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Optimal Control Strategies and Cost Effectiveness Analysis of a Malaria Transmission Model

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Abstract
In this paper, a non-linear model with three control parameters for household of malaria has been study. The disease free equilibrium is obtained and the basic reproduction number is computed using the next generation matrix. We carry out cost evaluation of the model to optimize the cost of the intervention in the objective functional using Pontryagins's Maximum Principle (PMP). We apply the optimal control strategy to investigate and analyze the optimal cost for controlling the transmission of malaria using treated bednets, treatment and indoor residual spray as parameters. Numerical simulation has been carry out using Runge-Kutta of order four to calculate the incremental cost effectiveness ratio (*ICER*) for the implementation of various combinations of the parameters to determine the most cost effective strategy that check the spread of the disease. Our findings show that the most cost-effective strategy to check the spread of malaria is strategy F (the combination of treatment of infected individuals and indoor residual spray parameters).
Keywords: Optimal Control, Malaria Transmission, Cost-Effectiveness, Treated Bednets, Treatment, Indoor Spray

1. Introduction

Malaria is one of the deadliest infectious diseases that have claimed millions of lives around the globe. Malaria in human beings is caused by five species of parasites belonging to the genus *Plasmodium*. Four of these – *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae* and *Plasmodium ovale* – species affect human beings and are spread from one person to another via the bite of female mosquitoes of the genus *Anopheles*. There are about 400 different species of *Anopheles* mosquitoes, but only 30 of these are major vectors. Recently, human infections of malaria due to *Plasmodium knowlesi* have been recorded – these species of malaria are usually found among monkeys in certain forested areas of South-East Asia. Current information suggests that *Plasmodium knowlesi* malaria is not spread from person to person, but rather occurs in people when an *Anopheles* mosquito bites an infected monkey and transmits it to humans (zoonotic transmission) (WHO, 2015). They also reported that about 3.2 billion people or almost half of the world's population remain at risk of infection by the malaria parasite. Chitnis, Cushing & Hyman (2006) presented a model using ordinary differential equation for the spread of malaria in both human and mosquito populations. Obabiyi & Olaniyi (2016) formulated a model with discrete-age-structured human population which incorporated a class of vigilant human beings who adhered to the vector control measures. Mwanga, Haario & Nannyonga (2014) presented proposal to study the robustness of optimal control solutions under such parameter uncertainty. For the given model simulation, they created data so that a plausible variability of the epidemiological dynamics was covered. Kim *et al.* (2012) presented a plasmodium vivax malaria transmission model using a deterministic system of differential equations and investigated the optimal control strategy for Plasmodium Vivax malaria transmission in Korea. Their work shows that, if the cost of reducing the reproduction rate of the mosquito population was more than that of prevention measures which aimed to minimize mosquito-human contacts, the time optimal control of mosquito-human contacts needed longer time. Malarial infection could be controlled or prevented through drug treatment of malaria infected patients which would then reduce transmission of the disease, use of insecticide-treated nets (ITNs), indoor residual spraying and, in specific settings, larval control (WHO, 2012). Otieno, Koske & Mutiso (2016) studied a deterministic model for malaria transmission was studied and incorporated the intervention strategies for the most at risk groups (pregnant women and children under five years of age). Analyses of the model for cost effectiveness of the control strategies were undertaken. Silva & Torres (2013) studied a Mathematical model for the effects of insecticide treated nets (ITNs) on the transmission dynamics of malaria infection which took into account human behavior and introduced a supervision control, representing information, education, communication (IEC) campaigns for improving the ITN usage. They proposed an optimization model whose aim was to minimize the number of infected human beings while keeping the cost low. They found that an effective and optimal use of preventive measure without the use of larvacide is not possible if total elimination is the objective (Ozair *et al.* 2012). Seidu, Makinde & Daabo (2016) examined the implementation of various combinations of the parameters in order to determine the cost effective strategy that minimized spread of the diseases. An incremental cost-effective ratio was employed for the various control strategies which showed that the strategy that involved all the control parameters was the most cost effective strategy. This revealed that the fight against the disease should be multidimensional, to include

treatment, educational, sensitization and others. Bhatia, Fox-Rushby & Mills (2004) compared ITNs with IRS and found that the total costs of ITNs were greater than those of IRS, which was also reflected in the higher cost per capita (Rs. 56 versus Rs. 51). This was mainly due to the cost of mosquito nets and despite 74% of the total insecticide cost being attributed to IRS. Goodman & Mills (1999) assessed the range and quality of the evidence based on the cost-effectiveness of malaria prevention and treatment in sub-Saharan Africa.
Mathematical models are used as a tool to study and determine the optimal control strategy against malarial infection. This work attempts to study a mathematical model in order to determine the optimal cost control strategy using cost effectiveness of insecticide-treated nets (ITNs), indoor residual spraying (IRS), and drug treatment of malarial infection as parameters.

2. Model Formulation

In this paper, we partition the population of human (also referred to as host) at time t, denoted by $N_h(t)$ into the following sub-populations: susceptible population $S_h(t)$, exposed population $E_h(t)$, and infected population $I_h(t)$, Similarly, we partitioned the mosquitoes population (also referred to as vector) at time t, denoted by $N_v(t)$ into susceptible population $S_v(t)$, exposed population $E_v(t)$, and Infected sub-population $I_v(t)$,
The humans are recruited into the Susceptible population at constant rates Λ_h Susceptible individuals became exposed following contact with infected mosquito at a rates β. Exposed $E_h(t)$, individuals became infected at a rate ε_h. The Susceptible and Exposed populations die naturally at a rate μ_h. Those infected with malaria recovered after treatment at a rate σ_h and recover spontaneously at a rate γ_h Infected individuals may die naturally at a rate μ_h or due to the disease induced death rate δ_h. Similarly, the mosquitoes are recruited into the Susceptible population at constant rates Λ_v. Susceptible mosquitoes became exposed following contact with infected human. Those exposed to the parasite will move to the Infected class at a rate ε_v. However, the Infected mosquito may transmit the disease following contact with Susceptible humans who are not using the nets at a rate $(1-u_1(t))$. All susceptible, exposed and infected mosquitoes can may naturally or due to indoor spray of insecticide at a rate μ_{vb}. Below are the assumptions of the model with three control parameters;

(i) Susceptible individuals infected with malaria will move to exposed class before progressing to infectious class for both humans and mosquitoes.
(ii) Individuals infected with malaria will be effectively treated from the infection.
(iii) Treatment of infected individuals reduces the transmission of the disease.
(iv) Infectious individuals recover spontaneously.
(v) Susceptible and exposed individuals die naturally.
(vi) Infectious individuals die naturally and also due to the malaria disease.

