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A MATHEMATICAL ANALYSIS OF THE EFFECTS OF CONTROL OF PLASMODIUM *KNOWLESI* MALARIA

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ABSTRACT

This paper considers a mathematical model for the spread of *Plasmodium knowlesi* malaria. The model incorporates recruitment of human, mosquito and macaque populations through a constant immigration, with a fraction of infective immigrants. The basic properties of model and equilibriums for the models are analyzed rigorously. The sensitivity analysis of the model is carried out to recognize the most sensitive parameters for the disease transmission. Thus, control strategy is presented and studied. Optimal control theory is applied to investigate optimal strategies for controlling the spread of the malaria using quarantine, insecticide spray and culling as the control variables. The results obtained from numerical simulation of the model show possible significant reduction of the disease spread using the combine control strategies.

KEY WORDS

Plasmodium knowlesi malaria; Control; infective immigrants**;** Drug Resistance.

1. INTRODUCTION

Malaria is mostly ignored in the South-East Asia, although it has the highest figure of populace more vulnerable to the disease [1]. In the Region the disease exhibits strange epidemiological rareness such as "jungle malaria" and malaria due to movement across intercontinental borders [1]. Others include rising resistance to drugs and insecticides, detecting and treating *Plasmodium knowlesi* malaria. Broader challenges around health system capacity also exists which impact on the ability of countries to sustain control activities and work towards eradication of the disease (Malaria 2012) [2]. Its eradication is now a target of a lot of countries in the region and the Western Pacific. However, huge reduction in the disease occurrence has been achieved [3, 4]. The major challenge lingers, and though the threats of artemisinin resistance have been the center of much intercontinental concern, zoonotic malaria species (*Plasmodium knowlesi* malaria) have received less consideration [3, 4]. *Plasmodium knowlesi* malaria is the most significant emerging vector-borne infectious disease [4]. Presently, this malaria species is prevalent in Southeast Asia where the mosquito and its reservoir host, the macaque, are abundant [5-7]. In 1931, the parasite was first recognized in India from an imported long-tailed macaque from Singapore [8]. Its capability to transmit a disease to humans was earliest depicted in 1932, after Knowles and Das Gupta effectively transmitted the parasite to two human who offer themselves on free will by blood passages from infected macaques [8].

The management of the disease is still unknown, and the malaria cure guidelines by WHO malaria reports (2012) do not provide any suggestions for its treatment [9, 10]. The infectivity has been treated effectively with mefloquine, quinine and chloroquine [10, 11]. The disease is transmitted by Anopheles *leucosphyrus* to human and macaques, where the macaques serve as the origin and the reservoirs of the parasite [12]. Human can be infected everywhere within the distribution restrictions of Anopheles *leucosphyrus* mosquitoes if the infected macaques are present [13]. Forest dwelling mosquitoes of the *Anopheles leucosphyrus* group, such as *Anopheles latens*, *Anopheles leucosphyrus*, and *Anopheles dirus* are responsible for the disease transmission from human to human only [14]. Countries such as Malaysia, Thailand, China, Singapore, Philippines, Vietnam, Myanmar and Indonesian have recorded human infections of the disease [14].

Traditionally, human movements have added to the stretch of diseases [15, 16]. Failure to reflect on this reason contributed to decline of success of malaria eradication fights in the 1950s and 1960s [17]. Humans often travel across national borders, and national malaria control efficacy can be compromised by imported malaria [18]. Imported malaria cases transmit parasites, as well as resistant strains, even when at asymptomatic stage [19]. Although *Plasmodium knowlesi* malaria infection among western travelers returning from prevalent area has been reported intermittently for years, there has been no logical description of the clinical pattern of *Plasmodium knowlesi* malaria infection among travelers [5]. The international transfer of malaria can come about during the movement of an infected mosquito into a non endemic-disease area; this is described as airport malaria [15]. The mosquitoes are typically moved into non endemic-disease nations on an intercontinental flight. For instance, accidental search of aircrafts at Gatwick Airport (London) established that 12 of 67 aircrafts from tropical nations contained mosquitoes [15, 20]. After leaving the plane, mosquito might live long enough to take a blood meal and spread the disease, habitually in the neighborhood of an airport [15, 20]. Though the occurrence of these circumstances is low, they account for the majority of the disease spread in developed countries [5]. A traveler infected with the disease can aid 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 [21, 22].

Some malaria models have been developed for drug resistance and effect of infective immigrants. These include the studies of Aneke, (2002) [23] that formulated a deterministic model which illustrates the incident of drug resistant malaria in a hyper prevalent region by a scheme of ordinary differential equations models. Meanwhile, no control strategy is incorporated into the model. Koella & Antia (2003) [24] derived a model to examine the spread of anti-malarial resistance. The authors concluded that the models developed in their work are an initial stage in thoughtful of the causes of malaria drug resistance and assessing measures to ease the stretch of resistance. Although, this is one of the earliest drug resistance malaria model, but the precise suggestion for the management of resistance were not given due to unavailability of data. Chiyaka *et al.*, (2009) [25] formulated and analyzed a model for management and stretch of drug resistance in a population with partly resistant humans. The model extends the model of (Aneke, 2002; Koella & Antia 2003; Bacaër & Sokhna 2005) [23, 24, 26] by including discrete time delays on the dormant stage in both vectors and humans and fractional

resistance. They also reflect on occasions where the treated humans are contagious and while they are not transmittable. They concluded that the stretch of drug resistance with management as a control measure relies on the fraction of the contagious time of treated and untreated humans. Also the spread rates from infectious humans with resistant and sensitive strains. The shortcomings of the model includes: not considering the recovered humans and the return path from infected humans to the susceptible.

Esteva *et al.,* (2009) [27] derived a deterministic model for examining the effect of drug resistance on the spread of malaria in humans. The model extends the earlier work of (Koella & Antia 2003; Aneke, 2002) [23, 24] this is by including the infectious mosquitoes as a variable and also allows treated humans with the wild strain to advance to the resistance strain. The aim was to observe the epidemiological impact of the anti-malarial drug in dropping the infection saddle in known inhabitants. Also to observe the impact predisposed by the development of resistance in addition to the suitability of the resistant strain. The authors concluded that while the two strains *exist* together, the fraction of humans with the resistant strain at equilibrium-state reduces with growing scale of resistance. However, no control strategies were suggested. Tumwiine *et al.,* (2010) [28] formulated a human-mosquito model for the transmission of malaria that includes humans recruitment via a steady migration, with a portion of infective migrants. The model extended the earlier model by Tumwiine *et al.,* (2007) [29] where recruitment into the humans was via birth. They established that because of immigration of infective humans, a steady state with a positive portion of infectivity is constantly present. Therefore, the disease-free steady state of the model will not exist and only the endemic steady state where the infection perseveres in the population for an extended period. However, the model does not consider any control strategies and infective immigrants in the mosquito population. Tchuenche *et al.,* (2011) [30] formulated and analyzed a deterministic model for malaria with effect of treatment and they recognized three classes of resistance in individuals. The model includes in cooperated responsive and resistant strains of the parasites in humans and the mosquitoes. The authors established that the model exhibits backward bifurcation and that with specific model suppositions; when medication is increased it would have an inadequate advantage, particularly in setting with extraordinary transference rate. The aim of this work thus, is to build a model that would illustrate the essential procedures of the progress and the dependent investigation of the equilibrium points. Their conclusions entail that more advanced stages of medication will possibly guide to amplify endemic extent and the scope to which this happens relies on additional issues, for instance the degree of medication and resistance advancement. However, efficiency of the anti-malarial medications or medication sensitivity is not included into the medication section of the model and no control strategy was considered.

Makinde & Okosun (2011) [31] developed and investigated a deterministic model that illustrates the dynamics of the disease infectivity with the conscription of infected migrants, management of infective and the use of insecticides to counter the vectors in the inhabitants. The work aimed at developing a deterministic model with infected and transmittable migrants such that they examine the function of introduction of infected migrants in the disease spread. They applied Pontryagin's Maximum Principle, to obtain the best possible approaches for the disease management. However, they concluded that

infected migrants have no robust effect in the spread of the infection, if there is an efficient management system and the vector control. Although, the model considered the control measures and sensitivity analysis but the model is more suitable for *Plasmodium falciparium*. Furthermore, infected immigrants are some sources of resistance strain the disease. Okosun & Makinde (2012) [32] derived and analyzed a mathematical model that differs from those earlier works on drug-resistant anti-malaria; since it includes the compartments of both humans and mosquitoes with drug-resistant strain parasites. The study aimed at addressing the extent of lack of basic amenities and drug resistance strains manipulating the spread of malaria disease. The authors examined and established the likely effect of control measures on the stretch of the disease. They established the conditions necessary for best possible management of the disease applying the Pontryagin's maximum principle to establish best possible management for the stretch of the infection. They concluded that using best possible management actions can lead the disease to a stable disease free equilibrium state (*DFE*). Although, control strategies were suggested and sensitivity analysis evaluated, the model is more suitable for *Plasmodium falciparium*.

Tumwiine *et al.,* (2014) [32] extended the model of Tumwiine *et al.,* (2007) [29], by adding to human population drug resistance and drug sensitive humans. The model was formulated and analyzed. The authors concluded that, model can help out in determining control measures and can present broad assessment of model assumptions that manipulate decisions. However, the model does not suggest any control strategy. Although, the mosquito population ought to have both drug resistance and drug sensitive due to their interaction with human population.

Few studies have been carried out to quantify the impact of *Plasmodium knowlesi* malaria infection in human and macaques [34, 35]. From the work of [34] they formulated a deterministic system of differential equations with three classes with infected humans, mosquitoes and macaques to study the vector preference and host competence. The work of [35] use a deterministic system of differential equations to study the impact of treatment, biological and chemical control strategies in controlling the spread of *Plasmodium knowlesi* malaria in a model. In this paper, culling as a control strategy for dislodging mosquitoes and it larvae as used in [36, 37], and also for macaques control by removing the macaques from the endemic areas to a reserved area. Then, the time dependent control measure using optimal control theory is considered. The theory has been applied with malaria model see for example [36-40]. Imai et al., (2014) [41] the authors developed a new model that is the extension of an earlier model of the disease by Yakob et al., (2010) [35]. The extension includes addition of three characteristic geographical sites (forest (J), farm (F) and village (V)) in which exposure to infection and transmission can occur. The model is aimed at how helpful currently accessible malaria control strategies are against the disease was as well a vital concern that was explored using the model. The authors use the model to assess the probable impact of rapid treatment and the use of insecticide-treated bed nets in preventing wider spread of this rising infectivity. The authors conclude that their outcome demonstrated that continued human-vector or human transmission is unlikely to be taking place at present. As ecological alteration continues, there is the possible for the occurrence of the disease to amplify and to turn out to be an important public health crisis. These outcomes

also draw attention to the need for continued control and alertness of this zoonotic malaria mostly as Malaysia enters the pre-elimination phase for other malaria species.

The aim is to develop a deterministic mathematical model and suggest possible optimal control for the disease. This is to incorporate the effect of immigrations (humans, mosquitoes and macaques) and drug resistance. The extension to consider the effect of infective immigrants is motivated by some earlier work on malaria (see, for instance, Tumwiine *et al.,* 2010; Makinde & Okosun 2011; Okosun & Makinde 2012; Tumwiine *et al.,* 2014) [28, 31-33]. And effect of drug resistance is inspired by the work of (Aneke, 2002; Koella & Anita 2003; Chiyaka *et al.,* 2009; Esteve *et al.,* 2009; Tumwiine *et al.,* 2011) [23-25, 27] The sensitivity analysis of the model will be carried out to recognize the most sensitive parameters for the disease transmission. This is inspired by the some recent research on malaria epidemics (see, for instance, Okosun & Makinde 2013; Okosun *et al.,* 2013) [42, 43]. The paper is organized as follows: Section 2 is dedicated to model depiction and equilibrium analysis. Sensitivity analysis of the model is presented in section 3. In section 4, the existence of control problem stated and then applies the Pontryagin's Maximum Principle to find the necessary conditions for optimal control. Numerical simulations of the models are carried out in section 5 and finally conclusion in section 6.

