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Optimal Control Analysis of an Age-Structured Malaria Model Incorporating Children under Five Years and Pregnant Women

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Authors' contributions

This work was carried out in collaboration among all authors. Author GTAT designed the study, performed the analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors FTO and GAO managed the analyses of the study. Author GTAT managed the literature searches. All authors read and approved the final manuscript.

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Abstract

In this article, we apply the optimal control theory to a new age-structured malaria model with three infectious compartments for people under five years, over five years and pregnant women. The model is formulated for malaria endemic areas in the world and the following malaria control strategies ITN, IRS, Chemoprophylaxis and Improved Clinical Treatment were examined and analysed on the mode. The Cost-effectiveness Analysis points out that more attention should be given Insecticide -Treated bed nets (ITNs) in order to eliminate the malaria disease globally because the female Anopheles mosquitoes need human blood to lay their eggs. The expression for the effective reproduction number (R_e) has been derived by using the next-generation method. The impact of the controls on the R_e was studied and it came out that all the four controls have a positive impact such that the ITNs can reduce R_e to zero as the value of ITNs approaches one. Pontryagin's Maximum Principle was applied to analyse the optimal control model theoretically and the optimality system was solved numerically through an iterative scheme.

The optimal plots (Figs. 4-8) reveal that best control strategies for malaria elimination is the combination of ITN, Chemoprophylaxis and Improved Clinical Treatment. However, the Cost-effectiveness Analysis points out that ITN is economically best solution for fighting malaria in poor malaria endemic areas.

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Keywords: Insecticide Treated bed nets (ITNs); Indoor Residual Spraying (IRS); chemoprophylaxis; improved clinical treatment; effective reproduction number.

1 Introduction

Optimal Control Theory (OCT) is a powerful mathematical tool which is used in making fruitful decisions in dynamical systems [1,2]. It has also been applied in disease modelling [3], however, not much has been done in the area of malaria modelling, Even the few applications of the theory to existing malaria modelling do not include models having separate compartments for children under 5years and pregnant women [4,5,6,7]. The technique behind applying Optimal Control Theory to malaria modelling is to minimise the infected humans and vector population while maximizing the recovered human population using limited resources available [2]. The technique for analyzing disease models when one is applying Optimal Control Theory comes from the Pontryagin Maximum Principle (PMP). PMP is a classical result from optimal control theory which provides a necessary condition that must be satisfied by an optimal solution [3,8]. We extend the existing malaria models on the time-optimal control of the SI epidemic model with compartments for children under five years and pregnant women. The control strategies to be incorporated in our model are Insecticide Treated bed nets (ITNs), Indoor Residual Spraying (IRS), Chemoprophylaxis and Improved Antimalarial drugs. Stability analysis has carried out on the model in this article in a previous article entitled "Analysis of an Age-Structured Malaria Model Incorporating Infants and Pregnant Women" [9]. Sensitivity analysis in the previous article proved that malaria can be controlled or eliminated if the following parameters such as biting rates, recruitment rate and density-dependent natural mortality rate for mosquitoes and clinical recovery rates for humans are controlled. Therefore, the focus of this article is to apply optimal control theory to the said new model.

2. Previous Work

Makinde and Okosun, [10] established the optimal strategies for malaria control with infected immigrants. Also, Okosun, [11], Makinde and Okosun, [10], and Okosun et al. [6] applied optimal control theory to a continuous malaria model that includes treatment and vaccination with waning immunity to study the impact of possible vaccination with treatment strategies in controlling the spread of malaria. Silva and Torres [12] presented an optimal control approach to malaria prevention via ITNs in which supervision control was introduced representing information, education, communication (IEC) campaigns for improving the ITN usage. The optimal control problem was developed and solved with the aim of minimizing the number of infected humans while keeping the cost low. The numerical results showed the effectiveness of the optimal control interventions. Only one prevention strategy, that is, ITN, was investigated. Furthermore, Rafikov et al. [13] formulated a continuous model for malaria vector control with the aim of studying how genetically modified mosquitoes should be introduced in the environment using optimal control problem strategies.

Okosun et al. [6] showed that a possible vaccination combined with an effective treatment regime would reduce the spread of the disease. Their research based on the combined vaccination and treatment strategy. Optimal control strategy for Plasmodium vivax malaria transmission in Korea was investigated using a deterministic system of differential equations. This work suggested that if the cost of reducing the reproduction rate of the mosquito population is more than that of prevention measures to minimize mosquito-human contacts, the control of mosquito-human contacts needs to be taken for a longer period of time, comparing the other situations [14]. Magombedze et al. [15] studied optimal control of malaria chemotherapy in which an intra-host mathematical model of malaria that describes the interaction of the immune system with the blood stage malaria merozoites was done. The model was modified by incorporating the effects of malaria drugs that target blood stage parasites. The optimal control represented percentage effects of the chemotherapy of chloroquine in combination with chlorpheniramine on the reproduction of merozoites in erythrocytes. Their results indicated that highly toxic drugs and small dosage sizes have the potential of improving the quality of life and reduce economic costs of therapy.

Mwamtobe in his Ph.D. thesis applied optimal control theory to study optimal intervention strategies for

malaria epidemic in Karonga district in Malawi. Prevention strategies such as insecticide treated bed-nets (ITNs) and indoor residual spraying (IRS) and treatment of infected individuals were the control strategies considered in the study. Analysis of the model suggested that effective control or eradication of malaria can be achieved by the combination of protection and treatment measures. The work also suggested that making control strategies readily available to both populations can play an important role in reducing or eradicating malaria disease in Karonga District or in the entire Malawi nation. His work finally recommended that a model with children under five years and pregnant women could shed more light on which intervention strategy to prioritize to the specific groups [4]. Otieno et al. [16] study transmission dynamics and optimal control of malaria in Kenya. Their model use SEIRS type for the human population with temporary immunity after recovery and the mosquito population was described by the SEI model. The susceptible humans consist of children under the age of five and pregnant women. The following control strategies were considered in this model: (i) the use of treated bed nets, (ii) treatment of infective humans, (iii) spray of insecticides and (iv) treatment to protect pregnant women and their newborn children: intermittent preventive treatment for pregnant women (IPTp). The work suggested that the optimal control strategy for malaria control in endemic areas is the combined use of treatment and IRS; in epidemic-prone areas, it is the use of treatment and IRS; in seasonal areas, it is the use of treatment, and in low - risk areas, is the use of ITNs and treatment. The work finally concluded that following these strategies can effectively reduce the spread of malaria disease in different malaria transmission settings in Kenya.

3 Model Description and Formulation

The model proposed in this paper is an Age-Structured Malaria model having separate Infectious Compartments for people under 5 years, over 5 years, and Pregnant women. Two populations, that is, humans and adult female Anopheles mosquitoes are considered in the model (1). The human population is partition into susceptible S_H , infected humans under 5years I_I , infected humans over 5years I_A and infected pregnant women I_P . The mosquito population is also divided into Susceptible S_M and infected mosquitoes. I_M . The total population sizes at time t for humans and mosquitoes are denoted by $N_H(t)$ and $N_M(t)$ respectively. We employ the SIS type model for humans to describe the disease with malaria acquired immunity for those over 5years as long as they continue to live in malaria endemic areas and for mosquitoes, we use SI model type since mosquitoes do not recovery from the parasite infection. We incorporate four time-dependent control measures simultaneously: (1) Insecticide Treated bed nets (ITNs), (2) Indoor Residual Spraying (IRS), (3) Chemoprophylaxis and (4) Improved Antimalarial drugs. Detailed description of the control functions is given in Table 1. $S_H(t)$ represents the number of individuals not yet infected with the malaria parasite at time t and $I_I(t)$, $I_A(t)$ and $I_p(t)$ represent those who are infected malaria parasites and are capable of transmitting the parasites to susceptible mosquitoes. The susceptible humans consist of individual under 5 years, over 5years and pregnant women. It is assumed every infected person recovers after a one-time period and also through antimalarial drugs (clinical treatment). The immunity can be lost through interruption of exposure, that is, if an immune person migrates to a non- endemic malaria region where the exposure to the disease is not available, then he or she automatically loses their immunity. The immunity can be restored through numerous years of repeated infections, therefore a person living in malaria endemic area cannot lose his or her immunity as long as they continue to stay in the area and the exposure to the disease continues. The advantage of those with malaria immunity is that frequency of the malaria infections is reduced, which could delay the frequency of malaria infections in those over 5years [17]. Newborns have malaria immunity up to the first 3–6 months of their lives due to passive transfer of maternal antibodies through the placenta. After these months, they are vulnerable to clinical malaria episodes until they develop their own immunity [18]. People enter the human population through the susceptible (S_H) compartment at per capita recruitment rate (Z_H). When the malaria infection begins in humans, the individuals under 5years move to I_I compartment, over 5years who are not pregnant move to I_A compartment and pregnant women move to I_P compartment. Those in infectious compartments I_I and I_A and I_P are clinically treated (that is, gametocytes are completely cleared) at the rates Λ_I , Λ_A and Λ_P respectively, before they return to S_H compartment for re-infection. . Also, the infectious individuals can exit the human population through disease-induced deaths at the rates $(\boldsymbol{\pi_I})$, $(\boldsymbol{\pi_A})$ and $(\boldsymbol{\pi_P})$ respectively**.** The infectious under 5years can join the infectious over 5years at the

rate (ϕ) when they attain aged 5 and also infectious over 5years can join the infectious pregnant women compartment at the rate (Ω) when they become pregnant. It is assumed that infectious pregnant women cannot join the infectious over 5years compartment since most infectious pregnant women are clinically treated before they give birth. Humans can also exit their population through density-dependent mortality rate (μ_H) in each compartment.