2.1 Model diagram

The schematic diagram for the model with treated bednet, treatment of infected individual and indoor residence spray as control parameters is presented below:

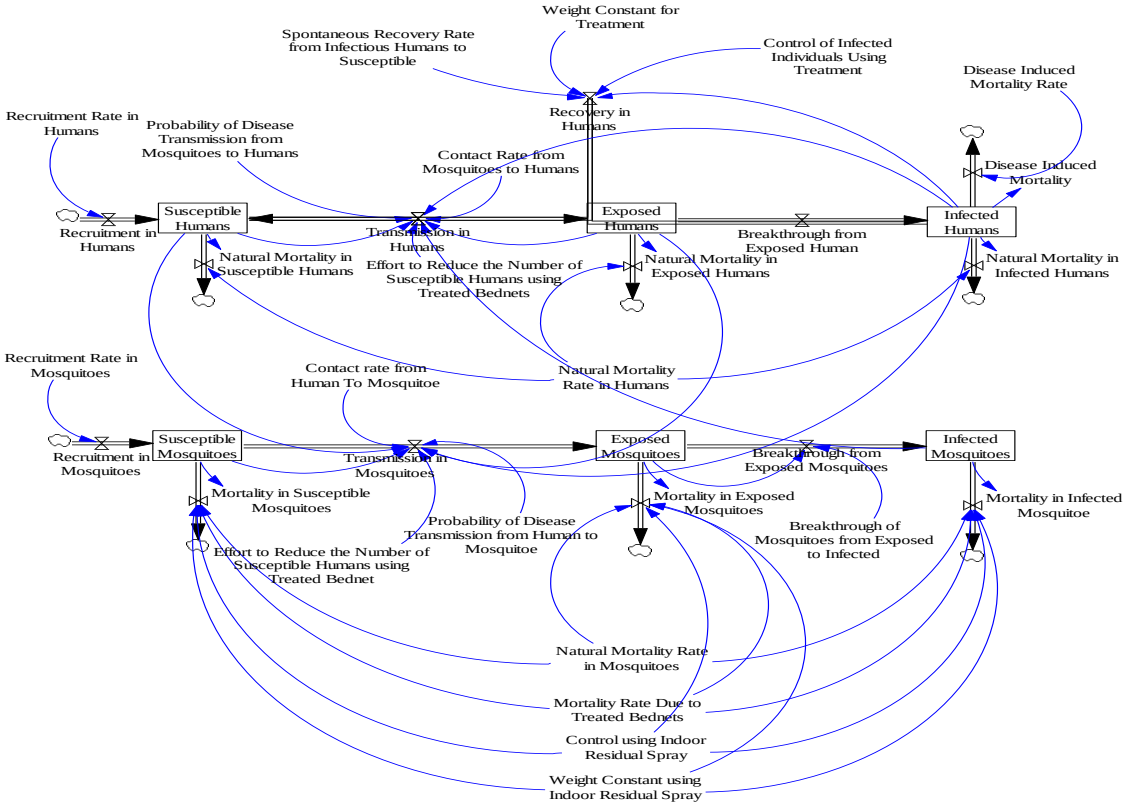

Figure 1: Flow diagram for the model with three control parameters

2.3 Model equations

$$\dot{S}_h(t) = \Lambda_h - [1-u_1(t)]\frac{p_1\beta I_v(t)}{N_h(t)}S_h(t) + [\gamma_h + \sigma_h u_2(t)]I_h(t) - \mu_h S_h(t) \quad (1)$$

$$\dot{E}_h(t) = [1-u_1(t)]\frac{p_1\beta I_v(t)}{N_h(t)}S_h(t) - \varepsilon_h E_h(t) - \mu_h E_h(t) \quad (2)$$

$$\dot{I}_h(t) = \varepsilon_h E_h(t) - [\gamma_h + \sigma_h u_2(t)]I_h(t) - (\mu_h + \delta_h)I_h(t) \quad (3)$$

$$\dot{S}_v(t) = \Lambda_v - [1-u_1(t)]\frac{p_2\beta I_h(t)}{N_h(t)}S_v(t) - (u_3\theta + \mu_{vb})S_v(t) \quad (4)$$

$$\dot{E}_v(t) = [1-u_1(t)]\frac{p_2\beta I_h(t)}{N_h(t)}S_v(t) - \varepsilon_h E_h(t) - (u_3\theta + \mu_{vb})E_v(t) \quad (5)$$

$$\dot{I}_v(t) = \varepsilon_v E_v(t) - (u_3\theta + \mu_{vb})I_v(t) \quad (6)$$

The rate of change of the total populations for human and mosquito are given by

$$\dot{N}_h(t) = \Lambda_h - \mu_h N_h(t) - \delta_h I_h(t) \quad (7)$$

$$\dot{N}_v(t) = \Lambda_v - (u_3 + \mu_{vb})N_v(t) \quad (8)$$

Table 1: Parameters and variables descriptions and values used in the model

Symbols	Description	Estimated values	References
Λ_h	Recruitment rate in humans	$10^3/(70\times365)$	Silva and Torres (2013)
Λ_v	Recruitment rate in mosquitoes	$10^4/21$	Silva and Torres (2013)
μ_h	Natural mortality rate in humans	$1/(70\times365)$	Silva and Torres (2013)
μ_{vb}	Natural mortality rate of mosquitoes	$1/21$	Silva and Torres (2013)
δ_h	Disease induced mortality rate in humans	10^{-3}	Silva and Torres (2013)
γ_h	Spontaneous recovery for humans	0.005	Okosun (2013)
p_1	Probability of disease transmission from mosquito to human	1	Silva and Torres (2013)
p_2	Probability of disease transmission from human to mosquito	1	Silva and Torres (2013)
σ_h	Weight constant for the use of treatment in humans	$1/4$	Silva and Torres (2013)
θ	Weight constant for the use of indoor spray	2.5	Okosun (2013)
ε_h	Progression rate from the exposed humans to infected humans	$1/17$	Okosun (2013)
ε_v	Progression rate from the total population of mosquitoes	$1/18$	Okosun (2013)
β	Biting rate of mosquito	0.3	Agusto (2012)
φ	Discount rate	$(3/365 \text{ to } 5/365)\%$	Okosun (2013)
A_1	Weight constant on infectious humans	25	Silva and Torres (2013)
A_2	Weight constant on the total population of mosquitoes	25	Silva and Torres (2013)
C_1	relative cost of the intervention associated with the control using ITNs	20	Okosun (2013)
C_2	relative cost of the intervention associated with the control using treatment	65	Okosun (2013)
C_3	relative cost of the intervention associated with the control using indoor residual spray	10	Okosun (2013)
C_{tb}	Cost of treated bednet per unit	\$(2.5-5)	Okosun (2013)
C_{tr}	Cost of treatment per unit	\$2 or more	Okosun (2013)
C_{S_v}	Cost of IRS per unit area	\$1.5	Okosun (2013)
$S_h(0)$	Susceptible humans initial value	800	Silva and Torres (2013)
$E_h(0)$	Exposed humans initial value	20	Okosun (2013)
$I_h(0)$	Infected humans initial value	0	Okosun (2013)
$S_v(0)$	Susceptible mosquitoes initial value	9500	Okosun (2013)
$E_v(0)$	Exposed mosquitoes initial value	20	Okosun (2013)
$I_v(0)$	Infected mosquitoes initial value	30	Okosun (2013)

