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. Tchuene 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 falciparum. 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 falciparum.

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 \( \left(S_h(t)\right) \), human infected with parasite sensitive to artemisinin \( \left(I_{hs}(t)\right) \), human infected with parasite that is artemisinin resistant strain \( \left(I_{hr}(t)\right) \) and recovered or immune human \( \left(R_h(t)\right) \). 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 \( \left(S_m(t)\right) \), macaque infected with parasite sensitive to artemisinin \( \left(I_{ms}(t)\right) \), macaque infected with parasite that is artemisinin resistant strain \( \left(I_{mr}(t)\right) \) and the recovered or immune macaque \( \left(R_m(t)\right) \). 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 \( N_v(t) \), into the following sub populations of susceptible mosquitoes \( \left(S_v(t)\right) \) mosquito infected by the parasites sensitive to artemisinin \( \left(I_{vs}(t)\right) \), and mosquitoes infected by malaria parasites with artemisinin resistant strain \( \left(I_{vr}(t)\right) \). 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 $\pi_h$. 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 $\Lambda_h$. A fraction $\phi_{hs}$ is human infected with parasite sensitive to artemisinin, a fraction $\phi_{hr}$ is human infected with parasite with artemisinin resistance strain and the remaining fraction $\left(1-(\phi_{hs}+\phi_{hr})\right)$ is susceptible human. The human population suffers a natural death at a rate $\mu_h$ and disease induced death at a rate $\mu_0$. Susceptible humans infected with parasites sensitive to artemisinin are moved to the infected humans with parasite sensitive to artemisinin $(I_{hs}(t))$ class at a rate $\beta_{hs}c_si_{vs}$, where $\beta_{hs}$ 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 $(I_{vr}(t))$ move to infected humans with artemisinin resistant strain at a rate $\beta_{hr}c_rI_{vr}$, where $\beta_{hr}$ 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 $(1-d)\tau$. 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, $\delta_h$ and returned to the susceptible class.

The mosquito population is recruited at a rate $\Lambda_v$. A fraction $\phi_{vs}$ is mosquito infected with parasite sensitive to artemisinin, a fraction $\phi_{vr}$ is mosquito infected with parasite with artemisinin resistance strain. The remaining fraction $\left(1-(\phi_{vs}+\phi_{vr})\right)$ is susceptible mosquito. Mosquito population suffers a natural death at a rate $\mu_v$. The susceptible mosquitoes $S_h$ move to infected class at a rate $\beta_{vs}c_s(I_{hs}+I_{ms})$ and $\beta_{vr}c_r(I_{hr}+I_{mr})$ where $\beta_{vs}$ 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 $I_{hr}$. $\beta_{vr}$ 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 $\Lambda_m$. A fraction $\phi_{ms}$ is macaque infected with parasite sensitive to
artemisinin. A fraction $\phi_{mr}$ is macaque infected with parasite with to artemisinin resistance strain and the remaining fraction $\left(1-(\phi_{ms}+\phi_{mr})\right)$ is a susceptible macaque. The macaque population suffers a natural death at a rate $\mu_m$ and disease induced death at a rate $\mu_1$. Susceptible macaque infected with the parasites sensitive to artemisinin are then moved to the infected humans with parasite sensitive to artemisinin ($I_{ms}(t)$) class at a rate $\beta_{ms}c_sI_{vs}$, where $\beta_{ms}$ 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 ($I_{mr}(t)$) moved to infected humans with artemisinin resistant strain at a rate $\beta_{mr}c_rI_{vr}$, where $\beta_{mr}$ 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 $\gamma_m$. The recovered macaques lose their immunity at a constant rate, $\delta_m$ 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).

\[
\begin{align*}
\frac{dS_h}{dt} &= \left(1-(\phi_{hs}+\phi_{hr})\Lambda_h\right) + \pi_h + \delta_hR_h - (\beta_{hs}c_sI_{vs} + \beta_{hr}c_rI_{vr} + \mu_h)S_h \\
\frac{dI_{hs}}{dt} &= \phi_{hs}\Lambda_h + \beta_{hs}c_sI_{vs}S_h - (\tau + \mu_0 + \mu_h)I_{hs} \\
\frac{dI_{hr}}{dt} &= \phi_{hr}\Lambda_h + \beta_{hr}c_rI_{vr}S_h + d\tau I_{hs} - (\mu_{hr} + \mu_h)I_{hr} \\
\frac{dR_h}{dt} &= (1-d)\tau I_{hs} - (\delta_h + \mu_h)R_h \\
\frac{dS_v}{dt} &= \left(1-(\phi_{vs}+\phi_{vr})\Lambda_v\right) - \left(\beta_{vs}c_s\left(I_{hs} + I_{ms}\right) + \beta_{vr}c_r\left(I_{hr} + I_{mr}\right) + \mu_v\right)S_v \\
\frac{dI_{vs}}{dt} &= \phi_{vs}\Lambda_v + \beta_{vs}c_s\left(I_{hs} + I_{ms}\right)S_v - \mu_vI_{vs} \\
\frac{dI_{vr}}{dt} &= \phi_{vr}\Lambda_v + \beta_{vr}c_r\left(I_{hr} + I_{mr}\right)S_v - \mu_vI_{vr} \\
\frac{dS_m}{dt} &= \left(1-(\phi_{ms}+\phi_{mr})\Lambda_m\right) + \pi_m + \delta_mR_m - (\beta_{ms}c_sI_{vs} + \beta_{mr}c_rI_{vr} + \mu_m)S_m \\
\frac{dI_{ms}}{dt} &= \phi_{ms}\Lambda_m + \beta_{ms}c_sI_{vs}S_m - (\mu_1 + \mu_m + \gamma_m)I_{ms} \\
\frac{dI_{mr}}{dt} &= \phi_{mr}\Lambda_m + \beta_{mr}c_rI_{vr}S_m - (\mu_{mr} + \mu_m)I_{mr} \\
\frac{dR_m}{dt} &= \gamma_mI_m - (\mu_m + \delta_m)R_m
\end{align*}
\]
where;
\[ \lambda_{hs} = \beta_{hs} e_{hs} c_s I_{vs} \]
\[ \lambda_{hr} = \beta_{hr} e_{hr} c_r I_{vr} \]
\[ \lambda_{vs} = \beta_{vs} e_{vs} c_s \left( I_{hs} + I_{ms} \right) \]
\[ \lambda_{vr} = \beta_{vr} e_{vr} c_r \left( I_{hr} + I_{mr} \right) \]
\[ \lambda_{ms} = \beta_{ms} e_{ms} c_s I_{vs} \]
\[ \lambda_{mr} = \beta_{mr} e_{mr} c_r I_{vr} \]