The adult female Anopheles mosquito becomes infectious when it bites gametocyte carriers (that is, infectious humans) and ingests the gametocytes. The mosquito in the S_M compartment becomes infectious and moves to the I_M compartment only when the malaria parasites becomes mature and moves to the mosquito's salivary glands and remains in the infectious status for life. The mosquito exits its population through density-dependent mortality at the rate (μ_M) or mortality due to insecticides but cannot die directly from the malaria parasite infection [19]. Female mosquitoes enter their population through the susceptible compartment at per capita recruitment rate (Z_M). It is assumed that there is no immigration of infectious individuals in the human population.

Table 1. Control functions

Control functions	Description
$\boldsymbol{u_1}$	It is a control variable which represents the fraction of individuals using the Insecticide Treated bed nets (ITNs). The impact of the control on the model is that, it will prevent the mosquitoes from biting the human population in sleeping areas and also reduce recruitment rate for mosquitoes, because the mosquitoes need blood to lay their eggs. In order to simplify the model, the force of infections are multiplied It by the factor $(1-u_1(t))$, .which represents the failure rate of using ITNs [5]. It benefits the members of the human population equally or uniformly.
$\boldsymbol{u_2}$	It is a control variable representing the fraction of mosquitoes killed by indoor residual spraying (IRS). The IRS will reduce the mosquito population by killing the mosquitoes, especially those that rest indoors after taken a blood meal (so called endophilic mosquitoes) [20]. The mosquito population is reduced by $-\beta u_2(t)S_M$ in susceptible population and $-\beta u_2(t)I_M$ in infectious population It benefits the members of the human population equally or uniformly, where β is the rate at which mosquitoes are killed by insecticides application.
$\boldsymbol{u_3}$	It is a control variable which represents the fraction of people under 5years using Chemoprophylaxis. It will prevent the malaria parasite from developing and growing in the human body. Therefore, when one takes Chemoprophylaxis, he or she will not develop malaria infection during the period. In order to simplify the model, the infectious people under 5years population is decreased by $u_3(t)I_I$ and susceptible human population is increased by $u_3(t)I_I$
$\boldsymbol{u_4}$	It is a control variable which represents the fraction of people over 5years using Chemoprophylaxis. The infectious people over 5years population is decreased by $u_4(t)I_A$ and susceptible human population is increased by $u_4(t)I_A$.
$\boldsymbol{u_5}$	It is a control variable which represents the fraction of pregnant women population using Chemoprophylaxis. The infectious pregnant women population is decreased by $u_5(t)I_P$ and susceptible human population is increased by $u_5(t)I_P$.
$\boldsymbol{u_6}$	It is a control variable which represents the effort to increase the current recovery rate for people under 5years through the use of improved Antimalarial drugs
$\boldsymbol{u_7}$	It is a control variable which represents the effort to increase the current recovery rate for people over 5years through the use of improved Antimalarial drugs
$\boldsymbol{u_8}$	It is a control variable which represents the effort to increase the current recovery rate for pregnant women through the use of improved Antimalarial drugs

The Flow Chart for malaria transmission dynamics without the four control strategies is given below as Fig. 1.

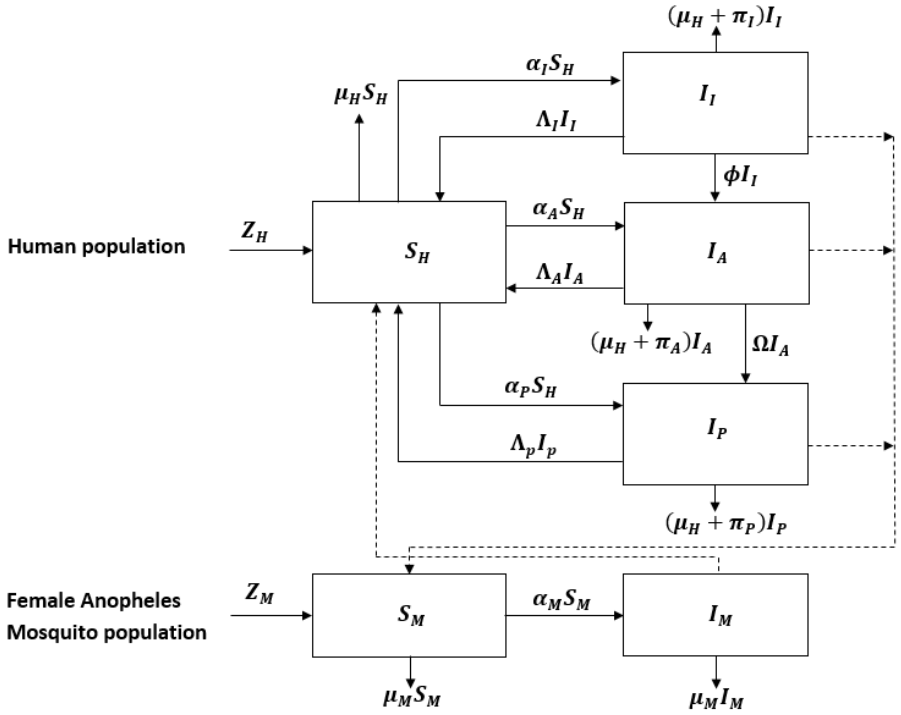

Fig. 1. Flow Chart for the malaria transmission dynamics without the four control strategies

The Flow Chart for malaria transmission dynamics with the four control strategies is given below as Fig. 2.

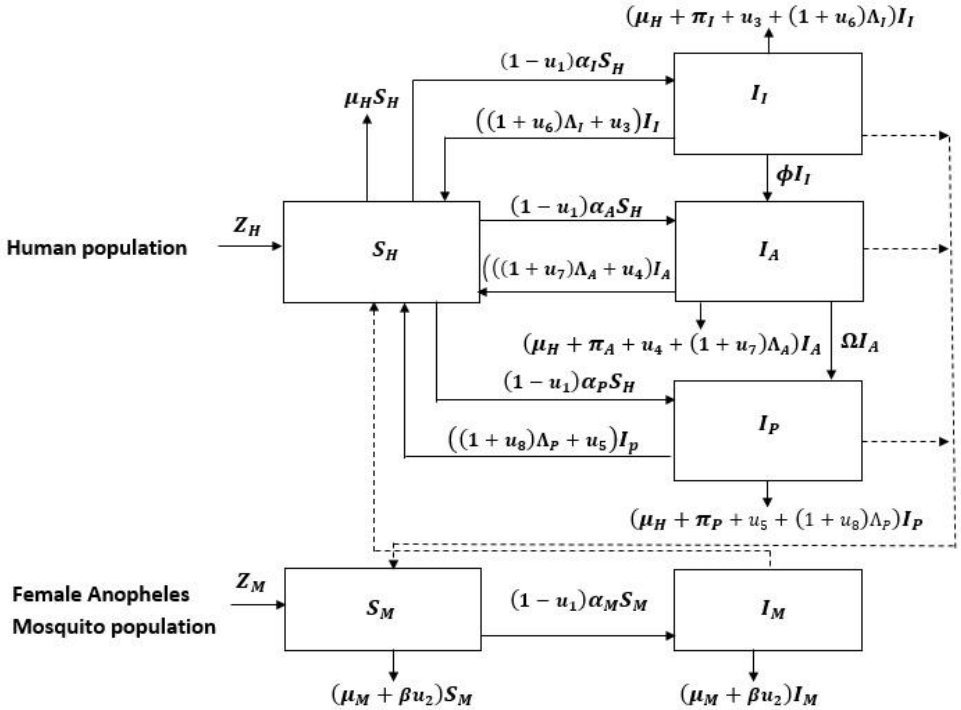

Fig. 2. Flow Chart for the malaria transmission dynamics with the four control strategies

The flow chart demonstrates the interactions between human and mosquito populations and the movement of individuals from one compartment to another. The solid arrows show progression of individuals from one compartment to another and the dotted arrows show how the humans and mosquitoes interact and infect each other. Susceptible humans in S_H get infected when infectious mosquitoes from I_M bite them. They then progress to I_I , I_A and I_P when they are infectious. Humans in I_I , I_A and I_P move to S_H compartment for re-infection after clinical treatment. Susceptible mosquitoes in S_M get infected when they bite humans in I_I , I_A and I_P compartments and then move to I_M when they are infectious. Mosquitoes remain in I_M until they die through density-dependent mortality or insecticide (IRS). Humans exit their population through density-dependent mortality and disease-induced mortality. Mosquitoes enter their population at per capita recruitment rate and Humans enter through birth or immigration. Chemoprophylaxis and Improved Antimalarial drugs will reduce the number of humans in I_I , I_A and I_P compartments and increase the number of people in S_H compartment. IRS will reduce the mosquitoes in both S_M and I_M compartments and ITNs will also reduce the force of infections (α_I , α_A , α_P and α_M).

Detailed description of the parameters and their values of figure 1 are given in Table 2 below.

