Optimal Prevention And Treatment Control Of Malaria Model With Resistance Drug

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Abstract : This paper presents an optimal control model for malaria resistant to antimalarial drugs. Optimal control measures included: control on the use of mosquito nets to prevent contact with mosquitoes, treatments, and spraying mosquitoes with insecticides as a system variable. The application was performed with the fourth-order Runge-Kutta approach. The strategy of using a set of optimal controls was found significantly more effective to reduce the number of individuals infected and mosquito vectors, compared to the optimal control separately.

Index Terms: Optimal control, antimalarial drug resistance, malaria, treatment, spray of mosquito insecticide.

1. INTRODUCTION

Malaria is an infectious disease caused by the plasmodium parasite which is transmitted to humans through female mosquito bites. Individuals infected are characterized by symptoms including chills, fever, headache, anemia, nausea, and vomiting [1]. The parasite develops inside the mosquito's body and is then transferred to the mosquito's salivary glands. Infected mosquitoes suck human blood, inject parasites (sporozoites) into the human body and constitute the malaria life cycle [2]. In 2017, WHO estimated that Plasmodium falciparum was the malaria parasite occurring in Africa 99.7%, in regions in Southeast Asia (62.8%), the Eastern Mediterranean (69%) and the Western Pacific (71.9%). While the main parasitic Plasmodium vivax occurred in regions in America, representing 74.1% of malaria cases [3]. The carrying out of exacting and sustainable preventive measures is very important to reduce the spread of malaria. These steps must stop the worsening malaria situation. For example, insulated mosquito nets have been effectively and safely used to control malaria epidemics in Africa and the Western Pacific region [4]. Although the mathematical model is an abstract simplification of reality; but can still capture the main features of the system and are more able to accept experiments or analysis.

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From here, mathematicians have promoted an important and powerful tool, namely through the malaria mathematical model. With a mathematical model, it can provide insight into interactions between hosts and vector populations, malaria dynamics, how to control malaria transmission, and finally how to control it [5]. Ross (1911) examined the model of malaria mosquito population distribution and the malaria eradication model to a certain extent. A few years later, Macdonald (1957) improved Ross's model, exhibit that minimizing the number of mosquitoes effectively affected the spread of epidemiology in areas of malaria transmission [6]. Another study is with a fractional model of controlling malaria transmission control strategy [5]. The authors in [7] used a simple mathematical model of SEIR of malaria transmission. Mathematical modeling of the global dynamics of malaria transmission: considering the initial stages before a malaria host occurs [8]. Obabiyi et al. (2019) analyzed the global stability of the dynamics of malaria transmission with latent compartments [1]. Malaria control model studies have been reviewed by several researchers. In [1], optimal control is used to examine the dynamics of malaria transmission and treatment. The optimal control of malaria has also been assessed with regard to the rainy season [9], with standard events [10], the problem of optimal control in Colombia has also been studied in [11]. The authors in [12] have developed the malaria model by incorporate optimal control to investigate the effect of mass treatment and insecticide. This study have been extended in [13] by adding the factor of malaria resistance. The authors in [2] studied the optimal control of the malaria model by taking into account drug resistance and the presence of indeterminate parameters. This paper discusses optimal control of the malaria model by looking at latent infected sub-populations, infected with malaria that is resistant to antimalarial drugs, and has been invaded or immune to malaria. This study provides control, namely the use of mosquito nets to prevent contact with mosquitoes, treatment, and spraying of insecticides on mosquito vectors. paper is organized as follows. The introduction is outlined first. Then, the mathematical model of the malaria spread is formulated and analyzed. Third, the control problems and objective functions are described, followed by the application of the Pontryagin Maximum Principle to the conditions needed for optimal control. In Section 4, numerical simulation results show the effect of optimal control on the dynamics of human and mosquito populations.

2. MODEL FORMULATION

In this section, we consider two populations, namely human and mosquitoes population. The total human population at time t, denoted by $N_h(t)$, is divided into the susceptible individuals $(S_h(t))$, the exposed individual which is sensitive to antimalarial drugs $(E_{hs}(t))$, individuals with malaria symptoms which is sensitive to antimalarial drugs $(I_{hs}(t))$, the exposed individual which is resistant to antimalarial drugs $(E_{hr}(t))$, individuals with malaria symptoms which is resistant to antimalarial drugs $(I_{hr}(t))$, and recovered individuals which is partially immune human $(R_h(t))$. So that

$N_h(t) = S_h(t) + E_{hs}(t) + I_{hs}(t) + E_{hr}(t) + I_{hr}(t) + R_h(t)$.

The total mosquito population at time t, denoted by $N_v(t)$, is divided into the susceptible mosquitoes $(S_v(t))$, infectious mosquitoes which is sensitive to antimalarial drugs $(I_{vs}(t))$ and infectious mosquitoes which is resistant to antimalarial drugs $(I_{vr}(t))$. Thus,

$$N_v(t) = S_v(t) + I_{vs}(t) + I_{vr}(t).$$

It is assumed that the rate of recruitment in the human population enters the susceptible sub-population at a constant rate of Λ_h, and each human sub-population dies naturally at the same rate of μ_h. Individuals in the susceptible sub-population can become infected with malaria after contact with infected mosquitoes (at the rate of $\beta_{H1} = \beta_{h1}b_{h1}\varphi_1$), where β_{h1} is the probability of transmission per bite and b_{h1} is the bite level of mosquitoes that are sensitive to antimalarial drugs, φ_1 is the contact rate of the mosquito vector which is still sensitive to antimalarial drugs per human per unit time. Individuals in the susceptible sub-population becoming infected with malaria enter the latent infected sub-population. However, they are still sensitive to antimalarial drugs (E_{hs}) at the rate β_{H1}. Then, from the E_{hs} sub-population, after some time the malaria germ actively enters the infectious population, which is still sensitive to antimalarial drugs at a rate of α. If treated, individuals in latent subpopulations who are sensitive to antimalarial drugs can recover at a rate of t_1, $0 \le t_1 \le 1$. The rate of recovery naturally individuals of sub-population I_{hs} enter the recovered sub-population at a rate of γ, $0 \le \gamma < t_1$, and individuals infected with malaria who are still sensitive to antimalarial drugs can die from disease (at a rate of d_1).