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
\[ \Omega = \left\{ \left( S_h, I_{hs}, I_{hr}, R_h, S_v, I_{vs}, I_{vr}, S_m, I_{ms}, I_{mr}, R_m \right) \in \mathbb{R}^{11} : \right\} \]

\[ S_h + I_{hs} + I_{hr} + R_h \leq \frac{\Lambda_h + \pi_h}{\mu_h}, S_v + I_{vs} + I_{vr} \leq \frac{\Lambda_v}{\mu_v}, \]

\[ S_h + I_{hs} + I_{hr} + R_h \leq \frac{\Lambda_h + \pi_h}{\mu_h}, \]

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:

\[ \frac{dN_h}{dt} = \Lambda_h + \pi_h - \mu_h N_h - \mu_0 I_{hs} - \mu_{hr} I_{hr} \quad (2) \]

\[ \frac{dN_v}{dt} = \Lambda_v - \mu_v N_v \quad (3) \]

and

\[ \frac{dN_m}{dt} = \Lambda_m + \pi_m - \mu_m N_m - \mu_1 I_{ms} - \mu_{mr} I_{mr} \quad (4) \]

Assuming \( I_{hs} = I_{hr} = I_{ms} = I_{mr} = 0 \) 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 \( \frac{dN_h}{dt} \leq \Lambda_h + \pi_h - \mu_h N_h \), \( \frac{dN_v}{dt} \leq \Lambda_v - \mu_v N_v \) and \( \frac{dN_m}{dt} \leq \Lambda_m + \pi_m - \mu_m N_m \), it follows that \( \frac{dN_h}{dt} < 0 \), \( \frac{dN_v}{dt} < 0 \) and \( \frac{dN_m}{dt} < 0 \), if \( N_h > \frac{\Lambda_h + \pi_h}{\mu_h} \), \( N_v > \frac{\Lambda_v}{\mu_v} \) 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

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

and

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

In particular, \( N_h \leq \frac{\Lambda_h + \pi_h}{\mu_h} \), \( N_v \leq \frac{\Lambda_v}{\mu_v} \) and \( N_v \leq \frac{\Lambda_m + \pi_m}{\mu_m} \), if \( N_h(0) \leq \frac{\Lambda_h + \pi_h}{\mu_h} \), \( N_v(0) \leq \frac{\Lambda_v}{\mu_v} \) and \( N_v(0) \leq \frac{\Lambda_m + \pi_m}{\mu_m} \), respectively. Thus, \( \Omega \) 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 \( \Omega \) 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 \( I_{hI}, I_{hR}, I_{vS}, I_{vR}, I_{mI} \) and \( I_{mR} \) approached zero. Hence \( \Omega \) is attracting (that is, all solutions in \( \mathbb{R}_+^{11} \) eventually enter \( \Omega \)). Thus, in \( \Omega \), the model is well-posed epidemiologically and mathematically. Hence it is sufficient to study the dynamics of the model in \( \Omega \).

### 6.2.2 Disease Free Equilibrium (DFE)

The \textit{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:
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,

\[
E_0 = \left( S_h^*, I_h^*, I_v^*, R_h^*, S_v^*, I_v^*, I_m^*, S_m^*, I_m^*, R_m^* \right)
\]

\[
= \left( \frac{\Lambda_h + \pi_h}{\mu_h}, 0, 0, \frac{\Lambda_v}{\mu_v}, 0, 0, \frac{\Lambda_m + \pi_m}{\mu_m}, 0, 0, 0 \right),
\]

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:

\[
\begin{align*}
(1 - (\phi_{hs} + \phi_{hr}) \Lambda_h) + \pi_h + \delta_h R_h - (\beta_{hs} c_s I_{vs} + \beta_{hr} c_r I_{vr} + \mu_h) S_h &= 0 \\
\phi_{hs} \Lambda_h + \beta_{hs} c_s I_{vs} S_h - (\tau + \mu_0 + \mu_h) I_{hs} &= 0 \\
\phi_{hr} \Lambda_h + \beta_{hr} c_r I_{vr} S_h + d \tau I_{hs} - (\mu_{hr} + \mu_h) I_{hr} &= 0 \\
(1 - d) \tau I_{hs} - (\delta_h + \mu_h) R_h &= 0 \\
(1 - (\phi_{vs} + \phi_{vr}) \Lambda_v) - (\beta_{vs} c_s (I_{hs} + I_{ms}) + \beta_{vr} c_r (I_{hr} + I_{mr}) + \mu_v) S_v &= 0 \\
\phi_{vs} \Lambda_v + \beta_{vs} c_s (I_{hs} + I_{ms}) S_v - \mu_v I_{vs} &= 0 \\
\phi_{vr} \Lambda_v + \beta_{vr} c_r (I_{hr} + I_{mr}) S_v - \mu_v I_{vr} &= 0 \\
(1 - (\phi_{ms} + \phi_{mr}) \Lambda_m) + \pi_m + \delta_m R_m - (\beta_{ms} c_s I_{vs} + \beta_{mr} c_r I_{vr} + \mu_m) S_m &= 0 \\
\phi_{ms} \Lambda_m + \beta_{ms} c_s I_{vs} S_m - (\mu_1 + \mu_m + \gamma_m) I_{ms} &= 0 \\
\phi_{mr} \Lambda_m + \beta_{mr} c_r I_{vr} S_m - (\mu_{mr} + \mu_m) I_{mr} &= 0 \\
\gamma_m I_m - (\mu_m + \delta_m) R_m &= 0
\end{align*}
\]
It follows that the drug sensitive basic reproduction number of the model equation (1) denoted by $R_s$. And given by:

$$R_s = \sqrt{\frac{\beta_{vs} c_s \left(\Lambda_h + \pi_h\right)}{\mu_h} \left(\tau + \mu_0 + \mu_h\right) \left(\mu_1 + \mu_m + \gamma_m\right) \left(\Lambda_m + \pi_m\right)}$$

and the drug resistance basic reproduction number is:

$$R_r = \sqrt{\frac{c_r^2 \left(\mu_m \beta_{hr} \left(\mu_m + \mu_r\right) \left(\Lambda_h + \pi_h\right) + \mu_h \beta_{ms} \left(\mu_h + \mu_m\right) \left(\Lambda_m + \pi_m\right)\right)\beta_{vr}}{\left(\mu_{hr} + \mu_h\right)\left(\mu_{mr} + \mu_m\right)\mu_h^2}}$$

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 $R_s$ is locally asymptotically stable (LAS) if $R_s < 1$, and unstable if $R_s > 1$.

**3. SENSITIVITY ANALYSIS OF MODEL PARAMETERS**

Sensitivity of each parameter is examined with respect to the basic reproduction number $R_r$. 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, $R_r$ 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:

$$
\gamma_{R_r}^{\beta_{mr}} = \frac{\partial R_r}{\partial \beta_{mr}} \times \frac{\beta_{mr}}{R_r}
$$

**6.3.1 Sensitivity indices of $R_r$**

Thus, the Sensitivity of $R_r$ 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;

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

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

$$
\begin{align*}
\gamma_{R_0}^{\mu_v} := \frac{\partial R_0}{\partial \mu_v} \times \frac{\mu_v}{R_0} &= -1, \\
\gamma_{R_0}^{c_r} := \frac{\partial R_0}{\partial c_r} \times \frac{c_r}{R_0} &= 1, \\
\gamma_{R_0}^{\beta_{vr}} := \frac{\partial R_0}{\partial \beta_{vr}} \times \frac{\beta_{vr}}{R_0} &= \frac{1}{2}, \\
\gamma_{R_0}^{\Lambda_v} := \frac{\partial R_0}{\partial \Lambda_v} \times \frac{\Lambda_v}{R_0} &= \frac{1}{2}.
\end{align*}
$$

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Sensitivity Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>$c_r$</td>
<td>0.502</td>
<td>+1</td>
</tr>
<tr>
<td>$\mu_v$</td>
<td>0.04</td>
<td>-1</td>
</tr>
<tr>
<td>$\mu_m$</td>
<td>0.02</td>
<td>-0.7245</td>
</tr>
<tr>
<td>$\beta_{vr}$</td>
<td>0.83</td>
<td>+0.5</td>
</tr>
<tr>
<td>$\Lambda_v$</td>
<td>0.071</td>
<td>+0.5</td>
</tr>
<tr>
<td>$\beta_{mr}$</td>
<td>0.83</td>
<td>+0.4830</td>
</tr>
<tr>
<td>$\Lambda_m$</td>
<td>0.2</td>
<td>+0.4812</td>
</tr>
<tr>
<td>$\mu_{mr}$</td>
<td>0.02</td>
<td>-0.2415</td>
</tr>
<tr>
<td>$\mu_h$</td>
<td>0.0004</td>
<td>-0.01715</td>
</tr>
<tr>
<td>$\beta_{hr}$</td>
<td>0.17</td>
<td>+0.01701</td>
</tr>
<tr>
<td>$\mu_{hr}$</td>
<td>0.05</td>
<td>-0.01688</td>
</tr>
<tr>
<td>$\pi_h$</td>
<td>0.00076</td>
<td>+0.01486</td>
</tr>
<tr>
<td>$\Lambda_h$</td>
<td>0.00011</td>
<td>+0.002151</td>
</tr>
<tr>
<td>$\pi_m$</td>
<td>0.00076</td>
<td>+0.001828</td>
</tr>
</tbody>
</table>

