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Modeling and Optimal Control of Plasmodium Knowlesi Malaria Spread from Infected Humans to Mosquitoes

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Authors' contributions

This work was carried out in collaboration between all authors. Author MBA designed the study. Author YAH performed the Simulation and numerical analysis. Author FAA wrote the protocol and author MBA wrote the first draft of the manuscript. Authors YAH and FAA managed the analyses of the study. Author FAA managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Malaria as among vector-borne diseases is reemerging in areas where control efforts were once effective and emerging in areas though free of the disease as a consequence of human migration and rapid growth of international traffic from malaria prevalent areas of the world to malaria free zone. In this paper we develop a mathematical model for the spread of *Plasmodium knowlesi* malaria from infected humans to mosquitoes. The stability

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analysis of the model is investigated rigorously. The model is extended to assess the impact of time dependent preventive (biological and chemical control) against the mosquitoes and treatment for infected humans. The existence of optimal control is established analytically by the use of optimal control theory. Numerical simulations of the problem, suggest that applying the three control measure can effectively reduce if not eliminate the spread of *Plasmodium knowlesi* malaria in a community.

Keywords: Modeling; optimal control; infected humans; mosquitoes; Plasmodium knowlesi.

1. INTRODUCTION

Malaria has been infecting and killing millions of humans for a long time [1]. It's even more life threatening with the emergence of its newest, deadliest form which is known as *Plasmodium knowlesi* malaria [2]. A short delay in accurate diagnosis and treatment could lead to onset of complications, including liver and kidney failure and finally death [2,3]. Researchers warn that since tourism is booming in Southeast Asia, it is not far for the new malaria (*Plasmodium knowlesi*) to infect western countries [3]. The contribution of human movement to the transmission of malaria exceeds the limit of the dispersal of mosquito on spatial scales [4].The rapid growth of international traffic is faced with new problems of vector borne disease in many countries [5]. These problems are malaria (*Plasmodium knowlesi*) and dengue which are being diagnosed increasingly in the western countries in travelers returning from Southeast Asia [6]. A traveler infected with malaria can serve as a reservoir and seed localized outbreaks or epidemics in those areas, and thus infected travelers become "active transmitters" of infection in low transmission areas [7,8].

The female anopheles mosquitoes are infected with malaria when they take a blood meal from an infected human, gametocytes and asexual erythrocytic parasite stage circulating in the peripheral bloodstream are ingested, together with other components of the infected human blood [9,10]. The parasite passes through stages of development within the mosquito, which includes the parasites version of sexual reproduction and bursting out of the parasite into the posterior mid-gut lumen of the Anopheles mosquito [10]. This ultimately results in the formation of sporozoites in the mosquito's salivary glands that render the mosquito infectious and ready to be injected into a new host [11,12].

Female anopheles mosquitoes required blood meal as it needs protein for egg production. However, in every 3-4 days feeding and reproduction process is repeated in its life span [13]. From its position statement World health organization/Global malaria program (WHO/GMP) [14], it is necessary to carry out mathematical modeling studies to determine the impact of various combinations of control strategies on the dynamics of *Plasmodium knowlesi* malaria. In this paper, we use treatment for infected human to prevent the spread of *Plasmodium knowlesi* to mosquitoes; biological and chemical control measure of mosquitoes. We consider the time dependent control measures (treatment and biological control) using optimal control theory. Numerous studies dealing with the optimal control theory on vector-borne disease are quite extensive. Many models of Mosquito- borne disease have been developed such as [15-20].

Our main objective is to develop mathematical model for infected human – mosquito interaction with the aim of investigation the role of treatment of infected human and using biological control for mosquitoes. To determine optimal control strategies using various combinations of the control measures for controlling the spread of *Plasmodium knowlesi*

malaria. The paper is organized as follows; Section 2 describes the model and its basic properties. Strategies of control problem are formulated in section 3. Section 4 explains the existence of control problem. In section 5, the simulation that illustrates the result of the dynamics is shown. Finally, in section 6 we have conclusion.

2. MODEL FORMULATION

To formulate the model of *Plasmodium knowlesi* malaria spread from infected humans to mosquitoes, as shown in Fig. 1, [see, for instance, [21-23] we considered the two interacting populations, namely the infected humans and the mosquitoes, the total infected human population I_H at a time t, denoted by $N_H(t)$, hence;

$$N_H(t) = I_H(t)$$

While, the total mosquito population at time t, denoted by $N_M(t)$, is split into susceptible mosquitoes $(S_M(t))$ and infected mosquitoes $(I_M(t))$. Hence,

$$N_M(t) = S_M + I_M.$$

Susceptible mosquitoes are generated (at a rate Λ_M) and diminished by natural death (at a rate μ_M), or by infection, as a result of the susceptible mosquitoes taking a blood meal from infected human (I_H) at a rate β_1. Thus

$$\frac{dS_M}{dt} = \Lambda_M - (\beta_1 I_H + \mu_M) S_M \tag{1}$$

Infected mosquitoes are generated following the development of different stages of the parasite in the susceptible mosquito resulting in the formation of sporozoites in the mosquito's salivary glands that render the mosquito infectious to humans (at a rate β_1). It remains infectious until death (at a rate μ_M). This gives

$$\frac{dI_M}{dt} = \beta_1 I_H S_M - \mu_M I_M \tag{2}$$

The infected human population is generated by infected migrated (at a rate Λ_H) which has interacted with the infected mosquitoes I_M. It diminished by natural death (at the rate μ_H) and disease- induced death (at a rate μ_0). Hence,

$$\frac{dI_H}{dt} = \Lambda_H I_M - (\mu_H + \mu_0) I_H \tag{3}$$

Thus, the basic model of spread of *Plasmodium knowlesi* malaria from infected humans to mosquitoes is given by the following system of differential equations:

$$\begin{cases} \dfrac{dS_M}{dt} = \Lambda_M - (\beta_1 I_H + \mu_M) S_M \\ \dfrac{dI_M}{dt} = \beta_1 I_H S_M - \mu_M I_M \\ \dfrac{dI_H}{dt} = \Lambda_H I_M - (\mu_H + \mu_0) I_H \end{cases} \tag{4}$$

