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A MATHEMATICAL MODEL FOR MALARIA WITH OPTIMAL CONTROL AND COST-EFFECTIVENESS ANALYSIS

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Abstract

Many infectious diseases including malaria are preventable, yet they remain endemic in many communities due to lack of proper, adequate and timely control policies. In this paper, we formulated an human-mosquito malaria model by introducing a new compartment for immuned human population, a partially immune compartment to account for waning immunity and also incorporate a vector reduction parameter in the vector population. The impact of vaccination and vector reduction were further investigated by incorporating time dependent controls using Pontryagin's Maximum Principle (PMP). We apply the optimal control strategy to investigate and analyze the optimal cost for controlling the transmission of malaria using vaccination, treatment and indoor residual spray as control parameters. Some numerical simulations were carried out to confirm the analytic results and possible behavior of the model. The result of the optimal control and cost effectiveness analysis shows clearly that malaria can best be controlled with the combination of vaccination and indoor residual spraying (vector reduction).

Keywords: Incremental cost effective ratio, Pontryagin's Maximum Principle, Optimal cost, Indoor residual spray.

1. Introduction

Malaria is an infectious disease caused by protozoan of genius Plasmodium parasite and transmitted between humans through bites of female Anopheles mosquitoes. It remains one of the most prevalent and lethal human infections throughout the world. An estimated 40% of the world's population lives in malaria endemic areas. Most cases and deaths occur in sub-Saharan Africa. It causes an estimated 300 to 500 million cases and 1.5 to 2.7 million deaths each year worldwide. Africa shares 80% of the cases and 90% of deaths [1]. Children under the age of five and pregnant women are the most vulnerable to the severe forms of malaria. Each year 2-3 million children die from *Plasmodium falciparum* malaria and up to 500 million people throughout the world suffer from malaria clinical disease [2]. Four species of the parasite, namely: P. falciparum, P. vivax, P. ovale, and P. malariae infects humans. Malaria remains the most important of the tropical diseases, being widespread throughout the tropics also occurring in many temperate regions. Reductions in malaria deaths have contributed substantially to progress towards achieving MDG Target 4A, which was to reduce the under-5 mortality rate by two thirds between 1990 and 2015 [3]. The parasite requires two hosts to complete its life cycle - the vector female *Anopheles* mosquito and human.

The bites/blood meals of infected mosquitoes are the mode of transmission of the parasite between the human hosts. The symptoms in an infected human include bouts of fever, headache, vomiting flu-like, anemia (destroying red blood cell) and malaria can kill by clogging the capillaries that carry blood to the brain (cerebral malaria) or other vital organs. On the average the incubation period of Plasmodium falciparum is about 12 days in humans. Infection can be expressed in three ways. Prevalence of infection, or parasite rate, describes the proportion of the population harboring malaria parasites. Parasitaemia describes the density of parasites within a host, and is thought to be an important factor determining the severity of disease in humans [4]. Intensity of infection describes the number of separate infections received by a host. Since different strains of parasites differ in their antigenic properties [5], intensity is certainly important in determining the level of acquired immunity. It might also contribute to severity of disease possibly by determining the probability of a human becoming infected with a virulent parasite strain [6].

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In the recent years, global eradication and control efforts have led to a surge of activities leading to many studies and publications[7]. Control strategies and intervention program have been adopted worldwide. Some of which include the use of anti-malaria vaccines, insecticides-treated bed nets (ITNs), control of breeding environment, and biological control among others. These are largely used in malaria endemic countries especially those in Sub-Saharan Africa and have somewhat led to the reduction in the spread of the disease. The proportion of the population sleeping under an ITN increased from less than 2% in 2000 to an estimated 55% in 2015 (range: 50–58%). Ensuring access to ITNs has been critical to increasing the proportion of the population sleeping under an ITN. Nearly 500 million ITNs were delivered to countries in sub-Saharan Africa between 2013 and 2015, and the proportion of the population with access to an ITN increased to an estimated 67% in 2015 (range: 61–71%) [3].

Mathematical modeling has been an important tool in understanding the dynamics of disease transmission and also in decision making process regarding intervention mechanisms for disease control. The study of epidemiology of malaria was heralded by Ross [8] where he developed the first mathematical model for malaria transmission. His focus was on mosquito control and he showed that for the disease to be eliminated, the mosquito population should be brought below a certain. It is of great importance and tasking to review all types of models in one article. In this article a historical path has been considered, and an attempt is made to take into account some of those mathematical models, which are primarily focused on the transmission dynamics of the infection in the host and vector populations, using the epidemiological compartment modeling approach [9,10]. Koella and Boete [11] derive a model where humans move through multiple Susceptible Exposed-Infectious-Recovered (SEIR) stages, where history is kept of previous infections. They included a sub model for the mosquito population with subdivisions for juveniles and adults. They used the steady state value for the adult mosquito population, from this sub model, as the input into their model for malaria transmission. They introduced dependence of the parameters for the mosquito population sub model on an environmental parameter (e.g. temperature or rainfall) and calculated the dependence of the reproductive number, for the full malaria model, on this environmental parameter.

Other relevant studies include Koella and Anita [12] who incorporated a latent class for mosquito population. They considered different control strategies to curb the spread of the resistance and studied the sensitivity of their results to the parameters. Anderson and May [13] formulated a malaria model with the assumption that acquired immunity in malaria is independent of exposure duration. Christopher and Jorge [14] derived a simple two-dimensional SIS (susceptible-infected-susceptible) model with vaccination and multiple endermic states. Guihua and Zhen [15] studied the global trends of an SEIR (susceptible-exposed-infected-recovered) epidemic model in which latent and immune states were infective. However, very few studies have been carried out with consideration to the impact of vaccination and waning immunity to malaria models

Incorporating vaccines to the malaria disease-fighting mix could make a significant impact in our health challenges. Thus, introducing a vaccination compartment, vector reduction parameter in existing malaria model of the authors in [16] is one of the major focus of this research work as these can help to gain more insight in the dynamics and control of malaria and also make our models more realistic. Although, malaria vaccines have not yet been licensed commercially for use, its prospect is quite good news. This new initiative could likely make a significant impact in our health challenges especially in a time like this where the piloting of the injectable vaccines had just been launched by the World Health Organization in three of African countries (Malawi, Ghana and Kenya), to hundreds of thousands of young children, who have been at high risk of death [17]. Among the potential malaria vaccines, the RTS,S also known as Mosquirix, is the furthest along. The vaccine, which for now has partial effectiveness, has the potential to save tens of thousands of lives if used with existing measures [17]. The challenge however, is whether impoverished countries can deliver the required four doses of the vaccines, given through intramuscular injection, to each child. The vaccines will be tested on children between the ages of 5 - 17 months old to see whether its preventive effect shown so far in clinical trials can hold up under real-life conditions. At least 120,000 children in each of the three countries will receive the vaccine which has taken decades of work and hundreds of millions of dollars to develop [3]. Kenya, Ghana and Malawi were chosen for the vaccines pilot because all have strong prevention and vaccination programs but continue to have high number of malaria cases [17]. The countries will deliver the vaccines through their existing vaccination program. The malaria vaccine has been developed by pharmaceutical company GlaxoSmithKline, and the $49 million for the first phase of the first pilot is being funded by the global vaccine alliance GAVI, UNITAID and the Global fund to fight AIDS, Tuberculosis and Malaria. In this paper, we gleaned and modified the existing model of authors in [16] by introducing entirely new compartment (Immuned compartment, partially immuned compartment as well as vector reduction parameter and carry out cost-effectiveness analysis to determine the optimal cost for controlling malaria via prevention and treatment as new control strategies in combating the disease.