Table 2. The parameters for the model 1 [21]

Parameter	Value	Description
Z_H	414521	Recruitment for the human population. Dimension: Humans × Time^{-1}
Z_M	134267979835	Recruitment rate for mosquitoes. Dimensions: Time^{-1}
μ_H	0.016	Density-dependent natural mortality rate for humans. Dimensions: Time^{-1}
μ_M	0.058176	Density-dependent natural mortality rate for adult female Anopheles mosquitoes. Dimensions: Time^{-1}
π_I	0.020605	Per capita disease-induced mortality rate for people under 5 years. Dimensions: Time^{-1}
π_A	0.19113	Per capita disease-induced mortality rate for people over 5 years Dimensions: Time^{-1}
π_P	0.49273	Per capita disease-induced mortality rate for pregnant women Dimensions: Time^{-1}
Λ_I	0.11855	Clinical recovery rate for people under 5 years. Dimensions: Time^{-1}
Λ_A	0.14348	Clinical recovery rate for people over 5 years. Dimensions: Time^{-1}
Λ_P	0.14154	Clinical recovery rate for the pregnant women. Dimensions: Time^{-1}
θ_{MH}	0.00016937	Fraction of bites that successfully infect humans
θ_{HM}	0.00454	Fraction of bites that successfully infect mosquitoes.
Φ_I	0.33575	Number of bites on people under 5 years per female mosquito per unit time. Dimensions: Time^{-1}
Φ_A	0.98982	Number of bites on people over 5 years per female mosquito per unit time. Dimensions: Time^{-1}
Φ_P	0.012704	Number of bites on pregnant women per female mosquito per unit time. Dimensions: Time^{-1}
ϕ	0.10743	Rate of progression from I_I to I_A compartment. Dimensions: Humans × Time^{-1}
Ω	0.016744	Rate of progression from I_A to I_p compartment. Dimensions: Humans × Time^{-1}

4 Malaria Models

Putting the assumptions and the ideas together, the malaria model without the four control is given by a system of six (6) differential equations as stated in (1) below.

$$\left.\begin{aligned}
\frac{dS_H}{dt} &= Z_H + \Lambda_I I_I + \Lambda_A I_A + \Lambda_P I_P - \alpha_I S_H - \alpha_A S_H - \alpha_P S_H - \mu_H S_H \\
\frac{dI_I}{dt} &= \alpha_I S_H - \Lambda_I I_I - (\mu_H + \pi_I) I_I - \phi I_I \\
\frac{dI_A}{dt} &= \alpha_A S_H + \phi I_I - (\mu_H + \pi_A) I_A - \Lambda_A I_A - \Omega I_A \\
\frac{dI_P}{dt} &= \alpha_P S_H + \Omega I_A - (\mu_H + \pi_P) I_P - \Lambda_P I_P \\
\frac{dS_M}{dt} &= Z_M - \alpha_M S_M - \mu_M S_M \\
\frac{dI_M}{dt} &= \alpha_M S_M - \mu_M I_M
\end{aligned}\right\} \ldots\ldots (1)$$

The malaria model with the four controls is given below as (2)

$$\left.\begin{aligned}
\frac{dS_H}{dt} &= Z_H + \big((1+u_6)\Lambda_I + u_3\big) I_I + \big((1+u_7)\Lambda_A + u_4\big) I_A + \big((1+u_8)\Lambda_P + u_5\big) I_P \\
&\quad -(\mathbf{1}-\boldsymbol{u_1})\alpha_I S_H - (\mathbf{1}-\boldsymbol{u_1})\alpha_A S_H - (\mathbf{1}-\boldsymbol{u_1})\alpha_P S_H - \mu_H S_H \\
\frac{dI_I}{dt} &= (\mathbf{1}-\boldsymbol{u_1})\alpha_I S_H - (\mu_H + \pi_I + u_3 + (1+u_6)\Lambda_I + \phi) I_I \\
\frac{dI_A}{dt} &= (\mathbf{1}-\boldsymbol{u_1})\alpha_A S_H + \phi I_I - (\mu_H + \pi_A + u_4 + (1+u_7)\Lambda_A + \Omega) I_A \\
\frac{dI_P}{dt} &= (\mathbf{1}-\boldsymbol{u_1})\alpha_P S_H + \Omega I_A - (\mu_H + \pi_P + u_5 + (1+u_8)\Lambda_P) I_P \\
\frac{dS_M}{dt} &= Z_M - (\mathbf{1}-\boldsymbol{u_1})\alpha_M S_M - [\mu_M + \beta u_2] S_M \\
\frac{dI_M}{dt} &= (\mathbf{1}-\boldsymbol{u_1})\alpha_M S_M - [\mu_M + \beta u_2] I_M
\end{aligned}\right\} \ldots (2)$$

Applying the definitions of the force of infections as stated in the model of Addawe and Lope [22] the force of infections for infants, adults and pregnant women are

$$\alpha_I = \frac{\Phi_I \theta_{MH} I_M'}{N_H}, \quad \alpha_A = \frac{\Phi_A \theta_{MH} I_M}{N_H} \text{ and } \alpha_P = \frac{\Phi_P \theta_{MH} I_M}{N_H} . \qquad \ldots\ldots\ldots\ldots (3)$$

The force of infection for mosquitoes is

$$\alpha_M = \frac{(\Phi_I I_I + \Phi_A I_A + \Phi_P I_P)\theta_{HM}}{N_H} . \qquad \ldots\ldots\ldots\ldots (4)$$

Substituting (3) and (4) into (2) , leads to (5) .

$$\left.\begin{aligned}
\frac{dS_H}{dt} &= Z_H + \big((1+u_6)\Lambda_I + u_3\big)I_I + \big((1+u_7)\Lambda_A + u_4\big)I_A + \big((1+u_8)\Lambda_P + u_5\big)I_P \\
&\quad - \frac{(\Phi_I + \Phi_A + \Phi_P)(\mathbf{1}-\boldsymbol{u_1})\theta_{MH} I_M S_H}{N_H} - \mu_H S_H \\
\frac{dI_I}{dt} &= \frac{\Phi_I(\mathbf{1}-\boldsymbol{u_1})\theta_{MH} I_M S_H}{N_H} - (\mathrm{A}_1 + u_3 + u_6\Lambda_I)I_I \\
\frac{dI_A}{dt} &= \frac{\Phi_A(\mathbf{1}-\boldsymbol{u_1})\theta_{MH} I_M S_H}{N_H} + \phi I_I - (\mathrm{A}_2 + u_4 + u_7\Lambda_A)I_A \\
\frac{dI_P}{dt} &= \frac{\Phi_P(\mathbf{1}-\boldsymbol{u_1})\theta_{MH} I_M S_H}{N_H} + \Omega I_A - (\mathrm{A}_3 + u_5 + u_8\Lambda_P)I_P \\
\frac{dS_M}{dt} &= Z_M - \frac{(\Phi_I I_I + \Phi_A I_A + \Phi_P I_P)(\mathbf{1}-\boldsymbol{u_1})\theta_{HM} S_M}{N_H} - [\mu_M + \beta u_2]S_M \\
\frac{dI_M}{dt} &= \frac{(\Phi_I I_I + \Phi_A I_A + \Phi_P I_P)(\mathbf{1}-\boldsymbol{u_1})\theta_{HM} S_M}{N_H} - [\mu_M + \beta u_2]I_M
\end{aligned}\right\} \ldots (5)$$

where $\mathrm{A}_1 = (\mu_H + \pi_I + \Lambda_I + \phi)$, $\mathrm{A}_2 = (\mu_H + \pi_A + \Lambda_A + \Omega)$ and $\mathrm{A}_3 = (\mu_H + \pi_P + \Lambda_P)$.

There initial state variables are $S_H(0) = 15475505$, $I_I(0) = 1\,303685$, $I_A(0) = 2045843$, $I_P(0) = 102834$, $S_M(0) = 246{,}498{,}646{,}800$ and $I_M(0) = 2{,}061{,}060{,}114{,}000$. .

5 Invariant Region

The invariant region is a region where solutions of the model (5) exist biologically [23].

Biological entities cannot be negative, therefore all the solutions of the model (5) are positive for all time $t \geq 0$. [24]

The total population sizes N_H and N_M can be defined by $N_H = S_H + I_I + I_A + I_P$ and $N_M = S_M + I_M$.

In absence of the malaria disease, the differential equation for N_H is given as

$$\frac{dN_H}{dt} \leq Z_H - \mu_H N_H \qquad \ldots\ldots\ldots\ldots (6)$$

The differential equation for N_M is also given as

$$\frac{dN_M}{dt} < Z_M - [\mu_M + \beta u_2]N_M \qquad \ldots\ldots\ldots\ldots (7)$$

Lemma 1. The model (5) has feasible solutions which are contained in the proper subset

$\Psi = \Psi_H \times \Psi_M$.

Proof

Let $(S_H, I_I, I_A, I_P, S_M, I_M) \in R_+^6$ be any solution of the system with non-negative initial conditions. Using (6)

$$\frac{dN_H}{dt} \leq Z_H - \mu_H N_H \quad \Longrightarrow \int d(N_H e^{\mu_H}) \leq Z_H \int e^{\mu_H t}\, dt$$

$$N_H \leq \frac{Z_H}{\mu_H} + \left(N_{H0} - \frac{Z_H}{\mu_H}\right) e^{-\mu_H t} \qquad \ldots\ldots\ldots\ldots\ldots\ldots (8)$$

Therefore, as $t \longrightarrow \infty$, the human population N_H approaches $\frac{Z_H}{\mu_H}$ and it follows that [23]

$$\lim_{t \to \infty} \sup\, N_H(t) \leq \frac{Z_H}{\mu_H} \quad \text{and} \quad \lim_{t \to \infty} \sup\, N_M(t) \leq \frac{Z_M}{[\mu_M + \beta u_2]}\ .$$

Therefore, the feasible solution set for the model (5) is given by

$$\Psi = \left\{ \begin{array}{c} (S_H\ ,\ I_I\ ,\ I_A\ ,\ I_P\ ,\ S_M\ ,\ I_M) \in R_+^6 : (S_H\ ,\ S_M) > 0 \\ \\ (I_I\ ,\ I_A\ ,\ I_P\ ,\ I_M) \geq 0\ ;\ S_H + I_I + I_A + I_P \leq \frac{Z_H}{\mu_H}\ ;\ S_M + I_M \leq \frac{Z_M}{[\mu_M + \beta u_2]} \end{array} \right\}$$

6 Disease-Free Equilibrium Point

Definition 1 A disease-free equilibrium point (DFE) is a steady state solution of the model for which there is no malaria disease in the population. It is obtained by setting (5) to zero [23].