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 $\mu_v$. This is followed by death rate of macaques $\mu_m$ and recruitment rate of mosquitoes $\Lambda_v$. Other important parameters include probability of infection of macaques with artemisinin resistant strain mosquitoes $\beta_{mr}$, immigration rate of macaques $\Lambda_m$ and the least sensitive is the birth rate of macaques $\pi_m$. The sensitivity index of $\mathcal{R}_r$ with respect to probability of mosquitoes getting infected with artemisinin resistant strain ($\beta_{vr}$) is +0.5, this implies that decreasing (or increasing) the ($\beta_{vr}$) by 20%, decreases (or increases) $\mathcal{R}_r$ by 10% is the same with recruitment rate of mosquitoes, $\Lambda_v$. Since $\gamma c_r = -1$, 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 \(1 - (\phi_{hs} + \phi_{hr})u_t \Lambda_h\) where \(\phi_{hs}\) and \(\phi_{hr}\) are the fractions of humans infected with the parasite sensitive to artemisinin and resistance artemisinin respectively and \(u_t\) \((0 \leq u_t \leq 1)\) is the control efforts of immigrants (quarantine). Susceptible humans get infected following contact with infected mosquitoes with both strains at a rate \((1-u_1)(\beta_{hs}c_s I_{vs} + \beta_{hr}c_r I_{vr})\). And \(u_2\) \((0 \leq u_2 \leq 1)\) is the control on the use of insecticide spray.

The mosquitoes are recruited at a rate \(1 - (\phi_{vs} + \phi_{vr})u_2 \Lambda_v\) where \(\phi_{vs}\) and \(\phi_{vr}\) are the fractions of mosquitoes infected with the parasite sensitive to artemisinin and resistance artemisinin respectively and \(u_2\) \((0 \leq u_2 \leq 1)\) 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 \((1-u_2)(\beta_{vs}c_s (I_{hs} + I_{ms})S_v, (1-u_2)\beta_{vr}c_r (I_{hr} + I_{mr})S_v)\) respectively.

The macaques are recruited at a rate \(1 - (\phi_{ms} + \phi_{mr})u_1 \Lambda_m\) where \(\phi_{ms}\) and \(\phi_{mr}\) are the fractions of macaques infected with the parasite sensitive to artemisinin and resistance artemisinin respectively and \(u_1\) \((0 \leq u_1 \leq 1)\) is the control efforts of immigrants (quarantine). Susceptible macaques get infected following contact with infected mosquitoes with both strains at a rate \((1-u_3)(\beta_{ms}c_s I_{vs} + \beta_{mr}c_r I_{vr})\). And \(u_3\) \((0 \leq u_3 \leq 1)\) 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;
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:

\[
J = \min_{u_1, u_2, u_3} \int_0^T \left( A_1 I_{hr} + A_2 I_{mr} + A_3 u_1^2 + A_4 u_2^2 + A_5 u_3^2 \right) dt
\]

where \( A_i, i = 1, \ldots, 5 \) 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 \( J(u_1, u_2, u_3) \); 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 \( u_1(t), u_2(t) \) and \( u_3(t) \). Therefore, an optimal control \( u_1^*, u_2^*, u_3^* \) is obtained such that:

\[
J \left( u_1^*, u_2^*, u_3^* \right) = \min_{u_1, u_2, u_3} \left\{ J \left( u_1, u_2, u_3 \right) \mid u_1, u_2, u_3 \in Y \right\}
\]

where the control set:

\[
Y = \left\{ u_i : [0, T] \rightarrow [0,1], \text{ Lebesgue measurable } i = 1, 2, 3 \right\}.
\]
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 $i=1,\ldots,11$. The Hamiltonian for the present optimal control problem is given by:

$$
H = A_1 I_{hr} + A_2 I_{mr} + A_3 u_1^2 + A_4 u_2^2 + A_5 u_3^2 \\
+ \lambda_1 \left\{ \left(1 - (\phi_{hs} + \phi_{hr}) u_1 \Lambda_h\right) + \pi_h + \delta_h R_h \right\} \\
+ \lambda_2 \left\{ (1 - u_2) \left( \beta_{hs} c_s I_{vs} + \beta_{hr} c_r I_{vr} \right) S_h - \mu_h S_h \right\} \\
+ \lambda_3 \left\{ \phi_{hr} u_1 \Lambda_h + (1 - u_2) \beta_{hs} c_s I_{vs} S_h - (\tau + \mu_0 + \mu_h) I_{hs} \right\} \\
+ \lambda_4 \left\{ (1 - d) \tau I_{hs} - (\delta_h + \mu_h) R_h \right\} \\
+ \lambda_5 \left\{ (1 - (\phi_{vs} + \phi_{vr}) u_2 \Lambda_v) - (1 - u_2)\right\} \\
+ \lambda_6 \left\{ \phi_{vs} u_2 \Lambda_v + (1 - u_2) \beta_{vs} c_s (I_{hs} + I_{ms}) S_v - (\mu_v + u_2) I_{vs} \right\} \\
+ \lambda_7 \left\{ \phi_{vr} u_2 \Lambda_v + (1 - u_2) \beta_{vr} c_r (I_{hr} + I_{mr}) S_v - (\mu_v + u_2) I_{vr} \right\} \\
+ \lambda_8 \left\{ (1 - (\phi_{ms} + \phi_{mr}) u_1 \Lambda_m) + \pi_m + \delta_m R_m \right\} \\
+ \lambda_9 \left\{ (1 - u_3) \left( \beta_{ms} c_s I_{vs} + \beta_{mr} c_r I_{vr} \right) - \mu_m S_m \right\} \\
+ \lambda_10 \left\{ \phi_{mr} u_1 \Lambda_m + (1 - u_3) \beta_{ms} c_s I_{vs} S_m - (\mu_1 + \mu_m + \gamma_m) I_{ms} \right\} \\
+ \lambda_11 \left\{ \phi_{mr} u_1 \Lambda_m + (1 - u_3) \beta_{mr} c_r I_{vr} S_m - (\mu_{mr} + \mu_m) I_{mr} \right\} \\
+ \lambda_11 \left\{ \gamma_m I_m - (\mu_m + \delta_m) R_m \right\}
$$