2. Model Equation with Time-Dependent Control

The objective functional for the modified model of the authors in [16] with vaccination, treatment of infected individual and mass reduction of the mosquitoes (indoor residual spraying) as control parameters with their corresponding time dependent

preventive control (u_1, u_3) and treatment (u_3) aimed at controlling the transmission of the malaria infection is formulated and presented below:

$$\left.\begin{aligned}
\dot{x}_1 &= \lambda_h - (1-u_1)\frac{b\beta_h x_1 y_3}{1+v_h y_3} - (\mu_h+\varphi_h)x_1 + \sigma x_6 \\
\dot{x}_2 &= (1-u_1)\frac{b\beta_h x_1 y_3}{1+v_h y_3} - (\mu_h+\alpha_h)x_2 \\
\dot{x}_3 &= \alpha_h x_2 - (u_2 r + l + \delta_h + \mu_h)x_3 \\
\dot{x}_4 &= u_2 r x_3 - (\mu_h+\rho)x_4 \\
\dot{x}_5 &= \varphi_h x_1 - (\mu_h+e)x_5 \\
\dot{x}_6 &= l x_3 + \rho x_4 - (\mu_h+\sigma)x_6 + e x_5 \\
\dot{y}_1 &= \lambda_m - (1-u_1)\frac{b\beta_m y_1 x_3}{1+v_m x_3} - (\mu_m+u_3 k_m)y_1 \\
\dot{y}_2 &= (1-u_1)\frac{b\beta_m y_1 x_3}{1+v_m x_3} - (\alpha_m+\mu_m+u_3 k_m)y_2 \\
\dot{y}_3 &= \alpha_m y_2 - (\delta_m+\mu_m+u_3 k_m)y_3
\end{aligned}\right\} \quad (1)$$

However, the optimal level of efforts needed to control the transmission of malaria (at minimum cost implication) were investigated by minimizing the objective functional.

$$J(u_1,u_2,u_3) = \int_0^{t_f}\left(A_1 x_3(t) + A_2 N_v(t) + \frac{C_1}{2}u_1^2(t) + \frac{C_2}{2}u_2^2(t) + \frac{C_3}{2}u_3^2(t)\right)dt \quad (2)$$

Given the objective function (2), where t_f is the final time and the coefficients C_1, C_2, C_3 are the positive weights to balance the factors. Our aim is to minimize the number of infected humans $x_3(t)$ and the total population of mosquitoes $N_v(t)$, while minimizing the cost of implementing $u_1(t)$, $u_2(t)$ and $u_3(t)$ respectively. A_1 is the cost of treatment associated with the infected human and A_2 is the cost associated with the control of total population of the mosquitoes while $\frac{C_1}{2}u_1^2, \frac{C_2}{2}u_2^2$ and $\frac{C_3}{2}u_3^2$ represent the costs for the use of vaccination, treatment of infected human and use of indoor residual spray respectively.

If the elimination of malaria in unachievable as a result of costs or social and environmental reason, then we need to investigate the optimal level of efforts that will be needed in reducing the disease transmission, i.e. we analyze the objective functional in (1). Our aim is to minimize the number of infected human at the least cost with the respect to the control parameters $u_1(t)$, $u_2(t)$ and $u_3(t)$ We seek cost optimal control u_1^*, u_2^* and u_3^* such that

$$J(u_1^*,u_2^*,u_3^*) = \min_{u_1,u_2,u_3\in\prod} J(u_1,u_2,u_3) \quad (3)$$

where $\prod$ is the bounded interval $\prod < [0,1]$ such that $u_i(t) \in \prod \forall t \in [0,t_f]$ and $i = 1,2,3$. The necessary conditions for an optimal control is determined by Pontryagins's Maximum Principle [18]

Theorem 1

Given a non-linear control system $\overset{*}{x} = f(t,x,u)$; the necessary condition for optimal control is that the following Pontryagins Hamiltonian $H(\psi,x,t,u) = \psi f(t,x,u)$: then consider $\overset{*}{x} = \frac{\partial H}{\partial \psi}$ and $\overset{*}{\psi} = \frac{\partial H}{\partial x} = -\psi f_x(t,x,u)$ and $\psi(t) = \eta' X^{-1}(t)$ is the general solution.

Pontryagin Maximum Principle states that if u^* is the optimal control. Then u^* is satisfied where $u^*(t) = \text{sgn}[\psi f_u(t,x,u)] = \text{sgn}[\eta' X^{-1}(t) f_u(t,x,u)]$

Having introduced into the model (4.0), time dependent preventive strategies $u_1(t)$, $u_2(t)$ and treatment $u_3(t)$, our Hamiltonian becomes

$$
\begin{aligned}
H = {} & A_1 x_3(t) + A_2 N_v(t) + \frac{C_1}{2} u_1^2 e^{-\alpha t} + \frac{C_2}{2} u_2^2 e^{-\alpha t} + \frac{C_3}{2} u_3^2 e^{-\alpha t} \\
& + \pi_{x_1}\left[\lambda_h - (1-u_1)\frac{b\beta_h x_1 y_3}{1+v_h y_3} - (\mu_h + \varphi_h)x_1 + \sigma x_6\right] \\
& + \pi_{x_2}\left[(1-u_1)\frac{b\beta_h x_1 y_3}{1+v_h y_3} - (\mu_h + \alpha_h)x_2\right] \\
& + \pi_{x_3}\left[\alpha_h x_2 - (u_2 r + l + \delta_h + \mu_h)x_3\right] \\
& + \pi_{x_4}\left[u_2 r x_3 - (\mu_h + \rho)x_4\right] \\
& + \pi_{x_5}\left[\varphi_h x_1 - (\mu_h + e)x_5\right] \\
& + \pi_{x_6}\left[l x_3 + \rho x_4 - (\mu_h + \sigma)x_6 + e x_5\right] \\
& + \pi_{y_1}\left[\lambda_m - (1-u_1)\frac{b\beta_m y_1 x_3}{1+v_m x_3} - (\mu_m + u_3 k_m)y_1\right] \\
& + \pi_{y_2}\left[(1-u_1)\frac{b\beta_m y_1 x_3}{1+v_m x_3} - (\alpha_m + \mu_m + u_3 k_m)y_2\right] \\
& + \pi_{y_3}\left[\alpha_m y_2 - (\delta_m + \mu_m + u_3 k_m)y_3\right] \\
& + \pi_{C_f}\left[C_{vc} u_1 x_1 + C_{tr} r u_2 x_3 + C_{sp} k_m u_3 y_1 + C_{sp} k_m u_3 y_2 + C_{sp} k_m u_3 y_3\right]
\end{aligned}
\qquad (4)
$$

where $\pi_{x_1}\ \pi_{x_2}\ \pi_{x_3}\ \pi_{x_4}\ \pi_{x_5}\ \pi_{x_6}\ \pi_{y_1}\ \pi_{y_2}\ \pi_{y_3}$ and π_{C_f} are the adjoint variables or co-state variables.