The disease-free equilibrium E_0 of (5) is given by

$$E_0 = \left(\frac{Z_H}{\mu_H}\ ,\ 0\ ,\ 0\ ,\ 0\ ,\ \frac{Z_M}{[\mu_M + \beta u_2]}\ ,\ 0 \right)$$

7 The Effective Reproduction Number R_e

The effective reproduction number is the basic reproduction number of the model with the four controls (5). The basic reproduction number is defined as the expected number of secondary infection cases produced by a single infectious individual in a completely susceptible population. The next generation method is used to derive the basic reproduction number ([22], [25]).

The effective reproduction number is

$$\mathrm{R}_e = \sqrt{\frac{\phi\Omega L_1 L_6 + \phi L_1 L_5 L_9 + \Omega L_2 L_6 L_7 + L_1 L_4 L_8 L_9 + L_2 L_5 L_7 L_9 + L_3 L_6 L_7 L_8}{L_7 L_8 L_9 L_{10}}}$$

where $L_1 = (1-u_1)\Phi_I \theta_{MH}$, $L_2 = (1-u_1)\Phi_A \theta_{MH}$, $L_3 = (1-u_1)\Phi_P \theta_{MH}$, $L_4 = \frac{(1-u_1)\Phi_I \theta_{HM} \mu_H Z_M}{[\mu_M + \beta u_2] Z_H}$, $L_5 = \frac{(1-u_1)\Phi_A \theta_{HM} \mu_H Z_M}{[\mu_M + \beta u_2] Z_H}$, $L_6 = \frac{(1-u_1)\Phi_P \theta_{HM} \mu_H Z_M}{[\mu_M + \beta u_2] Z_H}$, $L_7 = (\mathrm{A}_1 + u_3 + u_6 \Lambda_I)$, $\mathrm{L}_8 = (\mathrm{A}_2 + u_4 + u_7 \Lambda_A)$, $\mathrm{L}_9 = (\mathrm{A}_3 + u_5 + u_8 \Lambda_P)$ and $L_{10} = [\mu_M + \beta u_2]$,

8 The Impact of the Control Strategies on the Effective Reproduction Number

The effective reproduction number is plotted against the four (4) control strategies in order to show graphically the impact of the controls.

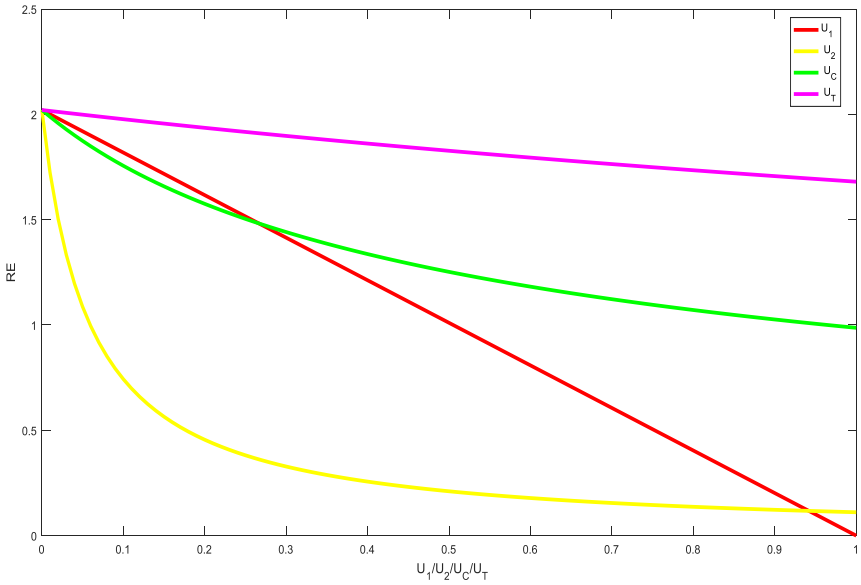

Fig. 3. Shows the plots of the effective reproduction number against the controls: plot of R_e against only ITNs (red line), plot of R_e against only IRS (yellow line), plot of R_e against only Chemoprophylaxis (green line), and plot of R_e against Improved Treatment effort (magenta line).

In Fig. 3, it can be seen that as each control approaches one (1), the value of R_e decreases which means the controls have positive impact on the model. The use of ITNs (u_1) can even reduce the value of R_e to zero at $\boldsymbol{u_1 = 1}$, which makes it the most effective control on R_e . The next effective control is the use of IRS (u_2) , which can reduce the value of R_e to approximately 0.1 at $u_2 = 1$. Chemoprophylaxis (u_C) also has positive impact on the value of R_e , as it can decrease R_e to approximately 1 at $u_T = 1$. And finally, the use of Treatment effort. (u_T) can reduce the value of R_e to approximately 1.68 at $u_T = 1$. Therefore, all the control strategies have positive impact on the effective reproduction number as shown in Fig. 3.

9 Objective Function

The goal is to minimise the infected human and female Anopheles mosquito populations while maximizing the susceptible human population. The control functions are practised in the time interval [0 , T] . Therefore, we can define the objective function as

$$J[\boldsymbol{u_1}, \boldsymbol{u_2}, \boldsymbol{u_3}, \boldsymbol{u_4}, \boldsymbol{u_5}, \boldsymbol{u_6}, \boldsymbol{u_7}, \boldsymbol{u_8}] = \int_0^T \left[D_1 + \frac{1}{2} D_2\right] dt \qquad \ldots\ldots (9)$$

where $D_1 = Y_1 I_I + Y_2 I_A + Y_3 I_P + Y_4 N_M$ and

$$D_2 = Z_1 u_1^2 + Z_2 u_2^2 + Z_3 u_3^2 + Z_4 u_4^2 + Z_5 u_5^2 + Z_6 u_6^2 + Z_7 u_7^2 + Z_8 u_8^2$$

The infectious people under 5years (I_I) , infectious people over 5years (I_A) , infectious pregnant women (I_P) and the total female Anopheles mosquito ($N_M = S_M + I_M$) populations are included in the objective function, because we want to minimise these populations. The terms Y_1 , Y_2 , Y_3 and Y_4 are positive weights to balance the factors of I_I , I_A , I_P and N_M , while Z_1 , Z_2 , Z_3 , Z_4 , Z_5 , Z_6 , Z_7 and Z_8 are also positive weights constants which measure the relative costs of implementing the respective strategies. The term $\frac{1}{2}Z_1 u_1^2$ represents the cost of implementing ITNs, $\frac{1}{2}Z_2 u_2^2$ also represents the cost of implementing indoor residual spraying (IRS), $\frac{1}{2}(Z_3 u_3^2 + Z_4 u_4^2 + Z_5 u_5^2)$ represent the cost of implementing of Chemoprophylaxis and finally, $\frac{1}{2}(Z_6 u_6^2 + Z_7 u_7^2 + Z_8 u_8^2)$ represents the cost of implementing of Improved clinical treatment (improved Antimalarial drugs).

We seek an optimal control $u_1^*(t)$, $u_2^*(t)$, $u_3^*(t)$, $u_4^*(t)$, $u_5^*(t)$, $u_6^*(t)$, $u_7^*(t)$ and $u_8^*(t)$ such that [26]

$$\mathrm{J}(u_1^*,\ u_2^*,\ u_3^*,\ u_4^*,\ u_5^*,\ u_6^*,\ u_7^*,\ u_8^*) = \min_{\mathrm{W}_1 \in \mathrm{U}} \{\ \mathrm{J}(\mathrm{W}_1) \mid \mathrm{W}_1 \in \mathrm{U}\},$$

where $\mathrm{W}_1 = u_1,\ u_2,\ u_3,\ u_4,\ u_5,\ u_6,\ u_7,\ u_8$ and U is the control set.

The control set U is defined as

$$\mathrm{U} = \{\ u_i \text{ is lebesgue measurable}, 0 \le u_i \le 1,\ i = 1,\ldots,8 \text{ ,for } t \in [\,0\ ,\mathrm{T}\,] \to [\,0\ ,1\,]\}.$$