Individuals in the susceptible sub-population can be infected after having contact with an infected mosquito that is resistant to antimalarial drugs (at a rate of $\beta_{H2} = \beta_{h2}b_{h2}\varphi_2$). β_{h2} is the probability of transmission per bite and b_{h2} is the rate of a mosquito bite which is resistant to antimalarial drugs, φ_2 is the level of contact of mosquito vectors per human per unit time. Individuals in the susceptible subpopulation enter the latent infected sub-population that is already resistant to antimalarial drugs (E_{hr}) at the level β_{H2}. Then from the sub-population E_{hr} after some time the germ becomes active and enters the infectious sub-population that is resistant to antimalarial drugs at a rate of σ. Individuals in latent infected sub-populations who are resistant to antimalarial drugs are treated and can recover with a cure rate of t_2, with $0 \le t_2 \le 1$. Individuals in malaria infected sub-populations who are resistant to antimalarial drugs can die of disease at a rate d_2. Assuming that individuals in the sub-population are recovered, their immunity can be lost and enter the susceptible sub-population at a rate of ρ.The transmission diagrams of the malaria model is given in Figure 1.

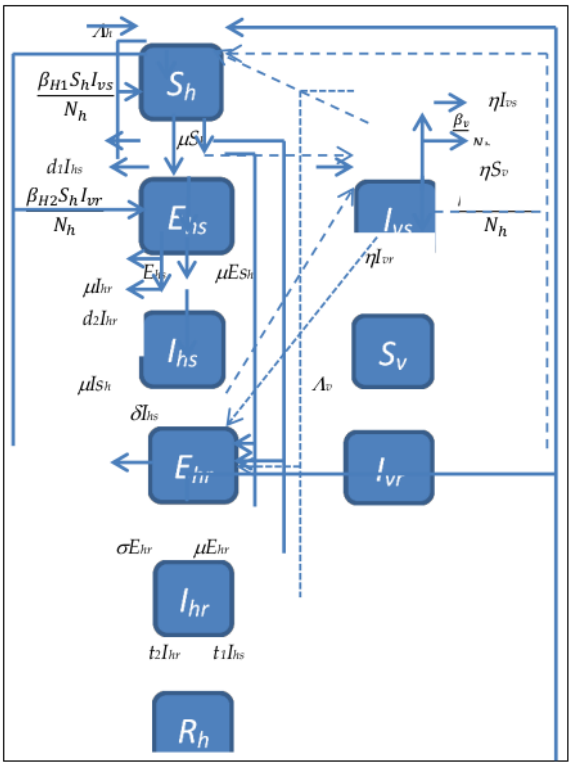

Figure 1: *Transmission diagram in human population and vector population*

Susceptible mosquitoes (S_v) are generated at the rate Λ_v and get malaria infection at a rate $\beta_{V1}(I_{h1} + \tau_1 R_h)$, with $\beta_{V1} = \beta_{v1}b_{v1}\varphi$. The effective contacts with the infectious human which is resistant to antimalarial drugs at a rate $\beta_{V2}(I_{hr} + \tau_2 R_h)$, with $\beta_{V2} = \beta_{v2}b_{v2}\varphi$. The parameters β_{v1} and β_{v2} are the probability of a vector getting infected through the infectious human, while b_{v1} and b_{v2} are the biting rate of mosquitoes which are sensitive and resistant to antimalarial drugs respectively. Thus, τ_1, τ_2 are the modification parameter with $\tau_1, \tau_2 \in [0, 1)$. The natural death rate of mosquitoes is denoted by η.

The model of malaria transmission is given by the system of the nonlinear differential equation as follows.

$$\frac{dS_h}{dt} = \Lambda_h + \rho R - \frac{\beta_{H1}S_hI_{vs}}{N_h} - \frac{\beta_{H2}S_hI_{vr}}{N_h} - \mu S_h$$

$$\frac{dE_{hs}}{dt} = \frac{\beta_{H1}S_hI_{vs}}{N_h} - (\mu + \alpha)E_{hs}$$

$$\frac{dI_{hs}}{dt} = \alpha E_{hs} - (\mu + d_1 + \delta + t_1 + \gamma)I_{hs}$$

$$\frac{dE_{hr}}{dt} = \frac{\beta_{H2}S_hI_{vr}}{N_h} + \delta I_{hs} - (\mu + \sigma)E_{hr}$$

$$\frac{dI_{hr}}{dt} = \sigma E_{hr} - (\mu + d_2 + t_2)I_{hr}$$
$$\frac{dR_h}{dt} = \gamma I_{hs} + t_1 I_{hs} + t_2 I_{hr} - (\mu + \rho)R_h$$
$$\frac{dS_v}{dt} = \Lambda_v - \frac{\beta_{V1} S_v (I_{hs} + \tau_1 R_h)}{N_h} - \frac{\beta_{V2} S_v (I_{hr} + \tau_2 R_h)}{N_h} - \eta S_v \quad (1)$$
$$\frac{dI_{vs}}{dt} = \frac{\beta_{V1} S_v (I_{hs} + \tau_1 R_h)}{N_h} - \eta I_{vs}$$
$$\frac{dI_{vr}}{dt} = \frac{\beta_{V2} S_v (I_{hr} + \tau_2 R_h)}{N_h} - \eta I_{vr}.$$

2.1 The Positivity and Boundedness of the Solution

The malaria model (1) is well posed in the region

$$\Omega = \Omega_h \times \Omega_v \subset R_+^6 \times R_+^3, \quad (2)$$

where, $\Omega_h = \{(S_h, E_{hs}, I_{hs}, E_{hr}, I_{hr}, R_h) \in R_+^6 : S_h + E_{hs} + I_{hs} + E_{hr} + I_{hr} + R_h \leq \frac{\Lambda_h}{\mu}\}$ and

$\Omega_v = \{(S_v, I_{vs}, I_{vr}) \in R_+^3 : S_v + I_{vs} + I_{vr} \leq \frac{\Lambda_v}{\eta}\}$.

We use the following theorem to proof the positivity and boundedness of the solution.

Theorem 1 If $S_h(0)$, $E_{hs}(0)$, $I_{hs}(0)$, $E_{hr}(0)$, $I_{hr}(0)$, $R_h(0)$, $S_v(0)$, $I_{vs}(0)$, $I_{vr}(0)$ are non-negative, then so are $S_h(t)$, $E_{hs}(t)$, $I_{hs}(t)$, $E_{hr}(t)$, $I_{hr}(t)$, $R_h(t)$, $S_v(t)$, $I_{vs}(t)$, $I_{vr}(t)$ for all time $t > 0$.

Furthermore, $\frac{\Lambda_h}{\mu+d_1+d_2} \leq lim_{n\to\infty} N_h \leq \frac{\Lambda_h}{\mu}$ and $lim_{n\to\infty} N_v \leq \frac{\Lambda_v}{\mu}$ with $N_h = S_h + E_{hs} + I_{hs} + E_{hr} + I_{hr} + R_h$ and $N_v = S_v + I_{vs} + I_{vr}$..