Theorem 2

Given an optimal control u_1^*, u_2^*, u_3^* and the relation $x_1^*, x_2^*, x_3^*, x_4^*, x_5^*, x_6^*, y_1^*, y_2^*, y_3^*$ of the corresponding system (1) that minimizes $J(u_1, u_2, u_3)$ over $[0, t_f]$. Then there exists adjoint variables $\pi_{x_1}, \pi_{x_2}, \pi_{x_3}, \pi_{x_4}, \pi_{x_5}, \pi_{x_6}, \pi_{y_1}, \pi_{y_2}, \pi_{y_3}$ satisfying

$$
\begin{aligned}
-\frac{d\pi_{x_1}}{dt} &= -\begin{bmatrix} -(1-u_1)\frac{b\beta_h y_3}{1+v_h y_3}\pi_{x_1} - (\mu_h + \varphi_h)\pi_{x_1} \\ +(1-u_1)\frac{b\beta_h y_3}{1+v_h y_3}\pi_{x_2} + \varphi_h \pi_{x_5} + C_{vc} u_1 \pi_{C_f} \end{bmatrix} \\
-\frac{d\pi_{x_2}}{dt} &= -\left[-(\mu_h + \alpha_h)\pi_{x_2} + \alpha_h \pi_{x_3}\right] \\
-\frac{d\pi_{x_3}}{dt} &= -\begin{bmatrix} A_1 - (u_2 r + l + \delta_h + \mu_h)\pi_{x_3} + u_2 r \pi_{x_4} + l\pi_{x_6} \\ -(1-u_1)\left(\frac{(1+v_m x_3)(b\beta_m y_1) - (b\beta_m y_1 x_3)v_m}{(1+v_m x_3)^2}\right)\pi_{y_1} \\ +(1-u_1)\left(\frac{(1+v_m x_3)(b\beta_m y_1) - (b\beta_m y_1 x_3)v_m}{(1+v_m x_3)^2}\right)\pi_{y_2} + C_{tr} r u_2 \pi_{C_f} \end{bmatrix} \\
-\frac{d\pi_{x_4}}{dt} &= -\left[-(\mu_h + \rho)\pi_{x_4} + \rho\pi_{x_6}\right] \\
-\frac{d\pi_{x_5}}{dt} &= -\left[-(\mu_h + e)\pi_{x_5} + e\pi_{x_6}\right] \\
-\frac{d\pi_{x_6}}{dt} &= -\left[-(\mu_h + \sigma)\pi_{x_6} + \sigma\pi_{x_1}\right] \\
-\frac{d\pi_{y_1}}{dt} &= -\begin{bmatrix} A_2 - (1-u_1)\frac{b\beta_m x_3}{1+v_m x_3}\pi_{y_1} - (u_m + u_3 k_m)\pi_{y_1} \\ +(1-u_1)\frac{b\beta_m x_3}{1+v_m x_3}\pi_{y_2} + C_{sp} k_m u_3 \pi_{C_f} \end{bmatrix} \\
-\frac{d\pi_{y_2}}{dt} &= -\left[A_2 - (\alpha_m + \mu_m + u_3 k_m)\pi_{y_2} + \alpha_m \pi_{y_3} + C_{sp} k u_3 \pi_{C_f}\right] \\
-\frac{d\pi_{y_3}}{dt} &= -\begin{bmatrix} A_2 - (1-u_1)\left(\frac{(1+v_h y_3)b\beta_h x_1 - (b\beta_h x_1 y_3)v_h}{(1+v_h y_3)^2}\right)\pi_{x_1} \\ +(1-u_1)\left(\frac{(1+v_h y_3)b\beta_h x_1 - (b\beta_h x_1 y_3)v_h}{(1+v_h y_3)^2}\right)\pi_{x_2} \\ -(\delta_m + \mu_m + u_3 k_m)\pi_{y_3} + C_{sp} k u_3 \pi_{C_f} \end{bmatrix} \\
-\frac{d\lambda_{C_f}}{dt} &= 0
\end{aligned}
\qquad (5)
$$

with transversality conditions:

$$\lambda_{x_1}(t_f)=\lambda_{x_2}(t_f)=\lambda_{x_3}(t_f)=\lambda_{x_4}(t_f)=\lambda_{x_5}(t_f)=\lambda_{x_6}(t_f)=\lambda_{y_1}(t_f)=\lambda_{y_2}(t_f)=\lambda_{y_3}(t_f)=0 \tag{6}$$

And the controls u_1^*, u_2^* and u_3^* satisfy the optimality conditions:

$$\left.\begin{aligned}
u_1^* &= \max\left\{0, \min\left(1, \frac{\dfrac{b\beta_h x_1^* y_3^*}{1+v_h y_3^*}(\pi x_2-\pi x_1)+\dfrac{b\beta_m y_1^* x_3^*}{1+v_h x_3^*}(\pi y_2-\pi y_1)-C_{vc}x_1^*\pi c_f}{c_1 e^{-\varphi t}}\right)\right\}\\
u_2^* &= \max\left\{0, \min\left(1, \frac{rx_3^*(\pi x_3-\pi x_4)-C_{tr}rx_3^*\pi c_f}{c_2 e^{-\varphi t}}\right)\right\}\\
u_3^* &= \max\left\{0, \min\left(1, \frac{k_m\left(y_1^*\pi y_1+y_2^*\pi y_2+y_3^*\pi y_3\right)-k_m C_{spr}\pi c_f\left(y_1^*+y_2^*+y_3^*\right)}{c_3 e^{-\varphi t}}\right)\right\}
\end{aligned}\right\} \tag{7}$$

Proof

The differentiable equations governing the adjoint variables are obtained by differentiating the (4) and evaluated at the control parameter. Then the adjoint system can thus be written as

$$\frac{d\lambda_{x_1}}{dt}=-\frac{\partial H_c}{\partial x_1},\frac{d\lambda_{x_2}}{dt}=-\frac{\partial H_c}{\partial x_2},\frac{d\lambda_{x_3}}{dt}=-\frac{\partial H_c}{\partial x_3},\frac{d\lambda_{x_4}}{dt}=-\frac{\partial H_c}{\partial x_4},\frac{d\lambda_{x_5}}{dt}=-\frac{\partial H_c}{\partial x_5},\frac{d\lambda_{x_6}}{dt}=-\frac{\partial H_c}{\partial x_6}, \tag{8}$$

$$\frac{d\lambda_{y_1}}{dt}=-\frac{\partial H_c}{\partial y_1},\frac{d\lambda_{y_2}}{dt}=-\frac{\partial H_c}{\partial y_2},\frac{d\lambda_{y_3}}{dt}=-\frac{\partial H_c}{\partial y_3}$$