2. MODEL FORMULATION

The model sub-divides the total human population at a time t, denoted by $N_h(t)$, into the following sub populations of susceptible human $(S_h(t))$, human infected with parasite sensitive to artemisinin $(I_{hs}(t))$, human infected with parasite that is artemisinin resistant strain $(I_{hr}(t))$ and recovered or immune human $(R_h(t))$. Thus,

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

The model sub-divides the total macaque population at a time t, denoted by $N_m(t)$, into the following sub populations of susceptible macaque $(S_m(t))$, macaque infected with parasite sensitive to artemisinin $(I_{ms}(t))$, macaque infected with parasite that is artemisinin resistant strain $(I_{mr}(t))$ and the recovered or immune macaque $(R_h(t))$. So that,

$$N_m(t) = S_m + I_{ms} + I_{mr} + R_m$$

The model sub-divides the total mosquito population at a time t, denoted by $N_m(t)$, into the following sub populations of susceptible mosquitoes $(S_v(t))$ mosquito infected by the parasites sensitive to artemisinin $(I_{vs}(t))$, and mosquitoes infected by malaria parasites with artemisinin resistant strain $(I_{vr}(t))$. Therefore, mosquito populations are given by;

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

It is assumed that humans are born susceptible without infection at a rate π_h. The model with flow into the population that is either infected with the parasite that is sensitive to artemisinin or parasite with artemisinin resistant strain or susceptible humans is considered. This flow is assumed to occur through immigration at constant rate Λ_h. A fraction ϕ_{hs} is human infected with parasite sensitive to artemisinin, a fraction ϕ_{hr} is human infected with parasite with artemisinin resistance strain and the remaining fraction $\left(1-\left(\phi_{hs}+\phi_{hr}\right)\right)$ is susceptible human. The human population suffers a natural death at a rate μ_h and disease induced death at a rate μ_0. Susceptible humans infected with parasites sensitive to artemisinin are moved to the infected humans with parasite sensitive to artemisinin $\left(I_{hs}(t)\right)$ class at a rate $\beta_{hs}c_s I_{vs}$, where β_{hs} is the transmission probability per bite, c_s is the contact rate of human with mosquitoes with parasite sensitive to artemisinin. Susceptible human infected with parasites with artemisinin resistant strain $\left(I_{vr}(t)\right)$ move to infected humans with artemisinin resistant strain at a rate $\beta_{hr}c_r I_{vr}$, where β_{hr} is the transmission probability per bite, c_r is the contact rate of human with artemisinin resistant strain mosquitoes. A fraction of humans with parasites sensitive to artemisinin after treatment progress to the recovered/immune class with at a rate $\left(1-d\right)\tau$. The fraction $d\tau$ of treated infected humans who develop artemisinin resistant strains are moved to the infected human with artemisinin resistant strain class. The recovered individuals lose their immunity at a constant rate, δ_h and returned to the susceptible class.

The mosquito population is recruited at a rate Λ_v. A fraction ϕ_{vs} is mosquito infected with parasite sensitive to artemisinin, a fraction ϕ_{vr} is mosquito infected with parasite with artemisinin resistance strain. The remaining fraction $\left(1-\left(\phi_{vs}+\phi_{vr}\right)\right)$ is susceptible mosquito. Mosquito population suffers a natural death at a rate μ_v. The susceptible mosquitoes S_h move to infected class at a rate $\beta_{vs}c_s\left(I_{hs}+I_{ms}\right)$ and $\beta_{vr}c_r\left(I_{hr}+I_{mr}\right)$ where β_{vs} is the transmission probability per bite of either the humans infected with parasite sensitive to artemisinin I_{hs} or macaques infected with the parasites with sensitive to artemisinin I_{ms}. Other possibility is macaques infected with parasites resistance to artemisinin I_{mr} or infected human with artemisinin resistant strain I_{hr}. β_{vr} is the transmission probability per bite of either the humans infected with parasite resistance to artemisinin. Susceptible mosquitoes infected with malaria parasites sensitive to artemisinin are moved to the class of infected mosquitoes with malaria parasite sensitive to artemisinin I_{vs}. And those susceptible mosquitoes infected with parasites with artemisinin -resistant strain are moved to the class of infected mosquitoes with drug-resistant strain I_{vr}.

It is assumed that the macaque population, increased through birth or immigration at constant rate Λ_m. A fraction ϕ_{ms} is macaque infected with parasite sensitive to

artemisinin. A fraction ϕ_{mr} is macaque infected with parasite with to artemisinin resistance strain and the remaining fraction $\left(1-\left(\phi_{ms}+\phi_{mr}\right)\right)$ is a susceptible macaque. The macaque population suffers a natural death at a rate μ_m and disease induced death at a rate μ_1. Susceptible macaque infected with the parasites sensitive to artemisinin are then moved to the infected humans with parasite sensitive to artemisinin $\left(I_{ms}(t)\right)$ class at a rate $\beta_{ms}c_s I_{vs}$, where β_{ms} is the transmission probability per bite, c_s is the contact rate of macaque with mosquitoes with parasite sensitive to artemisinin. Susceptible macaque infected with parasites with artemisinin resistant strain $\left(I_{mr}(t)\right)$ moved to infected humans with artemisinin resistant strain at a rate $\beta_{mr}c_r I_{vr}$, where β_{mr} is the transmission probability per bite, c_r is the contract rate with artemisinin resistant strain. Infected macaque recovers from the disease by acquiring immunity at a rate γ_m. The recovered macaques lose their immunity at a constant rate, δ_m and return to the susceptible class. These assumptions lead to the following coupled system of ordinary differential equations which describe the progress of the disease (see Table 1 and 2 for the variables description and numerical values of the parameters of the model).

$$
\begin{cases}
\dfrac{dS_h}{dt} = \left(1-\left(\phi_{hs}+\phi_{hr}\right)\Lambda_h\right)+\pi_h+\delta_h R_h-\left(\beta_{hs}c_s I_{vs}+\beta_{hr}c_r I_{vr}+\mu_h\right)S_h \\
\dfrac{dI_{hs}}{dt} = \phi_{hs}\Lambda_h+\beta_{hs}c_s I_{vs}S_h-\left(\tau+\mu_0+\mu_h\right)I_{hs} \\
\dfrac{dI_{hr}}{dt} = \phi_{hr}\Lambda_h+\beta_{hr}c_r I_{vr}S_h+d\tau I_{hs}-\left(\mu_{hr}+\mu_h\right)I_{hr} \\
\dfrac{dR_h}{dt} = \left(1-d\right)\tau I_{hs}-\left(\delta_h+\mu_h\right)R_h \\
\dfrac{dS_v}{dt} = \left(1-\left(\phi_{vs}+\phi_{vr}\right)\Lambda_v\right)-\left(\beta_{vs}c_s\left(I_{hs}+I_{ms}\right)+\beta_{vr}c_r\left(I_{hr}+I_{mr}\right)+\mu_v\right)S_v \\
\dfrac{dI_{vs}}{dt} = \phi_{vs}\Lambda_v+\beta_{vs}c_s\left(I_{hs}+I_{ms}\right)S_v-\mu_v I_{vs} \\
\dfrac{dI_{vr}}{dt} = \phi_{vr}\Lambda_v+\beta_{vr}c_r\left(I_{hr}+I_{mr}\right)S_v-\mu_v I_{vr} \\
\dfrac{dS_m}{dt} = \left(1-\left(\phi_{ms}+\phi_{mr}\right)\Lambda_m\right)+\pi_m+\delta_m R_m-\left(\beta_{ms}c_s I_{vs}+\beta_{mr}c_r I_{vr}+\mu_m\right)S_m \\
\dfrac{dI_{ms}}{dt} = \phi_{ms}\Lambda_m+\beta_{ms}c_s I_{vs}S_m-\left(\mu_1+\mu_m+\gamma_m\right)I_{ms} \\
\dfrac{dI_{mr}}{dt} = \phi_{mr}\Lambda_m+\beta_{mr}c_r I_{vr}S_m-\left(\mu_{mr}+\mu_m\right)I_{mr} \\
\dfrac{dR_m}{dt} = \gamma_m I_m-\left(\mu_m+\delta_m\right)R_m
\end{cases}
\tag{1}
$$

where;

$$\lambda_{hs} = \beta_{hs}\varepsilon_{hs}c_s I_{vs}$$
$$\lambda_{hr} = \beta_{hr}\varepsilon_{hr}c_r I_{vr}$$
$$\lambda_{vs} = \beta_{vs}\varepsilon_{vs}c_s \left(I_{hs} + I_{ms}\right)$$
$$\lambda_{vr} = \beta_{vr}\varepsilon_{vr}c_r \left(I_{hr} + I_{mr}\right)$$
$$\lambda_{ms} = \beta_{ms}\varepsilon_{ms}c_s I_{vs}$$
$$\lambda_{mr} = \beta_{mr}\varepsilon_{mr}c_r I_{vr}$$

refer to mass action force of infection for infected human with strain sensitive to artemisinin, infect human with artemisinin resistant strain, mosquito infected with sensitive strain to artemisinin, mosquito infected with resistance strain to artemisinin, macaques infected with sensitive strain to artemisinin and macaques infected with resistance strain to artemisinin respectively.

2.1 Basic Properties

In this section, the basic dynamical features of the model (1) will be explored. The next is asserted;

Lemma 1:

The closed set

$$\Omega = \left\{\left(S_h, I_{hs}, I_{hr}, R_h, S_v, I_{vs}, I_{vr}, S_m, I_{ms}, I_{mr}, R_m\right) \in \square_+^{11} : \right.$$
$$S_h + I_{hs} + I_{hr} + R_h \le \frac{\Lambda_h + \pi_h}{\mu_h}; S_v + I_{vs} + I_{vr} \le \frac{\Lambda_v}{\mu_v};$$
$$\left. S_h + I_{hs} + I_{hr} + R_h \le \frac{\Lambda_h + \pi_h}{\mu_h} \right\},$$

is positively-invariant and attracting with respect to the basic model (1).

Proof:

Adding the first four equations for humans, the next three equations for mosquitoes and the last four equations for the macaques in the model respectively yields:

$$\frac{dN_h}{dt} = \Lambda_h + \pi_h - \mu_h N_h - \mu_0 I_{hs} - \mu_{hr} I_{hr} \tag{2}$$

$$\frac{dN_v}{dt} = \Lambda_v - \mu_v N_v \tag{3}$$

and

$$\frac{dN_m}{dt} = \Lambda_m + \pi_m - \mu_m N_m - \mu_1 I_{ms} - \mu_{mr} I_{mr} \tag{4}$$

Assuming $\left(I_{hs} = I_{hr} = I_{ms} = I_{mr} = 0\right)$ thus, equation model equation (2) and (4) becomes;

$$\frac{dN_h}{dt} = \Lambda_h + \pi_h - \mu_h N_h$$
$$\frac{dN_v}{dt} = \Lambda_v - \mu_v N_v$$
$$\frac{dN_m}{dt} = \Lambda_m + \pi_m - \mu_m N_m$$

Since $\frac{dN_h}{dt} \le \Lambda_h + \pi_h - \mu_h N_h, \frac{dN_v}{dt} \le \Lambda_v - \mu_v N_v$ and $\frac{dN_m}{dt} \le \Lambda_m + \pi_m - \mu_m N_m,$ it follows that $\frac{dN_h}{dt} < 0, \frac{dN_v}{dt} < 0$ and $\frac{dN_m}{dt} < 0,$ if $N_h > \frac{\Lambda_h + \pi_h}{\mu_h}, \quad N_v > \frac{\Lambda_v}{\mu_v}$ and $N_v > \frac{\Lambda_m + \pi_m}{\mu_m},$ respectively.