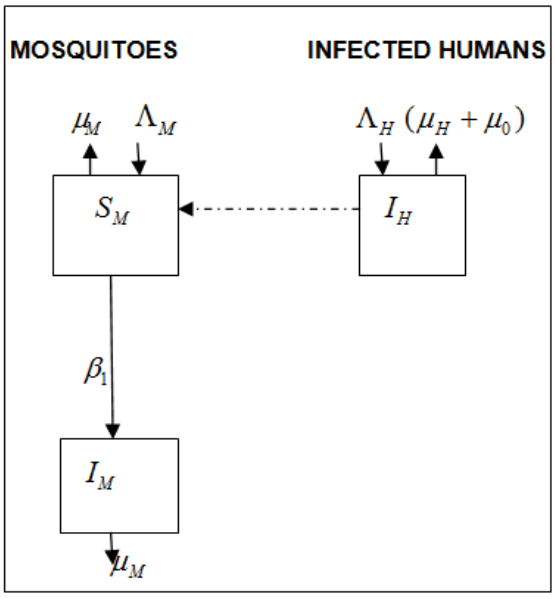

Fig. 1. Schematic illustration of infected human – mosquito interaction

The parameters and variables are non-negative since the model (4) monitors the population dynamics of the infected humans and the mosquito population at a time $t \geq 0$, the model variables and parameters are described in Table 1 and 2 respectively.
The basic model equation (4) is an extension of some standard models for vector- borne diseases, such as [15-20], by

(i) Incorporating only infected humans returning from an area of high transmission to an area of low transmission.
(ii) Including only transmission from infected humans to the mosquito population.

Moreover, the model equation (4) will be extended in section 3 to include time dependent preventive and treatment effort to curtail the spread of the *Plasmodium knowlesi* malaria. In addition to the extensions of the earlier models, this study contributes to literature by offering rigorous analysis of the resulting models.

2.1 Basic Properties of the Model

Theorem 1 The feasible region Ω defined by

$$\Omega=\left\{S_M(0)>0,(I_M(0),I_H(0)\geq 0)\in \square_+^3 : N_M \leq \frac{\Lambda_M}{\mu_M}\right\}$$

With initial conditions $S_M(0)>0,(I_M(0),I_H(0))\geq 0$, is positively invariant.

Proof: Since the infected human has one equation; we add the last two equations of the mosquito population of the model equation (4), thus

$$\frac{dN_M}{dt}=\Lambda_M-\mu_M N_M \tag{5}$$

The solution $N_M(t)$ of the differential equation of the system (5) has the following properties,

$$0\leq N_M(t)\leq N_M(0)e^{-(\mu_M)t}+\frac{\Lambda_S}{\mu_M}(1-e^{-(\mu_M)t}).$$

Where $N_H(0)\ and\ N_M(0)$ represents the initial values of variables. As $t\to\infty, 0\leq N_M\leq \frac{\Lambda_M}{\mu_M}.$

This implies that $\frac{\Lambda_M}{\mu_M}$ is the upper bound of N_M .However, if $N_M>\frac{\Lambda_M}{\mu_M}$, then $N_M(t)$ will decrease to $\frac{\Lambda_M}{\mu_M}$. This implies that if $N_M>\frac{\Lambda_M}{\mu_M}$, then the solutions $(S_M(t),I_M(t),I_H(t))$ enters Ω or approach it asymptotically. Hence, the region Ω attracts all solutions in $\square_+^3$. Since the region Ω is positively- invariant and attracting, the model equation (4) is well-posed epidemiologically and mathematically. Thus it is sufficient to study the dynamics of the model in Ω.

2.2 Positivity of Solutions

Lemma 1 Let the initial data be

$$\{S_M(0)>0,(I_M(0),I_H(0))\geq 0\}\in\Omega.$$

Then the solution set $\{S_M,I_H,I_H\}(t)$ of the model system (4) is positive for all $t>0.$

Proof: The first equation of the model (1) gives

$$\begin{cases} \dfrac{dS_M}{dt} = \Lambda_M - (\beta_1 I_H + \mu_M) S_M \\ \dfrac{dS_M}{dt} \geq -(\beta_1 I_H + \mu_M) S_M \\ \int \dfrac{1}{S_M} dS_M \geq -\int (\beta_1 I_H + \mu_M) dt \\ S_M(t) \geq S_M(0) e^{-(\beta_1 I_H + \mu_M)t} \\ S_M(t) \geq 0. \end{cases}$$

From the second equation of (4) we have;

$$\begin{cases} \dfrac{dI_M}{dt} = \beta_1 I_H S_M - \mu_M I_M \\ \dfrac{dI_M}{dt} \geq -\mu_M I_M \\ \int \dfrac{1}{I_M} dS_M \geq -\int \mu_M I_M \, dt \\ I_M(t) \geq I_M(0) e^{-(\mu_M)t} \\ I_M(t) \geq 0. \end{cases}$$

Similarly it can be shown that $I_H(0) \geq 0$ for all $t > 0$. This completes the proof.