$$\left.\begin{aligned}
\frac{dH}{dx_1} &= \left[(1-u_1)\frac{b\beta_h y_3}{1+v_h y_3}\left(\pi_{x_1}-\pi_{x_2}\right)+\left(\mu_h+\varphi_h\right)\pi_{x_1}-\varphi_h\pi_{x_5}-C_{vc}u_1\pi_{C_f}\right]\\
\frac{dH}{dx_2} &= \left[\left(\mu_h+\alpha_h\right)\pi_{x_2}-\alpha_h\pi_{x_3}\right]\\
\frac{dH}{dx_3} &= \left[\begin{aligned}&(1-u_1)\left(\frac{(1+v_m x_3)(b\beta_m y_1)-(b\beta_m y_1 x_3)v_m}{(1+v_m x_3)^2}\right)\left(\pi_{y_1}-\pi_{y_2}\right)\\&+\left(u_2 r+l+\delta_h+\mu_h\right)\pi_{x_3}-u_2 r\pi_{x_4}-l\pi_{x_6}-C_{tr}ru_2\pi_{C_f}-A_1\end{aligned}\right]\\
\frac{dH}{dx_4} &= \left[\left(\mu_h+\rho\right)\pi_{x_4}-\rho\pi_{x_6}\right]\\
\frac{dH}{dx_5} &= \left[\left(\mu_h+e\right)\pi_{x_5}-e\pi_{x_6}\right]\\
\frac{dH}{dx_6} &= \left[\left(\mu_h+\sigma\right)\pi_{x_6}-\sigma\pi_{x_1}\right]\\
\frac{dH}{dy_1} &= \left[\begin{aligned}&(1-u_1)\frac{b\beta_m x_3}{1+v_m x_3}\left(\pi_{y_1}-\pi_{y_2}\right)+\left(u_m+u_3k_m\right)\pi_{y_1}\\&-C_{sp}k_m u_3\pi_{C_f}-A_2\end{aligned}\right]\\
\frac{dH}{dy_2} &= \left[\left(\alpha_m+\mu_m+u_3k_m\right)\pi_{y_2}-\alpha_m\pi_{y_3}-C_{sp}ku_3\pi_{C_f}-A_2\right]\\
\frac{dH}{dy_3} &= -\left[\begin{aligned}&(1-u_1)\left(\frac{(1+v_h y_3)b\beta_h x_1-(b\beta_h x_1 y_3)v_h}{(1+v_h y_3)^2}\right)\left(\pi_{x_1}-\pi_{x_2}\right)\\&+\left(\delta_m+\mu_m+u_3k_m\right)\pi_{y_3}-C_{sp}ku_3\pi_{C_f}-A_2\end{aligned}\right]\\
\frac{dH}{dC_f} &= 0
\end{aligned}\right\} \tag{9}$$

with transversality conditions:

$$\pi_{x_1}(t_f)=\pi_{x_2}(t_f)=\pi_{x_3}(t_f)=\pi_{x_4}(t_f)=\pi_{x_5}(t_f)=\pi_{x_6}(t_f)=\pi_{y_1}(t_f)=\pi_{y_2}(t_f)=\pi_{y_3}(t_f)=0 \tag{10}$$

Hence, solving $\frac{\partial H}{\partial u_1}=0,\ \frac{\partial H}{\partial u_2}=0,\ \frac{\partial H}{\partial u_3}=0,$ gives the characterization of the control parameters.

$$\left.\begin{aligned} u_1^* &= \left(\frac{\frac{b\beta_h x_1^* y_3^*}{1+v_h y_3^*}(\pi x_2-\pi x_1)+\frac{b\beta_m y_1^* x_3^*}{1+v_h x_3^*}(\pi y_2-\pi y_1)-C_{vc}x_1^*\pi c_f}{c_1}\right)e^{-\varphi t} \\ u_2^* &= \left(\frac{rx_3^*(\pi x_3-\pi x_4)-C_{tr}rx_3^*\pi c_f}{c_2}\right)e^{-\varphi t} \\ u_3^* &= \left(\frac{k_m\left(y_1^*\pi y_1+y_2^*\pi y_2-y_3^*\pi y_3\right)-k_m C_{spr}\pi c_f\left(y_1^*+y_2^*+y_3^*\right)}{c_3}\right)e^{-\varphi t} \end{aligned}\right\} \tag{11}$$

The optimality condition via Pontryagin's Maximum Principle states that

$$u_1^*=\operatorname{sgn}\left[\eta^{'}X^{-1}(t)f_u(t,x,u)\right]=\begin{cases}-1, & if \quad f_u(t,x,u)<0\\ 0, & if \quad f_u(t,x,u)=0\\ 1, & if \quad f_u(t,x,u)>0\end{cases}$$

As a result of the aprioribondedness of the solutions of both the state and the adjoint equations, we obtain the uniqueness of the system (5-7). The restriction on the length of time interval $[0,t_f]$ in the order to guarantee the uniqueness of the system. This is due to the opposite time orientations (5-7); the state problem has initial values while the adjoint problems has final values. This restriction is common in control problems [19,20,21].

3. Model Analysis

Here we present the various cost evaluation analysis for our control strategies

The cost evaluation for the control parameters were analyzed using the objective functional given as

$$C_f=\min_{u_1,u_2,u_3}\int_0^{t_f}\left(C_{vc}u_1(t)x_1(t)+C_{tr}ru_2(t)x_3(t)+k_mC_{sp}u_3(t)\left(y_1(t)+y_2(t)+y_3(t)\right)\right)e^{-\varphi t}dt \tag{12}$$

subject to (1). Therefore, the corresponding Hamiltonian is given as

$$\left.\begin{aligned} H_C = {} & \left[C_{vc}u_1x_1+C_{tr}ru_2x_3+C_{sp}k_mu_3y_1+C_{sp}k_mu_3y_2+C_{sp}k_mu_3y_3\right]e^{-\varphi t} \\ & +\pi_{x_1}\left[\lambda_h-(1-u_1)\frac{b\beta_h x_1y_3}{1+v_hy_3}-(\mu_h+\varphi_h)x_1+\sigma x_6\right] \\ & +\pi_{x_2}\left[(1-u_1)\frac{b\beta_h x_1y_3}{1+v_hy_3}-(\mu_h+\alpha_h)x_2\right] \\ & +\pi_{x_3}\left[\alpha_hx_2-(u_2r+l+\delta_h+\mu_h)x_3\right] \\ & +\pi_{x_4}\left[u_2rx_3-(\mu_h+\rho)x_4\right] \\ & +\pi_{x_5}\left[\varphi_hx_1-(\mu_h+e)x_5\right] \\ & +\pi_{x_6}\left[lx_3+\rho x_4-(\mu_h+\sigma)x_6+ex_5\right] \\ & +\pi_{y_1}\left[\lambda_m-(1-u_1)\frac{b\beta_m y_1x_3}{1+v_mx_3}-(\mu_m+u_3k_m)y_1\right] \\ & +\pi_{y_2}\left[(1-u_1)\frac{b\beta_m y_1x_3}{1+v_mx_3}-(\alpha_m+\mu_m+u_3k_m)y_2\right] \\ & +\pi_{y_3}\left[\alpha_my_2-(\delta_m+\mu_m+u_3k_m)y_3\right] \end{aligned}\right\} \tag{13}$$

where $\pi_{x_1}, \pi_{x_2}, \pi_{x_3}, \pi_{x_4}, \pi_{x_5}, \pi_{x_6}, \pi_{y_1}, \pi_{y_2}, \pi_{y_3}$ are the shadow prices associated with their respective classes. The changes in the objective value of the optimal solution of an optimization problem are obtained by relaxing the constraint by one (1) unit. We use Pontryagin's Maximum Principle to obtain

$$-\frac{d\pi_{x_1}}{dt}=\frac{\partial H_c}{\partial x_1},-\frac{d\pi_{x_2}}{dt}=\frac{\partial H_c}{\partial x_2},-\frac{d\pi_{x_3}}{dt}=\frac{\partial H_c}{\partial x_3},-\frac{d\pi_{x_4}}{dt}=\frac{\partial H_c}{\partial x_4},-\frac{d\pi_{x_5}}{dt}=\frac{\partial H_c}{\partial x_5},-\frac{d\pi_{x_6}}{dt}=\frac{\partial H_c}{\partial x_6}, \tag{14}$$
$$-\frac{d\pi_{y_1}}{dt}=\frac{\partial H_c}{\partial y_1},-\frac{d\pi_{y_2}}{dt}=\frac{\partial H_c}{\partial y_2},-\frac{d\pi_{y_3}}{dt}=\frac{\partial H_c}{\partial y_3}$$