Proof: Let t_s = Sup $\{ t > 0 : S_h(t) > 0, E_{hs}(t) > 0, I_{hs}(t) > 0, E_{hr}(t) > 0, I_{hr}(t) > 0, R_h(t) > 0, S_v(t) > 0, I_{vs}(t) > 0, I_{vr}(t) > 0$. Since $S_h(0) > 0$, $E_{hs}(0) > 0$, $I_{hs}(0) > 0$, $E_{hr}(0) > 0$, $I_{hr}(0) > 0$, $R_h(0) > 0$, $S_v(0) > 0$, $I_{vs}(0) > 0$, $I_{vr}(0) > 0$, then, $t_s > 0$. If $t_s < \infty$, then $S_h, E_{hs}, I_{hs}, E_{hr}, I_{hr}$, or R_h, S_v, I_{vs}, I_{vr} is equal to zero at t_s . From the first equation of the system (1), we have

$$\frac{dS_h}{dt} = \Lambda_h + \rho R - \frac{\beta_{H1} S_h I_{vs}}{N_h} - \frac{\beta_{H2} S_h I_{vr}}{N_h} - \mu S_h.$$

Thus

$$\frac{d}{dt}\left\{S_h(t) \exp\left[\frac{\beta_{H1} I_{vs}}{N_h} + \frac{\beta_{H2} I_{vr}}{N_h} + \mu\right]\right\}$$
$$= (\Lambda_h + \rho R) exp\left[\left(\frac{\beta_{H1} I_{vs}}{N_h} + \frac{\beta_{H2} I_{vr}}{N_h} + \mu\right) v\right] dv,$$

Hence,

$$S_h(t_s) exp\left[\left(\frac{\beta_{H1} I_{vs}}{N_h} + \frac{\beta_{H2} I_{vr}}{N_h} + \mu\right) t\right] - S_h(0) =$$
$$\int_0^{t_s} (\Lambda_h + \rho R)\left[\left(\frac{\beta_{H1} I_{vs}}{N_h} + \frac{\beta_{H2} I_{vr}}{N_h} + \mu\right) v\right] dv,$$

so that

$$S_h(t_s) = S_h(0) exp\left[-\left(\frac{\beta_{H1} I_{vs}}{N_h} + \frac{\beta_{H2} I_{vr}}{N_h} + \mu\right) t_s\right] +$$
$$exp\left[-\left(\frac{\beta_{H1} I_{vs}}{N_h} + \frac{\beta_{H2} I_{vr}}{N_h} + \mu\right) t_s\right] \times$$
$$\int_0^{t_s} (\Lambda_h + \rho R)\left[\left(\frac{\beta_{H1} I_{vs}}{N_h} + \frac{\beta_{H2} I_{vr}}{N_h} + \mu\right) v\right] dv > 0.$$

It can similarly be shown that $E_{hs}(t) > 0$, $I_{hs}(t) > 0$, $E_{hr}(t) > 0$, $I_{hr}(t) > 0$, $R_h(t) > 0$, $S_v(t) > 0$, $I_{vs}(t) > 0$ and $I_{vr}(t) > 0$ for all t > 0.

Adding the first six equations and the last three equations of the model (1) gives

$$\frac{dN_h(t)}{dt} = \Lambda_h - \mu N_h(t) - d_1 I_{hs}(t) - d_2 I_{hr}(t),$$
$$\frac{dN_v(t)}{dt} = \Lambda_v - \eta N_v(t). \quad (3)$$

Thus,

$$\Lambda_h - \mu N_h(t) - d_1 I_{hs}(t) - d_2 I_{hr}(t) \leq \frac{dN_h(t)}{dt}$$
$$\leq \Lambda_h - \mu N_h(t),$$
$$\Lambda_v - \eta N_v(t) \leq \frac{dN_v(t)}{dt} \leq \Lambda_h - \eta N_v(t).$$

Hence respectively,

$$\frac{\Lambda_h}{\mu+d_1+d_2} \leq lim_{t\to\infty} \inf N_h(t) \leq lim_{t\to\infty} \sup N_h(t) \leq \frac{\Lambda_h}{\mu},$$

and

$$\frac{\Lambda_v}{\eta} \leq lim_{t\to\infty} \inf N_v(t) \leq lim_{t\to\infty} \sup N_v(t) \leq \frac{\Lambda_v}{\eta}.$$

2.2. Invariant regions

Next, we will analyze the biologically feasible region of the model (1) as follows. The following steps are done to prove the positive invariance of Ω (i.e., solutions in Ω remain in Ω for all t > 0). From equation (3), it follows that

$$\frac{dN_h(t)}{dt} \leq \Lambda_h - \mu N_h(t)$$
$$\frac{dN_v(t)}{dt} \leq \Lambda_h - \eta N_v(t) \quad (4)$$

Using Theorem 1, we obtain

$$N_h(t) \leq N_h(0) e^{-\mu t} + \frac{\Lambda_h}{\mu}(1 - e^{-\mu t}) \text{ and}$$
$$N_v(t) \leq N_v(0) e^{-\eta t} + \frac{\Lambda_v}{\eta}(1 - e^{-\eta t}).$$

In particular, $N_h(t) \leq \frac{\Lambda_h}{\mu}$ and $N_v(t) \leq \frac{\Lambda_v}{\eta}$ if $N_h(0) \leq \frac{\Lambda_h}{\mu}$ and $N_v(0) \leq \frac{\Lambda_v}{\eta}$ respectively.

Thus, the region Ω is positively-invariant. Hence, it is sufficient to consider the dynamics of the flow generated by (1) in Ω. In this region, the model (1) is well-posed [5]. Thus, every solution of the model (1) with initial conditions in Ω remains in Ω for all t > 0. Therefore, the ω-limit sets of the system (1) are contained in Ω. This result is summarized below.

Lemma 2. The region $\Omega = \Omega_h \times \Omega_v \subset R_+^6 \times R_+^3$ is positively-invariant for the basic model (1) with non-negative initial conditions in R_+^9.

