of minimizing pointwise a Hamiltonian H, with respect to (u_1, u_2)

$$\begin{aligned} H = {} & wI_v + mI_h + nu_1^2 + cu_2^2 + \lambda_{S_h}\{(1-u_1)\Lambda_h + \kappa R_h - \beta_1\epsilon\phi I_v S_h \\ & + \sigma V_h - \mu_h S_h + (1-\rho)(\theta + u_2\tau)I_h\} + \lambda_{E_h}\{\epsilon\phi I_v(\beta S_h + b\beta V_h) \\ & - (\alpha_1 + \mu_h)E_h\} + \lambda_{I_h}\{\alpha_1 E_h - (\theta + u_2\tau + \psi + \mu_h)I_h\} \\ & + \lambda_{R_h}\{\rho(\theta + u_2\tau)I_h - (\kappa + \mu_h)R_h\} + \lambda_{V_h}\{u_1\Lambda_h - (\mu_h + \sigma \\ & + b\beta\epsilon\phi I_v)V_h\} + \lambda_{S_v}\{\Lambda_v - \lambda\epsilon\phi(\eta R_h + I_h)S_v - \mu_v S_v\} \\ & + \lambda_{E_v}\{\lambda\epsilon\phi(\eta R_h + I_h)S_v - (\alpha_2 + \mu_v)E_v, \} + \lambda_{I_v}\{\alpha_2 E_v - \mu_v I_v\} \end{aligned} \tag{13}$$

where

$\lambda_{S_h}, \lambda_{E_h}, \lambda_{I_h}, \lambda_{R_h}, \lambda_{V_h}, \lambda_{S_v}, \lambda_{E_v}$ and λ_{I_v} are the adjoint variables or co-state variables solutions of the following adjoint system:

$$\begin{aligned} -\frac{d\lambda_{S_h}}{dt} &= ((\beta\epsilon\phi I_v) + \mu_h)\lambda_{S_h} - (\beta\epsilon\phi I_v)\lambda_{E_h} \\ -\frac{d\lambda_{E_h}}{dt} &= (\mu_h + \alpha_1)\lambda_{E_h} - \alpha_1\lambda_{I_h} \\ -\frac{d\lambda_{I_h}}{dt} &= -m + (q + \theta + u_2\tau + \mu_h + \psi)\lambda_{I_h} - \rho(\theta + u_2\tau)\lambda_{R_h} \\ & \quad -(1-\rho)(\theta + u_2\tau)\lambda_{R_h} + (\lambda\epsilon\phi S_v)\lambda_{S_v} - (\lambda\epsilon\phi S_v)\lambda_{E_v} \\ -\frac{d\lambda_{R_h}}{dt} &= -\kappa\lambda_{S_h} + (\mu_h + \kappa)\lambda_{R_h} + \lambda\epsilon\phi\eta S_v(\lambda_{S_v} - \lambda_{E_v}) \\ -\frac{d\lambda_{V_h}}{dt} &= -\sigma\lambda_{S_h} + (\sigma + \mu_h)\lambda_{V_h} + b\beta\epsilon\phi I_v(\lambda_{V_h} - \lambda_{E_h}) \\ -\frac{d\lambda_{S_v}}{dt} &= (\lambda\epsilon\phi(\eta R_h + I_h) + \mu_v)\lambda_{S_v} - \lambda\epsilon\phi(\eta R_h + I_h)\lambda_{E_v} \\ -\frac{d\lambda_{E_v}}{dt} &= (\alpha_2 + \mu_v)\lambda_{E_v} - \alpha_2\lambda_{I_v} \\ -\frac{d\lambda_{I_v}}{dt} &= -w + (\beta\epsilon\phi S_h)\lambda_{S_h} - \lambda_{E_h}(\beta\epsilon\phi(S_h + bV_h) \\ & \quad +\mu_v\lambda_{I_v} + b\beta\epsilon\phi V_h\lambda_{V_h} \end{aligned} \tag{14}$$

satisfying the transversality conditions

$$\begin{aligned} &\lambda_{S_h}(t_f) = \lambda_{E_h}(t_f) = \lambda_{I_h}(t_f) = \lambda_{R_h}(t_f) = \lambda_{V_h}(t_f) = 0 \\ &\lambda_{S_v}(t_f) = \lambda_{E_v}(t_f) = \lambda_{I_v}(t_f) = 0 \end{aligned} \tag{15}$$

By applying Pontryagin's Maximum Principle (Pontryagin et al., 1962) and the existence result for the optimal control from Fleming and Rishel (1975), we obtain

Theorem 2. *The optimal control pair $(u_1^\sharp, u_2^\sharp)$ that minimizes J over $\mathcal{U}$ is given by*

$$\begin{aligned} u_1^\sharp &= \max\left\{0, \min\left(1, \frac{(\lambda_{S_h} - \lambda_{V_h})\Lambda_h}{2n}\right)\right\} \\ u_2^\sharp &= \max\left\{0, \min\left(1, \frac{\tau(\lambda_{I_h} - \rho\lambda_{R_h} - (1-\rho)\lambda_{S_h})I_h^*}{2c}\right)\right\} \end{aligned} \tag{16}$$

where $\lambda_{S_h}, \lambda_{E_h}, \lambda_{I_h}, \lambda_{R_h}, \lambda_{V_h}, \lambda_{S_v}, \lambda_{E_v}$ and λ_{I_v} are the solutions of (14) and (15).