Thus solving (13), we have

$$\left.\begin{aligned}
-\frac{d\pi_{x_1}}{dt}&=-\begin{bmatrix} C_{vc}u_1e^{-\varphi t}-(1-u_1)\dfrac{b\beta_h y_3}{1+v_h y_3}\pi_{x_1}-(\mu_h+\varphi_h)\pi_{x_1} \\ +(1-u_1)\dfrac{b\beta_h y_3}{1+v_h y_3}\pi_{x_2}+\varphi_h\pi_{x_5}\end{bmatrix}\\
-\frac{d\pi_{x_2}}{dt}&=-\left[-(\mu_h+\alpha_h)\pi_{x_2}+\alpha_h\pi_{x_3}\right]\\
-\frac{d\pi_{x_3}}{dt}&=-\begin{bmatrix} C_{tr}ru_2e^{-\varphi t}-(u_2r+l+\delta_h+\mu_h)\pi_{x_3}+u_2r\pi_{x_4}+l\pi_{x_6} \\ -(1-u_1)\left(\dfrac{(1+v_m x_3)(b\beta_m y_1)-(b\beta_m y_1 x_3)v_m}{(1+v_m x_3)^2}\right)\pi_{y_1} \\ +(1-u_1)\left(\dfrac{(1+v_m x_3)(b\beta_m y_1)-(b\beta_m y_1 x_3)v_m}{(1+v_m x_3)^2}\right)\pi_{y_2}\end{bmatrix}\\
-\frac{d\pi_{x_4}}{dt}&=-\left[-(\mu_h+\rho)\pi_{x_4}+\rho\pi_{x_6}\right]\\
-\frac{d\pi_{x_5}}{dt}&=-\left[-(\mu_h+e)\pi_{x_5}+e\pi_{x_6}\right]\\
-\frac{d\pi_{x_6}}{dt}&=-\left[-(\mu_h+\sigma)\pi_{x_6}+\sigma\pi_{x_1}\right]\\
-\frac{d\pi_{y_1}}{dt}&=-\begin{bmatrix} C_{sp}k_m u_3e^{-\varphi t}-(1-u_1)\dfrac{b\beta_m x_3}{1+v_m x_3}\pi_{y_1}-(u_m+u_3k_m)\pi_{y_1} \\ +(1-u_1)\dfrac{b\beta_m x_3}{1+v_m x_3}\pi_{y_2}\end{bmatrix}\\
-\frac{d\pi_{y_2}}{dt}&=-\left[C_{sp}ku_3e^{-\varphi t}-(\alpha_m+\mu_m+u_3k_m)\pi_{y_2}+\alpha_m\pi_{y_3}\right]\\
-\frac{d\pi_{y_3}}{dt}&=-\begin{bmatrix} C_{sp}ku_3e^{-\varphi t}-(1-u_1)\left(\dfrac{(1+v_h y_3)b\beta_h x_1-(b\beta_h x_1 y_3)v_h}{(1+v_h y_3)^2}\right)\pi_{x_1} \\ +(1-u_1)\left(\dfrac{(1+v_h y_3)b\beta_h x_1-(b\beta_h x_1 y_3)v_h}{(1+v_h y_3)^2}\right)\pi_{x_2} \\ -(\delta_m+\mu_m+u_3k_m)\pi_{y_3}\end{bmatrix}
\end{aligned}\right\} \tag{15}$$

Cost evaluation for vaccination

Differentiating (13) partially with respect to u_1 (vaccination) as control parameter, we get

$$\frac{\partial H_C}{\partial u_1}=C_{vc}x_1e^{-\varphi t}+\frac{b\beta_h x_1 y_3}{1+v_h y_3}\left(\pi_{x_1}-\pi_{x_2}\right)+\frac{b\beta_m y_1 x_3}{1+v_m x_3}\left(\pi_{y_1}-\pi_{y_2}\right) \tag{16}$$

This expression $\left(\dfrac{b\beta_h x_1 y_3}{1+v_h y_3}\left(\pi_{x_1}-\pi_{x_2}\right)+\dfrac{b\beta_m y_1 x_3}{1+v_m x_3}\left(\pi_{y_1}-\pi_{y_2}\right)\right)$ in (16) is the total marginal benefit of the use of vaccination and the $C_{vc}x_1e^{-\varphi t}$ is the marginal cost. If the marginal cost of vaccination is equal to the marginal benefit, then the optimal policy is achieved.

$$\left.\begin{array}{lll} u_1(t)=0 & if & C_{vc}x_1e^{-\varphi t} > \dfrac{b\beta_h x_1 y_3}{1+v_h y_3}\left(\pi_{x_2}-\pi_{x_1}\right)+\dfrac{b\beta_m y_1 x_3}{1+v_m x_3}\left(\pi_{y_2}-\pi_{y_1}\right) \\ u_1(t)\in(0,1) & if & C_{vc}x_1e^{-\varphi t} = \dfrac{b\beta_h x_1 y_3}{1+v_h y_3}\left(\pi_{x_2}-\pi_{x_1}\right)+\dfrac{b\beta_m y_1 x_3}{1+v_m x_3}\left(\pi_{y_2}-\pi_{y_1}\right) \\ u_1(t)=1 & if & C_{vc}x_1e^{-\varphi t} < \dfrac{b\beta_h x_1 y_3}{1+v_h y_3}\left(\pi_{x_2}-\pi_{x_1}\right)+\dfrac{b\beta_m y_1 x_3}{1+v_m x_3}\left(\pi_{y_2}-\pi_{y_1}\right) \end{array}\right\} \quad (17)$$

This means that the use of vaccination in preventing malaria will be cost optimal only when the expected marginal benefit is greater than the marginal cost.

Cost evaluation for treated of infective human population

Similarly differentiating (13) partially with respect to u_2 (treatment) as control parameter, we get

$$\frac{\partial H_C}{\partial u_2} = C_{tr}rx_3e^{-\varphi t} + rx_3\left(\pi_{x_4}-\pi_{x_3}\right) \quad (18)$$

These expressions $C_{tr}rx_3e^{-\varphi t}$ and $rx_3\left(\pi_{x_4}-\pi_{x_3}\right)$ in (18) are the total marginal cost and benefit for treatment.

$$\left.\begin{array}{lll} u_2(t)=0 & if & C_{tr}rx_3e^{-\varphi t} > rx_3\left(\pi_{x_3}-\pi_{x_4}\right) \\ u_2(t)\in(0,1) & if & C_{tr}rx_3e^{-\varphi t} = rx_3\left(\pi_{x_3}-\pi_{x_4}\right) \\ u_2(t)=1 & if & C_{tr}rx_3e^{-\varphi t} < rx_3\left(\pi_{x_3}-\pi_{x_4}\right) \end{array}\right\} \quad (19)$$

If the marginal benefit is greater than the marginal cost, then the cost optimal target for treatment is achieved.