2.2. The disease-free equilibrium (DFE)

The malaria model (1) has a DFE, obtained by setting the right-hand sides of the equations in the model to zero, given by:

$$E_0 = (\frac{\Lambda_h}{\mu}, 0,0,0,0,0, \frac{\Lambda_v}{\eta}, 0,0)$$

The basic reproduction number established using the next generation operator method [14] on the system (1) at E_0, the matrices F (the new infection terms) and V (the remaining transfer terms), are, respectively, given by

$$F=\begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & -\beta_{H1} & -\beta_{H2} \\ \beta_{H1} & 0 & 0 & 0 & 0 & 0 & \beta_{H1} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \beta_{H2} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\beta_{V1} & 0 & -\beta_{V1} & 0 & 0 & 0 \\ 0 & 0 & \beta_{V1} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \beta_{V2} & 0 & 0 & 0 \end{bmatrix},$$

$$V=\begin{bmatrix} \mu & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \mu+\alpha & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -\alpha & \mu+d1+\delta+t1+\gamma & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\delta & \mu+\sigma & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -\sigma & \mu+d2+t2 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \eta & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \eta & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \eta \end{bmatrix}.$$

Next, the basic reproduction number is determined as spectral radius of FV^{-1}[15]. This method provides the reproduction number, R_{01}, and R_{02} for drug-sensitive and drug-resistant parasites infections as

$R_{01}=\sqrt{\frac{\sigma\beta_{H2}\beta_{V2}}{\eta(\mu+\sigma)(d_2+t_2+\mu)}}$, $R_{02}=\sqrt{\frac{\alpha\beta_{H1}\beta_{V1}}{\eta(\alpha+\mu)(d_1+\delta+\gamma+t_1+\mu)}}$.

The next step is using [16], the following results are specified. The basic reproduction number is defined as the number of secondary cases (infections) produced in a completely susceptible population, by a single infectious individual (human or mosquito). Square root shows that there are two phase of infection. Koella and Antia [17] state that due to natural selection, parasitic strains with a predominant number of reproductions attack parasitic populations with lower reproductive numbers, making R_0 = max {R_{01}, R_{02}}. The DFE E_0 of the model (1) is asymptotically stable if $R_{01}, R_{02} < 1$ or $R_0 < 1$ [15].

3. OPTIMAL CONTROL STRATEGIS

In this section, the equation system (1) is given control measures to see the effect on the dynamics of human populations and mosquitoes. Several control action strategies are given: mosquito-contact preventions, treatments and mosquito vectors with insecticides sprays. In the human population, mosquito nets are given as an effort to reduce human contact with infected mosquitoes by (1 – u_1). Efforts to improve recovery through malaria treatments in infected individuals who are still sensitive to antimalarial drugs are given u_2 control measures. To improve the healing treatment of malaria in individuals infected and resistant to antimalarial drugs, u_3 control actions are given. Assumed that mosquitoes can still bite humans outside netting, insecticides spraying as u_4 control is performed. Thus, each mosquito sub-population is reduced by insecticide spraying (at a rate of u_4(1 - p)). Given that (1 - p) is the proportion of the reduced mosquito vector population and $0 \le u_4 \le 1$, it is a control function that represents insecticide spray aimed at reducing the mosquito sub-population. We introduce into the model (1), time-dependent preventive control u_1 and treatment control u_2, u_3, insecticide spraying control u_4, $0 \le u_i \le 1$, i = 1, 2, 3, 4. Malaria model (1) becomes:

$$\frac{dS_h}{dt}=\Lambda_h+\rho R-\frac{(1-u_1)S_hI_{vs}}{N_h}-\frac{(1-u_1)\beta_{H2}S_hI_{vr}}{N_h}-\mu S_h$$
$$\frac{dE_{hs}}{dt}=\frac{(1-u_1)\beta_{H1}S_hI_{vs}}{N_h}-(\mu+\alpha)E_{hs}$$
$$\frac{dI_{hs}}{dt}=\alpha E_{hs}-(\mu+d_1+\delta+(t_1+u_2)+\gamma)I_{hs}$$
$$\frac{dE_{hr}}{dt}=\frac{(1-u_1)\beta_{H2}S_hI_{vr}}{N_h}+\delta I_{hs}-(\mu+\sigma)E_{hr}$$
$$\frac{dI_{hr}}{dt}=\sigma E_{hr}-(\mu+d_2+(t_2+u_3))I_{hr}$$
$$\frac{dR_h}{dt}=\gamma I_{hs}+(t_1+u_2)I_{hs}+(t_2+u_3)I_{hr}-(\mu+\rho)R_h \quad (5)$$
$$\frac{dS_v}{dt}=\Lambda_v-\frac{(1-u_1)\beta_{V1}S_v(I_{hs}+\tau_1R_h)}{N_h}-\frac{(1-u_1)\beta_{V2}S_v(I_{hr}+\tau_2R_h)}{N_h}-u_4(1-p)S_v-\eta S_v$$
$$\frac{dI_{vs}}{dt}=\frac{(1-u_1)\beta_{V1}S_v(I_{hs}+\tau_1R_h)}{N_h}-u_4(1-p)I_{vs}-\eta I_{vs}$$
$$\frac{dI_{vr}}{dt}=\frac{(1-u_1)\beta_{V2}S_v(I_{hr}+\tau_2R_h)}{N_h}-u_4(1-p)I_{vr}-\eta I_{vr}$$

The following performance index or cost function is given by

$$J(u_1,u_2,u_3,u_4)=\int_0^{t_f}[a_1I_{hs}+a_2I_{hr}+a_3I_{vs}+a_4I_{vr}+\frac{1}{2}c_1u_1^2+\frac{1}{2}c_2u_2^2+\frac{1}{2}c_3u_3^2+\frac{1}{2}c_4u_4^2]dt \quad (6)$$

where t_f is the final time and the coefficients a_1, a_2, a_3, a_4, c_1, c_2, c_3, c_4 are positive weights to balance the factors. Our aims is to minimize the number of infectious humans and also infectious mosquitoes while minimizing the cost of controls $u_1(t)$, $u_2(t)$, $u_3(t)$, $u_4(t)$. Thus, we seek an optimal control $u_1^*, u_2^*, u_3^*, u_4^*$ such that

$$J(u_1^*,u_2^*,u_3^*,u_4^*)=min_{u_1,u_2,u_3,u_4}\{J(u_1,u_2,u_3,u_4)|u_1,u_2,u_3,u_4 \in U\} \quad (7)$$

where the control set

$U=\{(u_1,u_2,u_3,u_4)|u_i:[0,t_f]\to[0,1]$, Lebesgue Measurable $,i=1,2,3,4\}$.