The Lagrangian for the control problem is defined as

$$\mathrm{L} = D_1 + \frac{1}{2}D_2$$

The necessary conditions that an optimal control must satisfy come from the Pontryagin Maximum Principle [2]. This principle converts (5) and (9) into a problem of minimising pointwise a Hamiltonian H , with respect to W_1

$$\mathrm{H} = \mathrm{L} + \lambda_{S_H}\frac{dS_H}{dt} + \lambda_{I_I}\frac{dI_I}{dt} + \lambda_{I_A}\frac{dI_A}{dt} + \lambda_{I_P}\frac{dI_P}{dt} + \lambda_{S_M}\frac{dS_M}{dt} + \lambda_{I_M}\frac{dI_M}{dt} \qquad \ldots\ldots(10)$$

$$\mathrm{H} = \left.\begin{array}{l} \mathrm{Y}_1 I_I + \mathrm{Y}_2 I_A + \mathrm{Y}_3 I_P + \mathrm{Y}_4 N_M + \\ \frac{1}{2}(Z_1 u_1^2 + Z_2 u_2^2 + Z_3 u_3^2 + Z_4 u_4^2 + Z_5 u_6^2 + Z_6 u_6^2 + Z_7 u_7^2 + Z_8 u_8^2) + \\ \lambda_{S_H}\left[\begin{array}{c} Z_H + \big((1+u_6)\Lambda_I + u_3\big)I_I + \big((1+u_7)\Lambda_A + u_4\big)I_A + \\ \big((1+u_8)\Lambda_P + u_5\big)I_P - \dfrac{(\Phi_I + \Phi_A + \Phi_P)(\mathbf{1}-\boldsymbol{u_1})\theta_{MH} I_M S_H}{N_H} - \mu_H S_H \end{array}\right] \\ + \lambda_{I_I}\left[\begin{array}{c} \dfrac{(\mathbf{1}-\boldsymbol{u_1})\Phi_I \theta_{MH} I_M S_H}{N_H} \\ -(\mathrm{A}_1 + u_3 + u_6\Lambda_I)I_I \end{array}\right] + \lambda_{I_A}\left[\begin{array}{c} \dfrac{(\mathbf{1}-\boldsymbol{u_1})\Phi_A \theta_{MH} I_M S_H}{N_H} + \\ \phi I_I - (\mathrm{A}_2 + u_4 + u_7\Lambda_A)I_A \end{array}\right] + \\ \lambda_{I_P}\left[\begin{array}{c} \dfrac{(\mathbf{1}-\boldsymbol{u_1})\Phi_P \theta_{MH} I_M S_H}{N_H} + \\ \Omega I_A - (\mathrm{A}_3 + u_5 + u_8\Lambda_P)I_P \end{array}\right] + \lambda_{S_M}\left[\begin{array}{c} Z_M - [\mu_M + \beta u_2]S_M - \\ \dfrac{(\Phi_I I_I + \Phi_A I_A + \Phi_P I_P)(\mathbf{1}-\boldsymbol{u_1})\theta_{HM} S_M}{N_H} \end{array}\right] \\ + \lambda_{I_M}\left[\begin{array}{c} \dfrac{(\Phi_I I_I + \Phi_A I_A + \Phi_P I_P)(\mathbf{1}-\boldsymbol{u_1})\theta_{HM} S_M}{N_H} \\ -[\mu_M + \beta u_2]I_M \end{array}\right] \end{array}\right\}$$

where the λ_{S_H} , λ_{I_I} , λ_{I_A} , λ_{I_P} , λ_{S_M} , λ_{I_M} are the adjoint variables or co-state variables. ([5] , [27], Corollary 4. 1) gives the existence of optimal control due to the convexity of the integrand of J with

respect to u_1, u_2, u_3, u_4, u_5, u_6, u_7 and u_8, a priori boundedness of the state solutions, and the Lipschitz property of the state system with respect to the state variables. Applying Pontryagin's Maximum Principle [28] and the existence result for the optimal control from [27], we obtain the following theorem.

Theorem 1

Given an optimal control u_1^*, u_2^*, u_3^*, u_4^*, u_5^*, u_6^*, u_7^*, u_8^* and S_H^*, I_I^*, I_A^*, I_P^*, S_M^*, I_M^* of the corresponding state system (5) that minimises $J(u_1, u_2, u_3, u_4, u_5, u_6, u_7, u_8)$ over U. Then there exists adjoint variables λ_{S_H}, λ_{I_I}, λ_{I_A}, λ_{I_P}, λ_{S_M}, λ_{I_M} satisfying

$$\left.\begin{aligned}\frac{d\lambda_{S_H}}{dt} = &\lambda_{S_H}\left[\frac{(\Phi_I+\Phi_A+\Phi_P)(\mathbf{1}-\boldsymbol{u_1})\theta_{MH}I_M}{N_H}\left(1-\frac{S_H}{N_H}\right)+\mu_H\right]\\ &-\frac{(\mathbf{1}-\boldsymbol{u_1})\theta_{MH}I_M}{N_H}\left(1-\frac{S_H}{N_H}\right)\left[\Phi_I\lambda_{I_I}+\Phi_A\lambda_{I_A}+\Phi_P\lambda_{I_p}\right]\\ &+\frac{(\Phi_I I_I+\Phi_A I_A+\Phi_P I_P)(\mathbf{1}-\boldsymbol{u_1})\theta_{HM}S_M\left(\lambda_{I_M}-\lambda_{S_M}\right)}{N_H^2}\end{aligned}\right\} \quad \ldots(11)$$

$$\left.\begin{aligned}\frac{d\lambda_{I_I}}{dt} = &-\left[\mathrm{Y}_1+\lambda_{S_H}\left((1+u_6)\Lambda_I+u_3\right)+\lambda_{I_A}\phi\right]+\lambda_{I_I}(\mathrm{A}_1+u_3+u_6\Lambda_I)+\\ &\frac{(\mathbf{1}-\boldsymbol{u_1})\theta_{MH}I_MS_H\left[\Phi_I\left(\lambda_{I_I}-\lambda_{S_H}\right)+\Phi_A\left(\lambda_{I_A}-\lambda_{S_H}\right)+\Phi_P\left(\lambda_{I_P}-\lambda_{S_H}\right)\right]}{N_H^2}\\ &+\frac{(\mathbf{1}-\boldsymbol{u_1})\theta_{HM}S_M\left(\lambda_{S_M}-\lambda_{I_M}\right)}{N_H}\left[\Phi_I-\frac{(\Phi_I I_I+\Phi_A I_A+\Phi_P I_P)}{N_H}\right]\end{aligned}\right\} \ldots(12)$$

$$\left.\begin{aligned}\frac{d\lambda_{I_A}}{dt} = &-\left[Y_2+\lambda_{S_H}\left((1+u_7)\Lambda_A+u_4\right)+\lambda_{I_P}\Omega\right]+\lambda_{I_A}(\mathrm{A}_2+u_4+u_7\Lambda_A)+\\ &\frac{(\mathbf{1}-\boldsymbol{u_1})\theta_{MH}I_MS_H\left[\Phi_I\left(\lambda_{I_I}-\lambda_{S_H}\right)+\Phi_A\left(\lambda_{I_A}-\lambda_{S_H}\right)+\Phi_P\left(\lambda_{I_P}-\lambda_{S_H}\right)\right]}{N_H^2}\\ &+\frac{(\mathbf{1}-\boldsymbol{u_1})\theta_{HM}S_M\left(\lambda_{S_M}-\lambda_{I_M}\right)}{N_H}\left[\Phi_A-\frac{(\Phi_I I_I+\Phi_A I_A+\Phi_P I_P)}{N_H^2}\right]\end{aligned}\right\} \ldots(13)$$

$$\left.\begin{aligned}\frac{d\lambda_{I_P}}{dt} = &-\left[Y_3+\lambda_{S_H}\left((1+u_8)\Lambda_P+u_5\right)\right]+\lambda_{I_P}(\mathrm{A}_3+u_5+u_8\Lambda_P)+\\ &\frac{(\mathbf{1}-\boldsymbol{u_1})\theta_{MH}I_MS_H\left[\Phi_I\left(\lambda_{I_I}-\lambda_{S_H}\right)+\Phi_A\left(\lambda_{I_A}-\lambda_{S_H}\right)+\Phi_P\left(\lambda_{I_P}-\lambda_{S_H}\right)\right]}{N_H^2}\\ &+\frac{(\mathbf{1}-\boldsymbol{u_1})\theta_{HM}S_M\left(\lambda_{S_M}-\lambda_{I_M}\right)}{N_H}\left[\Phi_P-\frac{(\Phi_I I_I+\Phi_A I_A+\Phi_P I_P)}{N_H^2}\right]\end{aligned}\right\} \ldots(14)$$

$$\left.\begin{aligned}\frac{d\lambda_{S_M}}{dt} = &-Y_4+\lambda_{S_M}\left[\frac{(\Phi_I I_I+\Phi_A I_A+\Phi_P I_P)(\mathbf{1}-\boldsymbol{u_1})\theta_{HM}}{N_H}+\left[\mu_M+\beta u_2\right]\right]\\ &-\frac{(\Phi_I I_I+\Phi_A I_A+\Phi_P I_P)(\mathbf{1}-\boldsymbol{u_1})\theta_{HM}\lambda_{I_M}}{N_H}\end{aligned}\right\} \ldots(15)$$

$$\frac{d\lambda_{I_M}}{dt} = \left.\begin{array}{l} -Y_4 + \lambda_{S_H}\left[\dfrac{(\Phi_I + \Phi_A + \Phi_P)(\mathbf{1}-\boldsymbol{u_1})\theta_{MH}S_H}{N_H}\right] - \\ \dfrac{(\mathbf{1}-\boldsymbol{u_1})\theta_{MH}S_H[\Phi_I\,\lambda_{I_I} + \Phi_A\lambda_{I_A} + \Phi_P\lambda_{I_P}]}{N_H} + \lambda_{I_M}[\mu_M + \beta u_2] \end{array}\right\} \ldots(16)$$