Cost evaluation for indoor residence spray

Similarly differentiating (13) partially with respect to u_3 (indoor residence spray) as control parameter, we get

$$\frac{\partial H_C}{\partial u_3} = C_{sp}k_me^{-\varphi t}\left(y_1+y_2+y_3\right) - k_m\left(y_1\pi_{y_1}+y_2\pi_{y_2}+y_3\pi_{y_3}\right) \quad (20)$$

The marginal cost of indoor spray against the total population of mosquitoes is given by $C_{sp}k_me^{-\varphi t}\left(y_1+y_2+y_3\right)$ while the marginal benefit derived as a result of indoor spray is $k_m\left(y_1\pi_{y_1}+y_2\pi_{y_2}+y_3\pi_{y_3}\right)$. The cost optimal target will be achieved if

$$\left.\begin{array}{lll} u_3(t)=0 & if & C_{sp}k_me^{-\varphi t}\left(y_1+y_2+y_3\right) > k_m\left(y_1\pi_{y_1}+y_2\pi_{y_2}+y_3\pi_{y_3}\right) \\ u_3(t)\in(0,1) & if & C_{sp}k_me^{-\varphi t}\left(y_1+y_2+y_3\right) = k_m\left(y_1\pi_{y_1}+y_2\pi_{y_2}+y_3\pi_{y_3}\right) \\ u_3(t)=1 & if & C_{sp}k_me^{-\varphi t}\left(y_1+y_2+y_3\right) < k_m\left(y_1\pi_{y_1}+y_2\pi_{y_2}+y_3\pi_{y_3}\right) \end{array}\right\} \quad (21)$$

If the marginal benefit for the cost optimal indoor residual spray is greater than the marginal cost of indoor residual, then the indoor residence spray is cost optimal.

4. Numerical Simulation, Results and Discussion

Numerically, we investigate the effect of the cost optimal control strategies on the spread of malaria in a population using parameters and variables values in table 2. The strategies are:

Strategy A: use of vaccination and treatment
Strategy B: use of vaccination and indoor residual spray
Strategy C: use of treatment and indoor residual spray
Strategy D: use of vaccination, treatment and indoor residual spray

Table 1 Parameters and description of the model

Parameters	Description	Values	Sources
λ_h	recruitment term of the susceptible humans	0.000215	[16]
λ_m	recruitment term of the susceptible mosquitoes	0.07	[16]
β_h	probability that a bite by an infectious mosquito results in transmission of disease to human	0.01	[16]
β_m	probability that a bite by an infectious human results in transmission of disease to mosquito	0.09	[16]

μ_h	per capita natural death rate of humans	0.07	[22]
μ_m	per capita natural death rate of the mosquitoes	$\frac{1}{15}$	[16]
δ_h	disease-induced death rate of infected human	0.089	[22]
δ_m	disease-induced death rate of infected mosquito	0.01	[22]
α_h	per capital rate of progression of humans from the exposed state to the infectious state	$\frac{1}{17}$	[22]
b	probability that a bite by an infectious mosquito results in transmission of disease to human	0.015	[23]
α_m	per capital rate of progression of mosquitoes from the exposed state to the infectious state	$\frac{1}{18}$	[22]
r	per capital recovery rate of humans from the infectious state to the recovered state	0.25	[24]
l	per capital rate at which human host acquire partial immunity due to natural recovery	0.17	[25]
υ_h	proportion of antibody produced by human in response to the incidence of infection caused by mosquito	0.5	Assumed
υ_m	proportion of antibody produced by mosquito in response to the incidence of infection caused by human	0.5	Assumed
φ_h	the 'vaccination rate' on human	0.5	Assumed
k_m	the per capital death induced rate of mosquitoes	0.5	Assumed
e	the per capita rate of loss of immunity from vaccinated human to partially immune human host to susceptible human	0.008333	Assumed
σ	the per capita rate of loss of immunity from partially immune human to susceptible human host to susceptible human	0.057	Assumed
ρ	the per capita rate of loss of immunity from recovered/immune human to partially immune human	0.015	Assumed
A_1	weight constant on infectious human	25	[26]
A_2	weight constant on the total population of mosquitoes	25	[26]
C_1	relative cost of intervention associated with the control using vaccination	20	[27]
C_2	relative cost of intervention associated with the control using treatment	65	[27]
C_3	relative cost of intervention associated with the control using indoor residual spray	10	[27]
C_{vc}	cost of vaccination per unit	\$2.5	Estimated
C_{tr}	cost of treatment per unit	\$2	[27]
C_{sp}	cost of IRS per unit area	\$1.5	[27]

The optimality system (5-7) is solved to obtain the optimal strategy. An iterative scheme has been used for solving the optimality system. Because of the transversality conditions (7), the adjoint equations are solved by the backward fourth order Runge-Kutta scheme using the iterative solutions of the state equation.

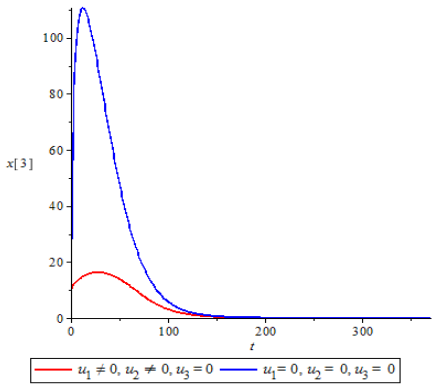

Fig 1a

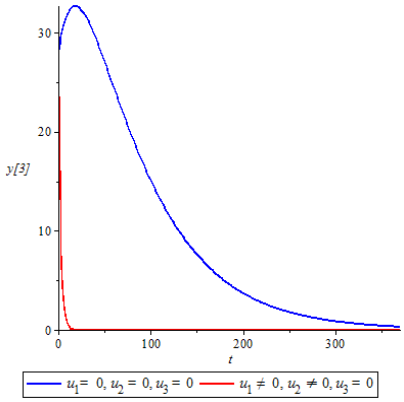

Fig 1b.