Thus, using the standard comparison theorem (Lakshmikantham et al., 1988) [44] it has been shown that

$$N_h(t) \le N_h(0)e^{-\mu_h(t)} + \frac{\Lambda_h + \pi_h}{\mu_h}\left[1 - e^{-\mu_h(t)}\right], N_v(t) \le N_v(0)e^{-\mu_v(t)} + \frac{\Lambda_v}{\mu_v}\left[1 - e^{-\mu_v(t)}\right]$$

and

$$N_m(t) \le N_m(0)e^{-\mu_m(t)} + \frac{\Lambda_m + \pi_m}{\mu_m}\left[1 - e^{-\mu_m(t)}\right].$$

In particular, $N_h \le \frac{\Lambda_h + \pi_h}{\mu_h}, N_v \le \frac{\Lambda_v}{\mu_v}$ and $N_v \le \frac{\Lambda_m + \pi_m}{\mu_m},$ if $N_h(0) \le \frac{\Lambda_h + \pi_h}{\mu_h},$ $N_v(0) \le \frac{\Lambda_v}{\mu_v}$ and $N_v(0) \le \frac{\Lambda_m + \pi_m}{\mu_m},$ respectively. Thus, Ω is positively-invariant. Moreover, if $N_h > \frac{\Lambda_h + \pi_h}{\mu_h}, N_v > \frac{\Lambda_v}{\mu_v}$ and $N_v > \frac{\Lambda_m + \pi_m}{\mu_m},$ then either the solution enter Ω in finite time, or $N_h(t)$ approaches $\frac{\Lambda_h + \pi_h}{\mu_h}$, $N_v(t)$ approaches $\frac{\Lambda_v}{\mu_v}$ and $N_m(t)$ approaches $\frac{\Lambda_m + \pi_m}{\mu_m}$, and the infected variables $I_{hs}, I_{hr}, I_{vs}, I_{vr}, I_{ms}$ and I_{mr} approached zero. Hence Ω is attracting (that is, all solutions in $\mathbb{R}_+^{11}$ eventually enter Ω). Thus, in Ω, the model is well-posed epidemiologically and mathematically. Hence it is sufficient to study the dynamics of the model in Ω.

6.2.2 Disease Free Equilibrium (DFE)

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

$$\begin{cases} \left(1-\left(\phi_{hs}+\phi_{hr}\right)\Lambda_h\right)+\pi_h+\delta_h R_h-\left(\beta_{hs}c_s I_{vs}+\beta_{hr}c_r I_{vr}+\mu_h\right)S_h=0 \\ \phi_{hs}\Lambda_h+\beta_{hs}c_s I_{vs}S_h-\left(\tau+\mu_0+\mu_h\right)I_{hs}=0 \\ \phi_{hr}\Lambda_h+\beta_{hr}c_r I_{vr}S_h+d\tau I_{hs}-\left(\mu_{hr}+\mu_h\right)I_{hr}=0 \\ \left(1-d\right)\tau I_{hs}-\left(\delta_h+\mu_h\right)R_h=0 \\ \left(1-\left(\phi_{vs}+\phi_{vr}\right)\Lambda_v\right)-\left(\beta_{vs}c_s\left(I_{hs}+I_{ms}\right)+\beta_{vr}c_r\left(I_{hr}+I_{mr}\right)+\mu_v\right)S_v=0 \\ \phi_{vs}\Lambda_v+\beta_{vs}c_s\left(I_{hs}+I_{ms}\right)S_v-\mu_v I_{vs}=0 \\ \phi_{vr}\Lambda_v+\beta_{vr}c_r\left(I_{hr}+I_{mr}\right)S_v-\mu_v I_{vr}=0 \\ \left(1-\left(\phi_{ms}+\phi_{mr}\right)\Lambda_m\right)+\pi_m+\delta_m R_m-\left(\beta_{ms}c_s I_{vs}+\beta_{mr}c_r I_{vr}+\mu_m\right)S_m=0 \\ \phi_{ms}\Lambda_m+\beta_{ms}c_s I_{vs}S_m-\left(\mu_1+\mu_m+\gamma_m\right)I_{ms}=0 \\ \phi_{mr}\Lambda_m+\beta_{mr}c_r I_{vr}S_m-\left(\mu_{mr}+\mu_m\right)I_{mr}=0 \\ \gamma_m I_m-\left(\mu_m+\delta_m\right)R_m=0 \end{cases} \tag{5}$$

The disease-free equilibrium points *(DFE)* are equilibrium-state solutions where there is no disease (*Plasmodium knowlesi* malaria). The "diseased" classes in the human, mosquito and macaque populations are equal to zero. Thus, the (*DFE)* of the basic model (1) is given by,

$$\begin{aligned} E_0 &= \left(S_h^*, I_{hs}^*, I_{hr}^*, R_h^*, S_v^*, I_{vs}^*, I_{vr}^*, S_m^*, I_{ms}^*, I_{mr}^*, R_m^*\right) \\ &= \left(\frac{\Lambda_h+\pi_h}{\mu_h}, 0, 0, 0, \frac{\Lambda_v}{\mu_v}, 0, 0, \frac{\Lambda_m+\pi_m}{\mu_m}, 0, 0, 0\right), \end{aligned}$$

This represents the state where there exist no infectivity in a community and it is acknowledged as the disease-free equilibrium point (*DFE*).

The linear stability of the disease can be established using the next generation operator method (Van den Driessche & Watmough 2002) [45] on the model equation (1), the matrix *F* and *V*, for the new infection terms and the remaining transfer terms, are respectively given by;

$$F=\begin{pmatrix} 0 & 0 & \frac{\beta_{hs}c_s\left(\Lambda_h+\pi_h\right)}{\mu_h} & 0 & 0 & 0 \\ d\tau & 0 & 0 & \frac{\beta_{hr}c_s\left(\Lambda_h+\pi_h\right)}{\mu_h} & 0 & 0 \\ \frac{\beta_{vs}c_s\Lambda_v}{\mu_v} & 0 & 0 & 0 & \frac{\beta_{vs}c_s\Lambda_v}{\mu_v} & 0 \\ 0 & \frac{\beta_{vr}c_r\Lambda_v}{\mu_v} & 0 & 0 & 0 & \frac{\beta_{vr}c_r\Lambda_v}{\mu_v} \\ 0 & 0 & \frac{\beta_{ms}c_s\left(\Lambda_m+\pi_m\right)}{\mu_m} & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{\beta_{mr}c_r\left(\Lambda_m+\pi_m\right)}{\mu_m} & 0 & 0 \end{pmatrix}$$

$$V=\begin{pmatrix} \tau+\mu_0+\mu_h & 0 & 0 & 0 & 0 & 0 \\ 0 & \mu_{hr}+\mu_h & 0 & 0 & 0 & 0 \\ 0 & 0 & \mu_v & 0 & 0 & 0 \\ 0 & 0 & 0 & \mu_v & 0 & 0 \\ 0 & 0 & 0 & 0 & \gamma_m+\mu_1+\mu_m & 0 \\ 0 & 0 & 0 & 0 & 0 & \mu_{mr}+\mu_m \end{pmatrix}$$

It follows that the drug sensitive basic reproduction number of the model equation (1) denoted by $\mathcal{R}_s$. And given by;

$$\mathcal{R}_s=\sqrt{\frac{\beta_{vs}\left(\mu_m\beta_{hs}\left(\mu_1+\mu_m+\gamma_m\right)\left(\Lambda_h+\pi_h\right)+\mu_h\beta_{ms}\left(\Lambda_m+\pi_m\right)\left(\tau+\mu_0+\mu_h\right)\right)\Lambda_v c_s^2}{\left(\tau+\mu_0+\mu_h\right)\left(\mu_1+\mu_m+\gamma_m\right)\mu_m\mu_h\mu_v^2}} \tag{6}$$

and the drug resistance basic reproduction number is;

$$\mathcal{R}_r=\sqrt{\frac{c_r^2\left(\mu_m\beta_{hr}\left(\mu_{mr}+\mu_m\right)\left(\Lambda_h+\pi_h\right)+\mu_h\beta_{mr}\left(\mu_{hr}+\mu_h\right)\left(\Lambda_m+\pi_m\right)\right)\beta_{vr}\Lambda_v}{\left(\mu_{hr}+\mu_h\right)\left(\mu_{mr}+\mu_m\right)\mu_m\mu_h\mu_v^2}} \tag{7}$$

Furthermore, using Theorem 2 of (Van den Driessche & Watmough 2002) [45] the following result is established.

Theorem 6.1.1

The *DFE* of the model (1), given by $\mathcal{R}_s$ is locally asymptotically stable (LAS) if $\mathcal{R}_s<1$, and unstable if $\mathcal{R}_s>1$.

3. SENSITIVITY ANALYSIS OF MODEL PARAMETERS

Sensitivity of each parameter is examined with respect to the basic reproduction number $\mathcal{R}_r$. In this way, the parameters that are more sensitive to the disease

transmission are identified. And by either reducing or increasing such parameters will as well reduce or increase the transmission of the disease. Sensitivity index of the basic reproduction number, $\mathcal{R}_r$ with respect to each parameter is computed as given in Table 1 for the model equation (1)

Definition:

The normalized forward sensitivity index of a variable with respect to a parameter is the ratio of the relative change in the variable to the relative change in the parameter. When the variable is a differentiable function of the parameter, the sensitivity index perhaps is on the other hand defined using partial derivatives as:

$$\Upsilon_{\beta_{mr}}^{\mathcal{R}_r} = \frac{\partial \mathcal{R}_r}{\partial \beta_{mr}} \times \frac{\beta_{mr}}{\mathcal{R}_r}$$

6.3.1 Sensitivity indices of $\mathcal{R}_r$

Thus, the Sensitivity of $\mathcal{R}_r$ to each of the (14) different parameters described in table 6.1 are determined using drug resistance basic reproduction number of the basic model (1) stated;

$$\mathcal{R}_r = \sqrt{\frac{c_r^2\left(\mu_m\beta_{hr}\left(\mu_{mr}+\mu_m\right)\left(\Lambda_h+\pi_h\right)+\mu_h\beta_{mr}\left(\mu_{hr}+\mu_h\right)\left(\Lambda_m+\pi_m\right)\right)\beta_{vr}\Lambda_v}{\left(\mu_{hr}+\mu_h\right)\left(\mu_{mr}+\mu_m\right)\mu_m\mu_h\mu_v^2}}$$

The Sensitivity indices of $\mathcal{R}_r$ with respect to $\mu_v, \beta_{vr}, \Lambda_v, c_r$ for example are,

$$\begin{cases} \Upsilon_{\mu_v}^{\mathcal{R}_0} := \dfrac{\partial \mathcal{R}_0}{\partial \mu_v} \times \dfrac{\mu_v}{\mathcal{R}_0} = -1, \\ \Upsilon_{c_r}^{\mathcal{R}_0} := \dfrac{\partial \mathcal{R}_0}{\partial c_r} \times \dfrac{c_r}{\mathcal{R}_0} = 1, \\ \Upsilon_{\beta_{vr}}^{\mathcal{R}_0} := \dfrac{\partial \mathcal{R}_0}{\partial \beta_{vr}} \times \dfrac{\beta_{vr}}{\mathcal{R}_0} = \dfrac{1}{2}, \\ \Upsilon_{\Lambda_v}^{\mathcal{R}_0} := \dfrac{\partial \mathcal{R}_0}{\partial \Lambda_v} \times \dfrac{\Lambda_v}{\mathcal{R}_0} = \dfrac{1}{2}. \end{cases} \tag{8}$$

These parameters do not depend on any parameter values, while the remaining parameter depends of other parameters for their values. The parameters values are given on Table 3

Table 3
Sensitivity Indices of $\mathcal{R}_r$

	Parameter	Value	Sensitivity Index
1	c_r	0.502	+1
2	μ_v	0.04	-1
3	μ_m	0.02	-0.7245
4	β_{vr}	0.83	+0.5
5	Λ_v	0.071	+0.5
6	β_{mr}	0.83	+0.4830
7	Λ_m	0.2	+0.4812
8	μ_{mr}	0.02	-0.2415
9	μ_h	0.0004	-0.01715
10	β_{hr}	0.17	+0.01701
11	μ_{hr}	0.05	-0.01688
12	π_h	0.00076	+0.01486
13	Λ_h	0.00011	+0.002151
14	π_m	0.00076	+0.001828

Table 3 above entails that an increase in the mosquito deaths has an optimistic impact in controlling the disease. The parameters are prearranged starting from the most sensitive to the least. The most sensitive parameters are c_r is the contact rate of human and macaques with artemisinin resistant strain mosquitoes and mosquito death rate μ_v. This is followed by death rate of macaques μ_m and recruitment rate of mosquitoes Λ_v. Other important parameters include probability of infection of macaques with artemisinin resistant strain mosquitoes β_{mr}, immigration rate of macaques Λ_m and the least sensitive is the birth rate of macaques π_m. The sensitivity index of $\mathcal{R}_r$ with respect to probability of mosquitoes getting infected with artemisinin resistant strain (β_{vr}) is +0.5, this implies that decreasing (or increasing) the (β_{vr}) by 20%, decreases (or increases) $\mathcal{R}_r$ by 10% is the same with *recruitment rate of mosquitoes,* Λ_v. Since $\Upsilon_{c_r}^{\mathcal{R}_0} = -1$, increasing (or decreasing) c_r by 20%, decreases (or increases) the $\mathcal{R}_0$ by 20%. Therefore, reducing the number of contacts between human and macaques with artemisinin resistant strain mosquitoes, through reducing the number of mosquitoes, will reduce the contact and biting rate with both human and macaques. Thus, the number of bits that human and macaques will receive will have a large effect on disease transmission.