2.3 Stability of the Disease Free Equilibrium (DFE)

The *Plasmodium Knowlesi* malaria model (4) has a DFE, obtained by setting the right-hand sides of the equations in the model (1) to zero, given by

$$\varepsilon_0 = (S_M^*, I_M^*, I_H^*) = \left(\frac{\Lambda_M}{\mu_M}, 0, 0 \right) \qquad (6)$$

The local stability of ε_0 can be explored using the next generation operator method [24] on the system (4), the matrices $F \ and \ V$, of new infection and of transition terms associated with the system (4) respectively, given by

$$F = \begin{bmatrix} 0 & \dfrac{\beta_1 \Lambda_M}{\mu_M} \\ \Lambda_H & 0 \end{bmatrix}$$

And

$$V = \begin{bmatrix} \mu_M & 0 \\ 0 & \mu_H + \mu_0 \end{bmatrix}$$

It follows that the basic reproduction number denoted by $\Re_0 = \rho(FV^{-1})$, where ρ denotes the spectral radius is given by

$$\Re_0 = \sqrt{\frac{\beta_1 \Lambda_M \Lambda_H}{(\mu_H + \mu_O)\mu_M^2}} \tag{7}$$

Further, using [24, theorem 2], the following is established.

Theorem 2 The DFE of the model (4), given by $\Re_0$, is locally asymptotically stable (LAS) if $\Re_0 < 1, \ and$ unstable if $\Re_0 > 1.$

2.4 Existence of Endemic Equilibrium Point (EEP)

When $I_M \neq 0 \ and \ I_H \neq 0,$ this implies that the *Plasmodium knowlesi* malaria still persists within infected human and the mosquito population. Therefore, the model equation (4) has an endemic equilibrium (EEP).

Let,

$$\varepsilon_1 = (S_M^{**}, I_M^{**}, I_H^{**}),$$

Represents any arbitrary endemic equilibrium of the model equation (4), Solving model (4) by setting the right-hand sides of the equations to zero is given by;

$$\begin{cases} S_M^{**} = \dfrac{\mu_M(\mu_H + \mu_0)}{\beta_1 \Lambda_H} \\ I_M^{**} = \dfrac{(-\mu_H - \mu_0)\mu_M^2 + \Lambda_M \beta_1 \Lambda_H}{\mu_M \beta_1 \Lambda_H} \\ I_H^{**} = \dfrac{(-\mu_H - \mu_0)\mu_M^2 + \Lambda_M \beta_1 \Lambda_H}{\mu_M \beta_1 (\mu_H + \mu_0)} \end{cases} \tag{8}$$

2.5 Global Stability of Endemic State

Lemma 2 The model equation (1) has a unique positive endemic equilibrium whenever $\Re_0 > 1,$ and no positive endemic equilibrium otherwise.

Proof: Let $\Re_0 > 1,$ so that the endemic equilibrium ε_1 exists. Consider the non-linear Lyapunov function

$$\begin{cases} V(S_M, I_M, I_H) = \left(S_M - S_M^{**} - S_M^{**} \log \dfrac{S_M}{S_M^{**}} \right) \\ \qquad\qquad + \left(I_M - I_M^{**} - I_M^{**} \log \dfrac{I_M}{I_M^{**}} \right) \\ \qquad\qquad + \left(I_H - I_H^{**} - I_H^{**} \log \dfrac{I_H}{I_H^{**}} \right) \end{cases}$$

The Lyapunov derivative is

$$\begin{cases} \dfrac{dV}{dt} = \left(\dfrac{S_M - S_M^{**}}{S_M} \right) \dfrac{dS_M}{dt} + \left(\dfrac{I_M - I_M^{**}}{I_M} \right) \dfrac{dI_M}{dt} \\ \qquad + \left(\dfrac{I_H - I_H^{**}}{I_H} \right) \dfrac{dI_H}{dt} \end{cases} \tag{9}$$

$$\begin{cases} \dfrac{dV}{dt} = \left(\dfrac{S_M - S_M^{**}}{S_M} \right) \left[\Lambda_M - (\beta_1 I_H + \mu_M) S_M \right] \\ \qquad + \left(\dfrac{I_M - I_M^{**}}{I_M} \right) \left[\beta_1 I_H S_M - \mu_M I_M \right] \\ \qquad + \left(\dfrac{I_H - I_H^{**}}{I_H} \right) \left[\Lambda_H I_M - (\mu_H + \mu_0) I_H \right] \end{cases}$$

Substituting

$$S_M = S_M - S_M^{**}, I_H = I_H - I_H^{**} and\ I_H = I_H - I_H^{**}$$

$$\begin{cases} \dfrac{dV}{dt} = \left(\dfrac{S_M - S_M^{**}}{S_M} \right) \left[\Lambda_M - (\beta_1 (I_H - I_H^{**}) + \mu_M)(S_M - S_M^{**}) \right] \\ \qquad + \left(\dfrac{I_M - I_M^{**}}{I_M} \right) \left[\beta_1 (I_H - I_H^{**})(S_M - S_M^{**}) - \mu_M (I_M - I_M^{**}) \right] \\ \qquad + \left(\dfrac{I_H - I_H^{**}}{I_H} \right) \left[\Lambda_H (I_M - I_M^{**}) - (\mu_H + \mu_0)(I_H - I_H^{**}) \right] \end{cases} \tag{10}$$