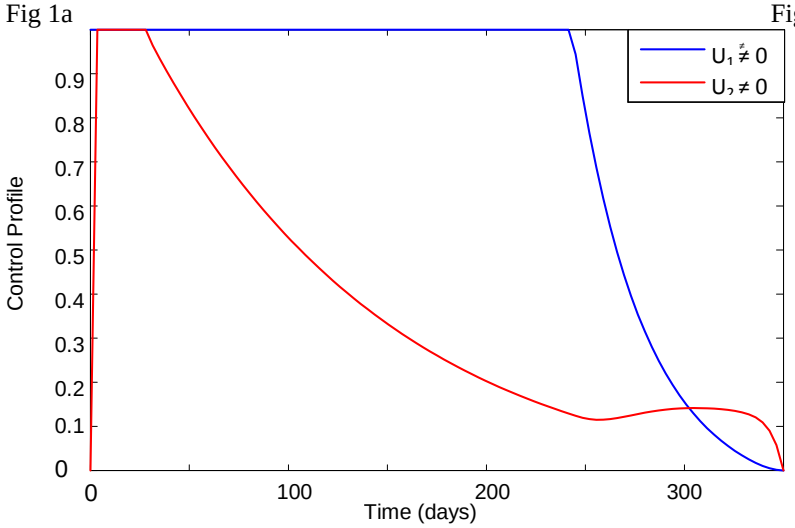

Fig 1c: *Simulations showing the effect of vaccination and treatment on infected human and mosquitoes population*

In this strategy, the vaccination (u_1) and the treatment (u_2) are used to optimize the cost objective functional (*J*) while we set the indoor spray (u_3) to zero. We observe a significant difference in the infected humans (x_3) and infected mosquitoes (y_3) with control when compared to (x_3) and (y_3) in the uncontrolled case, see figure 1a & 1b.

In the control profile in Fig 1c, the control u_1 is at upper bound for $t_f = 240 days$ and gradually reduces until reaching the lower bound, while control on treatment u_2 begins and maintain the upper bound for 25 days before falling gradually to the lower bound. The result indicates that a combination of vaccination outreach of 100% for 240 days and treatment outreach of 100% for 25 (days), the incidence of the disease will be minimized.

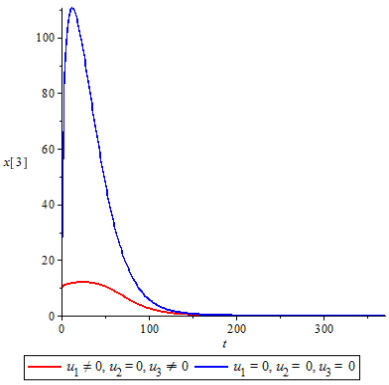

Fig 2a

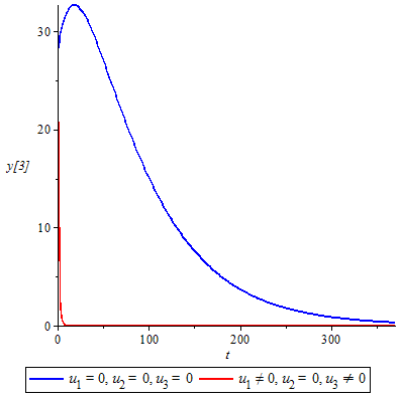

Fig 2b

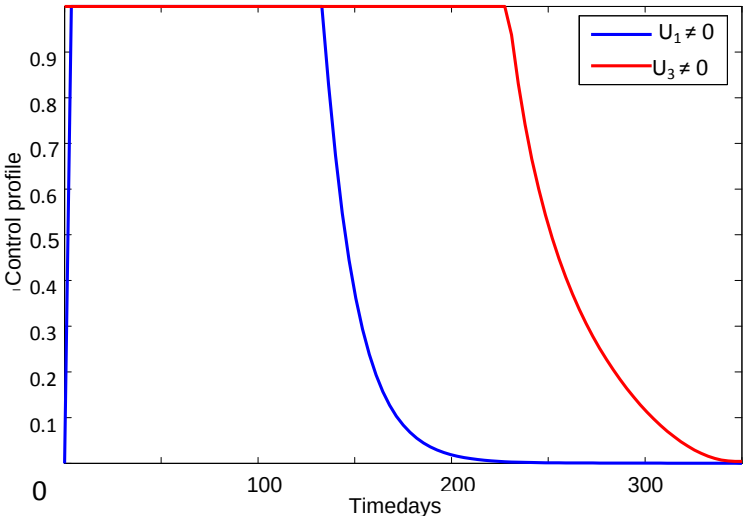

Fig 2c: *Simulations showing the effect of vaccination and spray of insecticide on infected human and mosquitoes population*

In this strategy, the vaccination parameter (u_1) and the indoor residual spray parameter (u_3) are used to optimize the cost objective functional (J) while we set the treatment parameter (u_2) at zero. We observed in figure 2a & 2b a significant difference in the infected humans (x_3) and infected mosquitoes (y_3) with control when compared to (x_3) and (y_3) in the uncontrolled state. The control profile in Figure 2c shows that the control on vaccination (u_1) is at upper bound for $t_f = 165 days$ while insecticide spray (u_3) is at upper bound for $t_f = 230 days$ before dropping to the lower bound.

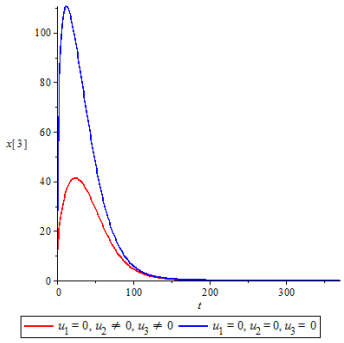

Fig 3a

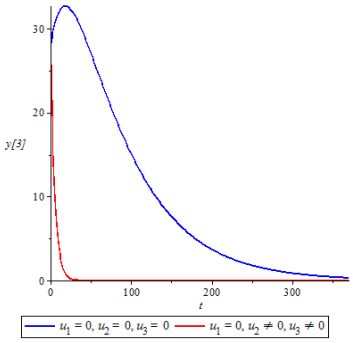

Fig 3b

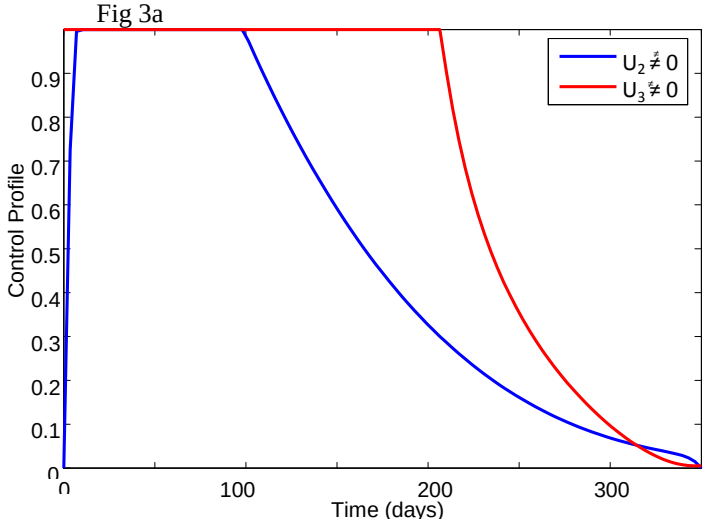

Fig 3c: *Simulations showing the effect of treatment and spray of insecticide on infected human and mosquitoes population*

In this strategy, the treatment parameter (u_2) and the indoor spray parameter (u_3) is used to optimize the cost objective functional (*J*) while we set the vaccination parameter (u_1) at zero. We observed in figure 3a & 3b, a significant difference in the infected humans (x_3) and infected mosquitoes (y_3) with control when compared to (x_3) and (y_3) in the uncontrolled state. The control profile as shown in figure 3c, shows that the optimal treatment control u_2 increases and maintain the upper bound to time $t_f = 100 days$, while the optimal insecticide spray u_3 is at the upper bound for $t_f = 90 days$ before falling gradually to the lower bound.