Proof. From Corollary 4.1 (Fleming and Rishel, 1975), the existence of optimal control results from the convexity of the integrand of J with respect to u_1 and u_2, a priori boundedness of the state solutions, and the *Lipschitz* property of the state system with respect to the state variables. System (14) is obtained by differentiating the Hamiltonian function, evaluated at the optimal control. Furthermore, by equating to zero the derivatives of the Hamiltonian with respect to the controls, we obtain (see Lenhart and Workman, 2007) $u_1 = \tilde{u}_1 := (\lambda_{S_h} - \lambda_{V_h})\Lambda_h/2n$ and $u_2 = \tilde{u}_2 := \tau(\lambda_{I_h} - \rho\lambda_{R_h} -$

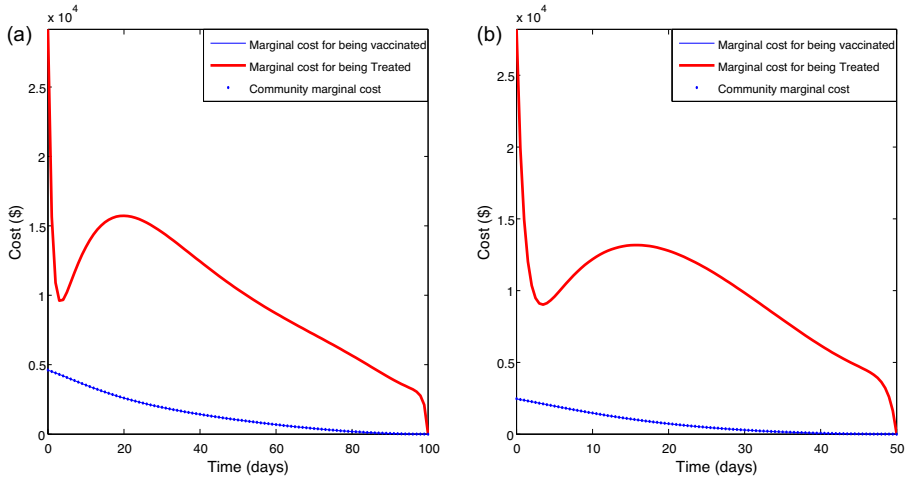

Fig. 2. Numerical simulations showing individual marginal cost for being vaccinated, individual marginal cost for being treated and the community cost, where $I_h = 20$ and the time durations are set to 100 and 50, the other parameter values are $\phi\epsilon = 0.1004$, $\mu_h = 0.00004$, $\mu_v = 0.1429$, $\alpha_1 = 100$, $\alpha_2 = 0.0981$, $\Lambda_h = 0.00099$, $\Lambda_v = 0.0089$, $\psi = 0.00013945392$, $\kappa = 0.7902$, $\rho = 0.023$, $\sigma = 0.005$, $\eta = 0.001$, $\theta = 0.005$, $r = 0.00656$.

$(1-\rho)\lambda_{S_h})I_h^*/2c$. By standard control arguments involving the bounds on the controls, we conclude

$$u_1^{\sharp} = \begin{cases} 0 & \text{if } \tilde{u}_1 \le 0 \\ \tilde{u}_1 & \text{if } 0 < \tilde{u}_1 < 1 \\ 1 & \text{if } \tilde{u}_1 \ge 1 \end{cases} \quad \text{and} \quad u_2^{\sharp} = \begin{cases} 0 & \text{if } \tilde{u}_2 \le 0 \\ \tilde{u}_2 & \text{if } 0 < \tilde{u}_2 < 1 \\ 1 & \text{if } \tilde{u}_2 \ge 1 \end{cases} \quad (17)$$

which leads to (16). Due to the a priori boundedness of the state and adjoint functions and the resulting Lipschitz structure of the ODE's, we obtain the uniqueness of the optimal control for small t_f. The uniqueness of the optimal control pair follows from the uniqueness of the optimality system, which consists of (1), (14), (15) and (16). □

There is a restriction on the length of time interval in order to guarantee the uniqueness of the optimality system. This is due to the opposite time orientations of the optimality system; the state problem has initial values and the adjoint problem has final values. This restriction is very common in control problems (see de Souza et al., 2000; Joshi, 2002; Kirschner et al., 1997; Lenhart and Bhat, 1992; Lenhart and Yong, 1997; Seierstad and Sydsaeter, 1987).

Next we discuss the numerical solutions of the optimality system and the corresponding optimal control pair, the parameter choices, and the interpretations from various cases.

5. Numerical Results

5.1. Optimal Eradication

Fig. 2 shows the individual marginal cost for being vaccinated, individual marginal cost for being treated and the community cost, when the initial number of infective humans $I_h = 20$. The individual's best strategy is to be vaccinated until time $t = 100$ days. The numerical also result shows that the control is sensitive to the final time, the shorter the period of control programme, the smaller the marginal cost of control.

Also, the control programme is found to be sensitive to the number of initial infective humans in the community, this is shown in Fig. 3.

In Fig. 4, we evaluate the shadow price at the start of malaria epidemic as a function of the numbers of vaccinated. Fig. 4(a) shows that the shadow price of susceptibles is less damaging compared to

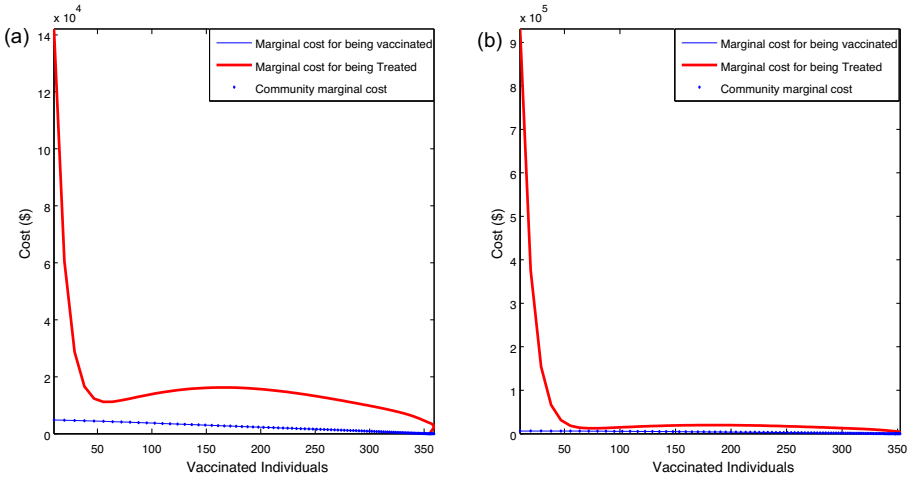

Fig. 3. Numerical simulations showing the model sensitivity to the initial number of infective individuals in the community, (a) ($I_h(0) = 100$) and (b) ($I_h(0) = 800$), the other parameter values are $\phi\epsilon = 0.1004$, $\mu_h = 0.00004$, $\mu_v = 0.1429$, $\alpha_1 = 100$, $\alpha_2 = 0.0981$, $\Lambda_h = 0.00099$, $\Lambda_v = 0.0089$, $\psi = 0.00013945392$, $\kappa = 0.7902$, $\rho = 0.023$, $\sigma = 0.005$, $\eta = 0.001$, $\theta = 0.005$, $r = 0.00656$.