Necessary conditions to set the optimal control u_1^*,u_2^*,u_3^*,u_4^* that satisfy the condition (7) with constraint model (5) will be solved by the Pontryagin's Maximum Principle [18]. This principle converts (5)-(7) into a problem of minimizing pointwise a Hamiltonian H, with respect to (u_1,u_2,u_3,u_4), that is

$$H=a_1I_{hs}+a_2I_{hr}+a_3I_{vs}+a_4I_{vr}+\frac{1}{2}c_1u_1^2+\frac{1}{2}c_2u_2^2+\frac{1}{2}c_3u_3^2+\frac{1}{2}c_4u_4^2$$
$$+\lambda_1\left(\Lambda_h+\rho R-\frac{(1-u_1)\beta_{H1}S_hI_{vs}}{N_h}-\frac{(1-u_1)\beta_{H2}S_hI_{vr}}{N_h}-\mu S_h\right)$$
$$+\lambda_2\left(\frac{(1-u_1)\beta_{H1}S_hI_{vs}}{N_h}-(\mu+\alpha)E_{hs}\right)$$
$$+\lambda_3(\alpha E_{hs}-(\mu+d_1+\delta+(t_1+u_2)+\gamma)I_{hs})$$
$$+\lambda_4\left(\frac{(1-u_1)\beta_{H2}S_hI_{vr}}{N_h}+\delta I_{hs}-(\mu+\sigma)E_{hr}\right)$$
$$+\lambda_5(\sigma E_{hr}-(\mu+d_2+(t_2+u_3))I_{hr})$$
$$+\lambda_6(\gamma I_{hs}+(t_1+u_2)I_{hs}+(t_2+u_3)I_{hr}-(\mu+\rho)R_h)$$
$$+\lambda_7(\Lambda_v-\frac{(1-u_1)\beta_{V1}S_v(I_{hs}+\tau_1R_h)}{N_h}-\frac{(1-u_1)\beta_{V2}S_v(I_{hr}+\tau_2R_h)}{N_h})-$$

$$\lambda_7 u_4(1-p)S_v - \eta S_v$$
$$+\lambda_8\left(\frac{(1-u_1)\beta_{V1}S_v(I_{hs}+\tau_1 R_h)}{N_h} - u_4(1-p)I_{vs} - \eta I_{vs}\right)$$
$$+\lambda_9\left(\frac{(1-u_1)\beta_{V2}S_v(I_{hr}+\tau_2 R_h)}{N_h} - u_4(1-p)I_{vr} - \eta I_{vr}\right). \quad (8)$$

Theorem 3

Let $u_i, i = 1,2,3,4$ be the optimal controls and $S_h^*, E_{hs}^*, I_{hs}^*, E_{hr}^*, I_{hr}^*, R_h^*, S_v^*, I_{vs}^*, I_{vr}^*$ are the solutions of the state system (5) that minimizes $J(u_1,u_2,u_3,u_4)$ over U. Then there exists adjoint variables $\lambda_i,\ i = 1,2,\dots,9$ satisfying

$$\frac{d\lambda_1}{dt} = (\lambda_1-\lambda_2)\frac{(1-u_1)\beta_{H1}I_{vs}}{N_h} + (\lambda_1-\lambda_4)\frac{(1-u_1)\beta_{H2}I_{vr}}{N_h} + \lambda_1\mu,$$
$$\frac{d\lambda_2}{dt} = (\lambda_2-\lambda_3)\alpha + \lambda_2\mu,$$
$$\frac{d\lambda_3}{dt} = -a_1 + (\lambda_3-\lambda_4)\delta + (\lambda_3-\lambda_6)(t_1+u_2+\gamma) + \lambda_3(\mu+d_1) + (\lambda_7-\lambda_8)(1-u_1)\frac{\beta_{V1}S_v}{N_h},$$
$$\frac{d\lambda_4}{dt} = (\lambda_4-\lambda_5)\sigma + \lambda_4\mu,$$
$$\frac{d\lambda_5}{dt} = -a_2 + (\lambda_5-\lambda_6)(t_2+u_3) + (\lambda_7-\lambda_9)\times(1-u_1)\frac{\beta_{V2}S_v}{N_h} + \lambda_5(\mu+d_2),$$
$$\frac{d\lambda_6}{dt} = (\lambda_6-\lambda_1)\rho + (\lambda_8+\lambda_9)(1-u_1)\frac{(-\tau_1-\tau_2)S_v}{N_h} + \lambda_6\mu, \quad (9)$$
$$\frac{d\lambda_7}{dt} = \lambda_7(1-u_1)\frac{(\beta_{V1}I_{hs}+\beta_{V2}I_{hr})}{N_h} + (u_4(1-p)+\eta)\lambda_7 - \lambda_8(1-u_1)\frac{\beta_{V1}(I_{hs}+\tau_1 R_h)}{N_h} - \lambda_9(1-u_1)\frac{\beta_{V2}(I_{hr}+\tau_2 R_h)}{N_h},$$
$$\frac{d\lambda_8}{dt} = -a_3 + (\lambda_1-\lambda_2)(1-u_1)\frac{\beta_{H1}S_h}{N_h} + (u_4(1-p)+\eta) + \lambda_8,$$
$$\frac{d\lambda_9}{dt} = -a_4 + (\lambda_1-\lambda_4)(1-u_1)\frac{\beta_{H2}S_h}{N_h} + (u_4(1-p)\eta + \lambda_8,$$

with transversality conditions

$\lambda_i(t_f) = 0, i = 1,2,\dots,9.$

Furthermore, the optimal control u_1^*, u_2^*, u_3^* and u_4^* are given by

$$u_1^* = \{1, \frac{(\lambda_2-\lambda_1)\beta_{H1}S_hI_{vs}+(\lambda_4-\lambda_1)\beta_{H2}S_hI_{vr}}{c_1N_h} + \frac{(\lambda_8-\lambda_7)\beta_{V1}S_v+(\lambda_9-\lambda_7)\beta_{V2}S_v(I_{vr}+\tau_2R_h)}{c_1N_h})\}$$
$$u_2^* = max\left\{0, min\left(1, \frac{(\lambda_6-\lambda_3)I_{hs}}{c_2}\right)\right\} \quad (10)$$
$$u_3^* = max\left\{0, min\left(1, \frac{(\lambda_6-\lambda_5)I_{hr}}{c_3}\right)\right\}$$
$$u_4^* = max\left\{0, min\left(1, \frac{(1-p)(\lambda_7S_v+\lambda_8I_{vs}+\lambda_9I_{vr})}{c_4}\right)\right\}.$$

Proof: The co-state system (9) is determined by taking the partial derivative of the Hamiltonian function H (8) with respect to each state variable. Thus,

$$\frac{d\lambda_1}{dt} = -\frac{\partial H}{\partial S_h}, \quad \frac{d\lambda_2}{dt} = -\frac{\partial H}{\partial E_{hs}}, \quad \frac{d\lambda_3}{dt} = -\frac{\partial H}{\partial I_{hs}}, \quad \frac{d\lambda_4}{dt} = -\frac{\partial H}{\partial E_{hr}}, \quad \frac{d\lambda_5}{dt} = -\frac{\partial H}{\partial I_{hr}}, \quad \frac{d\lambda_6}{dt} = -\frac{\partial H}{\partial R_h}, \frac{d\lambda_7}{dt} = -\frac{\partial H}{\partial S_v}, \quad \frac{d\lambda_8}{dt} = -\frac{\partial H}{\partial I_{vs}}, \quad \frac{d\lambda_9}{dt} = -\frac{\partial H}{\partial I_{vr}}.$$

$\lambda_i(t_f) = 0$, i = 1, 2, …, 9.