The above adjoint equations [1] (11) - (16) satisfy transversality conditions

$$\lambda_{S_H}(T) = \lambda_{I_I}(T) = \lambda_{I_A}(T) = \lambda_{I_P}(T) = \lambda_{S_M}(T) = \lambda_{I_M}(T) = 0 \qquad \ldots\ldots\ldots(17)$$

and the controls u_1^* , u_2^* , u_3^* , u_4^* , u_5^* , u_6^* , u_7^* and u_8^* satisfy the optimality condition

$$\left.\begin{array}{l} u_1^* = \max\left\{0 \;,\; \min\left(1 \;,\; \dfrac{1}{Z_1 N_H}(\theta_{MH}I_M^*S_H^*D_3 + D_4)\right)\right\} \\ u_2^* = \max\left\{0 \;,\; \min\left(1 \;,\; \dfrac{\beta}{Z_2}(\lambda_{S_M}S_M^* + \lambda_{I_M}I_M^*)\right)\right\} \\ u_3^* = \max\left\{0 \;,\; \min\left(1 \;,\; \dfrac{I_I^*}{Z_3}(\lambda_{I_I} - \lambda_{S_H})\right)\right\} \\ u_4^* = \max\left\{0 \;,\; \min\left(1 \;,\; \dfrac{I_A^*}{Z_4}(\lambda_{I_A} - \lambda_{S_H})\right)\right\} \\ u_5^* = \max\left\{0 \;,\; \min\left(1 \;,\; \dfrac{I_P^*}{Z_5}(\lambda_{I_P} - \lambda_{S_H})\right)\right\} \\ u_6^* = \max\left\{0 \;,\; \min\left(1 \;,\; \dfrac{\Lambda_I I_I^*}{Z_6}(\lambda_{I_I} - \lambda_{S_H})\right)\right\} \\ u_7^* = \max\left\{0 \;,\; \min\left(1 \;,\; \dfrac{\Lambda_A I_A^*}{Z_7}(\lambda_{I_A} - \lambda_{S_H})\right)\right\} \\ u_8^* = \max\left\{0 \;,\; \min\left(1 \;,\; \dfrac{\Lambda_P I_P^*}{Z_8}(\lambda_{I_P} - \lambda_{S_H})\right)\right\} \end{array}\right\} \ldots\ldots\ldots(18)$$

where $D_3 = \Phi_I(\lambda_{I_I} - \lambda_{S_H}) + \Phi_A(\lambda_{I_A} - \lambda_{S_H}) + \Phi_P(\lambda_{I_P} - \lambda_{S_H})$ and

$D_4 = (\Phi_I I_I^* + \Phi_A I_A^* + \Phi_P I_P^*)\theta_{HM}S_M^*(\lambda_{S_M} + \lambda_{I_M})$.

Proof

We can obtain u_1^* as follows:

$$\frac{\partial H}{\partial \boldsymbol{u_1}} = \left[\begin{array}{l} Z_1\boldsymbol{u_1} + \dfrac{(\Phi_I + \Phi_A + \Phi_P)\theta_{MH}I_M^*S_H^*\,\lambda_{S_H}}{N_H} \\ -\dfrac{\Phi_I\theta_{MH}I_M^*S_H^*\lambda_{I_I}}{N_H} - \dfrac{\Phi_A\theta_{MH}I_M^*S_H^*\lambda_{I_A}}{N_H} \\ -\dfrac{\Phi_P\theta_{MH}I_M^*S_H^*\lambda_{I_P}}{N_H} \\ -\dfrac{(\Phi_I I_I + \Phi_A I_A + \Phi_P I_P)\theta_{HM}S_M^*\lambda_{S_M}}{N_H} \\ -\dfrac{(\Phi_I I_I + \Phi_A I_A + \Phi_P I_P)\theta_{HM}S_M^*\lambda_{I_M}}{N_H} \end{array}\right] = 0$$

$$\Rightarrow \begin{bmatrix} Z_1 \boldsymbol{u_1} + \dfrac{(\Phi_I + \Phi_A + \Phi_P)\theta_{MH} I_M^* S_H^* \lambda_{S_H}}{N_H} \\ - \dfrac{\Phi_I \theta_{MH} I_M^* S_H^* \lambda_{I_I}}{N_H} - \dfrac{\Phi_A \theta_{MH} I_M^* S_H^* \lambda_{I_A}}{N_H} \\ - \dfrac{\Phi_P \theta_{MH} I_M^* S_H^* \lambda_{I_P}}{N_H} \\ - \dfrac{(\Phi_I I_I + \Phi_A I_A + \Phi_P I_P)\theta_{HM} S_M \lambda_{S_M}}{N_H} \\ - \dfrac{(\Phi_I I_I + \Phi_A I_A + \Phi_P I_P)\theta_{HM} S_M \lambda_{I_M}}{N_H} \end{bmatrix} = 0$$

$$\Rightarrow \quad Z_1 \boldsymbol{u_1} = \begin{matrix} - \dfrac{(\Phi_I + \Phi_A + \Phi_P)\theta_{MH} I_M^* S_H^* \lambda_{S_H}}{N_H} \\ + \dfrac{\Phi_I \theta_{MH} I_M^* S_H^* \lambda_{I_I}}{N_H} + \dfrac{\Phi_A \theta_{MH} I_M^* S_H^* \lambda_{I_A}}{N_H} \\ + \dfrac{\Phi_P \theta_{MH} I_M^* S_H^* \lambda_{I_P}}{N_H} \\ + \dfrac{(\Phi_I I_I + \Phi_A I_A + \Phi_P I_P)\theta_{HM} S_M \lambda_{S_M}}{N_H} \\ + \dfrac{(\Phi_I I_I + \Phi_A I_A + \Phi_P I_P)\theta_{HM} S_M \lambda_{I_M}}{N_H} \end{matrix}$$

$$\Rightarrow Z_1 \boldsymbol{u_1} = \begin{matrix} \dfrac{\Phi_I \theta_{MH} I_M^* S_H^* (\lambda_{I_I} - \lambda_{S_H})}{N_H} + \dfrac{\Phi_A \theta_{MH} I_M^* S_H^* (\lambda_{I_A} - \lambda_{S_H})}{N_H} \\ + \dfrac{\Phi_P \theta_{MH} I_M^* S_H^* (\lambda_{I_P} - \lambda_{S_H})}{N_H} \\ \dfrac{(\Phi_I I_I + \Phi_A I_A + \Phi_P I_P)\theta_{HM} S_M (\lambda_{S_M} + \lambda_{I_M})}{N_H} \end{matrix}$$

$$\Rightarrow Z_1 \boldsymbol{u_1} = \begin{matrix} \dfrac{\theta_{MH} I_M^* S_H^*}{N_H} [\Phi_I (\lambda_{I_I} - \lambda_{S_H}) + \Phi_A (\lambda_{I_A} - \lambda_{S_H}) + \Phi_P (\lambda_{I_P} - \lambda_{S_H})] \\ \dfrac{(\Phi_I I_I + \Phi_A I_A + \Phi_P I_P)\theta_{HM} S_M (\lambda_{S_M} + \lambda_{I_M})}{N_H} \end{matrix}$$

Let $D_3 = \Phi_I (\lambda_{I_I} - \lambda_{S_H}) + \Phi_A (\lambda_{I_A} - \lambda_{S_H}) + \Phi_P (\lambda_{I_P} - \lambda_{S_H})$ and

$D_4 = (\Phi_I I_I^* + \Phi_A I_A^* + \Phi_P I_P^*)\theta_{HM} S_M^* (\lambda_{S_M} + \lambda_{I_M})$.

$$\Rightarrow \boldsymbol{u_1} = \frac{\mathbf{1}}{Z_1} \left[\frac{\theta_{MH} I_M^* S_H^*}{N_H} [D_3] + \frac{D_4}{N_H} \right] = \frac{1}{Z_1 N_H} (\theta_{MH} I_M^* S_H^* D_3 + D_4)$$

$$u_1^* = \frac{1}{Z_1 N_H} (\theta_{MH} I_M^* S_H^* D_3 + D_4)$$

Similarly, the remaining control policies can be obtained by this method.

The next thing to consider is the numerical solutions of the optimality system.

10 Numerical Results

Numerical solution to the optimality system is obtained by solving optimality system using an iterative scheme. The solution process involves using an initial guess of the controls to solve the state equations with forward scheme. The resulting solution of the state equation together with guessed controls are used to solve the co-state equation with a backward scheme due to the nature of the transversality conditions, which are final time conditions. The controls are updated using a convex combination of their previous values and the values from the characterizations. This process is continued until the unknowns at the present iteration are sufficiently close to those in the previous one ([1], [29], [30]).

The following weights factors $\mathbf{Y_1 = 1000}$, $\mathbf{Y_2 = 600}$, $\mathbf{Y_3 = 800}$ **and** $\mathbf{Y_4 = 200}$ are used for the numerical simulations. The cost associated with $\boldsymbol{u_1}$ includes purchasing bed-net and insecticide chemicals for treating the bed-net and the cost associated with $\boldsymbol{u_2}$ will include the cost of buying insecticide chemical and labour cost of spraying. The cost associated with chemoprophylaxis ($\boldsymbol{u_3}$, $\boldsymbol{u_4}$ **and** $\boldsymbol{u_5}$) is the cost of buying the drugs for the whole year. And finally, the cost associated with clinical treatment ($\mathbf{u_6}$, $\mathbf{u_7}$ **and** $\mathbf{u_8}$) includes the cost of antimalarial drugs, pain relief drugs, laboratory test cost and medical consultation fee. Therefore, we have $\boldsymbol{Z_1 = \$6.00}$, $\boldsymbol{Z_2 = \$14.40}$, $\boldsymbol{Z_3 = \$196.4}$, $\boldsymbol{Z_4 = \$312}$, $\boldsymbol{Z_5 = \$1.67}$, $\boldsymbol{Z_6 = \$28.93}$, $\boldsymbol{Z_7 = \$19.28}$ **and** $\boldsymbol{Z_8 = \$24.10}$. The parameter $\boldsymbol{\beta = 0.00003}$

We begin by plotting the single controls, that is, plotting ITN only, IRS only, Chemoprophylaxis only and Clinical treatment only, in order to compare the impact of each control.