4. OPTIMAL CONTROL MODEL DESCRIPTION

In order to investigate the optimal control measures for the control of the disease, some control parameters are considered. Based on the sensitivity analysis result, the

following control strategies will be considered; quarantine, spray of insecticides and culling. The quarantine will be used against human immigrants and imported macaques, spray of insecticides against the mosquitoes and culling against the macaques. Model equation (1) will be extended to include the three control strategies stated above. Thus, the modified model description is given below;

Susceptible humans are recruited at a rate $\left(1-\left(\phi_{hs}+\phi_{hr}\right)u_1\Lambda_h\right)$ where ϕ_{hs} and ϕ_{hr} are the fractions of humans infected with the parasite sensitive to artemisinin and resistance artemisinin respectively and $u_1\ (0\le u_1\le 1)$ is the control efforts of immigrants (quarantine). Susceptible humans get infected following contact with infected mosquitoes with both strains at a rate $(1-u_2)\left(\beta_{hs}c_sI_{vs}+\beta_{hr}c_rI_{vr}\right)$. And $u_2\ (0\le u_2\le 1)$ is the control on the use of insecticide spray.

The mosquitoes are recruited at a rate $\left(1-\left(\phi_{vs}+\phi_{vr}\right)u_2\Lambda_v\right)$ where ϕ_{vs} and ϕ_{vr} are the fractions of mosquitoes infected with the parasite sensitive to artemisinin and resistance artemisinin respectively and $u_2\ (0\le u_2\le 1)$ is the use of insecticide spray. Susceptible mosquitoes (S_v) get infected following effective contacts with either from infected humans or infected macaques with sensitive to artemisinin and resistance artemisinin the disease at a rate $(1-u_2)\beta_{vs}c_s\left(I_{hs}+I_{ms}\right)S_v$, $(1-u_2)\beta_{vr}c_r\left(I_{hr}+I_{mr}\right)S_v$ respectively.

The macaques are recruited at a rate $\left(1-\left(\phi_{ms}+\phi_{mr}\right)u_1\Lambda_m\right)$ where ϕ_{hs} and ϕ_{hr} are the fractions of macaques infected with the parasite sensitive to artemisinin and resistance artemisinin respectively and $u_1\ (0\le u_1\le 1)$ is the control efforts of immigrants (quarantine). Susceptible macaques get infected following contact with infected mosquitoes with both strains at a rate $(1-u_3)\left(\beta_{ms}c_sI_{vs}+\beta_{mr}c_rI_{vr}\right)$. And $u_3\ (0\le u_3\le 1)$ is the control on the use of culling.

Therefore, putting the above formulations and assumptions together gives the following human – mosquito - macaque model, given by system of ordinary differential equations below as;

$$
\begin{cases}
\dfrac{dS_h}{dt} = \left(1-\left(\phi_{hs}+\phi_{hr}\right)u_1\Lambda_h\right)+\pi_h+\delta_h R_h-\left(1-u_2\right)\left(\beta_{hs}c_s I_{vs}+\beta_{hr}c_r I_{vr}\right)S_h-\mu_h S_h \\
\dfrac{dI_{hs}}{dt} = \phi_{hs}u_1\Lambda_h+\left(1-u_2\right)\beta_{hs}c_s I_{vs}S_h-\left(\tau+\mu_0+\mu_h\right)I_{hs} \\
\dfrac{dI_{hr}}{dt} = \phi_{hr}u_1\Lambda_h+\left(1-u_2\right)\beta_{hr}c_r I_{vr}S_h+d\tau I_{hs}-\left(\mu_{hr}+\mu_h\right)I_{hr} \\
\dfrac{dR_h}{dt} = \left(1-d\right)\tau I_{hs}-\left(\delta_h+\mu_h\right)R_h \\
\dfrac{dS_v}{dt} = \left(1-\left(\phi_{vs}+\phi_{vr}\right)u_2\Lambda_v\right)-\left(1-u_2\right)\beta_{vs}c_s\left(I_{hs}+I_{ms}\right) \\
\qquad\qquad S_v-\left(1-u_2\right)\beta_{vr}c_r\left(I_{hr}+I_{mr}\right)S_v-\left(\mu_v+u_2\right)S_v \\
\dfrac{dI_{vs}}{dt} = \phi_{vs}u_2\Lambda_v+\left(1-u_2\right)\beta_{vs}c_s\left(I_{hs}+I_{ms}\right)S_v-\mu_v I_{vs} \\
\dfrac{dI_{vr}}{dt} = \phi_{vr}u_2\Lambda_v+\left(1-u_2\right)\beta_{vr}c_r\left(I_{hr}+I_{mr}\right)S_v-\mu_v I_{vr} \\
\dfrac{dS_m}{dt} = \left(1-\left(\phi_{ms}+\phi_{mr}\right)u_1\Lambda_m\right)+\pi_m+\delta_m R_m-\left(1-u_3\right)\left(\beta_{ms}c_s I_{vs}+\beta_{mr}c_r I_{vr}\right)-\mu_m S_m \\
\dfrac{dI_{ms}}{dt} = \phi_{ms}u_1\Lambda_m+\left(1-u_3\right)\beta_{ms}c_s I_{vs}S_m-\left(\mu_1+\mu_m+\gamma_m\right)I_{ms} \\
\dfrac{dI_{mr}}{dt} = \phi_{mr}u_1\Lambda_m+\left(1-u_3\right)\beta_{mr}c_r I_{vr}S_m-\left(\mu_{mr}+\mu_m\right)I_{mr} \\
\dfrac{dR_m}{dt} = \gamma_m I_m-\left(\mu_m+\delta_m\right)R_m
\end{cases}
\tag{9}
$$

In investigating the optimal control efforts that would be needed to control the disease, it is necessary to consider an optimal control problem with the objective (cost) functional given by;

$$J=\min_{u_1,u_2,u_3}\int_0^T\left(A_1I_{hr}+A_2I_{mr}+A_3u_1^2+A_4u_2^2+A_5u_3^2\right) \tag{10}$$

where $A_i, i=1,...,5$ are positive weights. A quadratic cost on the controls is chosen that is similar to others in literature (see, for instance, Okosun & Makinde 2013; Okosun *et al*., 2013) [42, 43]. With the given objective function $J\left(u_1,u_2,u_3\right)$; this is aimed to minimize the number of infected humans with resistance artemisinin strain to I_{hr} and infected macaques with resistance artemisinin strain I_{mr}, while minimizing the cost of controls $u_1(t),u_2(t)\text{and}u_3(t)$. Therefore, an optimal control u_1^*,u_2^*,u_3^* is obtained such that;

$$J\left(u_1^*,u_2^*,u_3^*\right)=\min_{u_1,u_2,u_3}\left\{J\left(u_1,u_2,u_3\right)\middle|u_1,u_2,u_3\in Y\right\} \tag{11}$$

where the control set;

$$Y=\left\{\left(u_1^*,u_2^*,u_3^*\right)\middle|u_i:[0,T]\to[0,1],\,Lebesgue\ \ measurable\, i=1,2,3\right\}. \tag{12}$$

4.1 Pontryagin's Maximum Principle

The necessary conditions that an optimal control must satisfy come from the Pontryagin's Maximum Principle (Pontryagin *et al.*, 1964) [46]. The principle converts $(9)-(10)$ into a problem of minimizing point wise a Hamiltonian H, with respect to (u_1,u_2,u_3). Using the optimal control theory, let $\lambda_i(t)$, be adjoint variables with $i=1,...,11$. The Hamiltonian for the present optimal control problem is given by;

$$
\begin{cases}
H = A_1 I_{hr} + A_2 I_{mr} + A_3 u_1^2 + A_4 u_2^2 + A_5 u_3^2 \\
\quad + \lambda_1 \left\{ \begin{array}{l} \left(1-(\phi_{hs}+\phi_{hr})u_1\Lambda_h\right)+\pi_h+\delta_h R_h \\ \quad -(1-u_2)(\beta_{hs}c_s I_{vs}+\beta_{hr}c_r I_{vr})S_h-\mu_h S_h \end{array} \right\} \\
\quad + \lambda_2 \left\{ \phi_{hs}u_1\Lambda_h + (1-u_2)\beta_{hs}c_s I_{vs}S_h - (\tau+\mu_0+\mu_h)I_{hs} \right\} \\
\quad + \lambda_3 \left\{ \phi_{hr}u_1\Lambda_h + (1-u_2)\beta_{hr}c_r I_{vr}S_h + d\tau I_{hs} - (\mu_{hr}+\mu_h)I_{hr} \right\} \\
\quad + \lambda_4 \left\{ (1-d)\tau I_{hs} - (\delta_h+\mu_h)R_h \right\} \\
\quad + \lambda_5 \left\{ \begin{array}{l} \left(1-(\phi_{vs}+\phi_{vr})u_2\Lambda_v\right)-(1-u_2) \\ \left(\beta_{vs}c_s(I_{hs}+I_{ms})S_v+\beta_{vr}c_r(I_{hr}+I_{mr})S_v\right)-(\mu_v+u_2)S_v \end{array} \right\} \\
\quad + \lambda_6 \left\{ \phi_{vs}u_2\Lambda_v + (1-u_2)\beta_{vs}c_s(I_{hs}+I_{ms})S_v - (\mu_v+u_2)I_{vs} \right\} \\
\quad + \lambda_7 \left\{ \phi_{vr}u_2\Lambda_v + (1-u_2)\beta_{vr}c_r(I_{hr}+I_{mr})S_v - (\mu_v+u_2)I_{vr} \right\} \\
\quad + \lambda_8 \left\{ \begin{array}{l} \left(1-(\phi_{ms}+\phi_{mr})u_1\Lambda_m\right)+\pi_m+\delta_m R_m \\ \quad -(1-u_3)(\beta_{ms}c_s I_{vs}+\beta_{mr}c_r I_{vr})-\mu_m S_m \end{array} \right\} \\
\quad + \lambda_9 \left\{ \phi_{ms}u_1\Lambda_m + (1-u_3)\beta_{ms}c_s I_{vs}S_m - (\mu_1+\mu_m+\gamma_m)I_{ms} \right\} \\
\quad + \lambda_{10} \left\{ \phi_{mr}u_1\Lambda_m + (1-u_3)\beta_{mr}c_r I_{vr}S_m - (\mu_{mr}+\mu_m)I_{mr} \right\} \\
\quad + \lambda_{11} \left\{ \gamma_m I_m - (\mu_m+\delta_m)R_m \right\}
\end{cases}
\tag{13}
$$