The optimal controls (10) are calculated by finding the partial derivative of the Hamiltonian function H (8) with u_i^* where the derivative vanishes [19]. Thus

$$\frac{\partial H}{\partial u_i} = 0,\ i = 1,\ 2,\ 3,\ 4, \quad (11)$$

and solving for u_1^*, u_2^*, u_3^* and u_4^* subject to the constraints of the control parameters, the characterization equations (11) are obtained.

4 NUMERICAL SIMULATIONS OF OPTIMAL CONTROL

This section discusses numerical simulations with optimal control on malaria control models. Optimal control is obtained by completing an optimal dynamic control system, which consists of 9 ODE of the state and ad-joint equations. The first step is to solve the state equation from left to right. This is done with an initial guess on the control over time, which is simulated using the fourth-order Runge-Kutta method. The adjoint equation is also solved by the fourth-order Runge-Kutta method from right to left together with an iteration state solution. This process is repeated iteratively and stops if the variable values are converging [20]. In the malaria control model with prevention and treatment measures and given control, the effect is seen to optimal control on prevention and treatment of malaria transmission. The control strategy used uses one control at a time and four controls together at a time and compared without control. The weighting factors a_1, a_2, a_3, a_4 are respectively related to the value of handling the sub-population E_{hs}, I_{hs} , E_{hr}, I_{hr}, assumed $a_1 = 800$, $a_2 = 400$, $a_3 = 200$, $a_4 = 100$. The weighting factors c_1, c_2, c_3, c_4 are respectively related to the control costs u_1, u_2, u_3, u_4, assumed $c_1 = 600$, $c_2 = 300$, $c_3 = 150$, $c_4 = 50$. The initial number of human and mosquito populations is assumed as follows: $S_h(0) = 100000$, $E_{hs}(0) = 10000$, $I_{hs}(0) = 6000$, $E_{hs}(0) = 4000$, $I_{hr}(0) = 3000$, $R_h(0) = 0$, $S_v(0) = 500000$, $I_{vs}(0) = 50000$, and $I_{vr}(0) = 10000$.

***TABLE 1**. PARAMETER VALUES OF THE SIMULATION*

Parameter	Estimation value	References
Λ_h	50	Assumed
Λ_V	2000	Assumed
β_{h1}	0.03	[5]
b_{h1}	0.3	[5]
φ	0.6	[5]
β_{h2}	0.03	[5]
b_{h2}	0.3	[5]
β_{v1}	0.03 – 0.5	[Mwanga]
b_{v1}	0.09 – 0.5	[2]
β_{v2}	0.03 – 0.05	[2]
b_{v2}	0.09 – 0.5	[2]
α	0.01	Assumed
μ	0.0004	[5]
d_1	0.05	[5]
d_2	0.05	[5]
δ	0.15	Assumed
γ	0.005	[5]
σ	0.2	Assumed
t_1	0,6	[11]
t_2	0,6	[11]
τ_1	0.05	Assumed
τ_2	0.03	Assumed
ρ	0.0014	[5]
η	0.04	[5]

Numerical simulation results are given as follows. The values of the parameters used in numerical simulations are mostly taken from the journals in the references and some are assumed.

4.1 Sub Population exposed to malaria parasite which is sensitive to antimalarial drugs

This strategy, preventive only the control of sleeping under treated mosquito net to prevent direct contact and bite from infected mosquito (u_1^*) , only the the control on insecticide spray (u_4^*) and ($u_1^*, u_2^*, u_3^*, u_4^*$) together are employed to optimize the objective function J, while malaria treatment of infected individuals which is sensitive to antimalarial drugs (u_2^*) and malaria treatment of infected individuals which is resistant to antimalarial drugs (u_3^*) and are set to zero. Figure 2(a), 2(b) and 2(c) without control shows that the number of individuals in the sub-population E_{hs}(t) increased from initial time to time t = 100 days. Figure 2(a), in using controls using mosquito nets as prevention of contact ($u_1^*(t)$), it is seen that the number of individuals sub-population E_{hs}(t) decreased slowly from initial time to time t = 100 days. In Figure 2(b), using an insecticide spraying control ($u_4^*(t)$), the number of individuals from the beginning increased to time t = 5 days, whereas from time t = 5 days to t = 100 days the number of individuals E_{hs}(t) decreased. Figure 2(c) presents that the control $u_1^*(t)$, is more effective in reducing the number of individual sub-populations E_{hs}(t) compared to using the control $u_4^*(t)$,. Whereas, the controls $(u_1^*(t), u_2^*(t), u_3^*(t), u_4^*(t))$ together are more effective in significantly reducing the number of individual E_{hs}(t) subpopulations than controls $u_1^*(t)$, and $u_1^*(t)$.

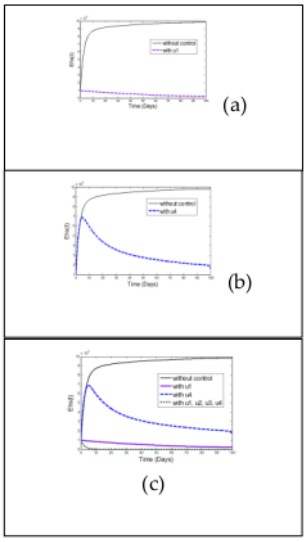

Figure 2. *Simulations on the E_{hs}(t) sub-population, without control and with controls $u_1^*(t)$, $u_4^*(t)$, and $(u_1^*(t), u_2^*(t), u_3^*(t), u_4^*(t))$ together.*

4.2 Sub population exposed to malaria parasite which is resistant to antimalarial drugs

Figure 3(a), 3(b) and 3(c) without control shows that the number of individuals in the sub-population E_{hr}(t) increased from initial time to time t = 100 days. Meanwhile, in using controls using mosquito nets as prevention of contact ($u_1^*(t)$,), In Figure 3(a), the number of individuals E_{hr}(t) increased from initial time to time t = 2 days, and the number of individuals decreased slowly from time t = 2 days to t = 100 days. Figure 3(b), by using the controls $u_2^*(t)$, the number of individuals E_{hr}(t) increased from initial time to time t = 4 days, whereas from time t = 4 days to t = 100 days the number of individuals decreased. Figure 3(c) presents that the control $u_1^*(t)$, is more effective in reducing the number of individual sub-populations E_{hs}(t) compared to using the control $u_1^*(t)$. Whereas, the controls $(u_1^*(t), u_2^*(t), u_3^*(t), u_4^*(t))$ together are more effective in significantly reducing the number of individual E_{hr}(t) subpopulations than controls $u_1^*(t)$, and $u_1^*(t)$.