3. Mathematical Analysis

3.1 Equilibrium State of the Model

In the absence of disease, we set equations (1) – (6) to zero and it is obtained as

$$M_0 = (S_h^*, E_h^*, I_h^*, S_v^*, E_v^*, I_v^*) = \left(\frac{\Lambda_h}{\mu_h}, 0, 0, \frac{\Lambda_v}{(u_3\theta + \mu_{vb})}, 0, 0 \right) \tag{10}$$

3.2 Basic Reproduction Number of the Model

The basic reproduction number can be defined as the average number of secondary infectious individual in a completely susceptible population. We use the next generation matrix method of computing R_0 described

by (Van den Driessche & Watmough, 2002) on the model (1) to (6). Let $x = (S_h, E_h, I_h, S_v, E_v, I_v)$, and $\frac{dx}{dt} = F(x) - V(x)$. Thus, $R_0 = \rho FV^{-1}$.

$$\left[\frac{\partial F_i(M_0)}{\partial X_j}\right]\left[\frac{\partial V_i(M_0)}{\partial X_j}\right]^{-1} = \nabla F_i \nabla V_i^{-1} \tag{11}$$

where

$$F = \begin{pmatrix} 0 & 0 & 0 & (1-u_1)p_1\beta \\ 0 & 0 & 0 & 0 \\ 0 & \frac{(u_1-1)p_2\beta\Lambda_v\mu_h}{\Lambda_h(\theta u_3+\mu_{vb})} & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \tag{12}$$

and

$$V = \begin{pmatrix} \varepsilon_h+\mu_h & 0 & 0 & 0 \\ -\varepsilon_h & \gamma_h+\sigma_h u_2+\mu_h+\delta_h & 0 & 0 \\ 0 & 0 & \varepsilon_v+\theta u_3+\mu_{vb} & 0 \\ 0 & 0 & -\varepsilon_v & \theta u_3+\mu_{vb} \end{pmatrix} \tag{13}$$

Using $V^{-1} = \frac{1}{\det V} \bullet adj(V)$, we have

$$FV^{-1} = \begin{pmatrix} 0 & 0 & (1-u_1)\frac{p_1\beta\varepsilon_v}{k_3k_4} & (1-u_1)\frac{p_1\beta}{k_4} \\ 0 & 0 & 0 & 0 \\ \frac{(1-u_1)p_2\beta\Lambda_v\mu_h\varepsilon_h}{k_1k_2\Lambda_h(\theta u_3+\mu_{vb})} & \frac{(1-u_1)p_2\beta\Lambda_v\mu_h}{k_2\Lambda_h(\theta u_3+\mu_{vb})} & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \tag{14}$$

Therefore,

$$R_0 = \sqrt{(1-u_1)^2 \frac{\Lambda_v p_1 p_2 \beta^2 \varepsilon_h \varepsilon_v \mu_h}{\Lambda_h(\varepsilon_h+\mu_h)(\gamma_h+\sigma_h u_2+\mu_h+\delta_h)(\varepsilon_v+\theta u_3+\mu_{vb})(\theta u_3+\mu_{vb})(\theta u_3+\mu_{vb})}} \tag{15}$$

3.3 Optimal Control

The objective functional for the model with treated bednet, treatment of infected individual and indoor residence spray is formulated and presented as control parameters aimed at controlling the transmission of the malaria infection. However, the optimal level of efforts needed to control the transmission of malaria at minimal cost had been investigated by minimizing the objective functional.

$$J(u_1, u_2, u_3) = \int_0^{t_f} (A_1 I_h(t) + A_2 N_v(t) + \frac{C_1}{2}u_1^2(t) + \frac{C_2}{2}u_2^2(t) + \frac{C_3}{2}u_3^2(t))dt \tag{16}$$

Given the objective functional (16), where t_f is the final time and the coefficients C_1, C_2, C_3 are the positive weights to balance the factors. The aim is to minimize the number of infected humans $I_h(t)$ and the total population of mosquitoes $N_v(t)$, while minimizing the cost of control 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 insecticide treated bednets, treatment of infected human and use of indoor residence spray respectively.

If the elimination of malaria is unachievable as a result of costs or social and environmental reasons, 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 (16). Our aim is to minimize the number of infected humans at the least cost

with 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

$$J(u_1^*, u_2^*, u_3^*) = \min_{u_1,u_2,u_3 \in \prod} J(u_1, u_2, u_3), \tag{17}$$

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 Pontryagin's Maximum Principle.

Theorem

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

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

Thus, our Hamiltonian is

$$\begin{aligned}
H \quad = \quad & A_1 I_h + A_2 N_v + \frac{C_1}{2} u_1^2 e^{-\varphi t} + \frac{C_2}{2} u_2^2 e^{-\varphi t} + \frac{C_3}{2} u_3^2 e^{-\varphi t} \\
+ \quad & \lambda_{S_h} \left[\Lambda_h - (1-u_1) \frac{p_1 \beta I_v}{N_h} S_h + (\gamma_h + \sigma_h u_2) I_h - \mu_h S_h \right] \\
+ \quad & \lambda_{E_h} \left[(1-u_1) \frac{p_1 \beta I_v}{N_h} S_h - \varepsilon_h E_h - \mu_h E_h \right] \\
+ \quad & \lambda_{I_h} \left[\varepsilon_h E_h - (\gamma_h + \sigma_h u_2) I_h - (\delta_h + \mu_h) I_h \right] \\
+ \quad & \lambda_{S_v} \left[\Lambda_v - (1-u_1) \frac{p_2 \beta I_h}{N_h} S_v - (\theta u_3 + \mu_{vb}) S_v \right] \\
+ \quad & \lambda_{E_v} \left[(1-u_1) \frac{p_2 \beta I_h}{N_h} S_v - \varepsilon_v E_v - (\theta u_3 + \mu_{vb}) E_v \right] \\
+ \quad & \lambda_{I_v} \left[\varepsilon_v E_v - (\theta u_3 + \mu_{vb}) I_v \right] \\
+ \quad & \lambda_{C_f} \left[C_{tb} u_1 S_h + C_{tr} u_2 I_h + C_{sv} \theta u_3 S_v + C_{sv} \theta u_3 E_v + C_{sv} \theta u_3 I_v \right]
\end{aligned} \tag{18}$$

where λ_{S_h}, λ_{E_h}, λ_{I_h}, λ_{S_v}, λ_{E_v}, λ_{I_v} and λ_{C_f} are the adjoint variables or co-state variables.