Theorem 1

For the optimal control triple u_1^*,u_2^*,u_3^* that minimizes $J(u_1,u_2,u_3)$ over Y, then there exists adjoint variables λ_i for $i=1,...,11$ satisfying

4.2 Adjoint System

$$
\begin{cases}
-\dfrac{d\lambda_1}{dt} = -\lambda_1\left(-(1-u_2)(\beta_{hs}c_sI_{vs}+\beta_{hr}c_rI_{vr})-\mu_h\right) \\
\qquad\qquad -\lambda_2(1-u_2)\beta_{hs}c_sI_{vs}-\lambda_3\beta_{hr}c_rI_{vr} \\
-\dfrac{d\lambda_1}{dt} = -\lambda_2(-\tau-\mu_0-\mu_h)-\lambda_3 d\tau-\lambda_4(1-d)\tau+\lambda_5(1-u_2)\beta_{hs}c_sS_v-\lambda_6\beta_{vs}c_sS_v \\
-\dfrac{d\lambda_3}{dt} = -A_1-c_rS_v(\lambda_5-\lambda_7)(u_2-1)\beta_{vr}-\lambda_{10}(-\mu_{mr}-\mu_m)-\lambda_3(-\mu_{hr}-\mu_h) \\
-\dfrac{d\lambda_4}{dt} = -\lambda_1\delta_h-\lambda_4(-\delta_h-\mu_h) \\
-\dfrac{d\lambda_5}{dt} = -\lambda_5\left(-(1-u_2)\beta_{vs}c_s(I_{hs}+I_{ms})-(1-u_2)\beta_{vr}c_r(I_{hr}+I_{mr})-\mu_v-u_2\right) \\
\qquad\qquad -\lambda_6\beta_{vs}c_s(I_{hs}+I_{ms})-\lambda_7(1-u_2)\beta_{vr}c_r(I_{hr}+I_{mr}) \\
-\dfrac{d\lambda_6}{dt} = \lambda_1(1-u_2)\beta_{hs}c_sS_h-\lambda_2(1-u_2)\beta_{hs}c_sS_h \\
\qquad\qquad -\lambda_6(-\mu_v-\mu_2)+\lambda_8(1-u_3)\beta_{ms}c_sS_m-\lambda_9(1-u_3)\beta_{ms}c_sS_m \\
-\dfrac{d\lambda_7}{dt} = \lambda_1(1-u_2)\beta_{hr}c_rS_h-\lambda_3\beta_{hr}c_rS_h-\lambda_7(-\mu_v-\mu_2) \\
\qquad\qquad +\lambda_8(1-u_3)\beta_{mr}c_rS_m-\lambda_{10}(1-u_3)\beta_{mr}c_rS_m \\
-\dfrac{d\lambda_8}{dt} = -\lambda_8\left(-(1-u_3)(\beta_{ms}c_sI_{vs}+\beta_{mr}c_rI_{vr})-\mu_m\right) \\
\qquad\qquad -\lambda_9(1-u_3)\beta_{ms}c_sI_{vs}-\lambda_{10}(1-u_3)\beta_{mr}c_rI_{vr} \\
-\dfrac{d\lambda_9}{dt} = -\lambda_9(\mu_1+\mu_m+\gamma_m)+\beta_{vs}S_v\left((-1+u_2)\lambda_5+\lambda_6\right)c_s+\lambda_{11}\gamma_m \\
-\dfrac{d\lambda_{10}}{dt} = -A_2+\lambda_5(1-u_2)\beta_{vr}c_rS_v-\lambda_7(1-u_2)\beta_{vr}c_rS_v \\
-\dfrac{d\lambda_{11}}{dt} = -\lambda_8\delta_m-\lambda_{11}(-\delta_m-\mu_m)
\end{cases}
\tag{14}
$$

As the optimal control just has initial conditions it is necessary to find the transversality conditions, that corresponds to a terminal condition in the adjoint equation,

4.3 Transversality Conditions

$$\lambda_i = 0,\ for\ i = 1,...,11 \tag{15}$$

4.4 Stationary Values

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

$$\begin{cases} u_1^* = \max\left\{0, \min\left(1, \dfrac{\lambda_1\left(\phi_{hs}+\phi_{hr}\right)\Lambda_h + \lambda_8\left(\phi_{ms}+\phi_{mr}\right)\Lambda_m}{2A_3}\right)\right\} \\ u_2^* = \max\left\{0, \min\left(1, \dfrac{1}{2A_4}\left[\left(-\beta_{vr}\left(I_{hr}+I_{mr}\right)c_r + 1 - c_s\left(I_{hs}+I_{ms}\right)\beta_{vs}\right)S_v \right.\right.\right. \\ \qquad \left. + \left(\phi_{vs}+\phi_{vr}\right)\Lambda_v\right]\lambda_5 \\ \qquad + c_r\beta_{vr}\lambda_7\left(I_{hr}+I_{mr}\right)S_v\lambda_1\beta_{hr}c_r I_{vr}S_h \\ \qquad \left.\left.\left. - \beta_{hs}I_{vs}S_h\left(\lambda_1-\lambda_2\right)c_s + \lambda_7 I_{vr} + \lambda_6 I_{vs}\right)\right)\right\} \\ u_3^* = \max\left\{0, \min\left(1, \dfrac{-S_m\left(c_r I_{vr}\left(\lambda_8-\lambda_{10}\right)\beta_{mr} + \beta_{ms}c_s I_{vs}\left(\lambda_8-\lambda_9\right)\right)}{2A_5}\right)\right\} \end{cases} \quad (16)$$

Proof:

The governing equations of the adjoints variables are solved via differentiation of the Hamiltonian function, estimated at the optimal control. Then the adjoint system can be written as;

$$
\begin{cases}
-\dfrac{d\lambda_1}{dt}=\dfrac{\partial H}{\partial S_h}=-\lambda_1\left(-\left(1-u_2\right)\left(\beta_{hs}c_sI_{vs}+\beta_{hr}c_rI_{vr}\right)-\mu_h\right)-\lambda_2\left(1-u_2\right)\beta_{hs}c_sI_{vs}-\lambda_3\beta_{hr}c_rI_{vr}\\
-\dfrac{d\lambda_1}{dt}=\dfrac{\partial H}{\partial I_{hs}}=-\lambda_2\left(-\tau-\mu_0-\mu_h\right)-\lambda_3d\tau-\lambda_4\left(1-d\right)\tau+\lambda_5\left(1-u_2\right)\beta_{hs}c_sS_v-\lambda_6\beta_{vs}c_sS_v\\
-\dfrac{d\lambda_3}{dt}=\dfrac{\partial H}{\partial I_{hr}}=-A_1-c_rS_v\left(\lambda_5-\lambda_7\right)\left(u_2-1\right)\beta_{vr}-\lambda_{10}\left(-\mu_{mr}-\mu_m\right)-\lambda_3\left(-\mu_{hr}-\mu_h\right)\\
-\dfrac{d\lambda_4}{dt}=\dfrac{\partial H}{\partial R_h}=-\lambda_1\delta_h-\lambda_4\left(-\delta_h-\mu_h\right)\\
-\dfrac{d\lambda_5}{dt}=\dfrac{\partial H}{\partial S_v}=-\lambda_5\left(-\left(1-u_2\right)\beta_{vs}c_s\left(I_{hs}+I_{ms}\right)-\left(1-u_2\right)\beta_{vr}c_r\left(I_{hr}+I_{mr}\right)-\mu_v-u_2\right)\\
\qquad\qquad -\lambda_6\beta_{vs}c_s\left(I_{hs}+I_{ms}\right)-\lambda_7\left(1-u_2\right)\beta_{vr}c_r\left(I_{hr}+I_{mr}\right)\\
-\dfrac{d\lambda_6}{dt}=\dfrac{\partial H}{\partial I_{vs}}=\lambda_1\left(1-u_2\right)\beta_{hs}c_sS_h-\lambda_2\left(1-u_2\right)\beta_{hs}c_sS_h-\lambda_6\left(-\mu_v-\mu_2\right)\\
\qquad\qquad +\lambda_8\left(1-u_3\right)\beta_{ms}c_sS_m-\lambda_9\left(1-u_3\right)\beta_{ms}c_sS_m\\
-\dfrac{d\lambda_7}{dt}=\dfrac{\partial H}{\partial I_{vr}}=\lambda_1\left(1-u_2\right)\beta_{hr}c_rS_h-\lambda_3\beta_{hr}c_rS_h-\lambda_7\left(-\mu_v-\mu_2\right)\\
\qquad\qquad +\lambda_8\left(1-u_3\right)\beta_{mr}c_rS_m-\lambda_{10}\left(1-u_3\right)\beta_{mr}c_rS_m\\
-\dfrac{d\lambda_8}{dt}=\dfrac{\partial H}{\partial S_m}=-\lambda_8\left(-\left(1-u_3\right)\left(\beta_{ms}c_sI_{vs}+\beta_{mr}c_rI_{vr}\right)-\mu_m\right)\\
\qquad\qquad -\lambda_9\left(1-u_3\right)\beta_{ms}c_sI_{vs}-\lambda_{10}\left(1-u_3\right)\beta_{mr}c_rI_{vr}\\
-\dfrac{d\lambda_9}{dt}=\dfrac{\partial H}{\partial I_{ms}}=-\lambda_9\left(\mu_1+\mu_m+\gamma_m\right)+\beta_{vs}S_v\left(\left(-1+u_2\right)\lambda_5+\lambda_6\right)c_s+\lambda_{11}\gamma_m\\
-\dfrac{d\lambda_{10}}{dt}=\dfrac{\partial H}{\partial I_{mr}}=-A_2+\lambda_5\left(1-u_2\right)\beta_{vr}c_rS_v-\lambda_7\left(1-u_2\right)\beta_{vr}c_rS_v\\
-\dfrac{d\lambda_{11}}{dt}=\dfrac{\partial H}{\partial R_m}=-\lambda_8\delta_m-\lambda_{11}\left(-\delta_m-\mu_m\right)
\end{cases}
\tag{17}
$$

and with transversality conditions

$$\lambda_i=0,\ for\, i=1,...,11$$

On the interior of the control set, where $0<\mu_i<1,\ for\, i=1,2,3$ yields

$$
\begin{cases}
0=\dfrac{\partial H}{\partial u_1}=2A_3u_1^*+\lambda_1\left(-\phi_{hs}-\phi_{hr}\right)\Lambda_h-\lambda_8\left(\phi_{ms}+\phi_{mr}\right)\Lambda_m\\
0=\dfrac{\partial H}{\partial u_2}=2A_4u_2^*-\left(\left(-\beta_{vr}\left(I_{hr}+I_{mr}\right)c_r+1-c_s\left(I_{hs}+I_{ms}\right)\beta_{vs}\right)S_v+\left(\phi_{vs}+\phi_{vr}\right)\Lambda_v\right)\lambda_5\\
\qquad\qquad +c_r\beta_{vr}\lambda_7\left(I_{hr}+I_{mr}\right)S_v\lambda_1\beta_{hr}c_rI_{vr}S_h-\beta_{hs}I_{vs}S_h\left(\lambda_1-\lambda_2\right)c_s+\lambda_7I_{vr}+\lambda_6I_{vs}\\
0=\dfrac{\partial H}{\partial u_3}=2A_5u_3^*+\lambda_8\left(\beta_{ms}c_sI_{vs}+\beta_{mr}c_rI_{vr}\right)S_m-\lambda_9\beta_{ms}c_sI_{vs}S_m-\lambda_{10}\beta_{mr}c_rI_{vr}S_m
\end{cases}
\tag{18}
$$