Factorizing and simplifying yields

$$\frac{dV}{dt}=-\frac{(S_M-S_M^{**})^2(\beta_1(I_H-I_H^{**})+\mu_M)}{S_M}+\frac{(S_M-S_M^{**})\Lambda_M}{S_M}-\frac{(I_M-I_M^{**})^2\mu_M}{I_M}$$
$$+\frac{(I_M-I_M^{**})(I_H-I_H^{**})(S_M-S_M^{**})}{I_M}-\frac{(I_H-I_H^{**})^2(\mu_H+\mu_0)}{I_H}+\frac{(I_H-I_H^{**})(I_M-I_M^{**})\Lambda_H}{I_H} \quad (11)$$

Let

$$A=\frac{(S_M-S_M^{**})\Lambda_M}{S_M},\ B=\frac{(I_M-I_M^{**})(I_H-I_H^{**})(S_M-S_M^{**})}{I_M}$$

$$C=\frac{(I_H-I_H^{**})(I_M-I_M^{**})\Lambda_H}{I_H}$$

And

$$X=-\frac{(S_M-S_M^{**})^2(\beta_1(I_H-I_H^{**})+\mu_M)}{S_M}$$

$$Y=-\frac{(I_M-I_M^{**})^2\mu_M}{I_M}$$

$$Z=-\frac{(I_H-I_H^{**})^2(\mu_H+\mu_0)}{I_H}$$

Therefore, $\frac{dV}{dt}\le 0$ if and only if $A+B+C\le X+Y+Z;$ Thus, the largest compact invariant set in $\left\{S_M,I_M,I_H\in\Omega:\frac{dV}{dt}=0\right\}$ is the singleton $\{\varepsilon_1\}$ where ε_1 is the endemic equilibrium point and because V' is a negative definite the Lyapunov theorem implies that the endemic equilibrium is globally asymptotically stable in the region.

2.6 Strategies of Optimal Control

In this section, we extend the model equation (4) by introducing the impact of some control measures namely; time dependent preventive (biological control) against mosquitoes larvae, chemical against the adult mosquitoes and treatment for infected humans. The reproduction rate of mosquito population is reduced by a factor of $(1-u_1)$. It was assumed that under the successful chemical control efforts the contact between mosquitoes and infected humans will be reduced by a factor $(1-u_2)$ and death rate of mosquito population increases at a

rate proportional to u_2, where $d > 0$ is at constant rate. The infection of the infected human travelers will be reduced by a factor $(1-u_3)$ and per capita recovery rate as a result of treatment is proportional to u_2, where control $a_1 > 0$ is a rate constant. The model equation (4) becomes

$$\begin{cases} \dfrac{dS_M}{dt} = \Lambda_M(1-u_1) - (1-u_2)\beta_1 I_H S_M - (\mu_M + du_2)S_M \\ \dfrac{dI_M}{dt} = (1-u_2)\beta_1 I_H S_M - (\mu_M + du_2)I_M \\ \dfrac{dI_H}{dt} = \Lambda_H I_M(1-u_3) - (\mu_H + \mu_0 + a_1 u_3)I_H \end{cases} \quad (13)$$

Furthermore, to investigate the optimal control level of efforts needed to control the spread of *Plasmodium knowlesi* malaria*,* our objective functional for the above system (13), is to minimize the number of infected mosquitoes I_M and the cost of control $u_1, u_2 \; and \; u_3$ is given by

$$J(u_1, u_2, u_3) = \int_0^T [A_1 I_H + A_2 S_M + A_3 I_H + B_1 u_1^2 + B_2 u_2^2 + B_2 u_3^2]dt \quad (14)$$

Where T is the final time and the coefficients $A_1, A_2, A_3, B_1, B_2, B_3$ are positive weights to balance the factors. Our aim is to minimize the number of infected mosquitoes $I_M(t)$, while minimizing the cost control $u_1(t), u_2(t) \; and \; u_3$. However, we seek to find an optimal control $u_1^*(t), u_2^*(t) \; and \; u_3^*(t)$ such that

$$J(u_1^*, u_2^*, u_3^*) = \min\{J(u_1, u_2, u_3), (u_1, u_2, u_3) \in U\} \quad (15)$$

Subject to the model equation (13), the control set is defined as

$$U = \{(u_1, u_2, u_3) \,|\, u_i(t) \text{ is Lebesgue measurable on } [0,1],\ 0 \le u_i(t) \le 1,\ i = 1,2,3\} \quad (16)$$

The term $A_1 I_H, A_2 S_M, A_3 I_M$ is the cost of infection while $B_1 u_1^2, B_2 u_2^2,$ and $B_3 u_3^2$ are the cost of using the control measures which consist of biological and chemical control used against mosquito and treatment of the infected humans respectively. The necessary conditions that optimal control must satisfy come from the Pontryagin's Maximum Principle [25]. This principle convert equation (13) and (14) into problem of minimizing point wise a Hamiltonian H, with respect to u_1, u_2 and u_3

$$\begin{cases} H = A_1 I_H + A_2 S_M + A_3 I_M + B_1 u_1^2 + B_2 u_2^2 + B_2 u_3^2 \\ \quad + \lambda_{S_M}\left[\Lambda_M (1-u_1) - (1-u_2)\beta_1 I_H S_M - (\mu_M + d u_2) S_M\right] \\ \quad + \lambda_{I_M}\left[(1-u_2)\beta_1 I_H S_M - (\mu_M + d u_2) I_M\right] \\ \quad + \lambda_{I_H}\left[\Lambda_H I_M (1-u_3) - (\mu_H + \mu_0 + a_1 u_3) I_H\right] \end{cases} \tag{17}$$

Where $\lambda_{S_M}, \lambda_{I_M}$ and λ_{I_H} are the adjoint variables, that will be used in the next section to show the existence of control problem.