Theorem

Given an optimal controls u_1^*, u_2^*, u_3^* and the relation $S_h^*, E_h^*, I_h^*, S_v^*, E_v^* I_v^*$ of the corresponding state systems (1) – (6) that minimizes $J(u_1, u_2, u_3)$ over $[0, t_f]$. Then there exists adjoint variables λ_{S_h}, λ_{E_h}, λ_{I_h}, λ_{S_v}, λ_{E_v}, λ_{I_v}, λ_{C_f} satisfying

$$\left.\begin{aligned}
-\frac{d\lambda_{S_h}}{dt} &= -\left[-(1-u_1)\frac{p_1\beta I_v}{N_h}\lambda_{S_h} - \mu_h\lambda_{S_h} + (1-u_1)\frac{p_1\beta I_v}{N_h}\lambda_{E_h} + C_{tb}u_1\lambda_{C_f}\right]\\
-\frac{d\lambda_{E_h}}{dt} &= -\left[-\varepsilon_h\lambda_{E_h} - \mu_h\lambda_{E_h} + \varepsilon_h\lambda_{I_h}\right]\\
-\frac{d\lambda_{I_h}}{dt} &= -\left[A_1 + (\gamma_h+\sigma_h u_2)\lambda_{S_h} - (\gamma_h+\sigma_h u_2)\lambda_{I_h} - (\delta_h+\mu_h)\lambda_{I_h} - (1-u_1)\frac{p_2\beta S_v}{N_h}\lambda_{S_v} + (1-u_1)\frac{p_2\beta S_v}{N_h}\lambda_{E_v} - C_{tr}\theta u_2\lambda_{C_f}\right]\\
-\frac{d\lambda_{S_v}}{dt} &= -\left[A_2 - (1-u_1)\frac{p_2\beta I_h}{N_h}\lambda_{S_v} - (\theta u_3+\mu_{vb})\lambda_{S_v} + (1-u_1)\frac{p_2\beta I_h}{N_h}\lambda_{E_v} + C_{sv}\theta u_3\lambda_{C_f}\right]\\
-\frac{d\lambda_{E_v}}{dt} &= -\left[A_2 - \varepsilon_h\lambda_{E_v} - (\theta u_3+\mu_{vb})\lambda_{E_v} + \varepsilon_v\lambda_{I_v} + C_{sv}\theta u_3\lambda_{C_f}\right]\\
-\frac{d\lambda_{I_v}}{dt} &= -\left[A_2 - (1-u_1)\frac{p_1\beta S_h}{N_h}\lambda_{S_h} + (1-u_1)\frac{p_1\beta S_h}{N_h}\lambda_{E_h} - (\theta u_3+\mu_{vb})\lambda_{I_v} + C_{sv}\theta u_3\lambda_{C_f}\right]\\
-\frac{d\lambda_{C_f}}{dt} &= 0
\end{aligned}\right\} \quad (19)$$

with transversality conditions:

$$\lambda_{S_h}(t_f) = \lambda_{E_h}(t_f) = \lambda_{I_h}(t_f) = \lambda_{S_v}(t_f) = \lambda_{E_v}(t_f) = \lambda_{I_v}(t_f) = 0 \quad (20)$$

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

$$\left.\begin{aligned}
u_1^* &= \max\left\{0,\ \min\left(1,\ \frac{\frac{p_1\beta I_v^* S_h^*}{N_h}\left(\lambda_{E_h}-\lambda_{S_h}\right) + \frac{p_2\beta I_h^* S_v^*}{N_h}\left(\lambda_{E_v}-\lambda_{S_v}\right) - C_{tb}S_h^*\lambda_{C_f}}{C_1 e^{-\varphi t}}\right)\right\}\\
u_2^* &= \max\left\{0,\ \min\left(1,\ \frac{\sigma_h I_h^*(\lambda_{I_h}-\lambda_{S_h}) - C_{tr}\sigma_h I_h^*\lambda_{C_f}}{C_2 e^{-\varphi t}}\right)\right\}\\
u_3^* &= \max\left\{0,\ \min\left(1,\ \frac{\theta(S_v^*\lambda_{S_v} + E_v^*\lambda_{E_v} + I_v^*\lambda_{I_v}) - \theta C_{S_v}\lambda_{C_f}(S_v^*+E_v^*+I_v^*)}{C_3 e^{-\varphi t}}\right)\right\}
\end{aligned}\right\} \quad (21)$$

Proof

The differentiable equations governing the adjoint variables are obtained by differentiating the (18) and evaluated at the control parameter. Then the adjoint system can be written as

$$\frac{d\lambda_{S_h}}{dt} = -\frac{\partial H_c}{\partial S_h},\quad \frac{d\lambda_{E_h}}{dt} = -\frac{\partial H_c}{\partial E_h},\quad \frac{d\lambda_{I_h}}{dt} = -\frac{\partial H_c}{\partial I_h},\quad \frac{d\lambda_{S_v}}{dt} = -\frac{\partial H_c}{\partial S_v},\quad \frac{d\lambda_{E_v}}{dt} = -\frac{\partial H_c}{\partial E_v},\quad \frac{d\lambda_{I_v}}{dt} = -\frac{\partial H_c}{\partial I_v},$$
$$\frac{d\lambda_{C_f}}{dt} = -\frac{\partial H_c}{\partial C_f} \quad (22)$$

$$\left.\begin{aligned}
\frac{\partial H}{\partial S_h} &= (1-u_1)\frac{p_1\beta I_v}{N_h}\left(\lambda_{S_h}-\lambda_{E_h}\right)+\mu_h\lambda_{S_h}-C_{tb}u_1\lambda_{C_f}\\
\frac{\partial H}{\partial E_h} &= \varepsilon_h(\lambda_{E_h}-\lambda_{I_h})+\mu_h\lambda_{E_h}\\
\frac{\partial H}{\partial I_h} &= (1-u_1)\frac{p_2\beta S_v}{N_h}\left(\lambda_{S_v}-\lambda_{E_v}\right)+(\gamma_h+\sigma_h u_2)(\lambda_{I_h}-\lambda_{S_h})+(\delta_h+\mu_h)\lambda_{I_h}-C_{tr}\sigma_h u_2\lambda_{C_f}-A_1\\
\frac{\partial H}{\partial S_v} &= (1-u_1)\frac{p_2\beta I_h}{N_h}\left(\lambda_{S_v}-\lambda_{E_v}\right)+(\theta u_3+\mu_{vb})\lambda_{S_v}-C_{sv}\theta u_3\lambda_{C_f}-A_2\\
\frac{\partial H}{\partial E_v} &= \varepsilon_v(\lambda_{E_v}-\lambda_{I_v})+(\theta u_3+\mu_{vb})\lambda_{E_v}-C_{sv}\theta u_3\lambda_{C_f}-A_2\\
\frac{\partial H}{\partial I_v} &= (1-u_1)\frac{p_1\beta S_h}{N_h}\left(\lambda_{S_h}-\lambda_{E_h}\right)+(\theta u_3+\mu_{vb})\lambda_{I_v}-C_{sv}\theta u_3\lambda_{C_f}-A_2\\
\frac{\partial H}{\partial C_f} &= 0
\end{aligned}\right\} \quad (23)$$

with transversality conditions:

$$\lambda_{S_h}(t_f)=\lambda_{E_h}(t_f)=\lambda_{I_h}(t_f)=\lambda_{S_v}(t_f)=\lambda_{E_v}(t_f)=\lambda_{I_v}(t_f)=0 \quad (24)$$