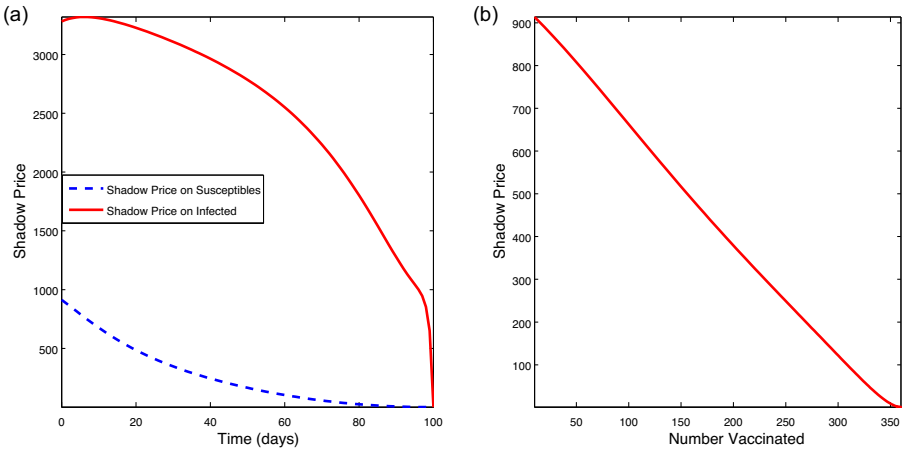

Fig. 4. Numerical simulations showing the shadow prices of susceptibles and infected using the following parameter values, $\phi\epsilon = 0.1004$, $\mu_h = 0.00004$, $\mu_v = 0.1429$, $\alpha_1 = 100$, $\alpha_2 = 0.0981$, $\Lambda_h = 0.00099$, $\Lambda_v = 0.0089$, $\psi = 0.00013945392$, $\kappa = 0.7902$, $\rho = 0.023$, $\sigma = 0.005$, $\eta = 0.001$, $\theta = 0.005$, $r = 0.00656$.

the shadow price of infected. This is, an indication that the shadow price of susceptibles has positive impact on the costs as the stock level of susceptibles decreases. Fig. 4(b) indicates that the shadow price on S_h tends to zero as the numbers of vaccinated susceptibles increases zero.

5.2. Optimal Control

In this section, we show the numerical simulations of the impacts of the optimal control strategies on malaria transmission. The optimal control is obtained by solving the optimality system that consists of the state system (1) and adjoint system (14). We use an iterative scheme to solve the optimality system. We first solve the state equations with a guess for the controls over the simulated time using fourth order Runge–Kutta scheme. Then, we use the current iterations solutions of the state equation to solve the adjoint equations by a backward fourth order Runge–Kutta scheme. Finally, we update the controls by using a convex combination of the previous controls and the value from the characterizations (16). This process is repeated and iterations are stopped if the values of the unknowns at the previous iterations are very close to the ones at the present iterations (Lenhart and Workman, 2007). We investigate and compare numerical results, with the following scenario (i) when vaccination u_1 was optimized while treatment u_2 is set to zero (ii) when treatment u_2 was optimized while we set u_1 to zero (iii) when both controls were optimized.

In Figs. 5–7, we use the same set of weight factors, $m = 150$, $n = 100$, $c = 500$ and initial state variables $S_h(0) = 700$, $E_h(0) = 220$, $I_h(0) = 100$, $R_h(0) = 60$, $V_h(0) = 10$, $S_v(0) = 3000$, $E_v(0) = 400$, $I_v(0) = 120$ to illustrate the effect of various optimal strategies on the spread of malaria. Other epidemiological and numerical parameters are presented in Table 1.

5.2.1. Vaccination

With this strategy, only the control u_1 on vaccination is used to optimize the objective function J, while the control u_2 on treatment is set to zero. Fig. 5 shows a significant difference in the number of infected humans I_h and infected mosquitoes I_v between the case with control and the case without. We observe in Fig. 5(a) and (b) that due to this strategy, the number of infected humans after an initial decrease, increases again and stabilize at $I_h = 37$ while the number of infected mosquitoes stabilizes at $I_v = 65$. The control profile is shown in Fig. 5(c), the control u_1 on vaccination is at the upper bound for 99 (days). This shows that an effective and optimal use of vaccination in the population without treatment will not be beneficial to the community on the long run in the control of the spread of the disease.

The results here suggest that, compared to the case without control, S_h is higher and I_h is far reduced when an optimal control strategy is adopted.

5.2.2. Treatment

With this strategy, we set the vaccination control, u_1, to zero and use only treatment control, u_2, to optimize the objective function J. In Fig. 6(a) and (b) show a significant difference in the infected humans I_h and infected mosquitoes I_v, respectively with control compared to the situation where there is no control. More specifically, we observe a decrease in I_h and I_v while an increase was observed in the uncontrolled cases. The control profile is shown

Table 1
Description of variables and parameters of the malaria model (1). The units of ϕ, μ_h, μ_v, α_1, α_2, Λ_h, Λ_v, ψ, κ, ρ, σ are day^{-1}, the other parameters are without units.