2.7 Existence of Optimal Problem

In this section, we consider the control of model equation (13) with initial conditions at $t = 0$ to show the existence of control problem, we state and prove the following theorem using the result by Fleming and Rishel [see, for instance, 19, 20, 26].

Theorem 3 There exist an optimal control $u_1^*, u_2^* \, and \, u_3^*$ and the solutions S_M, I_M, I_H of the corresponding state system (13) that minimizes $J(u_1, u_2)$ over U then there exist adjoint variables $\lambda_{S_M}, \lambda_{I_M}$ and λ_{I_H} satisfying

$$\begin{cases} -\dfrac{d\lambda_{I_H}}{dt} = -A_1 + \lambda_{S_M}(1-u_2)\beta_1 S_M + \lambda_{I_M}(1-u_2)\beta_1 S_M + \lambda_{I_H}(\mu_H + \mu_0 + a_1 u_3) \\ -\dfrac{d\lambda_{S_M}}{dt} = -A_2 - \lambda_{S_M}(-(1-u_2)\beta_1 I_H - \mu_M - d u_1) - \lambda_{I_M}(1-u_2)\beta_1 I_H \\ -\dfrac{d\lambda_{I_M}}{dt} = -A_3 + \lambda_{I_M}(-\mu_M + d u_2) + \lambda_{I_H}\Lambda_H (1-u_3) \end{cases} \tag{18}$$

And with transversality conditions

$$\lambda_{S_M}(T) = \lambda_{I_M}(T) = \lambda_{I_H}(T) = 0 \tag{19}$$

The controls u_1^*, u_2^* and u_3^* satisfy the optimality condition

$$\begin{cases} u_1^* = \max\left\{0, \min\left(1, \dfrac{\lambda_{S_M}\Lambda_M}{2B_1}\right)\right\} \\ u_2^* = \max\left\{0, \min\left(1, \dfrac{((\beta_1 I_H + d)\lambda_{S_M} - \lambda_{I_M}\beta_1 I_H) S_M + \lambda_{I_M} d I_M}{2B_2}\right)\right\} \\ u_3^* = \max\left\{0, \min\left(\dfrac{\lambda_{I_H}(\Lambda_H I_M + a_1 I_H)}{2B_3}\right)\right\} \end{cases} \tag{20}$$

Proof: To obtain the differential equation governing the adjoint variables, we differentiate the Hamiltonian function, then evaluate at the optimal control. Next adjoint system can be written as

$$\begin{cases} -\dfrac{d\lambda_{I_H}}{dt}\dfrac{dI_H}{dt} = -A_1 + \lambda_{S_M}(1-u_2)\beta_1 S_M + \lambda_{I_M}(1-u_2)\beta_1 S_M + \lambda_{I_H}(\mu_H + \mu_0 + a_1 u_3) \\ -\dfrac{d\lambda_{S_M}}{dt} = \dfrac{dS_M}{dt} = -A_2 - \lambda_{S_M}(-(1-u_2)\beta_1 I_H - \mu_M - du_1) - \lambda_{I_M}(1-u_2)\beta_1 I_H \\ -\dfrac{d\lambda_{I_M}}{dt} = \dfrac{dI_M}{dt} - A_3 + \lambda_{I_M}(-\mu_M + du_2) + \lambda_{I_H}\Lambda_H(1-u_3) \end{cases}$$

With transversality conditions

$$\lambda_{S_M}(T) = \lambda_{I_M}(T) = \lambda_{I_H}(T) = 0$$

On the interior of the control set, where $0 \le u_i(t) \le 1, i = 1,2,3$ we have

$$\begin{cases} 0 = \dfrac{\partial H}{\partial u_1} = 2B_1 u_1 - \lambda_{S_M}\Lambda_M \\ 0 = \dfrac{\partial H}{\partial u_2} = 2B_2 u_2 + \lambda_{S_M}(\beta_1 I_H S_M + dS_M) + \lambda_{I_M}(-\beta_1 I_H S_M + dL_M) \\ 0 = \dfrac{\partial H}{\partial u_3} = 2B_3 u_3 - \lambda_{I_H}(\Lambda_H I_M + a_1 I_H) \end{cases} \tag{21}$$

However, from [12,13] we obtained

$$\begin{cases} u_1^* = \dfrac{\lambda_{S_M}\Lambda_M}{2B_1}, \\ u_2^* = \dfrac{((\beta_1 I_H + d)\lambda_{S_M} - \lambda_{I_M}\beta_1 I_H)S_M + \lambda_{I_M} dI_M}{2B_2}, \\ u_3^* = \dfrac{\lambda_{I_H}(\Lambda_H I_M + a_1 I_H)}{2B_3} \end{cases} \tag{22}$$

And

$$\begin{cases} u_1^* = \max\left\{0, \min\left(1, \dfrac{\lambda_{S_M}\Lambda_M}{2B_1}\right)\right\} \\ u_2^* = \max\left\{0, \min\left(1, \dfrac{\left((\beta_1 I_H + d)\lambda_{S_M} - \lambda_{I_M}\beta_1 I_H\right)S_M + \lambda_{I_M} dI_M}{2B_2}\right)\right\} \\ u_2^* = \max\left\{0, \min\left(1, \dfrac{\lambda_{I_H}(\Lambda_H I_M + a_1 I_H)}{2B_3}\right)\right\} \end{cases}$$