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

$$u_1^*=\frac{\left[\frac{p_1\beta I_v^* S_h^*}{N_h}\left(\lambda_{E_h}-\lambda_{S_h}\right)+\frac{p_2\beta I_h^* S_v^*}{N_h}\left(\lambda_{E_v}-\lambda_{S_v}\right)-C_{tb}S_h^*\lambda_{C_f}\right]e^{\varphi t}}{C_1} \quad (25)$$

$$u_2^*=\frac{\left[\sigma_h I_h^*(\lambda_{I_h}-\lambda_{S_h})-C_{tr}\sigma_h I_h^*\lambda_{C_f}\right]e^{\varphi t}}{C_2} \quad (26)$$

$$u_3^*=\frac{\left[\theta(S_v^*\lambda_{S_v}+E_v^*\lambda_{E_v}+I_v^*\lambda_{I_v})-\theta C_{S_v}\lambda_{C_f}(S_v^*+E_v^*+I_v^*)\right]e^{\varphi t}}{C_3} \quad (27)$$

The optimality condition via Pontryagin's Maximum Principle states that

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

Because of the apriori boundedness of the solutions of both the state and the adjoint equations, we obtain the uniqueness of the system (19) – (21). The restriction on the length of time interval [0, t_f] in order to guarantee the uniqueness of the system. This is due to the opposite time orientations of (19) – (21); the state problem has initial values while the adjoint problems has final values. This restriction is common in control problems [14], [16] and [18].

3.4 Cost Evaluation Analysis

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

$$C_f=\min_{u_1,u_2,u_3}\int_0^{t_f}\left(C_{tb}u_1(t)S_h(t)+C_{tr}\sigma_h u_2(t)I_h(t)+\theta C_{sv}u_3(t)(S_v(t)+E_v(t)+I_v(t))\right)e^{-\varphi t}dt \quad (28)$$

subject to (1) – (6). Therefore, the corresponding Hamiltonian is given as

$$\left.\begin{aligned} H_C \quad = \quad & \left(C_{tb}u_1S_h + C_{tr}\sigma_h u_2 I_h + C_{sv}\theta u_3 S_v + C_{sv}\theta u_3 E_v + C_{sv}\theta u_3 I_v\right)e^{-\varphi t} \\ + \quad & \lambda_{S_h}\left[\Lambda_h - (1-u_1)\frac{p_1\beta I_v}{N_h}S_h + (\gamma_h + \sigma_h u_2)I_h - \mu_h S_h\right] \\ + \quad & \lambda_{E_h}\left[(1-u_1)\frac{p_1\beta I_v}{N_h}S_h - \varepsilon_h E_h - \mu_h E_h\right] \\ + \quad & \lambda_{I_h}\left[\varepsilon_h E_h - (\gamma_h + \sigma_h u_2)I_h - (\delta_h + \mu_h)I_h\right] \\ + \quad & \lambda_{S_v}\left[\Lambda_v - (1-u_1)\frac{p_2\beta I_h}{N_h}S_v - (\theta u_3 + \mu_{vb})S_v\right] \\ + \quad & \lambda_{E_v}\left[(1-u_1)\frac{p_2\beta I_h}{N_h}S_v - \varepsilon_v E_v - (\theta u_3 + \mu_{vb})E_v\right] \\ + \quad & \lambda_{I_v}\left[\varepsilon_v E_v - (\theta u_3 + \mu_{vb})I_v\right] \end{aligned}\right\} \tag{29}$$

where λ_{S_h}, λ_{E_h}, λ_{I_h}, λ_{S_v}, λ_{E_v}, λ_{I_v}, 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

$$-\frac{d\lambda_{S_h}}{dt} = \frac{\partial H_c}{\partial S_h},\quad -\frac{d\lambda_{E_h}}{dt} = \frac{\partial H_c}{\partial E_h},\quad -\frac{d\lambda_{I_h}}{dt} = \frac{\partial H_c}{\partial I_h},\quad -\frac{d\lambda_{S_v}}{dt} = \frac{\partial H_c}{\partial S_v},\quad -\frac{d\lambda_{E_v}}{dt} = \frac{\partial H_c}{\partial E_v},\quad -\frac{d\lambda_{I_v}}{dt} = \frac{\partial H_c}{\partial I_v} \tag{30}$$

Thus solving (29), we have

$$\left.\begin{aligned} -\frac{d\lambda_{S_h}}{dt} &= -\left[C_{tb}u_1e^{-\varphi t} - (1-u_1)\frac{p_1\beta I_v}{N_h}\lambda_{S_h} - \mu_h\lambda_{S_h} + (1-u_1)\frac{p_1\beta I_v}{N_h}\lambda_{E_h}\right] \\ -\frac{d\lambda_{E_h}}{dt} &= -\left[-\varepsilon_h\lambda_{E_h} - \mu_h\lambda_{E_h} + \varepsilon_h\lambda_{I_h}\right] \\ -\frac{d\lambda_{I_h}}{dt} &= -\left[C_{tr}\sigma_h u_2 e^{-\varphi t} + (\gamma_h + \sigma_h u_2)\lambda_{S_h} - (\gamma_h + \sigma_h u_2)\lambda_{I_h} - (\delta_h + \mu_h)\lambda_{I_h} - (1-u_1)\frac{p_2\beta S_v}{N_h}\lambda_{S_v} + (1-u_1)\frac{p_2\beta S_v}{N_h}\lambda_{E_v}\right] \\ -\frac{d\lambda_{S_v}}{dt} &= -\left[C_{sv}\theta u_3 e^{-\varphi t} - (1-u_1)\frac{p_2\beta I_h}{N_h}\lambda_{S_v} - (\theta u_3 + \mu_{vb})\lambda_{S_v} + (1-u_1)\frac{p_2\beta I_h}{N_h}\lambda_{E_v}\right] \\ -\frac{d\lambda_{E_v}}{dt} &= -\left[C_{sv}\theta u_3 e^{-\varphi t} - \varepsilon_h\lambda_{E_v} - (\theta u_3 + \mu_{vb})\lambda_{E_v} + \varepsilon_v\lambda_{I_v}\right] \\ -\frac{d\lambda_{I_v}}{dt} &= -\left[C_{sv}\theta u_3 e^{-\varphi t} - (1-u_1)\frac{p_1\beta S_h}{N_h}\lambda_{S_h} + (1-u_1)\frac{p_1\beta S_h}{N_h}\lambda_{E_h} - (\theta u_3 + \mu_{vb})\lambda_{I_v}\right] \end{aligned}\right\} \tag{31}$$