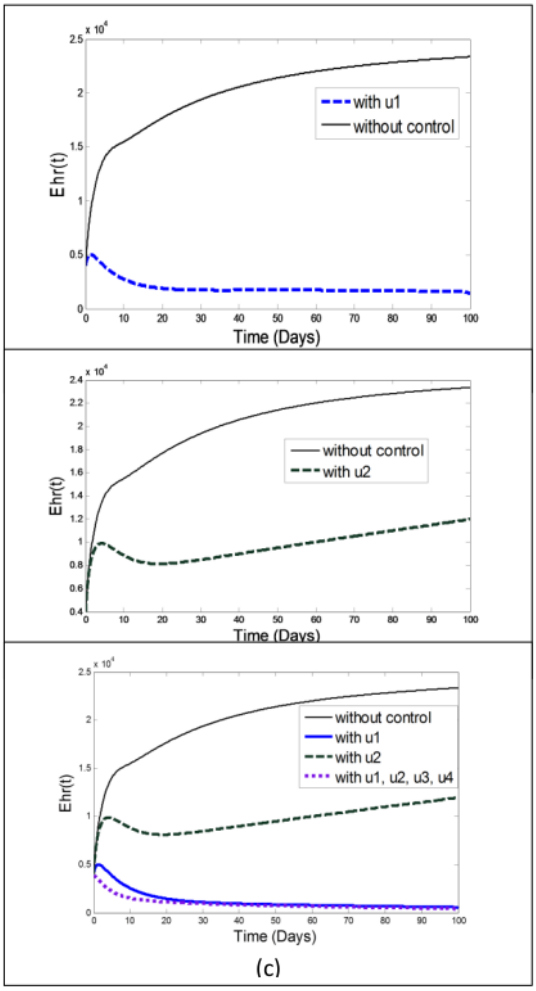

Figure 3. *Simulations on the E_{hr}(t) sub-population, without control and with controls $u_1^*(t)$, $u_2^*(t)$, and $(u_1^*(t), u_2^*(t), u_3^*(t), u_4^*(t))$ together*

4.3 Human sub-populations infected with active malaria that are sensitive to antimalarial drugs ($I_{hs}(t)$)

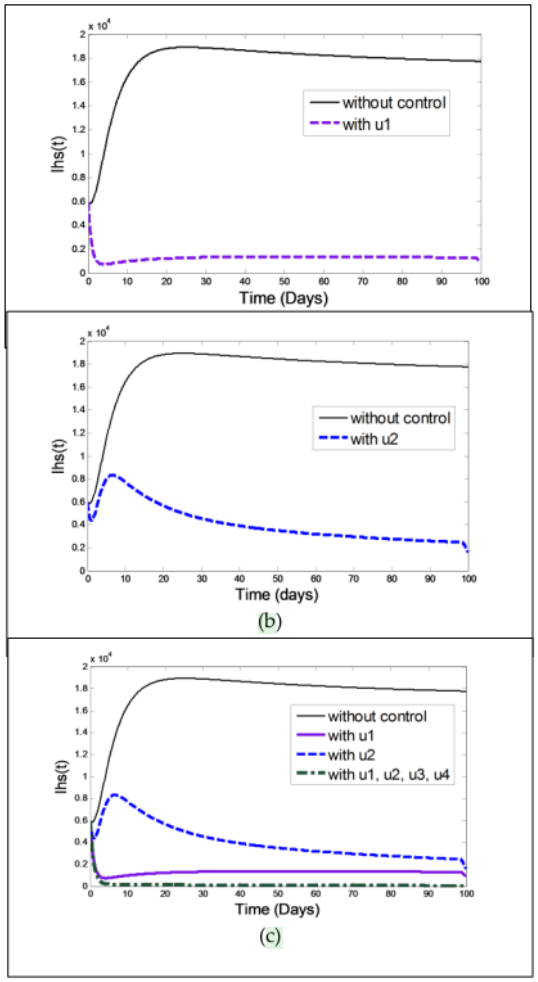

***Figure 4**. Simulation of $I_{hs}(t)$ sub-populations, without control and with controls $u_1^*(t), u_2^*(t)$, and $(u_1^*(t), u_2^*(t), u_3^*(t), u_4^*(t))$ together.*

Figures 4(a), 4(b) and 4(c) without control shows that the number of individuals in the $I_{hs}(t)$ sub-population increased from the initial time to the time of t = 100 days. Whereas, by using controls a prevention bed contact with mosquitoes $(u_1^*(t))$, in Figure 4(a) the number of individual sub-populations of $I_{hs}(t)$ decreases dramatically from the initial time to time t = 3 days, increasing very slowly from time t = 3 days to the time t = 22 days, and constant from time t = 22 days to time t = 100 days. In Figure 4(b), using the $u_2^*(t)$ treatment control the number of individuals sub-population $I_{hs}(t)$ from the initial time increased to time t = 7 days, whereas from time t = 7 days to t = 100 days the number of individuals decreased slowly. Figure 4(c) it is seen that the control $u_1^*(t)$ is more effective in reducing the number of individual sub-populations of $I_{hs}(t)$ compared to using the control $u_2^*(t)$, whereas the controls $(u_1^*(t), u_2^*(t), u_3^*(t), u_4^*(t))$ together are more effective in significantly reducing the number of individual sub-populations of $I_{hs}(t)$ compared to controls $u_1^*(t)$ and $u_2^*(t)$.