This in another clear form becomes

$$
\begin{cases}
-\dfrac{d\lambda_1}{dt} = -\lambda_1\left(-\left(1-u_2\right)\left(\beta_{hs}c_sI_{vs}+\beta_{hr}c_rI_{vr}\right)-\mu_h\right)-\lambda_2\left(1-u_2\right)\beta_{hs}c_sI_{vs}-\lambda_3\beta_{hr}c_rI_{vr}\\
-\dfrac{d\lambda_1}{dt} = -\lambda_2\left(-\tau-\mu_0-\mu_h\right)-\lambda_3 d\tau-\lambda_4\left(1-d\right)\tau+\lambda_5\left(1-u_2\right)\beta_{hs}c_sS_v-\lambda_6\beta_{vs}c_sS_v\\
-\dfrac{d\lambda_3}{dt} = -A_1-c_rS_v\left(\lambda_5-\lambda_7\right)\left(u_2-1\right)\beta_{vr}-\lambda_{10}\left(-\mu_{mr}-\mu_m\right)-\lambda_3\left(-\mu_{hr}-\mu_h\right)\\
-\dfrac{d\lambda_4}{dt} = -\lambda_1\delta_h-\lambda_4\left(-\delta_h-\mu_h\right)\\
-\dfrac{d\lambda_5}{dt} = -\lambda_5\left(-\left(1-u_2\right)\beta_{vs}c_s\left(I_{hs}+I_{ms}\right)-\left(1-u_2\right)\beta_{vr}c_r\left(I_{hr}+I_{mr}\right)-\mu_v-u_2\right)\\
\qquad\qquad -\lambda_6\beta_{vs}c_s\left(I_{hs}+I_{ms}\right)-\lambda_7\left(1-u_2\right)\beta_{vr}c_r\left(I_{hr}+I_{mr}\right)\\
-\dfrac{d\lambda_6}{dt} = \lambda_1\left(1-u_2\right)\beta_{hs}c_sS_h-\lambda_2\left(1-u_2\right)\beta_{hs}c_sS_h\\
\qquad\qquad -\lambda_6\left(-\mu_v-\mu_2\right)+\lambda_8\left(1-u_3\right)\beta_{ms}c_sS_m-\lambda_9\left(1-u_3\right)\beta_{ms}c_sS_m\\
-\dfrac{d\lambda_7}{dt} = \lambda_1\left(1-u_2\right)\beta_{hr}c_rS_h-\lambda_3\beta_{hr}c_rS_h-\lambda_7\left(-\mu_v-\mu_2\right)\\
\qquad\qquad +\lambda_8\left(1-u_3\right)\beta_{mr}c_rS_m-\lambda_{10}\left(1-u_3\right)\beta_{mr}c_rS_m\\
-\dfrac{d\lambda_8}{dt} = -\lambda_8\left(-\left(1-u_3\right)\left(\beta_{ms}c_sI_{vs}+\beta_{mr}c_rI_{vr}\right)-\mu_m\right)\\
\qquad\qquad -\lambda_9\left(1-u_3\right)\beta_{ms}c_sI_{vs}-\lambda_{10}\left(1-u_3\right)\beta_{mr}c_rI_{vr}\\
-\dfrac{d\lambda_9}{dt} = -\lambda_9\left(\mu_1+\mu_m+\gamma_m\right)+\beta_{vs}S_v\left(\left(-1+u_2\right)\lambda_5+\lambda_6\right)c_s+\lambda_{11}\gamma_m\\
-\dfrac{d\lambda_{10}}{dt} = -A_2+\lambda_5\left(1-u_2\right)\beta_{vr}c_rS_v-\lambda_7\left(1-u_2\right)\beta_{vr}c_rS_v\\
-\dfrac{d\lambda_{11}}{dt} = -\lambda_8\delta_m-\lambda_{11}\left(-\delta_m-\mu_m\right)
\end{cases}
$$

Thus, it is obtained that,

$$
\begin{cases}
u_1^* = \dfrac{\lambda_1\left(\phi_{hs}+\phi_{hr}\right)\Lambda_h+\lambda_8\left(\phi_{ms}+\phi_{mr}\right)\Lambda_m}{2A_3}\\
u_2^* = \dfrac{1}{2A_4}\begin{pmatrix}\left(\left(-\beta_{vr}\left(I_{hr}+I_{mr}\right)c_r+1-c_s\left(I_{hs}+I_{ms}\right)\beta_{vs}\right)S_v+\left(\phi_{vs}+\phi_{vr}\right)\Lambda_v\right)\lambda_5\\ +c_r\beta_{vr}\lambda_7\left(I_{hr}+I_{mr}\right)S_v\lambda_1\beta_{hr}c_rI_{vr}S_h\\ -\beta_{hs}I_{vs}S_h\left(\lambda_1-\lambda_2\right)c_s+\lambda_7I_{vr}+\lambda_6I_{vs}\end{pmatrix}\\
u_3^* = \dfrac{-S_m\left(c_rI_{vr}\left(\lambda_8-\lambda_{10}\right)\beta_{mr}+\beta_{ms}c_sI_{vs}\left(\lambda_8-\lambda_9\right)\right)}{2A_5}
\end{cases}
$$

By standard control arguments involving the bounds on the controls, it can be concluded that

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

$$u_2^* = \begin{cases} 0 \ \ if \ \xi_2^* \le 0 \\ \xi_2^* \ if \ 0 < \xi_2^* < 1 \\ 1 \ \ if \ \ \xi_2^* \ge 1 \end{cases} \tag{19}$$

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

where

$$\begin{cases} \xi_1^* = \dfrac{\lambda_1 \left(\phi_{hs} + \phi_{hr}\right)\Lambda_h + \lambda_8 \left(\phi_{ms} + \phi_{mr}\right)\Lambda_m}{2A_3} \\ \xi_2^* = \dfrac{1}{2A_4}\begin{pmatrix} \left(\left(-\beta_{vr}\left(I_{hr} + I_{mr}\right)c_r + 1 - c_s\left(I_{hs} + I_{ms}\right)\beta_{vs}\right)S_v + \left(\phi_{vs} + \phi_{vr}\right)\Lambda_v\right)\lambda_5 \\ + c_r\beta_{vr}\lambda_7\left(I_{hr} + I_{mr}\right)S_v\lambda_1\beta_{hr}c_r I_{vr}S_h \\ -\beta_{hs}I_{vs}S_h\left(\lambda_1 - \lambda_2\right)c_s + \lambda_7 I_{vr} + \lambda_6 I_{vs} \end{pmatrix} \\ \xi_3^* = \dfrac{-S_m\left(c_r I_{vr}\left(\lambda_8 - \lambda_{10}\right)\beta_{mr} + \beta_{ms}c_s I_{vs}\left(\lambda_8 - \lambda_9\right)\right)}{2A_5} \end{cases} \tag{20}$$

$$u_1^* = \min\left\{1, \xi_1^*\right\},\ u_2^* = \min\left\{1, \xi_2^*\right\}, u_3^* = \min\left\{1, \xi_3^*\right\}. \tag{21}$$

Subsequently, the numerical solutions of the optimality system and the corresponding optimal control pair, the parameter choices, and the interpretations from various cases are discussed.

5. NUMERICAL ANALYSIS

In this section, the effect of the optimal control strategies on the transmission of disease is investigated numerically. Using the iterative method, the optimality system, consisting of 11 ordinary differential equations from the state and adjoint equations, coupled with the three control characterizations is solved. 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 by (16). The process is repeated and the iterative process complete when the current state, adjoint, and control values converge sufficiently (Lenhart & Workman 2007) [47].

Then, the effect of the following optimal control strategies on the spread of the disease in a population is investigates numerically. Using two controls at a time while setting the other to zero and finally considering the three controls at same time.

- Strategy A: combination of use of quarantine and insecticide spray.
- Strategy B: combination of use of insecticide spray and culling.
- Strategy C: combination of use of quarantine and culling.
- Strategy D: combination of use of insecticide spray, quarantine and culling.

For the numerical simulation the following weight factors are used $A_i = 5, i = 1,...,5$ and use the parameter values from table 6.2. Initial states variables are chosen as $S_h(0) = 100, I_{hs}(0) = I_{hr}(0) = 0, R_h(0) = 0, S_v(0) = 1000, I_{vs}(0) = I_{vr}(0) = 0,\ S_m(0) = 100,$ $I_{ms}(0) = I_{mr}(0) = 0, R_m(0) = 0.$ Other parameter values are in table 6.2 to illustrate the effect of different optimal.

Table 1
Description of Variables

Var.	Description
S_h	*Susceptible human*
I_{hs}	Infected human with parasite sensitive to artemisinin
I_{hr}	Human infected with parasite that is artemisinin resistant strain
R_h	Recovered/immune human
S_v	*Susceptible mosquito*
I_{vs}	Infected *mosquito* with parasite sensitive to artemisinin
I_{vr}	Infected mosquito with parasite that is artemisinin resistant strain
S_m	*Susceptible macaque*
I_{ms}	Infected *macaque* with parasite sensitive to artemisinin
I_m	Infected macaque with parasite that is artemisinin resistant strain
R_m	Recovered/immune macaque

Table 2
Description of Parameters of Model (1)

Par.	Est. Value	Ref
Λ_h	*0.00011*	*Augusto et al., (2012) [38]*
π_h	*0.00076*	Chiyaka et al., (2008) [48]
Λ_v	0.071	*Augusto et al., (2012) [38]*
Λ_m	0.2	Assumed
π_m	*0.00076*	Assumed
μ_h	0.0004	Niger & Gumel, (2008) [49]
μ_{hr}	0.05	Okosun &Makinde (2012) [32]
μ_0	0.05	Hove-Musekwa, (2008) [50]
μ_m	0.02	Assumed
μ_{mr}	0.02	Assumed
μ_1	*0.06*	*Assumed*
δ_h	$\left(1/2\times 365\right)$	*Menach et al., (2005) [51]*
β_{hs}	0.03	*Menach et al., (2005) [51]*
β_{hr}	0.17	Chiyaka et al., (2008) [48]
c_s	0.6	Chitnis et al., (2006) [52]
d	0.02	Okosun &Makinde (2012) [32]
β_{vs}	0.09	*Menach et al., (2005) [51]*
β_{vr}	0.83	Chiyaka et al., (2008) [48]
β_{ms}	0.03	Assumed
β_{mr}	0.03	Assumed
c_r	0.502	Assumed
γ_m	0.5	Assumed
τ	0.8	*Augusto et al., (2012) [38]*
μ_v	0.04	Chiyaka et al., (2008) [48]
δ_m	$\left(1/2\times 365\right)$	Assumed
ϕ_{ms}	*0.0005*	Assumed
ϕ_{mr}	*0.0005*	Assumed
ϕ_{hs}	*0.00005*	Assumed
ϕ_{hr}	*0.00005*	Assumed
ϕ_{vs}	*0.036*	Assumed
ϕ_{vr}	*0.035*	Assumed

5.1 Optimal Use of the Quarantine (u_1) and Insecticide Spray (u_2)

With this control strategy, quarantine (u_1) and insecticide spray (u_2) are both used to optimize the objective functional J, while the control culling (u_3) is set to zero. In figure 1, the result shows a significant difference in the I_{hr}, I_{mr} and I_v with optimal control strategy compared to I_{hr}, I_{mr} and I_v without control. It was observed in Figure 1(a) that the infected humans with resistance artemisinin strain (I_{hr}) decrease as a result of control strategies against the increase in the uncontrolled case. In Figures 1(b) and 1(c), similar situation was also observed in the case of infected macaques with resistance artemisinin strain and infected mosquitoes.