Parameter	Estimated value	Reference
ϕ	0.502	Blayneh et al. (2009)
ϵ	0.2	Blayneh et al. (2009)
$\epsilon\phi$	0.1004, 0.58	Blayneh et al. (2009), Mukandavire et al. (2009)
β	0.03, 0.8333	Blayneh et al. (2009), Mukandavire et al. (2009)
λ	0.0057233, 0.09	Mukandavire et al. (2009), Blayneh et al. (2009)
μ_h	0.00004, 0.0000457	Mukandavire et al. (2009), Yang (2001)
μ_v	0.1429, 0.0667	Mukandavire et al. (2009), Chiyaka et al. (2008)
α_1	1/17, 100	Blayneh et al. (2009), Mukandavire et al. (2009)
α_2	1/18, 0.0981	Nakul et al. (2006), Mukandavire et al. (2009)
Λ_h	0.00099, 100	Mukandavire et al. (2009), Blayneh et al. (2009)
Λ_v	0.0089, 1000	Mukandavire et al. (2009), Blayneh et al. (2009)
ψ	0.00013945392, 0.02	Mukandavire et al. (2009), Blayneh et al. (2009)
κ	0.7902, $1/(2\times 365)$	Nakul et al. (2006), Blayneh et al. (2009)
η	0.001	Assumed
ρ	0.023	Assumed
r	0.00656	Mukandavire et al. (2009)
τ	0.7	Assumed
θ	0.005	Chiyaka et al. (2008)
σ	0.005	Assumed

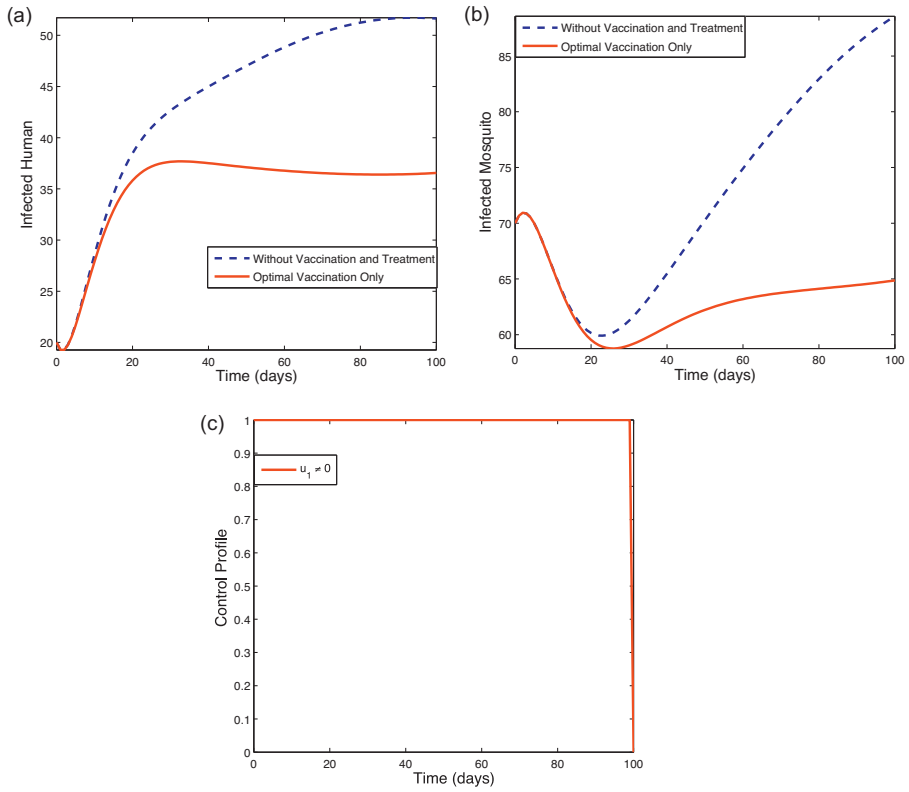

Fig. 5. Simulations of the malaria model showing impact of vaccination only using the following parameter values, $\phi = 0.502$, $\epsilon = 0.2$, $\mu_h = 0.0000457$, $\mu_v = 0.0667$, $\alpha_1 = 1/17$, $\alpha_2 = 1/18$, $\Lambda_h = 100$, $\Lambda_v = 1000$, $\psi = 0.02$, $\kappa = 1/(2 \times 365)$, $\rho = 0.023$, $\sigma = 0.005$, $\eta = 0.001$, $\theta = 0.005$, $r = 0.00656$.