3.4.1 Cost evaluation for treated bednet

Differentiating (29) partially with respect u_1 (treated bednet) as control parameter, we get

$$\frac{\partial H_C}{\partial u_1} = C_{tb}S_h e^{-\varphi t} + \frac{p_1\beta I_v S_h}{N_h}(\lambda_{S_h} - \lambda_{E_h}) + \frac{p_2\beta I_h S_v}{N_h}(\lambda_{S_v} - \lambda_{E_v}) \tag{31}$$

This expression $\left(p_1\beta I_v S_h(\lambda_{E_h} - \lambda_{S_h}) + p_2\beta I_h S_v(\lambda_{E_v} - \lambda_{S_v})\right)/N_h$ in (31), is the total marginal benefit of the use of treated bednets and the $C_{tb}S_h$ is the marginal cost. If the marginal cost of the treated bednets is equal to the marginal benefit, then the optimal policy is achieved.

$$\left.\begin{array}{lll} u_1(t)=0 \ if & C_{tb}S_h e^{-\varphi t} > \dfrac{p_1\beta I_v S_h}{N_h}(\lambda_{E_h}-\lambda_{S_h})+\dfrac{p_2\beta I_h S_v}{N_h}(\lambda_{E_v}-\lambda_{S_v}) \\ u_1(t)\in(0,1) & if \quad C_{tb}S_h e^{-\varphi t} = \dfrac{p_1\beta I_v S_h}{N_h}(\lambda_{E_h}-\lambda_{S_h})+\dfrac{p_2\beta I_h S_v}{N_h}(\lambda_{E_v}-\lambda_{S_v}) \\ u_1(t)=1 \ if & C_{tb}S_h e^{-\varphi t} < \dfrac{p_1\beta I_v S_h}{N_h}(\lambda_{E_h}-\lambda_{S_h})+\dfrac{p_2\beta I_h S_v}{N_h}(\lambda_{E_v}-\lambda_{S_v}) \end{array}\right\} \quad (32)$$

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

3.4.2 Cost evaluation for treatment of infective humans

Similarly, differentiating (29) partially with respect u_2 (treatment) as control parameter, we get

$$\frac{\partial H_C}{\partial u_2} = C_{tr}\sigma_h I_h e^{-\varphi t} + \sigma_h I_h(\lambda_{S_h}-\lambda_{I_h}) \quad (33)$$

These $C_{tr}\sigma_h I_h$ and $\sigma_h I_h(\lambda_{I_h}-\lambda_{S_h})$ are the respective marginal cost and marginal benefit for treatment.

$$\left.\begin{array}{lll} u_2(t)=0 \ if & C_{tr}\sigma_h I_h e^{-\varphi t} > \sigma_h I_h(\lambda_{I_h}-\lambda_{S_h}) \\ u_2(t)\in(0,1) & if \quad C_{tr}\sigma_h I_h e^{-\varphi t} = \sigma_h I_h(\lambda_{I_h}-\lambda_{S_h}) \\ u_2(t)=1 \ if & C_{tr}\sigma_h I_h e^{-\varphi t} < \sigma_h I_h(\lambda_{I_h}-\lambda_{S_h}) \end{array}\right\} \quad (34)$$

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

3.4.3 Cost evaluation for indoor residual spray

Differentiating (29) partially with respect u_3 (indoor residual spray) as control parameter, we get

$$\frac{\partial H_C}{\partial u_3} = C_{S_v}\theta e^{-\varphi t}(S_v+E_v+I_v) - \theta(S_v\lambda_{S_v}+E_v\lambda_{E_v}+I_v\lambda_{I_v}) \quad (35)$$

The marginal cost for indoor spray against the total population of mosquitoes is given by $C_{S_v}\theta(S_v+E_v+I_v)$ while $\theta(S_v\lambda_{S_v}+E_v\lambda_{E_v}+I_v\lambda_{I_v})$ being the marginal benefit derived as a result of the indoor spray. The cost optimal target will be achieved if

$$\left.\begin{array}{lll} u_3(t)=0 \ if & C_{S_v}\theta e^{-\varphi t}(S_v+E_v+I_v) > \theta(S_v\lambda_{S_v}+E_v\lambda_{E_v}+I_v\lambda_{I_v}) \\ u_3(t)\in(0,1) & if \quad C_{S_v}\theta e^{-\varphi t}(S_v+E_v+I_v) = \theta(S_v\lambda_{S_v}+E_v\lambda_{E_v}+I_v\lambda_{I_v}) \\ u_3(t)=1 \ if & C_{S_v}\theta e^{-\varphi t}(S_v+E_v+I_v) < \theta(S_v\lambda_{S_v}+E_v\lambda_{E_v}+I_v\lambda_{I_v}) \end{array}\right\} \quad (36)$$

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

4. Numerical simulation

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 1. The strategies are:

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

The optimality system (19) – (21) is solved to obtain the optimal strategy. An iterative scheme has been used for solving the optimality system. Because of the transversality conditions (21), the adjoint equations are solved by the backward fourth order Runge-Kutta scheme using the iterative solutions of the state equation.