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 $\lambda_i$ for $i=1,\ldots,11$ satisfying
4.2 Adjoint System

\[
\begin{align*}
-\frac{d\lambda_1}{dt} &= -\lambda_1 \left( -\left(1-u_2\right) \left( \beta_{hs} c_s I_{vs} + \beta_{hr} c_r I_{vr} \right) - \mu_h \right) \\
&\quad - \lambda_2 \left( 1-u_2 \right) \beta_{hs} c_s I_{vs} - \lambda_3 \beta_{hr} c_r I_{vr} \\
-\frac{d\lambda_2}{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_s S_v - \lambda_6 \beta_{vs} c_s S_v \\
-\frac{d\lambda_3}{dt} &= -\lambda_4 \left( 1-u_2 \right) \beta_{vs} c_s \left( \lambda_5 - \lambda_7 \right) \left( u_2 - 1 \right) \beta_{vr} - \lambda_{40} \left( -\mu_{mr} - \mu_m \right) - \lambda_3 \left( -\mu_{hr} - \mu_h \right) \\
-\frac{d\lambda_4}{dt} &= -\lambda_4 \delta_h - \lambda_4 \left( -\delta_h - \mu_h \right) \\
-\frac{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) \\
&\quad - \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) \\
-\frac{d\lambda_6}{dt} &= \lambda_1 \left( 1-u_2 \right) \beta_{hs} c_s S_h - \lambda_2 \left( 1-u_2 \right) \beta_{hs} c_s S_h \\
&\quad - \lambda_6 \left( -\mu_v - \mu_2 \right) + \lambda_8 \left( 1-u_3 \right) \beta_{ms} c_s S_m - \lambda_9 \left( 1-u_3 \right) \beta_{ms} c_s S_m \\
-\frac{d\lambda_7}{dt} &= \lambda_1 \left( 1-u_2 \right) \beta_{hr} c_r S_h - \lambda_3 \beta_{hr} c_r S_h - \lambda_7 \left( -\mu_v - \mu_2 \right) \\
&\quad + \lambda_8 \left( 1-u_3 \right) \beta_{mr} c_r S_m - \lambda_{10} \left( 1-u_3 \right) \beta_{mr} c_r S_m \\
-\frac{d\lambda_8}{dt} &= -\lambda_8 \left( -\left(1-u_3\right) \left( \beta_{ms} c_s I_{vs} + \beta_{mr} c_r I_{vr} \right) - \mu_m \right) \\
&\quad - \lambda_9 \left( 1-u_3 \right) \beta_{ms} c_s I_{vs} - \lambda_{10} \left( 1-u_3 \right) \beta_{mr} c_r I_{vr} \\
-\frac{d\lambda_9}{dt} &= -\lambda_9 \left( \mu_1 + \mu_m + \gamma_m \right) + \lambda_8 \beta_{vs} S_v \left( -1+u_2 \right) \lambda_5 + \lambda_6 \right) c_s + \lambda_{11} \gamma_m \\
-\frac{d\lambda_{10}}{dt} &= -A_2 + \lambda_5 \left( 1-u_2 \right) \beta_{vr} c_r S_v - \lambda_7 \left( 1-u_2 \right) \beta_{vr} c_r S_v \\
-\frac{d\lambda_{11}}{dt} &= -\lambda_8 \delta_m - \lambda_{11} \left( -\delta_m - \mu_m \right)
\end{align*}
\]

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

\[ \lambda_i = 0, \text{ for } i = 1, \ldots, 11 \]  

4.4 Stationary Values

The control \( u_1^*, u_2^* \) and \( u_3^* \) satisfy the optimality condition
A Mathematical Analysis of the Effects of Control of Plasmodium…

\[
\begin{align*}
\mathbf{u}_1^* &= \max \left\{ 0, \min \left( 1, \frac{\lambda_1 (\Phi_{hs} + \Phi_{hr}) \Lambda_h + \lambda_8 (\Phi_{ms} + \Phi_{mr}) \Lambda_m}{2A_3} \right) \right\} \\
\mathbf{u}_2^* &= \max \left\{ 0, \min \left( \frac{1}{2A_4} \left[ (\lambda_2 - \lambda_1) \beta_{vr} (I_{hr} + I_{mr}) c_r + 1 - c_s (I_{hs} + I_{ms}) \beta_{vs} \right] S_v \right) \right\} \\
\mathbf{u}_3^* &= \max \left\{ 0, \min \left( \frac{1}{2A_5} \left[ -S_m \left( c_r I_{vr} (\lambda_8 - \lambda_9) \beta_{mr} + \beta_{ms} c_s I_{vs} (\lambda_8 - \lambda_9) \right) \right] \right) \right\}
\end{align*}
\]