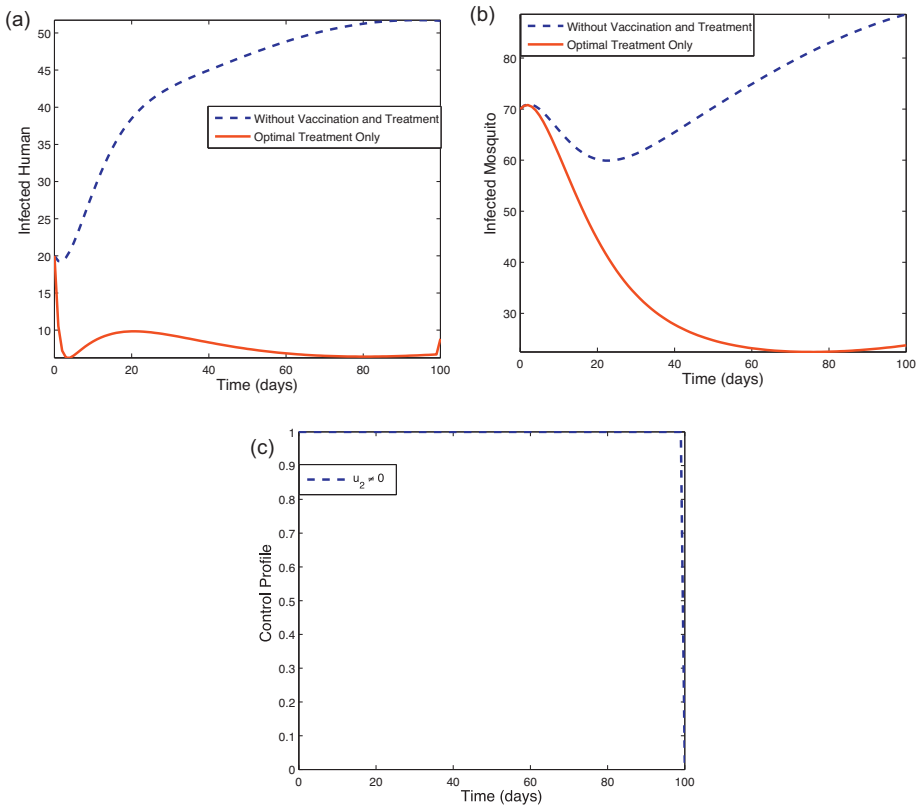

Fig. 6. Simulations of the malaria model showing impact of treatment only using the following parameter values, $\phi = 0.502$, $\epsilon = 0.2$, $\mu_h = 0.0000457$, $\mu_v = 0.0667$, $\alpha_1 = 1/17$, $\alpha_2 = 1/18$, $\Lambda_h = 100$, $\Lambda_v = 1000$, $\psi = 0.02$, $\kappa = 1/(2 \times 365)$, $\rho = 0.023$, $\sigma = 0.005$, $\eta = 0.001$, $\theta = 0.005$, $r = 0.00656$.

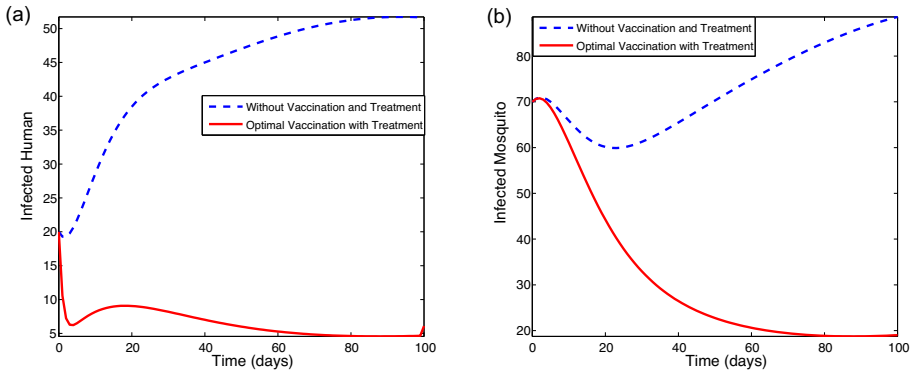

Fig. 7. Simulations of the malaria model showing effect of optimal strategies vaccination and treatment on the spread of malaria using the following parameter values, $\phi = 0.502$, $\epsilon = 0.2$, $\mu_h = 0.0000457$, $\mu_v = 0.0667$, $\alpha_1 = 1/17$, $\alpha_2 = 1/18$, $\Lambda_h = 100$, $\Lambda_v = 1000$, $\psi = 0.02$, $\kappa = 1/(2 \times 365)$, $\rho = 0.023$, $\sigma = 0.005$, $\eta = 0.001$, $\theta = 0.005$, $r = 0.00656$.

in Fig. 6(c), where we see that the optimal treatment control u_2 is at the upper bound for $t = 98$ (days). This strategy suggests that an additional effort is required on treatment under this strategy.

5.2.3. Optimal Vaccination and Treatment

With this strategy, the vaccination control u_1 and the treatment control u_2 are both used to optimize the objective function J. In Fig. 7(a) and (b), we observed that the control strategies resulted in a decrease in the number of infected humans (I_h), infected mosquitoes (I_v) and susceptible humans (S_h) while an increase is observed in the number of infected humans (I_h) and infected mosquitoes (I_v) in strategy without control.

6. Cost Effectiveness Analysis

Using cost effectiveness analysis, we want to determine the most cost effective strategy to use the control of malaria disease (vaccination only, treatment only, and vaccination with treatment). For this we need to compare the differences between the costs and health outcomes of these interventions. This is done by calculating the Incremental Cost-Effectiveness Ratio (ICER) which is generally described as the additional cost per additional health outcome. When comparing two competing intervention strategies incrementally, one intervention should be compared with the next-less-effective alternative. The ICER numerator includes the differences in intervention costs, averted disease costs, costs of prevented cases and averted productivity losses if applicable. While, the ICER denominator is the differences in health outcomes (e.g. total number of infection averted, number of susceptibility cases prevented)

Based on the model simulation results, we rank the strategies in increasing order of effectiveness, namely vaccination only (strategy A), treatment only (strategy B) and the combination of vaccination with treatment (strategy C).

The difference between the total infectious individuals without control and the total infectious individuals with control was used to determine the "total number of infection averted" used in the table of cost-effectiveness analysis

Strategy	Total infection averted	Total cost ($)
Strategy A	899.5042	17,100,000
Strategy B	3636.643	1,458,054

$$\begin{aligned} \text{ICER(A)} &= \frac{17,100,000}{899.5042} = 19,010 \\ \text{ICER(B)} &= \frac{1,458,054 - 17,100,000}{3636.643 - 899.5042} = -5714.7069 \end{aligned} \tag{18}$$

The comparison between ICER(A) and ICER(B) shows a cost saving of \$5714.7069 for strategy B over strategy A. The negative ICER for strategy B indicates the strategy A is "strongly dominated". That is, strategy A is more costly and less effective than strategy B. Therefore, strategy A, the strongly dominated is excluded from the set of alternatives so it does not consume limited resources.

We exclude strategy A and compare strategy B with C. From the numerical results we have

Strategy	Total infection averted	Total cost ($)
Strategy B	3636.643	1,458,054
Strategy C	3769.657	1,153,863

This leads to the following values for the ICER,

$$\begin{aligned} \text{ICER(B)} &= \frac{1,458,054}{3636.643} = 400.9341 \\ \text{ICER(C)} &= \frac{1,153,863 - 1,458,054}{3769.654 - 3636.643} = -2786.9612 \end{aligned} \tag{19}$$

The comparison between ICER(B) and ICER(C) shows a cost saving of \$2786.9612 for strategy C over strategy B. Similarly, the negative ICER for strategy C indicates the strategy B is "strongly dominated". That is, strategy B is more costly and less effective than strategy C. Therefore, strategy B, the strongly dominated is excluded.