4.1 Strategy A: use of treated bednets and treatment

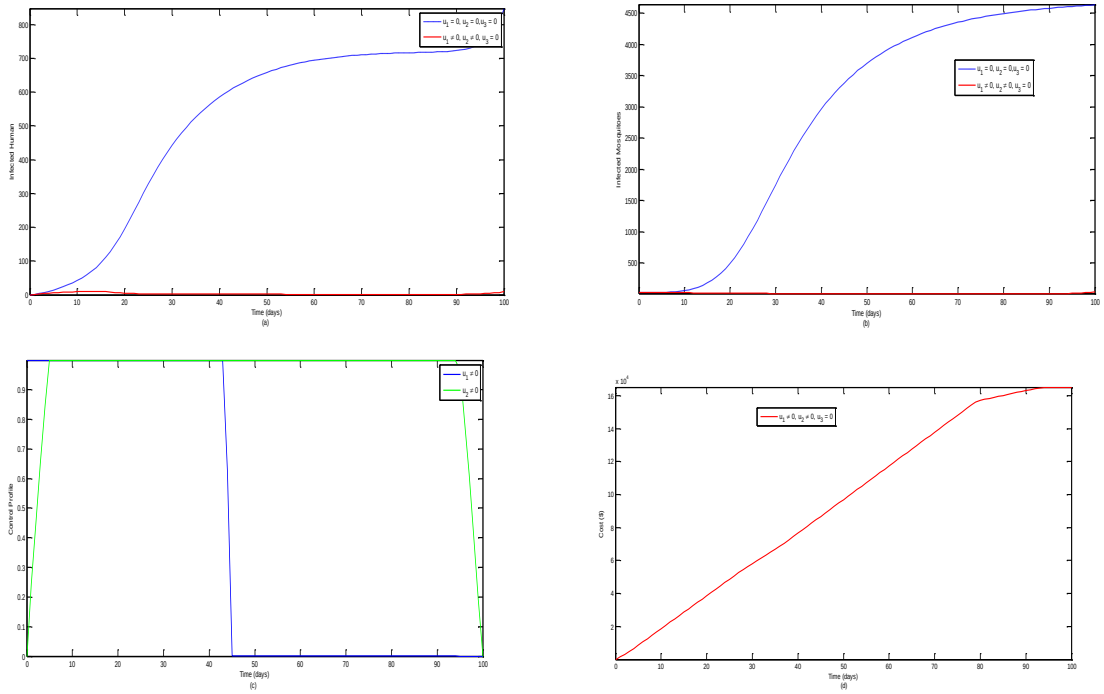

Figure 2. Implementing strategy (A) as the control parameter

In this strategy, the treated bednets (u_1) and the treatment (u_2) is 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 (I_h) and infected mosquitoes (I_h) with control when compared to (I_h) and (I_v) without control, see figure 2(a) – 2(d).

4.2 Strategy B: use of treated bednets and indoor residual spray

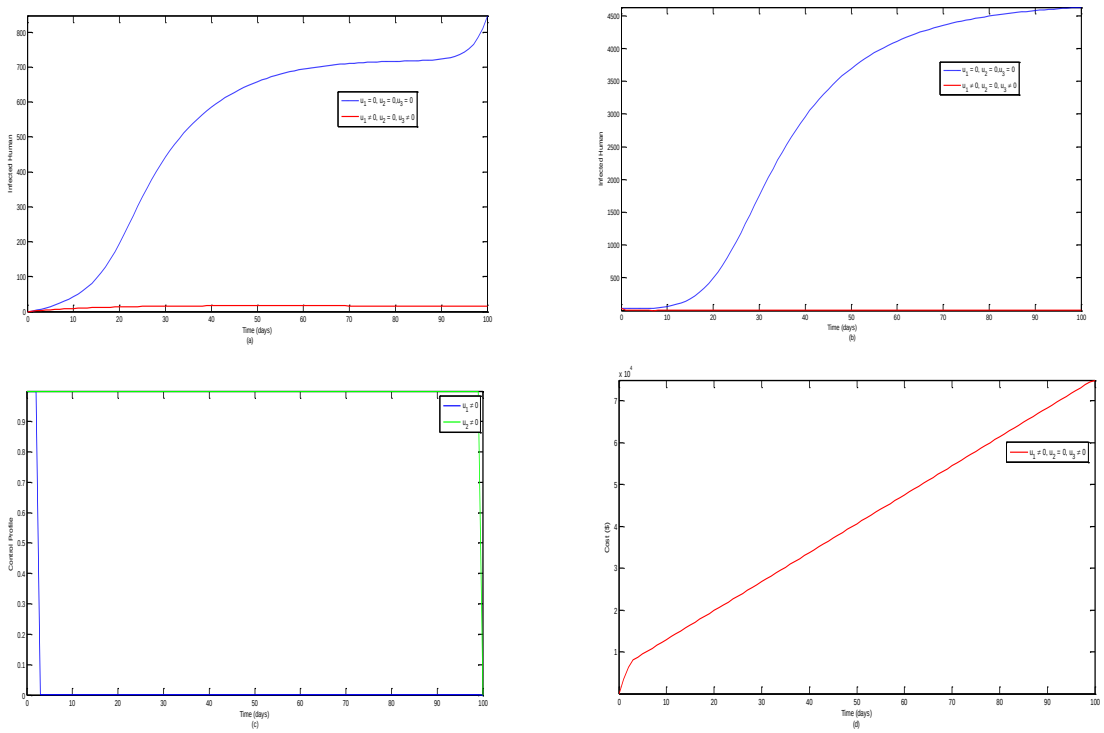

Figure 3. Implementing strategy (B) as the control parameter

In this strategy, the treated bednets parameter (u_1) and the indoor residual spray parameter (u_3) is used to optimize the cost objective functional (J) while we set the treatment parameter (u_2) at zero. We obseved in figure 3(a) – 3(d) a significant difference in the infected humans (I_h) and infected mosquitoes (I_h) with control when compared to (I_h) and (I_v) without control.

4.3 Strategy C: use of treatment and indoor residual spray

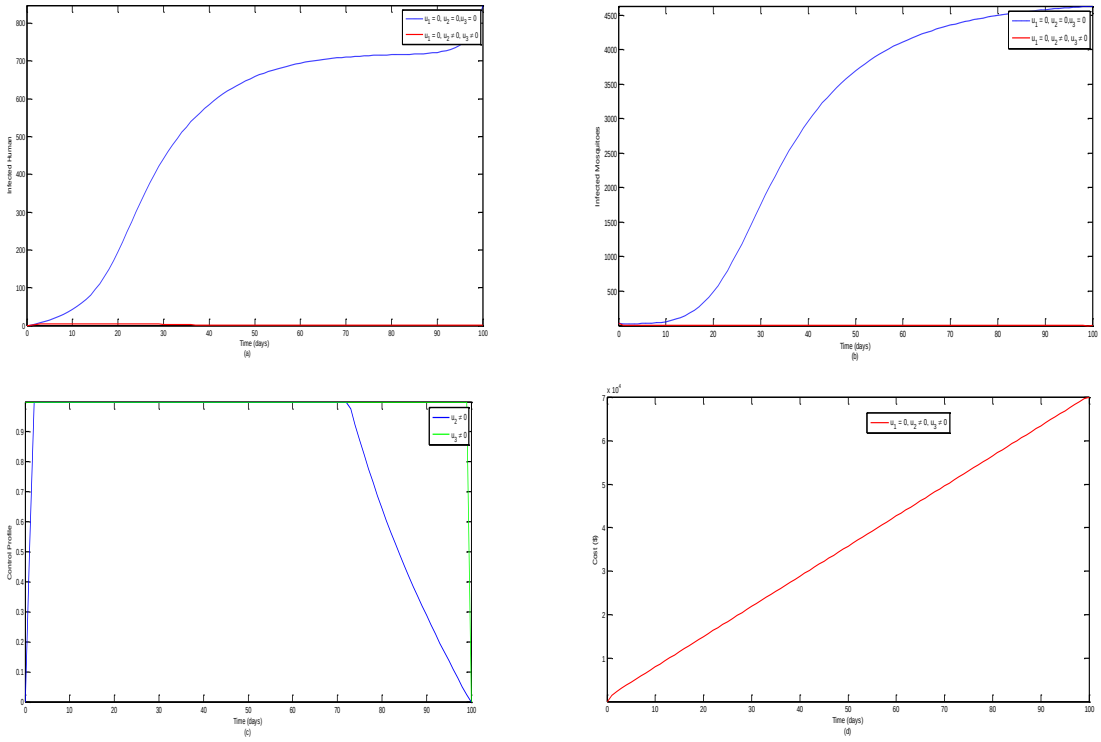

Figure 4. Implementing strategy (C) as the control parameter

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 treated bednets parameter (u_1) at zero. We observed in figure 4(a) – 4(d) a significant difference in the infected humans (I_h) and infected mosquitoes (I_v) with control when compared to (I_h) and (I_v) without control.