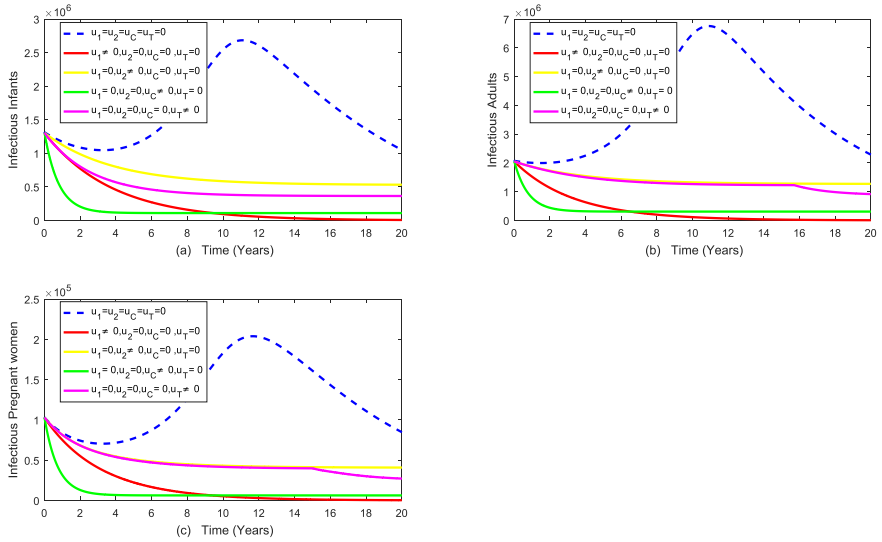

Fig. 4. Plots of model without control, ITN only, IRS only, Chemoprophylaxis only and Clinical treatment only

From Fig. 4, it can be seen that Chemoprophylaxis u_C (u_3, u_4, u_5) only as a single control has greatest impact on malaria prevention, that is, it can prevent approximately a total of 88,097,000 malaria infection cases in humans. It is followed by ITN (u_1) only which can also prevent 86,878,000 malaria infection cases. An improvement in Clinical treatment u_T (u_6, u_7, u_8) effort only can prevent 65,746,000 malaria infection cases. The control strategy with least malaria prevention is IRS only which can prevent 60,935,000 .

Therefore, we now move on to compare the impact of combining two control strategies such as ITN and IRS, ITN and Chemoprophylaxis, ITN and Clinical treatment, IRS and Chemoprophylaxis, IRS and Clinical treatment and Chemoprophylaxis and Clinical treatment. Their plots are given in Figs. 5 and 6.

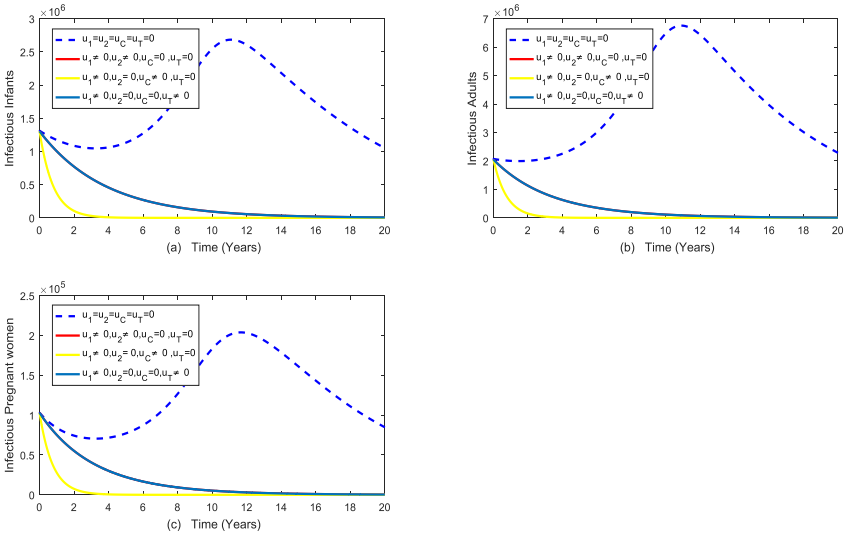

Fig. 5. Plots of model without control, ITN and IRS, ITN and Chemoprophylaxis, ITN and Clinical treatment

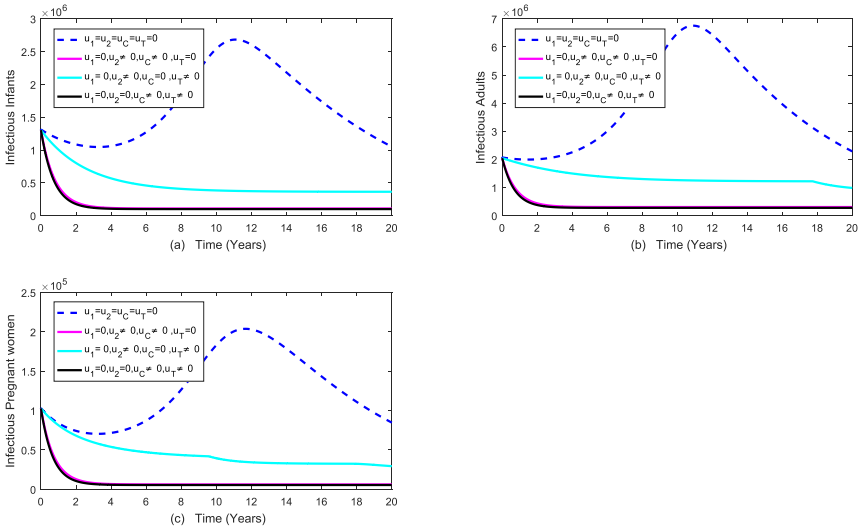

Fig. 6. Plots of model without control, IRS and Chemoprophylaxis, IRS and Clinical treatment and Chemoprophylaxis and Clinical treatment

From fig. 5 and 6, the combination with the highest malaria prevention cases is ITN and Chemoprophylaxis, it can prevent a total of 95,022,000 malaria infection cases in humans. It is followed by the combination of ITN and Treatment which can prevent 90,192,000 malaria infection cases. The combination of Chemoprophylaxis and Treatment can prevent 88,943,000 malaria infection cases. This is also followed by the combination of IRS and Chemoprophylaxis which can prevent 88,097,000 malaria infection cases. We also have the combination of ITN and IRS which can prevent 86,878,000 malaria infection cases. And finally, the combination of IRS and Treatment gives the least prevention, which is the sum total of 65,293,000 malaria infection cases.

Next, we consider the combination of three control strategies such as ITN, IRS and Chemoprophylaxis; ITN, IRS and Clinical treatment; ITN, Chemoprophylaxis and Clinical treatment and IRS, Chemoprophylaxis and Clinical treatment.

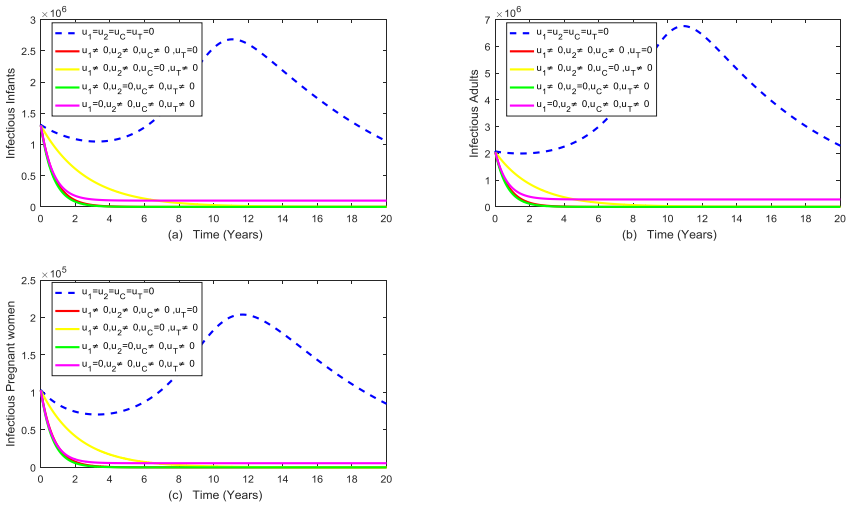

Fig. 7. Plots of model without control, ITN, IRS and Chemoprophylaxis; ITN, IRS and Clinical treatment; ITN, Chemoprophylaxis and Clinical treatment and IRS, Chemoprophylaxis and Clinical treatment

From Fig. 7, it can be seen that the combination of ITN, Chemoprophylaxis and Treatment improvement effort recorded the highest malarial prevention among the categories of the combining three control strategies. This combination can prevent a total of 95,237,000 malaria infection cases. This is followed by the combination of ITN, IRS and Chemoprophylaxis which can prevent 95,022,000 malaria infection cases. The combination of ITN, IRS and Treatment can also prevent 90,192,000 malaria infection cases. The combination of IRS, Chemoprophylaxis and Treatment gives the least malaria prevention in this category, which is 88,943,000 malaria infection cases.

Finally, we now consider the impact of combining all four control strategies on the optimality system.