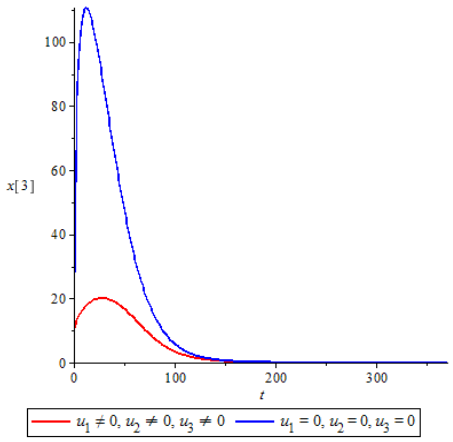

Fig 4a

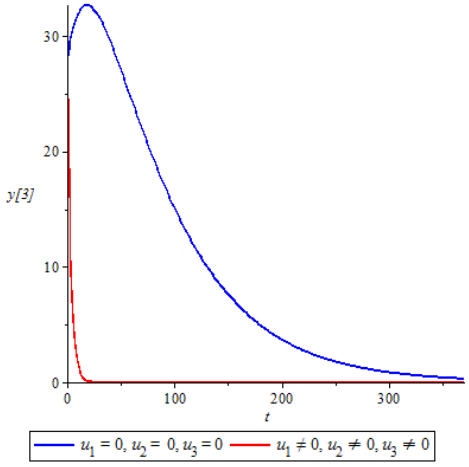

Fig 4b

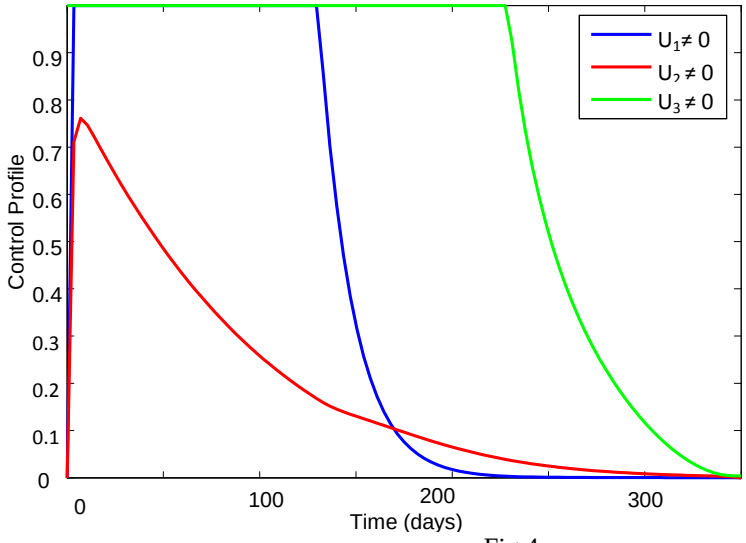

Fig 4c

Simulations showing the effect of vaccination,treatment and spray of insecticideon infected human and mosquitopopulations

In this strategy, the vaccination parameter (u_1), the treatment parameter (u_2) and the indoor spray parameter (u_3) are used to optimize the cost objective functional (*J*) with weight factors $C_1 = 25, C_2 = 65, C_3 = 10$ .We observe in figure 4a & 4b a significant difference in the infected humans (x_3) and infected mosquitoes (y_3) with control when compared to (x_3) and (y_3) in the uncontrolled case. The control profile shown in Figure 15c, shows that the control u_{11} is at upper bound for $t_f = 150 days$ while control u_2 starts high at about 77% and drops to the lower bound gradually over time. The control u_3 on the other hand is at upper bound for about $250 days$ before falling to the lower bound

Cost-Effectiveness Analysis

To measure the cost effectiveness of the control strategies, we consider the incremental cost effectiveness ratio (*ICER*). which allow comparing the cost-effectiveness of; combination of at least two (2) of the control parameter; use of vaccination, treatment of infected humans and the indoor residual spray. In *ICER*, when comparing two (2) competing intervention parameter incrementally, one intervention should be compared with the next-less-effective alternative. Based on the model simulation results, table 2 shows the strategies and their respective total infections averted and total costs of the strategies. The *ICER* is given by;

$$ICER = \frac{(C_c - C_0)}{(E_1 - E_0)} \quad (22)$$

Table 2: The Total Infection Averted and Total Costs for the Strategies

S/No	Strategies	Total Infection Averted	Total Cost ($)
i.	A	091.1213	29158.8160
ii.	B	104.0020	14560.2800
iii.	C	072.2802	15178.8420
iv.	D	090.0014	30150.4690

Table 3: Arrangement of Strategies in order of increasing effectiveness and incremental cost effectiveness ratio which was obtained using (22)

S/No	Strategies	Total Infection Averted	Total Cost ($)	*ICER*
i.	No Strategy	000.0000	0000.00000	-
ii.	C	072.2802	15178.8420	210.0000
iii.	D	090.0014	30150.4690	844.8427
iv.	A	91.1213	29158.8160	-885.4835
v.	B	104.0020	14560.2800	-1133.3651

The comparison of the strategies in table 6 indicates that strategy D is dominant over strategy C. Therefore, strategy D is costliest and less effective than strategy C. We therefore, eliminate D set of alternatives. We recalculate *ICER* in table 4

Table 4: The New *ICER* when strategy D is Eliminated

S/No	Strategies	Total Infection Averted	Total Cost ($)	*ICER*
i.	C	072.2802	15178.8420	210.0000
ii.	A	91.1213	29158.8160	741.9935
iii.	B	104.0020	14560.2800	-1133.3651

The comparison between strategies C and A shows that strategy A is costlier and less effective than strategy C. Therefore, we eliminate strategy A and recalculate *ICER* in table 5.

Table 5: The New *ICER* when strategy A is Eliminated

S/No	Strategies	Total Infection Averted	Total Cost ($)	ICER
i.	C	072.2802	15178.8420	210.0000
ii.	B	104.0020	14560.2800	-019.4996

With the result in table 5; we conclude that strategy C (combination of treatment of infected individuals and indoor residual spray) dominates in cost and less effective than strategy B. Therefore, we recommend strategy B (combination of vaccination and indoor spray) as the most cost-effective strategy.

5. Conclusion

This research considers 9 system of non-linear model equation with three control parameters for malaria transmission. We employed the optimal control to investigate and analyze the optimal strategies for controlling the transmission of malaria via vaccination, treatment and indoor residual spray as the control parameters and thus carried out cost evaluation of the model. We compared the cost of the intervention(s) in the cost objective functional using Pontryagin's Maximum Principle. We found out that if the marginal cost is greater than the marginal benefit, the strategy(s) will not be effective in controlling the malaria transmission. When equal, the strategy(s) could be applied and managed over a period of time as a control strategy.

However, whenever the marginal benefit of a strategy or combination of strategy(s) is greater than the marginal cost, then the strategy(s) could be considered as the best control strategy for controlling the transmission of the disease. Numerical simulations show how malaria transmission could be reduced whenever a control or combination(s) of the controls is/are applied. The incremental cost effectiveness ratio (*ICER*) is computed for the implementation of various combinations of the controls to determine the most cost effective strategy for controlling the disease. The *ICER* for the various control strategies shows that the most cost-effective strategy for the malaria control is the combination of vaccination and indoor residual spray.

Competing financial interests
The authors declare no competing financial interest

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