**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:
\[
\frac{d\lambda_i}{dt} = \begin{cases} 
\frac{\partial H}{\partial S_h} = -\lambda_1 \left( (1 - u_2) \left( \beta_{hs} c_s I_{hs} + \beta_{hr} c_r I_{hr} \right) - \mu_h \right) - \lambda_2 \left( 1 - u_2 \right) \beta_{hs} c_s I_{vs} - \lambda_3 \beta_{hr} c_r I_{hr} \\
\frac{d\lambda_2}{dt} = \frac{\partial H}{\partial I_{hs}} = -\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_s S_v - \lambda_6 \beta_{vs} c_r S_v \\
\frac{d\lambda_3}{dt} = \frac{\partial H}{\partial I_{hr}} = -A_1 c_r S_v \left( u_2 - 1 \right) \beta_{vr} c_r \left( I_{hr} + I_{mr} \right) - \lambda_5 \left(-\mu_{mr} - \mu_m \right) - \lambda_3 \left(-\mu_{hr} - \mu_h \right) \\
\frac{d\lambda_4}{dt} = \frac{\partial H}{\partial R_h} = -\lambda_4 \delta h - \lambda_4 \left( -\delta_h - \mu_h \right) \\
\frac{d\lambda_5}{dt} = \frac{\partial H}{\partial S_v} = -\lambda_5 \left(-\delta_h - \mu_h \right) \\
\frac{d\lambda_6}{dt} = \frac{\partial H}{\partial S_m} = \lambda_1 \left( 1 - u_2 \right) \beta_{hs} c_s S_h - \lambda_2 \left( 1 - u_2 \right) \beta_{hs} c_s S_h - \lambda_6 \left(-\mu_v - u_2 \right) \\
+ \lambda_8 \left( 1 - u_3 \right) \beta_{ms} c_s S_m - \lambda_9 \left( 1 - u_3 \right) \beta_{ms} c_s S_m \\
\frac{d\lambda_7}{dt} = \frac{\partial H}{\partial I_{vr}} = \lambda_1 \left( 1 - u_2 \right) \beta_{hr} c_r S_h - \lambda_3 \beta_{hr} c_r S_h - \lambda_7 \left(-\mu_v - u_2 \right) \\
+ \lambda_8 \left( 1 - u_3 \right) \beta_{mr} c_r S_m - \lambda_9 \left( 1 - u_3 \right) \beta_{mr} c_r S_m \\
\frac{d\lambda_8}{dt} = \frac{\partial H}{\partial I_{m}} = \lambda_1 \left( 1 - u_2 \right) \beta_{ms} c_I I_{vs} + \beta_{mr} c_r I_{vr} - \lambda_8 \left( 1 - u_3 \right) \beta_{ms} c_s I_{vs} \\
+ \lambda_3 \beta_{hr} c_r S_h - \lambda_7 \left( 1 - u_2 \right) \beta_{vr} c_r S_v \\
\frac{d\lambda_9}{dt} = \frac{\partial H}{\partial I_{m}} = \lambda_8 \left( 1 - u_3 \right) \beta_{ms} c_s I_{vs} - \lambda_9 \left( 1 - u_3 \right) \beta_{ms} c_s I_{vs} \\
\frac{d\lambda_{10}}{dt} = \frac{\partial H}{\partial R_m} = A_2 + \lambda_5 \left( 1 - u_2 \right) \beta_{vr} c_r S_v - \lambda_7 \left( 1 - u_2 \right) \beta_{vr} c_r S_v \\
\frac{d\lambda_{11}}{dt} = \frac{\partial H}{\partial R_m} = -\lambda_8 \delta_m - \lambda_9 \left(-\delta_m - \mu_m \right) \
\end{cases}
\]

and with transversality conditions
\[
\lambda_i = 0, \text{ for } i = 1, \ldots, 11
\]

On the interior of the control set, where \(0 < \mu_i < 1, \text{ for } i = 1, 2, 3\) yields
\[
\begin{cases}
0 = \frac{\partial H}{\partial u_1} = 2A_2 \mu_s^* + \lambda_1 \left( -\phi_{hs} - \phi_{hr} \right) \Lambda_h - \lambda_8 \left( \phi_{ms} + \phi_{mr} \right) \Lambda_m \\
0 = \frac{\partial H}{\partial u_2} = 2A_4 \mu_s^* \left( \left( -\beta_{vr} \left( I_{hr} + I_{mr} \right) c_r + 1 - c_s \left( I_{hs} + I_{ms} \right) \beta_{vs} \right) S_v + \left( \phi_{vs} + \phi_{vr} \right) \Lambda_v \right) \lambda_5 \\
+ c_s \beta_{vs} \lambda_7 \left( I_{hr} + I_{ms} \right) S_v \lambda_5 \beta_{hr} c_r I_{vr} S_h - \beta_{hs} I_{vs} S_h \left( \lambda_4 - \lambda_2 \right) c_s + \lambda_7 I_{vs} + \lambda_6 I_{vs} \\
0 = \frac{\partial H}{\partial u_3} = 2A_2 \mu_s^* + \lambda_8 \left( \beta_{ms} c_s I_{vs} + \beta_{mr} c_r I_{vr} \right) S_m - \lambda_6 \beta_{ms} c_s I_{vs} S_m - \lambda_10 \beta_{mr} c_r I_{vr} S_m
\end{cases}
\]
This in another clear form becomes