With this result, we therefore conclude strategy C (combination of vaccination u_1 with treatment of infective individuals (u_2) is most cost-effective of all the strategies for malaria disease control.

7. Conclusion

In this paper, we derived and analyzed a deterministic model for the transmission of malaria disease that includes treatment and vaccination with waning immunity, using mass action form of infection. We calculated the basic reproduction number, R_0, investigated the existence and stability of equilibria and performed optimal control analysis of the model. We found that the mass action system exhibits backward bifurcation. The epidemiological implication of this is that for effective eradication and control of malaria, R_0 should be less than a critical values less than one. Moreover, achieving this may be too costly, because it means that for constant controls, one needs to keep vaccinating and treating for infinite time. Therefore, we considered time dependent controls as a way out, to ensure the eradication of the disease in a finite time. In this light, we addressed the optimal control by deriving and analyzing the conditions for optimal eradication of the disease and in a situation where eradication is impossible or of less benefit compared with the cost of intervention, we also derived and analyzed the necessary conditions for optimal control of the

disease. From the analysis, we found that eradication will be possible and optimal when the community marginal costs is less than the community marginal benefit. But if this is impossible due to the budget/resource limitation, it is important that the disease is effectively and optimally controlled.

From the numerical results and cost effectiveness analysis we conclude that the optimal strategy to effectively control malaria is the combination of vaccination and treatment. However this conclusion must be taken with caution because of the uncertainties around the parameter values.

References

Ashrafi, M.N., Gumel, A.B., 2008. Mathematical analysis of the role of repeated exposure on malaria transmission dynamics. Differ. Equat. Dyn. Syst. 16 (3), 251–287.

Abdulla, S., Oberholzer, R., Juma, O., Kubhoja, S., Machera, F., Membi, C., Omari, S., Urassa, A., Mshinda, H., Jumanne, A., Salim, N., Shomari, M., Aebi, T., Schellenberg, D.M., Carter, T., Villafana, T., Demoiti, M.A., Dubois, M.C., Leach, M., Lievens, A., Vekemans, J., Cohen, J., Ballou, W.R., Tanner, 2008. Safety and immunogenicity of RTS,S/AS02 malaria vaccine in infants. N. Engl. J. Med. 359, 2533–2544.

Adams, B.M., Banks, H.T., Kwon, H., Tran, H.T., 2004. Dynamic multidrug therapies for HIV: optimal and STI control approaches. Math. Biosci. Eng. 1 (2), 223–241.

Ainseba, B., Benosman, C., 2010. Optimal control for resistance and suboptimal response in CML. Math. Biosci., 227, 81–93.

Alonso, P.L., Sacarlal, J., Aponte, J.J., Leach, A., Macete, E., Milman, J., Mandomando, I., Spiessens, B., Guinovart, C., Espasa, M., Bassat, Q., Aide, P., Ofori-Anyinam, O., Navia, M.M., Corachan, S., Ceuppens, M., Dubois, M.C., Demoiti, M.A., Dubovsky, F., Menndez, C., Tornieporth, N., Ballou, W.R., Thompson, R., Cohen, J., 2004. Efficacy of the RTS,S/AS02A vaccine against Plasmodium falciparum infection and disease in young African children: randomized controlled trial. Lancet 364 (9443), 1411–1420, 16–22.

Alonso, P.L., Sacarlal, J., Aponte, J.J., Leach, A., Macete, E., Aide, P., Sigauque, B., Milman, J., Mandomando, I., Bassat, Q., Guinovart, C., Espasa, M., Corachan, S., Lievens, M., Navia, N.M., Dubois, M.C., Menendez, C., Dubovsky, F., Cohen, J., Thompson, R., Ballou, W.R., 2005. Duration of protection with RTS,S/AS02A malaria vaccine in prevention of Plasmodium falciparum disease in Mozambican children: single-blind extended follow-up of a randomised controlled trial. Lancet 366 (9502), 2012–2018, 10.

Aponte, J.J., Aide, P., Renom, M., Mandomando, I., Bassat, Q., Sacarlal, J., Manaca, M.N., Lafuente, S., Barbosa, A., Leach, A., Lievens, M., Vekemans, J., Sigauque, B., Dubois, M.C., Demoiti, M.A., Sillman, M., Savarese, B., McNeil, J.G., Macete, E., Ballou, W.R., Cohen, J., Alonso, P.L., 2007. Safety of the RTS,S/AS02D candidate malaria vaccine in infants living in a highly endemic area of Mozambique: a double blind randomised controlled phase I/IIb trial. Lancet 370 (9598), 1543–1551.

Augas, R., White, L.J., Snow, R.W., Gabriela, M., Gomes, M., 2008. Prospects for malaria eradication in sub-Saharan Africa. PLoS One 3 (3), e1767.

Barrett, S., Hoel, M., 2007. Optimal disease eradication. Environ. Dev. Econ. 12, 627–652.

Bejon, P., Lusingu, J., Olotu, A., Leach, A., Lievens, M., Vekemans, J., Mshamu, S., Lang, J., Gould, J., Dubois, M.C., Demoiti, M.A., Stallaert, J.F., Vansadia, P., Carter, T., Njuguna, P., Awuondo, K.O., Malabeja, A., Abdul, O., Gesase, S., Mturi, N., Drakeley, C.J., Savarese, B., Villafana, T., Ballou, W.R., Cohen, J., Riley, E.M., Lemnge, M.M., Marsh, K., Von Seidlein, L., 2008. Efficacy of RTS,S/AS01E vaccine against malaria in children 5 to 17 months of age. N. Engl. J. Med. 359, 2521–2532.

Blayneh, K., Cao, Y., Hee-Dae, K., 2009. Optimal control of vector-borne diseases: treatment and prevention. Discrete Contin. Dyn. Syst. Ser. B 11, 587–611.