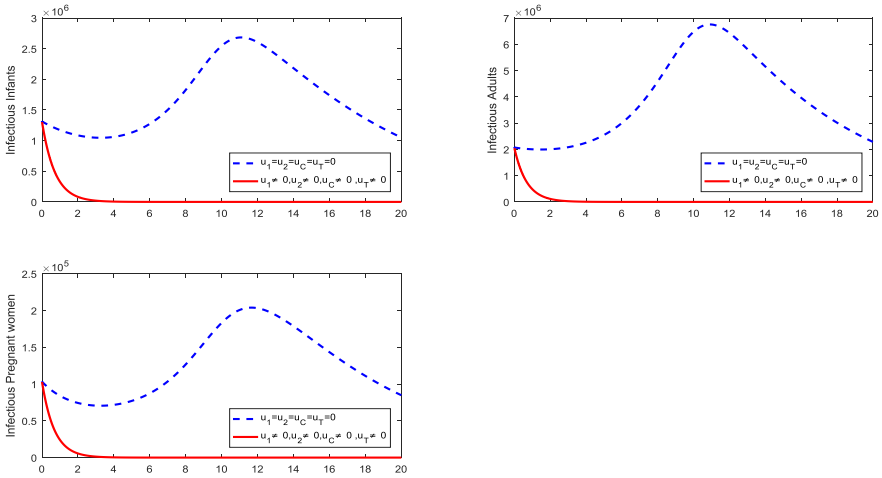

Fig. 8. Plots of model without control and the combination of all four control strategies on the model

From Fig. 8, the combination of all four control strategies can prevent approximately a total of 95,237,000 malaria infections cases in humans which is the same as the result produced by combining ITN, Chemoprophylaxis and Treatment in Fig. 7.

It can be seen that in Fig. 4, Chemoprophylaxis recoded the highest malaria prevention as a single control in the optimality system. It produces the same result as combining IRS and Chemoprophylaxis in Fig. 6 and produced a better result than the results produced by the combinations of ITN and IRS, and IRS and Treatment in Figs. 5 and 6 respectively. ITN as single control on the system in Fig. 4 produces the same result as the result recorded by the combination of ITN and IRS in Fig. 5 and better than the result produced by IRS and Treatment in Fig. 6. The result produced by the combination of ITN and Chemoprophylaxis in Fig. 5 is the same as the result produced by ITN, IRS and Chemoprophylaxis in Fig. 7 and better than the results recorded by the combinations of ITN, IRS and Treatment and IRS, Chemoprophylaxis and Treatment in Fig 7. It is not enough to use only graphs to determine the most efficient strategy, therefore, we employ a quantitative methodology such as cost effectiveness analysis to do that [30].

11 Cost Effectiveness Analysis

The CEA is a type of economic evaluation which compares the costs and outcomes of health programs when the interventions have a common health outcome but differ in effectiveness. In order to assess the extent to which our control intervention strategies are beneficial and cost effective, we employ the incremental cost-effectiveness ratio (ICER). The ICER is often defined as the additional cost per additional health outcome and provides a means of comparing intervention strategies so that we are able to determine which strategy is most cost-effective in controlling the disease.

Mathematically, the ICER between two strategies is defined in this work as:

$$\text{ICER} = \frac{\text{Differences in cost of interventions strategies}}{\text{Differences in number of infection averted by the strategies}} \quad \ldots\ldots (19)$$

The basic assumption in using the ICER is based on the understanding that the prime goal of using ITN, IRS, Chemoprophylaxis and an Improvement of the current Treatment is to reduce malaria infection. In order to use the ICER, we are required to rank all the intervention strategies according to their effectiveness on the basis of securing maximum effect rather than considering cost [4,31].

Based on the model simulation results, the strategies worth ranking in term of cost-effectiveness are stated in the Table 3.

Table 3. Ranking of the intervention strategies

Strategies	Total infection averted	Cost ($)
No strategy	0	0
IRS only	60,935,000	877,470.000
Treatment only	65,746,000	1,470,900,000
ITN only	86,878,000	417,020.000
Chemoprophylaxis only	88,097,000	23,854,000,000
ITN and Treatment	90,192,000	1,530,050,000

The ICER, is computed as follows:

$$\text{ICER(IRS only)} = \frac{877{,}470.000 - 0}{60{,}935{,}000 - 0} = \frac{877{,}470.000}{60{,}935{,}000} = 14.4$$

$$\text{ICER(Treatment only)} = \frac{1{,}470{,}900{,}000 - 877{,}470.000}{65{,}746{,}000 - 60{,}935{,}000} = \frac{593{,}430{,}000}{4{,}811{,}000} = 123.35$$

Comparing ICER(IRS only) and ICER(Treatment only) , it can be seen that there is a cost of \$14.4 for strategy IRS only over strategy Treatment only . The lower ICER for strategy IRS only shows that strategy Treatment only is strongly dominated. This makes strategy Treatment only more costly and less effective than strategy IRS only . Hence, strategy Treatment only is excluded from the set of alternatives so it does not consume limited resources. This leads to Table 4.

Table 4. Ranking of IRS only, ITN only, chemoprophylaxis only and ITN and treatment combination strategies

Strategies	Total infection averted	Cost (\$)
IRS only	**60,935,000**	**877,470.000**
ITN only	**86,878,000**	**417,020.000**
Chemoprophylaxis only	**88,097,000**	**23,854,000,000**
ITN and Treatment	**90,192,000**	**1,530,050,000**

We recalculate ICER,

$$\text{CER(IRS only)} = \frac{877{,}470.000}{60{,}935{,}000} = 14.4$$

$$\text{ICER(ITN only)} = \frac{417{,}020.000 - 877{,}470.000}{88{,}943{,}000 - 60{,}935{,}000} = \frac{-460{,}450{,}000}{27{,}162{,}000} = -16.95$$

Again, comparing CER(IRS only) and ICER(ITN only) , we have a cost saving of \$16.95 for strategy ITN only over IRS only .The negative ICER for strategy ITN only shows that strategy IRS only is strongly dominated. Therefore, strategy IRS only is excluded and this leads to Table 5.

Table 5. Ranking of ITN only, Chemoprophylaxis only and ITN and Treatment combination strategies

Strategies	Total infection averted	Cost (\$)
ITN only	**86,878,000**	**417,020.000**
Chemoprophylaxis only	**88,097,000**	**23,854,000,000**
ITN and Treatment	**90,192,000**	**1,530,050,000**

We recalculate ICER,

$$\text{ICER(ITN only)} = \frac{417{,}020.000}{86{,}878{,}000} = 4.8$$

$$\text{ICER(Chemoprophylaxis only)} = \frac{23{,}854{,}000{,}000 - 417{,}020.000}{88{,}097{,}000 - 86{,}878{,}000} = \frac{23{,}436{,}980{,}000}{1219000} = 19226.4$$

Hence, strategy Chemoprophylaxis only is excluded from the set of alternatives so it does not consume limited resources. This leads to Table 6.

Table 6. Ranking of ITN only and ITN and treatment combination strategies

Strategies	Total infection averted	Cost (\$)
ITN only	86,878,000	417,020.000
ITN and Treatment	90,192,000	1,530,050,000

We recalculate ICER,

$$\text{ICER(ITN only)} = \frac{417{,}020.000}{86{,}878{,}000} = 4.8$$

$$\text{ICER(ITN and Treatment)} = \frac{1{,}530{,}050{,}000 - 417{,}020.000}{90{,}192{,}000 - 86{,}878{,}000} = -\frac{1{,}113{,}030{,}000}{3314000} = 335.86$$

Hence, strategy ITN and Treatment is excluded from the set of alternatives so it does not consume limited resources. This leads to Table 7.

Table 7. ITN strategy only

Strategies	Total infection averted	Cost ($)
ITN only	86,878,000	417,020.000

Therefore, it can be seen that the strategy ITN only is best for controlling malaria in terms of cost. Therefore, I will recommend that policy makers on Malaria Control Programmes in endemic areas should advise their governments to subsidy ITN for its citizens or make it free and compulsory. However, this does not mean other strategies are not necessary, it is only telling us that more attention should be given to ITN. Although, the other strategies such as Chemoprophylaxis, IRS and Improved Treatment are good to avert malaria infections as seen in figures 4 to 8. However, their costs do not make them economically viable to assist malaria victims. For example, Chemoprophylaxis for those over 5years is about Twenty-Seven Ghana Cedis (6 US dollars) per week and for pregnant women it is free when they visit Anti-neonatal clinic and Seven Ghana Cedis and Fifty Pesewas (1.67 US dollars) at a Pharmaceutical shop in Ghana for a dosage during a pregnancy in the year 2018. Therefore, only privileged few of the malaria victims can afford it and also it is recommended for a short time and not for our whole life time.

Therefore, as the Cost-effectiveness Analysis points out in this work that ITN is economically best solution for fighting malaria in poor endemic areas, I will recommend that more attention should be given to the ITN; because personally I used one ITN for almost three (3) years at Navrongo in the Upper East region of Ghana which I received for free during a Malaria Control Programme.

12 Conclusion

In this article, we apply the optimal control theory to a new model formulated for malaria disease in endemic areas in the world. The following malaria control strategies ITN, IRS, Chemoprophylaxis and Improved Clinical Treatment were examined and analysed on the mode. The Cost-effectiveness Analysis points out that more attention should be given Insecticide -Treated bed nets (ITNs) in order to eliminate the malaria disease globally, because the female Anopheles mosquitoes need human blood to lay their eggs [8]. The expression for the effective reproduction number (R_e) has been derived by using the next-generation method. The impact of the controls on the R_e was studied and it came out that all four controls have positive impact. The epidemiological theory states if R_e is less than one, then the disease can easily be eliminated. An analysis of controls on R_e reveals that the ITNs can reduce R_e to zero as the value of ITNs approaches one. Pontryagin's Maximum Principle is applied to analyse the optimal control model theoretically and the optimality system is solved numerically through an iterative scheme. The optimal plots (Figs. 4-8) reveal that best control strategies for malaria elimination is the combination of ITN, Chemoprophylaxis and Improved Clinical Treatment. However, the Cost-effectiveness Analysis points out in this article that ITN is economically best solution for fighting malaria in poor endemic areas.

Competing Interests

Authors have declared that no competing interests exist.

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