\[
\begin{align*}
- \frac{d\lambda_1}{dt} &= -\lambda_1 \left( (1-u_2)(\beta_{hs}c_s I_{vs} + \beta_{hr} c_r I_{vr}) - \mu_h \right) - \lambda_2 \left( 1-u_2 \right) \beta_{hs} c_s I_{vs} - \lambda_3 \beta_{hr} c_r I_{vr} \\
- \frac{d\lambda_2}{dt} &= -\lambda_2 (\tau - \mu_0 - \mu_h) - \lambda_3 d \tau - \lambda_4 (1-d) \tau + \lambda_5 (1-u_2) \beta_{hs} c_s S_v - \lambda_6 \beta_{vs} c_r S_v \\
- \frac{d\lambda_3}{dt} &= -A_1 - c_r S_v \left( \lambda_5 - \lambda_7 \right) (u_2 - 1) \beta_{vr} - \lambda_10 (\mu_{mr} - \mu_m) - \lambda_3 (\mu_{hr} - \mu_h) \\
- \frac{d\lambda_4}{dt} &= -\lambda_4 \delta_h - \lambda_4 \delta_h - \delta_h - \mu_h \\
- \frac{d\lambda_5}{dt} &= -\lambda_5 \left( (1-u_2) \beta_{vs} c_s (I_{hs} + I_{ms}) - (1-u_2) \beta_{cr} c_r (I_{hr} + I_{mr}) - \mu_v - u_2 \right) \\
&\quad - \lambda_6 \beta_{vs} c_s (I_{hs} + I_{ms}) - \lambda_7 (1-u_2) \beta_{cr} c_r (I_{hr} + I_{mr}) \\
- \frac{d\lambda_6}{dt} &= \lambda_1 (1-u_2) \beta_{hs} c_s S_h - \lambda_2 (1-u_2) \beta_{hs} c_s S_h \\
&\quad - \lambda_6 (\mu_v - \mu_2) + \lambda_8 (1-u_3) \beta_{ms} c_s S_m - \lambda_9 (1-u_3) \beta_{ms} c_s S_m \\
- \frac{d\lambda_7}{dt} &= \lambda_1 (1-u_2) \beta_{hs} c_s S_h - \lambda_3 \beta_{hr} c_r S_h - \lambda_7 (\mu_v - \mu_2) \\
&\quad + \lambda_8 (1-u_3) \beta_{mr} c_r S_m - \lambda_{10} (1-u_3) \beta_{mr} c_r S_m \\
- \frac{d\lambda_8}{dt} &= -\lambda_8 \left( (1-u_3) \left( \beta_{ms} c_s I_{vs} + \beta_{mr} c_r I_{vr} \right) - \mu_m \right) \\
&\quad - \lambda_9 (1-u_3) \beta_{ms} c_s I_{vs} - \lambda_{10} (1-u_3) \beta_{mr} c_r I_{vr} \\
- \frac{d\lambda_9}{dt} &= -\lambda_9 (\mu_1 + \mu_m + \gamma_m) + \beta_{vs} S_v \left( (1-u_2) \lambda_5 + \lambda_6 \right) c_s + \lambda_1 \gamma_m \\
- \frac{d\lambda_{10}}{dt} &= -A_2 + \lambda_5 (1-u_2) \beta_{vs} c_s S_v - \lambda_7 (1-u_2) \beta_{vs} c_s S_v \\
- \frac{d\lambda_{11}}{dt} &= -\lambda_8 \delta_m - \lambda_11 (\delta_m - \mu_m)
\end{align*}
\]

Thus, it is obtained that,

\[
\begin{align*}
u_1^* &= \frac{\lambda_1 (\phi_{hs} + \phi_{hr}) \Lambda_h + \lambda_8 (\phi_{ms} + \phi_{mr}) \Lambda_m}{2A_3} \\
u_2^* &= \frac{1}{2A_3} \left( \left( -\beta_{vr} (I_{hr} + I_{mr}) c_r + 1 - c_s (I_{hs} + I_{ms}) \beta_{vs} \right) S_v + (\phi_{vs} + \phi_{vr}) \Lambda_v \right) \\
u_3^* &= -\frac{S_m (c_r I_{vr} (\lambda_8 - \lambda_{10}) \beta_{mr} + \beta_{ms} c_s I_{vs} (\lambda_8 - \lambda_9))}{2A_5}
\end{align*}
\]
By standard control arguments involving the bounds on the controls, it can be concluded that

\[
u_1^* = \begin{cases} 
0 & \text{if } \xi_1^* \leq 0 \\
\xi_1^* & \text{if } 0 < \xi_1^* < 1 \\
1 & \text{if } \xi_1^* \geq 1
\end{cases}
\]

\[
u_2^* = \begin{cases} 
0 & \text{if } \xi_2^* \leq 0 \\
\xi_2^* & \text{if } 0 < \xi_2^* < 1 \\
1 & \text{if } \xi_2^* \geq 1
\end{cases}
\]

\[
u_3^* = \begin{cases} 
0 & \text{if } \xi_3^* \leq 0 \\
\xi_3^* & \text{if } 0 < \xi_3^* < 1 \\
1 & \text{if } \xi_3^* \geq 1
\end{cases}
\]

where

\[
\xi_1^* = \frac{\lambda_1 (\phi_{hs} + \phi_{hr}) \Lambda_h + \lambda_6 (\phi_{ms} + \phi_{mr}) \Lambda_m}{2A_3}
\]

\[
\xi_2^* = \frac{1}{2A_4} \left( \left( \left(-\beta_{vr} (I_{hr} + I_{mr}) c_r + 1 - c_s (I_{hs} + I_{ms}) \beta_{vs} \right) S_v + (\phi_{us} + \phi_{vr}) \Lambda_v \right) \lambda_5 \right)
\]

\[
\xi_3^* = \frac{-S_m (c_r I_{vr} (\lambda_8 - \lambda_{10}) \beta_{mr} + \beta_{ms} c_s I_{vs} (\lambda_8 - \lambda_9))}{2A_5}
\]

\[
u_i^* = \min \left\{ 1, \xi_i^* \right\}, \quad u_2^* = \min \left\{ 1, \xi_2^* \right\}, \quad u_3^* = \min \left\{ 1, \xi_3^* \right\}.
\]