4.4 Strategy D: use of treated bednet, treatment and indoor residual spray

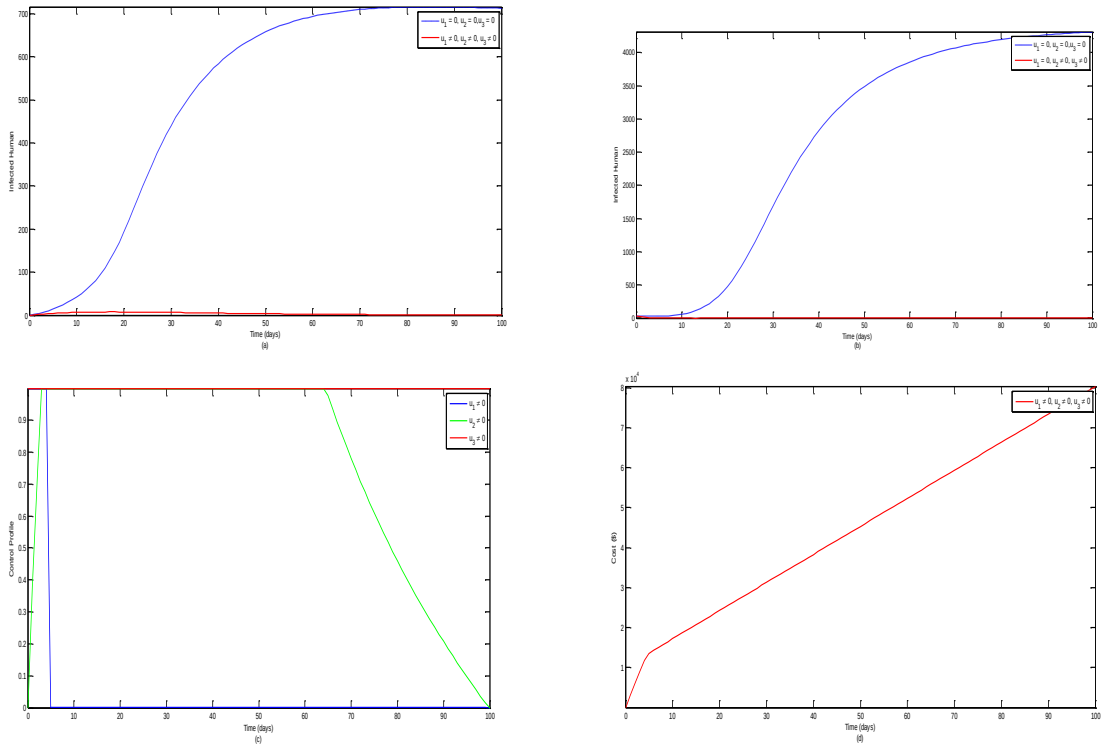

Figure 5. Implementing strategy (D) as the control parameter

In this strategy, the treated bednets parameter (u_1), the treatment parameter (u_2) and the indoor spray parameter (u_3) is used to optimize the cost objective functional (J). We observe in figure 5(a) – 5(d) a significant difference in the infected humans (I_h) and infected mosquitoes (I_v) with control when compared to (I_h) and (I_v) without control.

5. Cost-Effectiveness Analysis

We want to measure the cost effectiveness of the control strategies for the purpose of the study; 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 treated bednets, 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;

$$ICER = \frac{(C_c - C_0)}{(E_1 - E_0)} \tag{37}$$

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

S/N0	Strategies	Total infection averted	Total cost ($)
1	A	703.2915	164740
2	B	697.8022	84307
3	C	712.6687	71427
4	D	711.6938	73732

Table 3: Arrangement of Strategies in Order of Increasing Effectiveness and the Incremental Cost Effectiveness Ratio Which was Obtained Using (37)

S/N0	Strategies	Total infection averted	Total cost ($)	*ICER*
1	No strategy	0	0	-
2	EB	697.8022	84307	120.8179
3	DA	703.2915	164740	14652.6880
4	GD	711.6938	73732	-10831.32
5	FC	712.6687	71427	-2364.3451

Table 4: The New *ICER* when Strategy A is Eliminated

S/N0	Strategies	Total infection averted	Total cost ($)	*ICER*
1	B	697.8022	84307	120.8179
2	D	711.6938	73732	-761.2514
3	C	712.6687	71427	-2364.3451

The comparison of the strategies in table 4 indicates that strategy A is dominant over strategy B. Therefore, strategy A is costliest and less effective than strategy B. We therefore, eliminate A set of alternatives. We recalculate *ICER* in table 5.

Table 5: The *ICER* when strategy B is eliminated

S/N0	Strategies	Total Infection Averted	Total Cost ($)	*ICER*
1	D	711.6938	73732	103.6007
2	C	712.6687	71427	-2364.3451

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

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

6. Conclusion

This work considers a non-linear model with three control parameters of malaria transmission. We obtain disease free equilibrium (DFE) and the basic reproduction number R_0 of the model with three (3) control parameters using the next generation matrix. We carried out cost evaluation of the model and compared the cost of the intervention(s) in the cost objective functional using Pontryagin's Maximum Principle (PMP) where we found out that if the marginal cost is greater than the marginal benefit the strategy(s) will not be effective could not be consider in controlling the malaria transmission. Similarly, if the marginal cost is equal to the marginal benefit, the strategy(s) could be considered over a finite time as transmission control strategy. Furthermore, whenever the marginal benefit of strategy is larger than the marginal cost, then the strategy could be considered as the best prevention strategy for controlling the transmission. We applied the optimal control to investigate and analyze the optimal strategies for controlling the transmission of malaria using treated bednets, treatment and indoor spray as the control parameters. The results show significantly how the transmission is controlled whenever a control(s) is used. The numerical simulation using Runge-Kutta of order four, the result shows 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 that can control the disease. The *ICER* for the various control strategies shows that the most cost-effective strategy for the malaria control is the combination of treatment and indoor spray together, follow by the combination of all the three (3) control strategies.

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