4.4 Human sub-populations infected with active malaria which is resistant to antimalarial drugs ($I_{hr}(t)$)

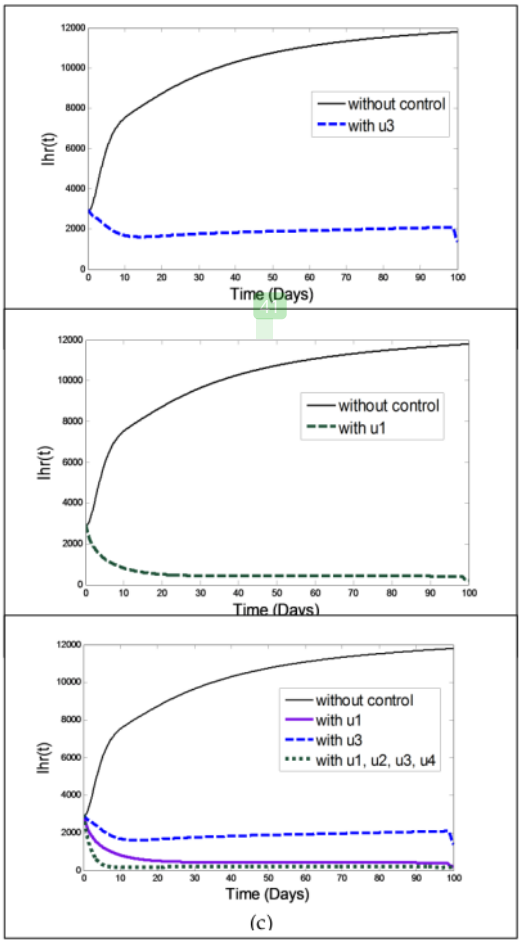

***Figure 5**. Simulation of $I_{hr}(t)$ sub-populations, without control and with controls $u_1^*(t), u_3^*(t)$, and $(u_1^*(t), u_2^*(t), u_3^*(t), u_4^*(t))$ together.*

Figures 5(a), 5(b) and 5(c) without control shows that the number of individuals in the $I_{hr}(t)$ sub-population increased from the initial time to the time of t = 100 days. Figure 5(a) using the $u_3^*(t)$, treatment control of individuals sub-population $I_{hr}(t)$, the number of individuals sub-population $I_{hr}(t)$ decreased from the initial time to the time of t = 15 days, and constans from time t = 15 days to the time of t = 100 days. Figure 5(b), by using controls a prevention bed contact with mosquitoes $(u_1^*(t))$, the number of individual sub-populations of $I_{hr}(t)$ decreases dramatically from the initial time to time t = 22 days, and constant from time t = 22 days to time t = 100 days. Figure 5(c) it is seen that the

control $u_1^*(t)$ is more effective in reducing the number of individual sub-populations of $I_{hr}(t)$ compared to using the control $u_3^*(t)$, whereas the controls $(u_1^*(t), u_2^*(t), u_3^*(t), u_4^*(t))$ together are more effective in significantly reducing the number of individual sub-populations of $I_{hr}(t)$ compared to controls $u_1^*(t)$ and $u_3^*(t)$.

4.5 Mosquito vector sub-populations $S_v(t)$, $I_{vs}(t)$, $I_{vr}(t)$ and control profiles $u_1^*, u_2^*, u_3^*, u_4^*$

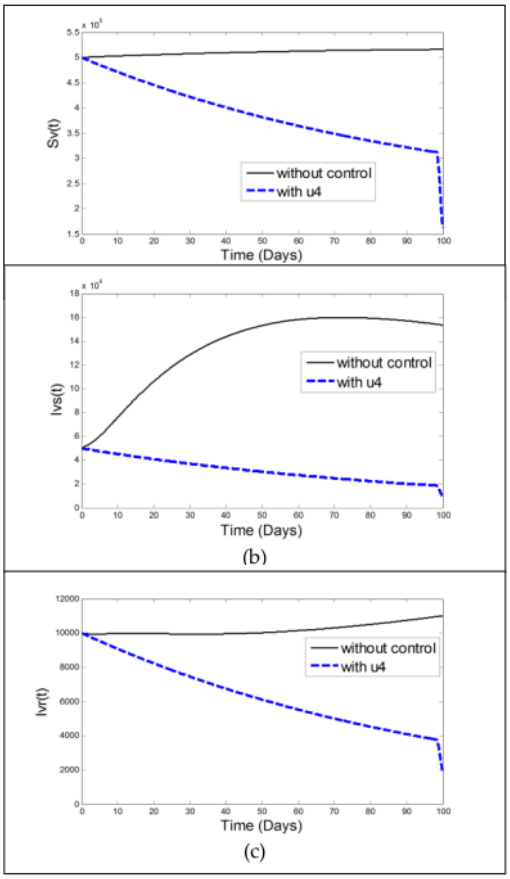

***Figure 6**. Simulations on the spread of $S_v(t)$, $I_{vs}(t)$ and $I_{vr}(t)$ sub-populations with control $u_4^*(t)$ and without control*

Figures 6(a), 6(b), and 6(c) show without control the number of mosquito vectors $S_v(t)$, $I_{vs}(t)$, and $I_{vr}(t)$ increased from initial time to time t = 100 day. Whereas with controls $u_4^*(t)$ or with controls $(u_1^*(t), u_2^*(t), u_3^*(t), u_4^*(t))$ together the number of mosquito vectors $S_v(t)$, $I_{vs}(t)$, and $I_{vr}(t)$ decreased significantly from initial time to time t = 100 days.

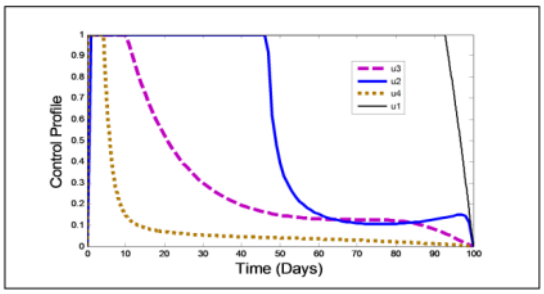

***Figure 7**. Simulations on $(u_1^*(t), u_2^*(t), u_3^*(t), u_4^*(t))$ together, and control profiles.*

The control profile in Figure 7, control of $u_1^*(t)$ was pursued optimally from the initial time to time t = 92.5 days, while $u_2^*(t)$ was pursued optimally from the initial time to time t = 46 days, $u_3^*(t)$ control was sought optimally from the initial time until t = 12 days, and $u_4^*(t)$ strived optimally from the initial time until the time t = 6 days.

5. CONCLUSIONS

In this paper, the study of the malaria model uses a deterministic system of differential equations, determining the stability of asymptotic local disease-free and the basic reproduction number. The control strategy on malaria control by using one control at a time was compared to a combination of four controls together at a time and then compared to without control. Numerical results show combination of four controls, mosquito prevention, treatment of infected individuals and still sensitive to antimalarial drugs, treatment of infected individuals who are resistant to antimalarial drugs and spraying insecticides on mosquitoes. Each of which has a significant impact on malaria prevention. Preventive control u_1^* more effective significantly reduced the number of individuals infected with malaria compared to u_2^*, u_3^* or u_4^*. Control $(u_1^*, u_2^*, u_3^*, u_4^*)$ together were more effective at significantly reducing the number of individuals infected with malaria and the number of mosquito vectors compared to individual controls.

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