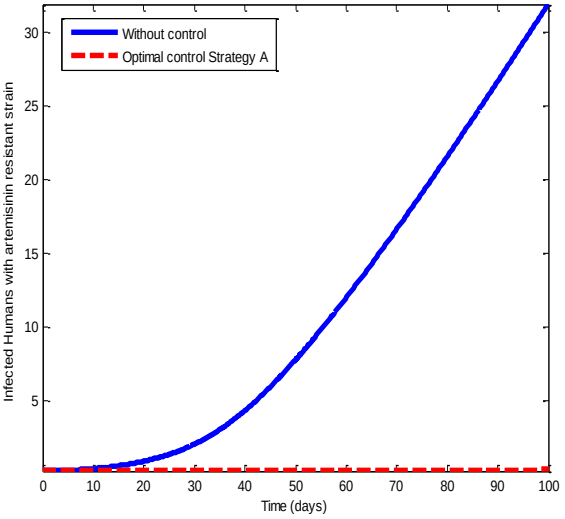

Figure 1(a)

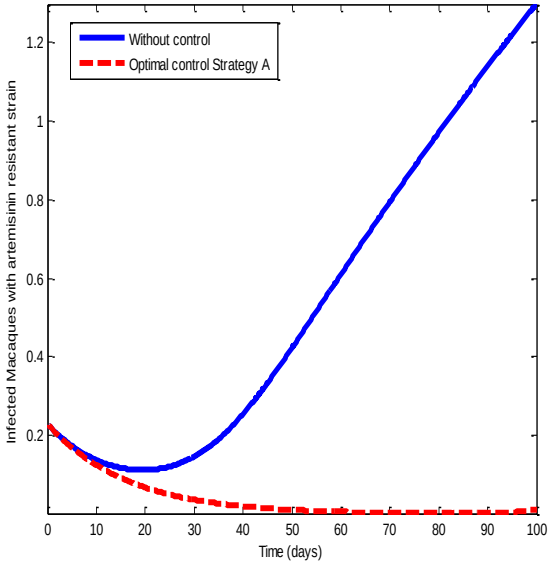

Figure 1(b)

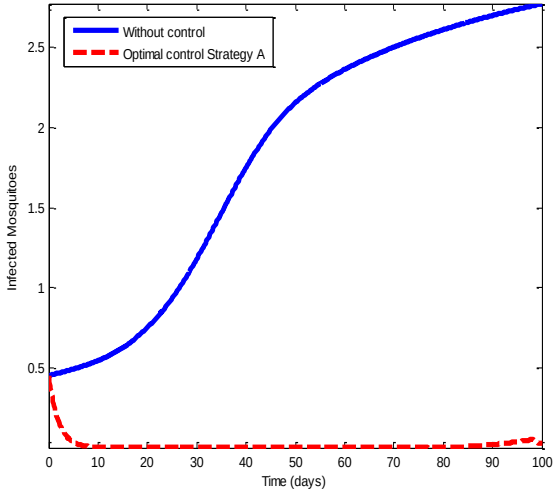

Figure 1(c)

Fig. 1: Simulations of the *Plasmodium Knowlesi* Malaria Model Showing Effect of Optimal Use of Quarantine and Insecticide Spray on the Spread of the Disease

5.2 Optimal use of the Insecticide Spray (u_2) and Culling (u_3)

In this control strategy, use of insecticide spray (u_2) and culling (u_3) are both used to optimize the objective functional J, while the control biological control (u_2) is set to zero. In figure 2, the result shows a significant difference in the I_{mr} and I_v with optimal

control strategy compared to I_{mr} and I_v without control. It was observed in Figure 2(a) that the infected macaques with resistance artemisinin strain (I_{mr}) decrease as a result of control strategies against the increase in the uncontrolled case. In Figure 2(b) similar situation been also observed in the case of infected mosquitoes.

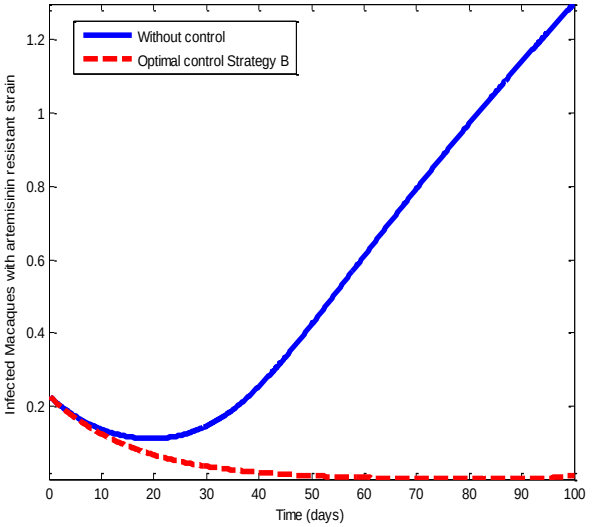

Figure 2(a)

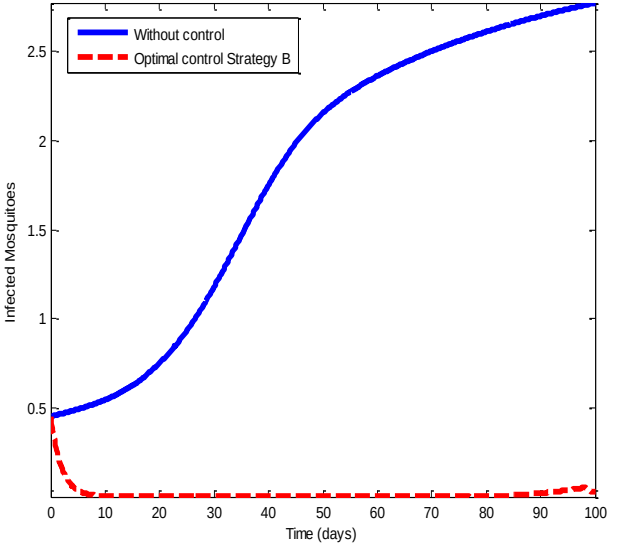

Figure 2 (b)

Fig. 2: Simulations of the *Plasmodium Knowlesi* Malaria Model Showing Effect of Optimal Use of Insecticide Spray and Culling on the Spread of the Disease

6.6.3 Optimal use of the Quarantine (u_1) and Culling (u_3)

In this control strategy, quarantine (u_1) and culling (u_3) are both used to optimize the objective functional J, while the control insecticide spray (u_2) is set to zero. In figure 3, the result shows a significant difference in the I_{hr} and I_{mr} with optimal control strategy compared to I_{hr} and I_{mr} without control. It was observed in Figure 3(a) infected humans with resistance artemisinin strain (I_{hr}) decrease as a result of control strategies against the increase in the uncontrolled case. In Figure 3(b) similar situations been also observed in the case of infected macaques with resistance artemisinin strain.

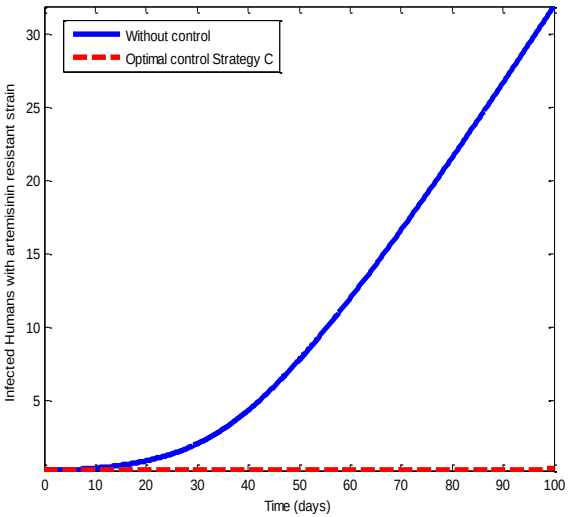

Figure 3(a)

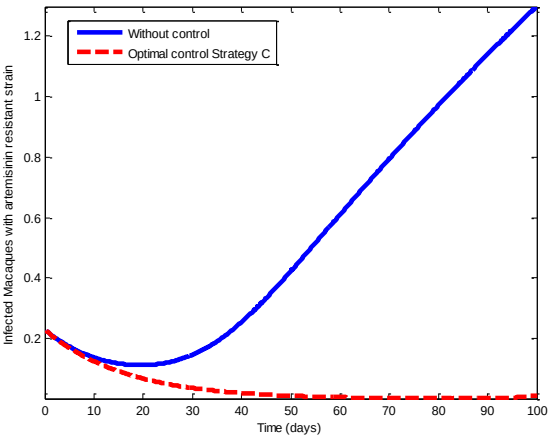

Figure 3(b)

Fig. 3: Simulations of the *Plasmodium Knowlesi* Malaria Model Showing Effect of Optimal Use of Quarantine and Culling on the Spread of the Disease

5.4 Optimal Use of the Quarantine (u_1), Insecticide spray (u_2) and Culling (u_3)

Here, all the control strategies (u_1, u_2, u_3) are used to optimize the objective functional J. In figure 4, the result shows a significant difference in the I_{hr}, I_v *and* I_{mr} with optimal control strategy compared to I_{hr}, I_v *and* I_{mr} without control. It was observed in figure 4(a) that the infected humans with resistance artemisinin strain (I_{hr}) decrease as a result of control strategies against the increase in the uncontrolled case. In Figures 4(b) and 4(c) similar situations been also observed in the case of infected macaques with resistance artemisinin strain and the infected mosquitoes.

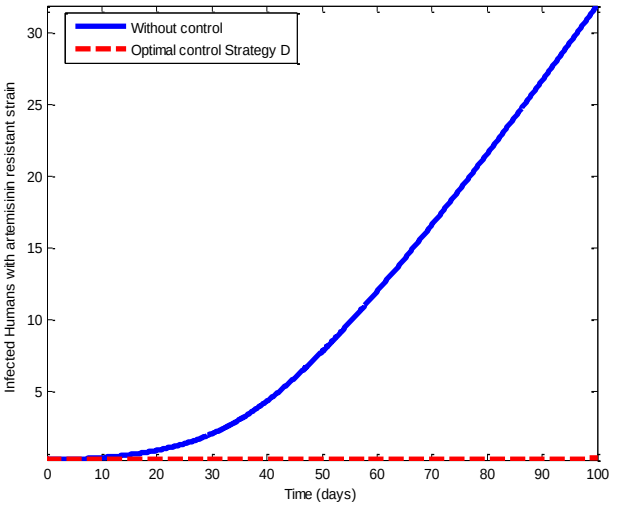

Figure 4(a)

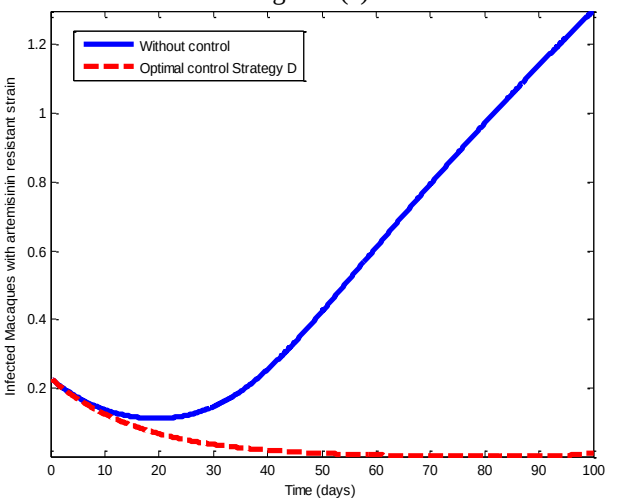

Figure 4(b)

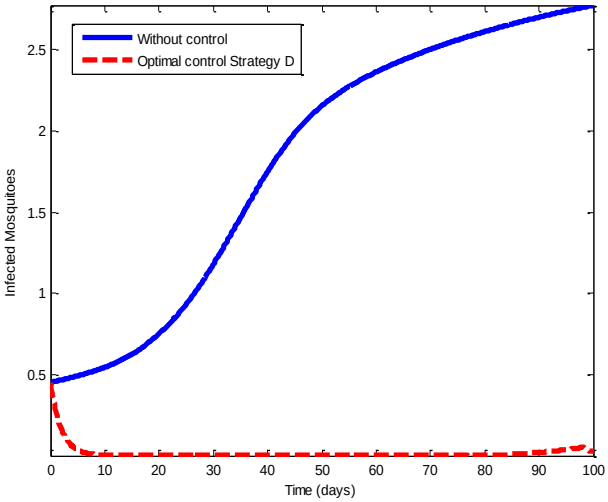

Figure 4(c)

Fig. 4: Simulations of the *Plasmodium Knowlesi* Malaria Model Showing Effect of Optimal Use of Insecticide Spray, Quarantine and Culling on the Spread of the Disease