By standard control arguments involving the bounds on the controls [14], we concluded that

$$u_1^* = \begin{cases} 0 \ \ if \ \xi_1 \le 0 \\ \xi_1 \ if \ 0 < \xi_1 < 1 \\ 1 \ \ if \ \ \xi_1 \ge 1 \end{cases} \tag{23}$$

$$u_2^* = \begin{cases} 0 \ \ if \ \xi_2 \le 0 \\ \xi_2 \ if \ 0 < \xi_2 < 1 \\ 1 \ \ if \ \ \xi_2 \ge 1 \end{cases} \tag{24}$$

$$u_3^* = \begin{cases} 0 \ \ if \ \xi_3 \le 0 \\ \xi_3 \ if \ 0 < \xi_3 < 1 \\ 1 \ \ if \ \ \xi_3 \ge 1 \end{cases} \tag{25}$$

Where

$$\xi_1 = \frac{\lambda_{S_M} \Lambda_M}{2B_1},$$

$$\xi_2 = \frac{\lambda_{S_M} dS_M - \lambda_{S_M} \beta_1 I_H S_M + dI_M}{2B_2},$$

$$\xi_3 = \frac{\lambda_{I_H} (\Lambda_H + a_1 I_H)}{2B_3}.$$

In addition, the second derivative of the Hamilton function with respect to $u_1^*, u_2^* \, and \, u_3^*$, yields

$$\begin{aligned} 0 &= \frac{\partial^2 H}{\partial u_1^2} = 2B_1 \\ 0 &= \frac{\partial^2 H}{\partial u_2^2} = 2B_2 \\ 0 &= \frac{\partial^2 H}{\partial u_3^2} = 2B_3 \end{aligned} \tag{26}$$

This shows that they are positive, which implies that the optimal problem exist and it is minimum at $u_1, u_2 \, and \, u_3$.

2.8 Numerical Simulation

In this section, we investigate numerically the effect of the optimal control strategies on the spread of *Plasmodium knowlesi* malaria from infected human to mosquitoes in a population. Using the iterative method, we solved the optimality system, consisting of 3 ordinary differential equations from the state and adjoint equations, coupled with the three control characterizations. The state differential equations, with initial estimates for controls and the state are solved using fourth order Runge-Kutta scheme. Using the result of state and the

given final time values, the adjoint system is then solved backward in time, using fourth order Runge-Kutta scheme. The state and the adjoints system are used to update the three control strategies using the characterizations given be equation (22). The process is repeated and the iterative process complete when the current state, adjoint, and control values converge sufficiently [27].

Next, we investigate numerically the effect of the following optimal control strategies on the spread of *Plasmodium knowlesi* malaria from infected human to mosquitoes in a population.

- Optimal use of the time dependent preventive biological control against the mosquito Larvae $u_1 \neq 0$, chemical control for adult mosquitoes $u_2 \neq 0$ and absent of treatment for infected humans $u_3 = 0$.
- Optimal use of treatment for infected humans $u_3 \neq 0$ and absence of optimal use the time dependent preventive (biological and chemical control) against the mosquitoes Larvae $u_1 = 0,$ adult mosquitoes $u_2 = 0$.
- Optimal use of the three control strategies $(u_1, u_2 \; and \; u_3).$

For the numerical simulation we have used the following weight factors $A_1 = 5,\ B_1 = 5,$ $B_2 = 5,\ \ B_3 = 5,$ and use the parameter values from Table 2. Initial states variables are chosen as $I_h(0) = 10, S_v(0) = 1000, I_v(0) = 0.$

2.9 Optimal use of the Biological Control (u_1) and Chemical Control for Adult Mosquitoes (u_2)

With this control strategy, use of *the* biological control (u_1) and chemical control for adult mosquitoes (u_2) are both used to optimize the objective functional J, while the treatment for infected humans (u_3) is set to zero. In Fig. 2, the result shows a significant difference in S_M and I_M with optimal control strategy compared to S_M and I_M without control. It was observed in Fig. 2(a) that the susceptible mosquitoes (S_M) decrease as a result of control strategies against the increase in the uncontrolled case. In Fig. 2(b), similar situation was also observed in the case of infected mosquitoes (I_M).

Table 1. Shows of variables

Variables	Description
S_M	Susceptible mosquitoes
I_M	Infected mosquitoes
I_H	Infected humans

Table 2. Shows the initial values of parameters

Parameter	Initial value	References
Λ_M	0.003200	Estimated
β_1	0.500000	Estimated
μ_M	0.000047	Estimated
Λ_H	0.001000	Estimated
μ_H	0.000045	Estimated
μ_0	0.000038	Estimated
Λ_M	0.003200	Estimated
u_1	variables	
u_2	variables	
u_3	variables	

2.10 Optimal use of Treatment for Infected Humans u_3

In this control strategy, use of *treatment for infected humans* u_3 is used to optimize the objective functional J, while use of *the* biological control (u_1) and chemical control for adult mosquitoes (u_2) are both set to zero. In Fig. 3, the result shows a significant difference in the I_H with optimal control strategy compared I_H without control. It was observed in Fig. 3, that the infected humans (I_H) decrease as a result of control strategies against the increase in the uncontrolled case.