Bojang, K.A., Milligan, P.J.M., Pinder, M., Vigneron, L., Allouecheb, A., Kester, K.E., Ballou, W.R., Conway, D.J., Reece, W.H.H., Gothard, P., Yamuah, L., Delchambre, M., Voss, G., Greenwood, B.M., Hill, A., McAdam, K.P.W.J., Tornieporth, N., Cohen, J.D., Doherty, T., for the RTS,S Malaria Vaccine Trial Team, 2001. Efficacy of RTS,S/AS02 malaria vaccine against Plasmodium falciparum infection in semi-immune adult men in The Gambia: a randomised trial. Lancet 358 (9297), 1927–1934.

Bojang, K., Milligan, P., Pinder, M., Doherty, T., Leach, A., Ofori-Anyinam, O., Lievens, M., Kester, K., Schaecher, K., Ballou, W.R., Cohen, J., 2009. Five-year safety and immunogenicity of GlaxoSmithKline's candidate malaria vaccine RTS,S/AS02 following administration to semi-immune adult men living in a malaria-endemic region of The Gambia. Hum. Vaccine 5 (4), 242–247.

Cesar, C., 2006. Optimal control of an epidemic through educational campaigns. Electron. J. Differ. Equat. 125, 1–11.

Chiyaka, C., Tchuenche, J.M., Garira, W., Dube, S., 2008. A mathematical analysis of the effects of control strategies on the transmission dynamics of malaria. Appl. Math. Comput. 195, 641–662.

Chiyaka, C., Garira, W., Dube, S., 2009. Effects of treatment and drug resistance on the transmission dynamics of malaria in endemic areas. Theor. Popul. Biol. 75, 14–29.

de Souza, F., Antonio Leonel Caetano, J.A.M., Yoneyama, T., 2000. Optimal control theory applied to the anti-viral treatment of AIDS. In: Proceeding of Conference on Decision and Control, Sydney.

Denis, K., Lenhart, S., Steve, S., 1997. Optimal control of the chemotherapy of HIV. J. Math. Biol. 35, 775–792.

Dietz, K., Molineaux, L., Thomas, A., 1974. A malaria model tested in the African savannah. Bull. World Health Organ. 50, 347–357.

Doedel, E.J., Paffenroth, R.C., Champneys, A.R., Fairgrieve, T.F., Kuznetsov, Y.A., Sandstede, B., Wang, X., 2002. AUTO 2000: Continuation and Bifurcation Software for Ordinary Differential Equations (with HomCont), v.0.9.7, 2002, online at http://sourceforge.net/projects/auto2000/.

Fleming, W.H., Rishel, R.W., 1975. Deterministic and Stochastic Optimal Control. Springer Verlag, New York.

Garba, S.M., Gumel, A.B., Abu, B., 2008. Backward bifurcations in dengue transmission dynamics. Math. Biosci. 215, 11–25.

Goldman, S.M., Lightwood, J., 2002. Cost optimisation in the SIS model of infectious disease with treatment. Top. Econ. Anal. Policy 2, article 4.

Gumel, A.B., Song, B., 2008. Existence of multiple-stable equilibria for a multi-drug-resistant model of Mycobacterium tuberculosis. Math. Biosci. Eng. 5, 437–455.

Gupta, N.K., Rink, R.E., 1973. Optimal control of epidemics. Math. Biosci. 18, 383–396.

Isao, K., Akira, S., Motoyoshi, M., 2004. Combining zooprophylaxis and insecticide spraying: a malaria-control strategy limiting the development of insecticide resistance in vector mosquitoes. Proc. R. Soc. Lond. 271, 301–309, doi:10.1098/rspb.2003.2575.

Joshi, H.R., Lenhart, S., Li, M.Y., Wang, L., 2006. Optimal control methods applied to disease models. Contemp. Math. 410, 187–207.

Joshi, H.R., 2002. Optimal control of an HIV immunology model. Optim. Control Appl. Math. 23, 199–213.

Kar, T.K., Batabyal, A., 2011. Stability analysis and optimal control of an SIR epidemic model with vaccination. Biosystems 104 (2/3), 127–135.

Karrakchou, J., Rachik, M., Gourari, S., 2006. Optimal control and infectiology: application to an HIV/AIDS model. Appl. Math. Comput. 177, 807–818.

Kirschner, D., Lenhart, S., Serbin, S., 1997. Optimal control of the chemotherapy of HIV. J. Math. Biol. 35, 775–792.

Koella, J.C., Anita, R., 2003. Epidemiological models for the spread of anti-malaria resistance. Malaria J. 2, 1–11.

Lenhart, S., Bhat, M.G., 1992. Application of distributed parameter control model in wildlife damage management. Math. Models Methods Appl. Sci. 2, 423–439.

Lenhart, S., Workman, J.T., 2007. Optimal Control Applied to Biological Models. Chapman and Hall.

Lenhart, S., Yong, J., 1997. Optimal Control for Degenerate Parabolic Equations with Logistic Growth. Preprint Institute for Mathematics and Application.

Li, J., 2008. A malaria model with partial immunity in humans. Math. Biosci. Eng. 5, 789–801.

Lindsay, S.W., Martens, W.J.M., 1998. Malaria in the African highlands: past, present and future. Bull. WHO 76, 33–45.

Lord, C.C., Woolhouse, M.E.J., Heesterbeek, J.A.P., 1996. Vector-borne diseases and the basic reproduction number: a case study of African horse sickness. Med. Vet. Entomol. 10, 19–28.

Maire, N., Aponte, J.J., Ross, A., Thompson, R., Alonso, P., Utzinger, J., Tanner, M., Smith, T., 2006. Modeling a field trial of the RTS,S/AS02A malaria vaccine. Am. J. Trop. Med. Hyg. 75 (2 Suppl.), 104–110.

Makinde, O.D., Okosun, K.O., 2011. Impact of chemo-therapy on optimal control of malaria disease with infected immigrants. Biosystems 104 (1), 32–41, doi:10.1016/j.biosystems.2010.12.010.