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>
<thead>
<tr>
<th>Var.</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S_h$</td>
<td>Susceptible human</td>
</tr>
<tr>
<td>$I_{hs}$</td>
<td>Infected human with parasite sensitive to artemisinin</td>
</tr>
<tr>
<td>$I_{hr}$</td>
<td>Human infected with parasite that is artemisinin resistant strain</td>
</tr>
<tr>
<td>$R_h$</td>
<td>Recovered/immune human</td>
</tr>
<tr>
<td>$S_v$</td>
<td>Susceptible mosquito</td>
</tr>
<tr>
<td>$I_{vs}$</td>
<td>Infected mosquito with parasite sensitive to artemisinin</td>
</tr>
<tr>
<td>$I_{vr}$</td>
<td>Infected mosquito with parasite that is artemisinin resistant strain</td>
</tr>
<tr>
<td>$S_m$</td>
<td>Susceptible macaque</td>
</tr>
<tr>
<td>$I_{ms}$</td>
<td>Infected macaque with parasite sensitive to artemisinin</td>
</tr>
<tr>
<td>$I_m$</td>
<td>Infected macaque with parasite that is artemisinin resistant strain</td>
</tr>
<tr>
<td>$R_m$</td>
<td>Recovered/immune macaque</td>
</tr>
</tbody>
</table>
Table 2

Description of Parameters of Model (1)

<table>
<thead>
<tr>
<th>Par.</th>
<th>Est. Value</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Lambda_h$</td>
<td>0.00011</td>
<td>Augusto et al., (2012) [38]</td>
</tr>
<tr>
<td>$\pi_h$</td>
<td>0.00076</td>
<td>Chiyaka et al., (2008) [48]</td>
</tr>
<tr>
<td>$\Lambda_v$</td>
<td>0.071</td>
<td>Augusto et al., (2012) [38]</td>
</tr>
<tr>
<td>$\Lambda_m$</td>
<td>0.2</td>
<td>Assumed</td>
</tr>
<tr>
<td>$\pi_m$</td>
<td>0.00076</td>
<td>Assumed</td>
</tr>
<tr>
<td>$\mu_h$</td>
<td>0.0004</td>
<td>Niger &amp; Gumel, (2008) [49]</td>
</tr>
<tr>
<td>$\mu_{hr}$</td>
<td>0.05</td>
<td>Okosun &amp; Makinde (2012) [32]</td>
</tr>
<tr>
<td>$\mu_0$</td>
<td>0.05</td>
<td>Hove-Musekwa, (2008) [50]</td>
</tr>
<tr>
<td>$\mu_m$</td>
<td>0.02</td>
<td>Assumed</td>
</tr>
<tr>
<td>$\mu_{mr}$</td>
<td>0.02</td>
<td>Assumed</td>
</tr>
<tr>
<td>$\mu_1$</td>
<td>0.06</td>
<td>Assumed</td>
</tr>
<tr>
<td>$\delta_h$</td>
<td>$(\frac{1}{2 \times 365})$</td>
<td>Menach et al., (2005) [51]</td>
</tr>
<tr>
<td>$\beta_{hs}$</td>
<td>0.03</td>
<td>Menach et al., (2005) [51]</td>
</tr>
<tr>
<td>$\beta_{hr}$</td>
<td>0.17</td>
<td>Chiyaka et al., (2008) [48]</td>
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<tr>
<td>$c_s$</td>
<td>0.6</td>
<td>Chitnis et al., (2006) [52]</td>
</tr>
<tr>
<td>$d$</td>
<td>0.02</td>
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</tr>
<tr>
<td>$\beta_{vs}$</td>
<td>0.09</td>
<td>Menach et al., (2005) [51]</td>
</tr>
<tr>
<td>$\beta_{vr}$</td>
<td>0.83</td>
<td>Chiyaka et al., (2008) [48]</td>
</tr>
<tr>
<td>$\beta_{ms}$</td>
<td>0.03</td>
<td>Assumed</td>
</tr>
<tr>
<td>$\beta_{mr}$</td>
<td>0.03</td>
<td>Assumed</td>
</tr>
<tr>
<td>$c_r$</td>
<td>0.502</td>
<td>Assumed</td>
</tr>
<tr>
<td>$\gamma_m$</td>
<td>0.5</td>
<td>Assumed</td>
</tr>
<tr>
<td>$\tau$</td>
<td>0.8</td>
<td>Augusto et al., (2012) [38]</td>
</tr>
<tr>
<td>$\mu_v$</td>
<td>0.04</td>
<td>Chiyaka et al., (2008) [48]</td>
</tr>
<tr>
<td>$\delta_m$</td>
<td>$(\frac{1}{2 \times 365})$</td>
<td>Assumed</td>
</tr>
<tr>
<td>$\phi_{ms}$</td>
<td>0.0005</td>
<td>Assumed</td>
</tr>
<tr>
<td>$\phi_{mr}$</td>
<td>0.0005</td>
<td>Assumed</td>
</tr>
<tr>
<td>$\phi_{hs}$</td>
<td>0.00005</td>
<td>Assumed</td>
</tr>
<tr>
<td>$\phi_{hr}$</td>
<td>0.00005</td>
<td>Assumed</td>
</tr>
<tr>
<td>$\phi_{vs}$</td>
<td>0.036</td>
<td>Assumed</td>
</tr>
<tr>
<td>$\phi_{vr}$</td>
<td>0.035</td>
<td>Assumed</td>
</tr>
</tbody>
</table>
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)](image-url)
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)](image1.png)

**Figure 3(a)**

![Figure 3(b)](image2.png)

**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.
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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