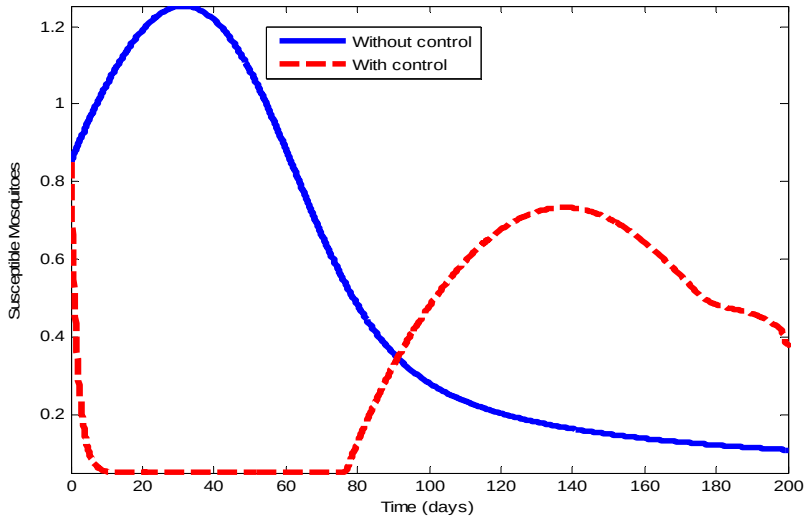

Fig. 2a. Susceptible mosquitoes

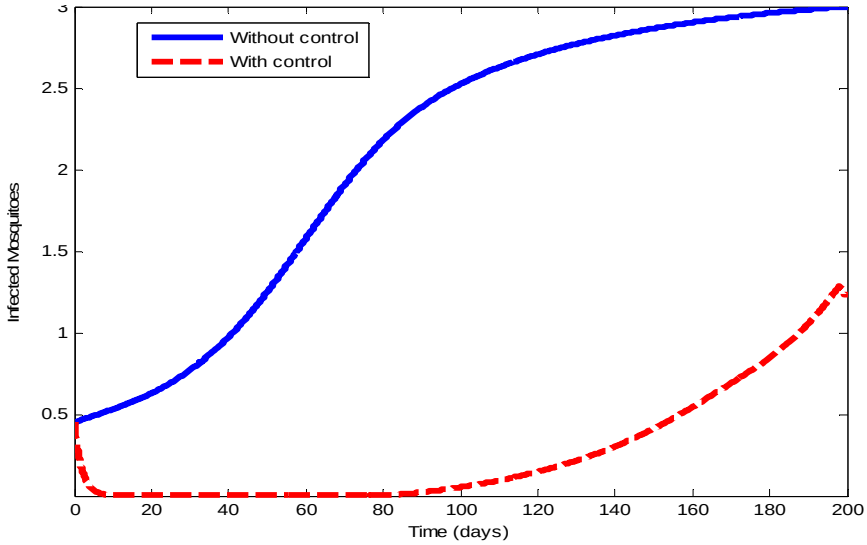

Fig. 2b. Infected mosquitoes

2.11 Optimal use of the Three Control Strategies $(u_1, u_2 \text{ and } u_3)$.

Here, all the control strategies (u_1, u_2, u_3) are used to optimize the objective functional J. In Fig. 4, the result shows a significant difference in the $S_M, I_M \text{and } I_H$ with optimal control strategy compared to $S_M, I_M \text{and } I_H$ without control. It was observed in Fig. 4(a) that the susceptible mosquitoes (S_M) decrease as a result of control strategies against the increase in the uncontrolled case. In Fig. 4(b) and 4(c), similar situations have also been observed in the case of infected mosquitoes and infected human.