CONCLUSIONS

In this paper, a mathematical model for the spread of *Plasmodium knowlesi* malaria is developed. The model incorporates recruitment rate of the three populations through a constant immigration, with a fraction of infective immigrants. The effect of drug resistance is also considered. The impact of a control measure, culling against larvae and macaques is considered. The sensitivity index of the model is investigated to understand the importance of each parameter to the disease transmission. The condition for optimal *Plasmodium knowlesi* malaria were derived and analyzed with time dependent preventive. The optimal control has a very desirable effect for reducing the *Plasmodium knowlesi* malaria. However, based on the results of the analysis, three control strategies were considered, insecticide spray, quarantine and culling**.** The numerical simulation results have shown that the best control strategies for control of the disease combination of the three control strategies (Strategy D). However, the implication of using all the controls is that additional cost will be incurred. This is because strategy D and insecticide spray and quarantine (strategy A) has same effect on this control of the disease. It can be concluded that to control the disease, the most cost-effective of all the strategies is the use of insecticide spray and quarantine (strategy A) in the presence of infective immigrations and drug resistance. 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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REFERENCES

1. Bharati, K. and Ganguly, N.K. (2013). Tackling the malaria problem in the South-East Asia Region: Need for a change in policy? *The Indian Journal of Medical Research*, 137(1), 36-47.
2. Lynch, C. and Hewitt, S. (2012). Malaria in the Asia-Pacific: Burden, success and challenges.
3. World Health Organization (2011). *World Malaria Report 2011*, World Health Organization, Geneva.
4. William, T., Rahman, H.A., Jelip, J., Ibrahim, M.Y., Menon, J., Grigg, M.J., Yeo, T.W. Anstey, N.M. and Barber B.E. (2013). Increasing incidence of Plasmodium Plasmodium knowlesi malaria following control of P. falciparum and P. vivax Malaria in Sabah, Malaysia. *PLoS Neglected Tropical Diseases*, 7(1), e2026. doi:10.1371/journal.pntd.0002026.
5. ÔàÓÑáØÑ, Ô. (2012). Plasmodium Plasmodium knowlesi malarial infection in western travelers returning from Southeast Asia. *Archives of Hellenic Medicine*, 29(1), 58-60.
6. Sabbatani, S., Fiorino, S. and Manfredi, R. (2010). The emerging of the fifth malaria parasite (Plasmodium Plasmodium knowlesi): A public health concern? *Brazilian Journal of Infectious Diseases*, 14(3), 299-309.
7. Vythilingam, I. (2010). Review Paper Plasmodium Plasmodium knowlesi in humans: a review on the role of its vectors in Malaysia. *Tropical Biomedicine*, 27(1), 1-12.
8. Jeslyn, W.P.S., Huat, T.C., Vernon, L., Irene, L.M.Z., Sung, L.K., Jarrod, L.P., Singh, B. and Ching, N.L. (2011). Molecular epidemiological investigation of Plasmodium Plasmodium knowlesi in humans and macaques in Singapore. *Vector-Borne and Zoonotic Diseases*, 11(2), 131-135.
9. William, T., Menon, J., Rajahram, G., Chan, L. Ma, G., Donaldson, S., Khoo, S., Fredrick, C., Jelip, J., Anstey, N.M. and Yeo, T.W. (2011). Severe Plasmodium knowlesi malaria in a tertiary care hospital, Sabah, Malaysia. *Emerg. Infect. Dis.*, 17(7), 1248-1255.
10. World Health Organization (2012). World Malaria Report 2012. Accessed 2nd October, 2013. http://www.who.int/malaria/publications/world_malaria_report_2012/report/en/
11. Bronner, U., Divis, P.C., Färnert, A. and Singh, B. (2009). Swedish traveller with Plasmodium knowlesi malaria after visiting Malaysian Borneo. *Malaria Journal*, 8(1), 15. doi:10.1186/1475-2875-8-15.
12. Jongwutiwes, S., Putaporntip, C., Iwasaki, T., Sata, T. and Kanbara, H. (2004). Naturally acquired Plasmodium knowlesi malaria in human, Thailand. *Emerging Infectious Diseases*, 10(12), 2211-2213.
13. Kantele, A., Marti, H., Felger, I., Müller, D. and Jokiranta, TS. (2008). Monkey malaria in a European traveler returning from Malaysia. *Emerging Infectious Diseases*, 14(9), 1434-1436.
14. Collins, W.E. and Barnwell, J.W. (2009). Plasmodium knowlesi: finally being recognized. *Journal of Infectious Diseases*, 199(8), 1107-1108.
15. Martens, P. and Hall, L. (2000). Malaria on the move: Human population movement and malaria transmission. *Emerging Infectious Diseases*, 6(2), 103-109.
16. Prothero, R.M. (1977). Disease and mobility: a neglected factor in epidemiology. *International Journal of Epidemiology*, 6(3), 259-267.

17. Bruce-Chwatt, L.J. (1968). Movements of populations in relation to communicable disease in Africa. *East African Medical Journal*, 45(5), 266-275.
18. Molineaux, L, Wernsdorfer, W.H. and McGregor, I. (1988). The epidemiology of human malaria as an explanation of its distribution, including some implications for its control. *Malaria: Principles and Practice of Malariology*, 2, 913-998.
19. Marques, A.C. (1986). Migrations and the dissemination of malaria in Brazil. *Memórias do Instituto Oswaldo Cruz*, 81, 17-30.
20. Curtis, C.F. and White, G.B. (1984). Plasmodium falciparum transmission in England: entomological and epidemiological data relative to cases in 1983. *Journal of Tropical Medicine and Hygiene*, 87(3), 101-114.
21. Lynch, C. and Roper, C. (2011). The transit phase of migration: circulation of malaria and its multidrug-resistant forms in Africa. *PLoS Medicine*, 8(5), e1001040.
22. Prothero R.M. (1987). Populations on the Move. *Third World Quarterly*, 9, 1282-1310.
23. Aneke, S.J. (2002). Mathematical modelling of drug resistant malaria parasites and vector populations. *Mathematical Methods in the Applied Sciences*, 25(4), 335-346.
24. Koella, J.C. and Antia, R. (2003). Epidemiological models for the spread of anti-malarial resistance. *Malaria Journal*, 2(1), 3. doi:10.1186/1475-2875-2-3.
25. Chiyaka, C., Garira, W. and Dube, S. (2009). Effects of treatment and drug resistance on the transmission dynamics of malaria in endemic areas. *Theoretical Population Biology*, 75(1), 14-29.
26. Bacaër, N. and Sokhna, C. (2005). A reaction-diffusion system modeling the spread of resistance to an antimalarial drug. *Math. Biosci. Eng.*, 2(2), 227-238.
27. Esteva, L., Gumel, A.B. and De LeóN, C.V. (2009). Qualitative study of transmission dynamics of drug-resistant malaria. *Mathematical and Computer Modelling*, 50(3), 611-630.
28. Tumwiine, J., Mugisha, J.Y.T. and Luboobi, L.S. (2010). A host-vector model for malaria with infective immigrants. *Journal of Mathematical Analysis and Applications*, 361(1), 139-149.
29. Tumwiine, J., Mugisha, J.Y.T. and Luboobi, L.S. (2007). A mathematical model for the dynamics of malaria in a human host and mosquito vector with temporary immunity. *Applied Mathematics and Computation*, 189(2), 1953-1965.
30. Tchuenche, J.M., Chiyaka, C., Chan, D., Matthews, A. and Mayer, G. (2011). A mathematical model for antimalarial drug resistance. *Mathematical Medicine and Biology*, 28(4), 335-355.
31. Makinde, O.D. and Okosun, K.O. (2011). Impact of Chemo-therapy on Optimal Control of Malaria Disease with Infected Immigrants. *BioSystems*, 104(1), 32-41.
32. Okosun, K.O. and Makinde, O.D. (2012). On a drug-resistant malaria model with susceptible individuals without access to basic amenities. *Journal of Biological Physics*, 38(3), 507-530.
33. Tumwiine, J., Hove-Musekwa, S.D. and Nyabadza, F. (2014). A Mathematical Model for the Transmission and Spread of Drug Sensitive and Resistant Malaria Strains within a Human Population. *International Scholarly Research Notices. ISRN Biomathematics*, 2014 Article ID 636973, 12 pages.
34. Yakob, L., Bonsall, M.B. and Yan, G. (2010). Modelling Plasmodium knowlesi malaria transmission in humans: vector preference and host competence. *Malaria Journal*, 9(1), 329.

35. Abdullahi, M.B., Hasan, Y.A. and Abdullah, F.A. (2014). Optimal Control of Plasmodium knowlesi Malaria in Human and Macaques. *British Journal of Mathematics & Computer Science*, 4(2), 16-31.
36. Gourley, S.A., Liu, R. and Wu, J. (2007). Eradicating vector-borne diseases via age-structured culling. *Journal of Mathematical Biology*, 54(3), 309-335.
37. Hu, X., Liu. Y and Wu, J. (2009). Culling structured hosts to eradicate vector-borne diseases. *Mathematical Biosciences and Engineering*, 6(2), 301-319.
38. Agusto, F.B., Marcus, N. and Okosun, K.O. (2012). Application of optimal control to the epidemiology of malaria. *Electronic Journal of Differential Equations*, 2012(81), 1-22.
39. Magombedze, G., Chiyaka, C. and Mukandavire, Z. (2011). Optimal control of malaria chemotherapy. *Nonlinear Anal. Modell. Contr.*, 16(4), 415-434.
40. Okosun, K.O., Rachid, O. and Marcus, N. (2013). Optimal control strategies and cost-effectiveness analysis of a malaria model. *Biosystems*, 111(2), 83-101.
41. Imai, N., White, M.T., Ghani, A.C. and Drakeley, C.J. (2014). Transmission and Control of *Plasmodium knowlesi*: A Mathematical Modelling Study. *PLoS Neglected Tropical Diseases*, 8(7), e2978.
42. Okosun, K.O. and Makinde, O.D. (2013). Optimal control analysis of malaria in the presence of non-linear incidence rate. *Applied and Computational Mathematics* (Impact Factor: 0.75), 12, 20-32.
43. Okosun, K.O., Rachid, O. and Marcus, N. (2013). Optimal control strategies and cost-effectiveness analysis of a malaria model. *Biosystems*, 111(2), 83-101.
44. Lakshmikantham, V., Leela, S. and Martyniuk, A.A. (1988). *Stability Analysis of Nonlinear Systems*. CRC Press.
45. Van den Driessche, P. and Watmough, J. (2002). Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Mathematical Biosciences*, 180(1), 29-48.
46. Pontryagin, L.S. Boltyanskii, V.G., Gamkrelidze, R.V. and Mishchenko, E. (1964). *The mathematical theory of optimal processes* (Translated by D.E. Brown) A Pergamon Press Book. The Macmillan Company New York pp 56-57.
47. Lenhart, S. and Workman, J.T. (2007). *Optimal control applied to biological models* (Vol. 15). CRC Press New York.
48. Chiyaka, C., Tchuenche, J.M., Garira, W and Dube, S. (2008). A mathematical analysis of the effects of control strategies on the transmission dynamics of malaria. *Applied Mathematics and Computation*, 195(2), 641-662.
49. Niger, A.M. and Gumel, A.B. (2008). Mathematical analysis of the role of repeated exposure on malaria transmission dynamics. *Differential Equations and Dynamical Systems*, 16(3), 251-287.
50. Hove-Musekwa, S.D. (2008). Determining effective spraying periods to control malaria via indoor residual spraying in sub-saharan Africa. *Advances in Decision Sciences*, 2008.
51. Menach, A.L., McKenzie, F.E., Flahault, A. and Smith, D.L. (2005). The unexpected importance of mosquito oviposition behaviour for malaria: non-productive larval habitats can be sources for malaria transmission. *Malaria Journal*, 4(1), 23.
52. Chitnis, N., Cushing, J.M. and Hyman, J.M. (2006). Bifurcation analysis of a mathematical model for malaria transmission. *SIAM Journal on Applied Mathematics*, 67(1), 24-45.