Marsh, K., 1998. Malaria disaster in Africa. Lancet 352, 924–925.

Mukandavire, Z., Gumel, A.B., Garira, W., Tchuenche, J.M., 2009. Mathematical analysis of a model for HIV-malaria co-infection. Math. Biosci. Eng. 6, 333–362.

Mushayabasa, S., Tchuenche, J.M., Bhunu, C.P., Ngarakana-Gwasira, E., 2011. Modelling gonorrhea and HIV co-interaction. J. Biosyst. 103, 27–37.

Nakul, C., Cushing, J.M., Hyman, J.M., 2006. Bifurcation analysis of a mathematical model for malaria transmission. SIAM J. Appl. Math. 67 (1), 24–45.

Nakul, C., Hyman, J.M., Cushing, J.M., 2008. Determining important parameters in the spread of malaria through the sensitivity analysis of a mathematical model. Bull. Math. Biol. 70, 1272–1296.

Nanda, S., Moore, H., Lenhart, S., 2007. Optimal control of treatment in a mathematical model of chronic myelogenous leukemia. Math. Biosci. 210, 143.

Owusu-Agyei, S., Ansong, D., Asante, K., Kwarteng Owusu, S., Owusu, R., Wireko Brobby, N.A., Dosoo, D., Osei Akoto, A., Osei-Kwakye, K., Adjei, E.A., Boahen, K.O., Sylverken, J., Adjei, G., Sambian, D., Apanga, S., Kayan, K., Vekemans, J., Ofori-Anyinam, O., Leach, A., Lievens, M., Demoitie, M.A., Dubois, M.C., Cohen, J., Ballou, W.R., Savarese, B., Chandramohan, D., Gyapong, J.O., Milligan, P., Antwi, S., Agbenyega, T., Greenwood, B., Evans, J., 2009. Randomized controlled trial of RTS,S/AS02D and RTS,S/AS01E malaria candidate vaccines given according to different schedules in Ghanaian children. PLoS One 4 (10), e7302.

Polhemus, M.E., Remich, S.A., Ogutu, B.R., Waitumbi, J.N., Otieno, L., Apollo, S., Cummings, J.F., Kester, K.E., Ockenhouse, C.F., Stewart, A., Ofori-Anyinam, O., Ramboer, I., Cahill, C.P., Lievens, M., Dubois, M.C., Demoitie, M.A., Leach, A., Cohen, J., Ballou, W.R., Heppner Jr., D.G., 2009. Evaluation of RTS,S/AS02A and RTS,S/AS01B in adults in a high malaria transmission area. PLoS One 4 (7), e6465.

Pontryagin, L.S., Boltyanskii, V.G., Gamkrelidze, R.V., Mishchenko, E.F., 1962. The Mathematical Theory of Optimal Processes. Wiley, New York.

Rafikov, M., Bevilacqua, L., Wyse, A.P.P., 2009. Optimal control strategy of malaria vector using genetically modified mosquitoes. J. Theor. Biol. 258, 418–425.

Sacarlal, J., Aponte, J.J., Aide, P., Mandomando, I., Bassat, Q., Guinovart, C., Leach, A., Milman, J., Macete, E., Espasa, M., Ofori-Anyinam, O., Thonnard, J., Corachan, S., Dubois, M.C., Lievens, M., Dubovsky, F., Ballou, W.R., Cohen, J., Alonso, P.L., 2008.

Safety of the RTS,S/AS02A malaria vaccine in Mozambican children during a Phase IIb trial. Vaccine 26 (2), 174–184.
Sacarlal, J., Aide, P., Aponte, J.J., Renom, M., Leach, A., Mandomando, I., Lievens, M., Bassat, Q., Lafuente, S., Macete, E., Vekemans, J., Guinovart, C., Sigaque, B., Sillman, M., Milman, J., Dubois, M.C., Demoiti, M.A., Thonnard, J., Menndez, C., Ballou, W.R., Cohen, J., Alonso, P.L., 2009. Long-term safety and efficacy of the RTS,S/AS02A malaria vaccine in Mozambican children. J. Infect. Dis. 200, 329–336.
Sachs, J.D., 2002. A new infected global effort to control malaria. Science 298, 122–124.
Seierstad, A., Sydsaeter, K., 1987. Optimal Control Theory with Economic Applications. North-Holland, Amsterdam.
Sethi, S.P., 1978. Optimal quarantine programmes for controlling an epidemic spread. J. Opl. Res. Soc. 29, 265–268.
Sethi, S.P., Staats, W.P., 1978. Optimal control of some simple deterministic epidemic models. J. Opl. Res. Soc. 29, 129–136.
Tumwiine, J., Mugisha, J.Y.Y., Luboobi, L.S., 2008. Threshhold and stability results for a malaria model in a population with protective intervention among high-risk groups. Math. Modell. Anal. 13, 443–460.
Van den Driessche, P., Watmough, J., 2002. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. Math. Biosci. 180, 29–48.
Vásquez Pinzón, J.U., Méndez-Sánchez, S.C., Duque Luna, J.E., 2003. Mathematical model for the analysis of vaccination and vector control in malaria incidence. Rev. Salud Publica (Bogota) 5 (2), 172–179.
WHO expert committee on malaria, 20th report, WHO Regional Office of Africa, 2003.
Wickwire, K., 1975. A note on the optimal control of carrier-borne epidemic. J. Appl. Probab. 12, 565–568.
Yang, H.M., 2000. Malaria transmission model for different levels of acquired immunity and temperature dependent parameters (vector). Rev. Saude Publica 34 (3), 223–231.
Yang, H.M., 2001. A mathematical model for malaria transmision relating global warming and local socioeconomic conditions. Rev. Saude Publica 35 (3), 224–231.
Zhixing, H., Sheng, L., Hui, W., 2008. Backward bifurcation of an epidemic model with standard incidence rate and treatment rate. Nonlinear Anal: Real World Appl. 9, 2302–2312.