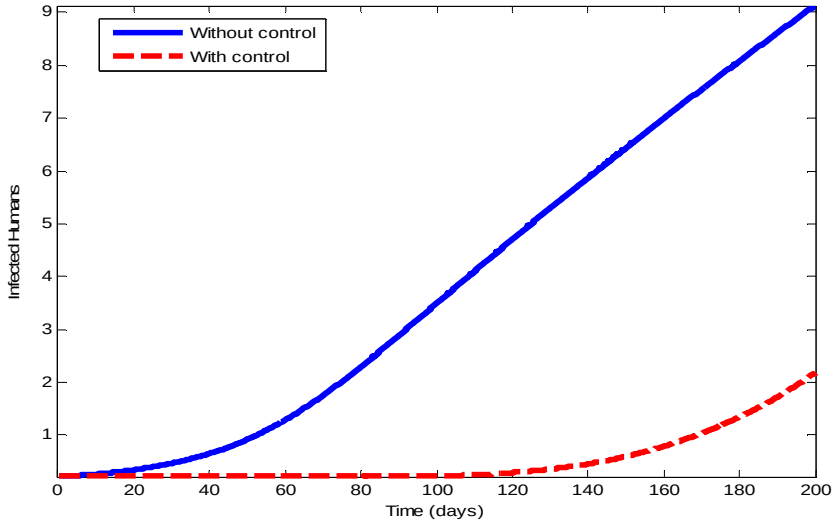

Fig. 3. Infected humans

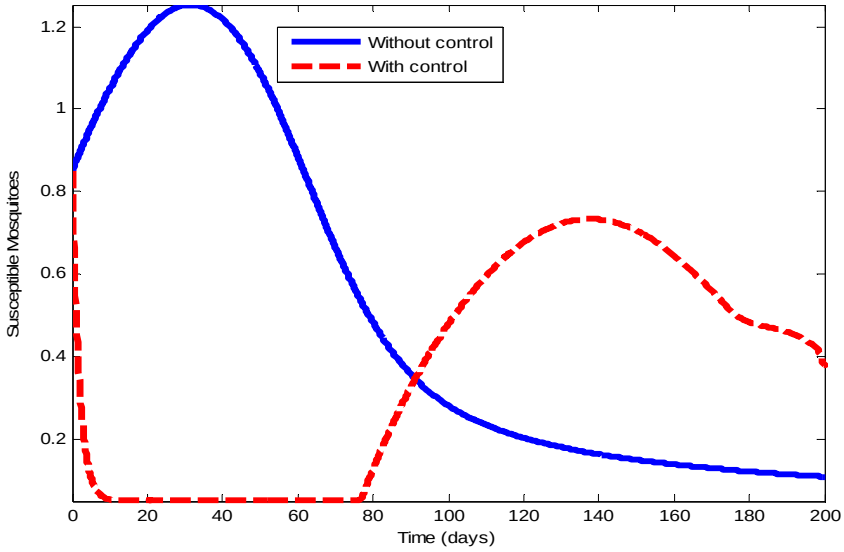

Fig. 4a. Susceptible mosquitoes

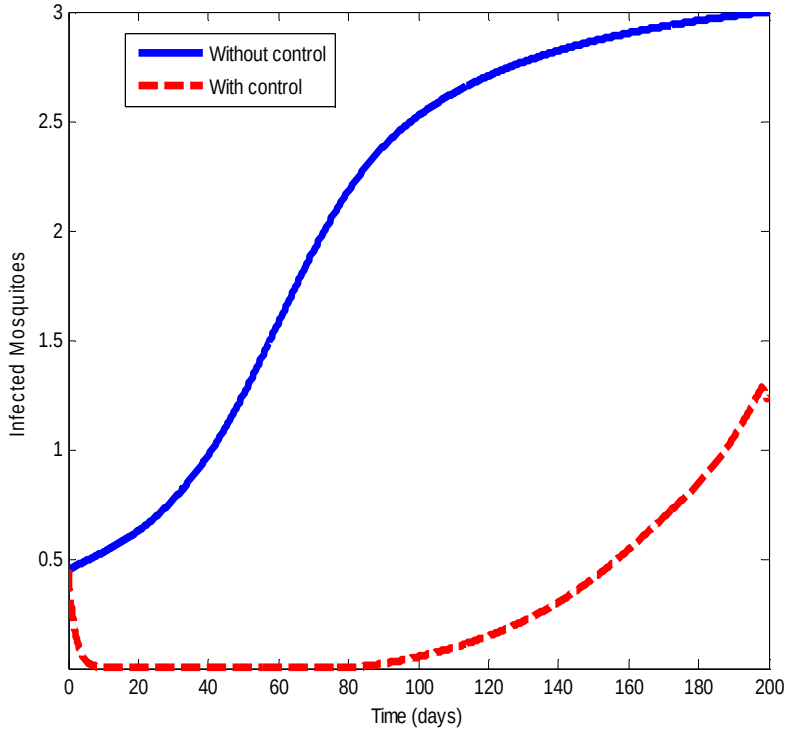

Fig. 4b. Infected mosquitoes

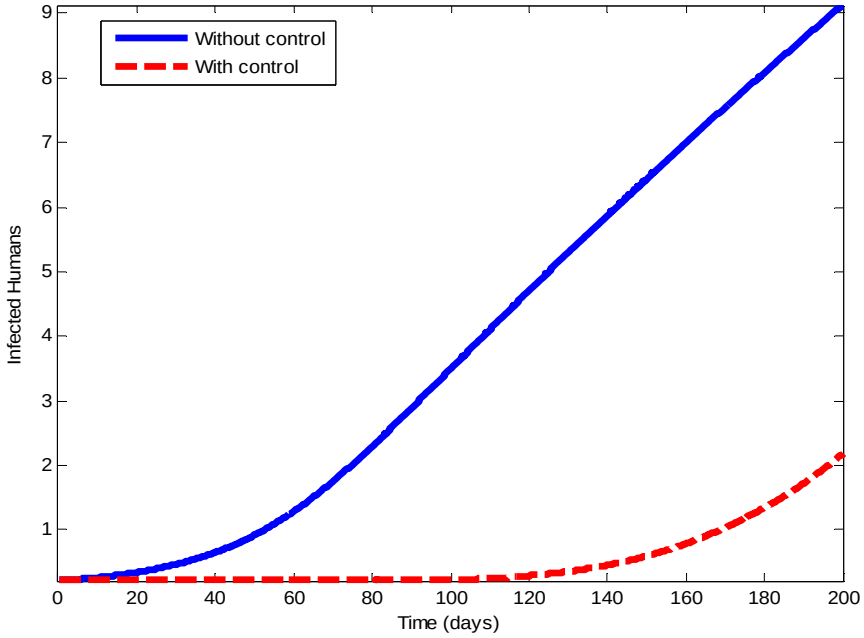

Fig. 4c. Infected humans

3. CONCLUSION

In this paper, a mathematical model for the spread of *plasmodium knowlesi* malaria was developed. It is derived from infected humans to mosquitoes and the model was analyzed rigorously. It was extended to assess the impact of some control measures, namely; time dependent preventive, biological control against mosquito Larvae, chemical control against the adult mosquitoes and treatment for infected humans. The conditions for optimal *plasmodium knowlesi* malaria were derived and analyzed with time dependent preventives and treatment. The optimal control has a very desirable effect for reducing the infected human and mosquito populations. However from the simulation result, it was found that using strategy in (5.1) where $u_1 \neq 0, u_2 \neq 0$ *and* $u_3 = 0$. It shows that mosquito control is one of the best strategies for controlling *Plasmodium Knowlesi* malaria. Moreover, an effective optimal use of the control programs that follow these strategies (5.3) that is $u_1 \neq 0, u_2 \neq 0$ and $u_3 \neq 0$ can effectively reduce if not eliminate the spread of the disease in a community. Although, the suggestion aggress with the result obtained in [1, 15, 16, 21], our result however shows two possible control strategies, each with two combinations of control strategies that are adequate to efficiently achieve and sustain interruption of transmission of the disease. This result addresses WHO [27] apprehension about the insufficiency of only a control strategy. Public health establishments ought to choose the appropriate control strategy where their situation lies in the scenarios discussed in the result.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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