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Optimal control with the effects of ivermectin and livestock availability on malaria transmission

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Abstract

Malaria remains a global threat and the conventional methods used for combating the disease leave out mosquitoes that feed outdoors. This study addresses the challenge posed by such mosquitoes based on a tool called ivermectin drug which is lethal to mosquitoes that ingest bloodmeal containing a concentration of it. We formulated a mathematical model with three control tools (insecticide treated nets, treatment of infective individuals and ivermectin drug on livestock and humans) for the transmission and control of malaria under optimal condition. The model's basic reproduction number, R_0 was estimated and the local and global stability analyses of the disease-free and endemic equilibrium points of the model were carried out. Sensitivity analysis carried out showed that R_0 is most sensitive to the mosquito biting rate and to the proportion of blood meal on human with cattle availability in such a way that any percent increase in the value of any of these parameters will lead to an equal percent increase in the value of R_0. The result of an optimal control analysis based on three time dependent controls suggests that the combination of all three controls gives the best result followed by the strategy that combines the use of ivermectin drug and the treatment of infective human. Depending on available resources, any of these is recommended to be adopted in malaria intervention programmes because of their effectiveness on both the infective human and mosquito populations with the potential of contributing significantly to the disease elimination within a minimal time frame.

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1. Introduction

Malaria, a preventable and curable disease remains a major public health threat especially in Sub-Saharan Africa. According to the 2022 World Malaria Report, an estimated global malaria death stood at 619 000 in 2021 with 247 million cases [1]. Despite the huge effort invested to achieve elimination and eradication, several obstacles undermine it. An important factor that contributes to the delay on achieving the prospect of malaria elimination and possible eradication is the behavioral changes in mosquito feeding and resting habits with an increase in outdoor activities for some species of the vector whereby an intervention that uses insecticide treated nets (ITNs) and indoor residual spraying (IRS) may not capture them. It was noted by Kiware *et al.* [2] that these vectors feed predominantly on animals and can sustain malaria transmission even if they only bite humans infrequently. As a result, there arose the need for new

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strategies that will address such gaps.

An intervention for controlling malaria known as zooprophylaxis that captures both zoophilic and zoophagic vectors was earlier proposed in Ref. [3]. This proposed strategy works in such a way that the attention of mosquitoes are diverted from humans to livestock for bloodmeal given that the malaria parasites that infect humans has no effect on livestock. In line with this, the malaria elimination community as reported in Ref. [4] is currently giving increased attention to the potential use of ivermectin (IVM), endo and ectoparasites in the livestock [5] and its role in increasing the mortality of Anopheles mosquitoes that ingest it in a blood meal was buttressed by the world health organization in 2016 [6] and also captured in Ref. [7]. It was also noted that modelling based on these studies indicates endectocides, as an additional vector control tool and this increasing attention is driven by the increased importance of outdoor/residual malaria transmission and the threat of insecticide resistance. The drug is used in treating livestock as it has the ability to reduce the burden of both endo and ectoparasite in the livestock [5]. It was also noted that modelling based on these studies indicates that mass drug administration (MDA) with IVM has the potential to reduce malaria transmission mainly by negatively impacting mosquito survival, fitness, and fertility, and also potentially inhibits sporogony. In this regard several studies that are based on mathematical models, with the aim of bringing down the malaria vector population and thereby reducing malaria transmission through the use of IVM have been carried out. One of such is an investigation on the potential impact of combining artemisinin-combination therapy (ACT) and IVM in MDA campaigns for the control of malaria [8].

It was noted in the study that the effect of adding ivermectin during individual malaria treatment led to a minimal additional transmission suppression while an accelerated time to elimination was the case when ivermectin MDA is added to antimalarial MDA. Extending and then validating a population-level mathematical model using a clinical and an entomological data, the effect of ivermectin mass drug administration on the malaria vector population and malaria transmission was further explored in Ref. [7]. It was estimated that MDA with ivermectin will reduce malaria prevalence and incidence, thereby suggesting the need for considering MDA with ivermectin malaria control in areas where the transmission of malaria is highly persistent with existing interventions not sufficient and also in those areas tending towards elimination. The use of ivermectin drug in the control of malaria was extended further on both human and livestock populations [9] based on mathematical model on which the effects of livestock on malaria transmission were observed to be non-linear. Although the strategy, according to the authors, is likely to be more beneficial to the people in areas where zoophilic malaria vectors are predominant, nevertheless applying it under certain conditions shows the possibility of bringing down the malaria burden substantially in areas with moderately zoophilic vectors like sub-Saharan Africa. A mathematical model consisting of ordinary differential equations for both human and mosquito populations was formulated by Yakob [10] and was used to explore the effect of endectocide treated-livestock and several mosquito biting hosts on malaria transmission and control. The model was based on an open population where no birth nor death were considered. It was observed that endectocides used on cattle had equivalent, and in some cases, improved efficacy over bed nets and spray in controlling the spread of malaria. Building on that work, Yakob *et al.* [11] then carried out an investigation on the combined use of endectocide-treated livestock with LLINs for malaria control. Based on the findings of that study, it was concluded that treating livestock with endectocides as a target for mosquito feeding serves as very useful complement to the use of LLINs for malaria control. The investigations of their study was without optimal control analysis which would be applied in the current study.

A parsimonious mathematical model that accounts for a diverse range of host-biting behaviors and also assesses their impact on combining LLINs with treating livestock with one of these endectocides was considered in Yakob *et al.* [11]. The result from simulations of the model showed marked differences across biting ecologies in the efficacy of both LLINs as a standalone tool and the combination of LLINs with endectocide-treated cattle. Furthermore, Waite *et al.* [12] observed a high propensity of mosquito to feed on livestock (cattle) and rest in outdoor structures such as cattle shelters. Unlike the studies earlier mentioned, in Ochigbo *et al.* [13] an explicit compartment representing a proportion of susceptible humans treated with ivermectin drug for the purpose of controlling malaria burden through the reduction of its vector population was formulated. The model was based on a system of ordinary differential equations which also captures the relapse of the infection in humans. Numerical simulations of the model showed that treatment alone, in the presence of relapse was not sufficient to bring about the desired elimination goal but the inclusion of ivermectin as a control tool was observed to bring down the vector population tremendously, thereby reducing transmission intensity. It was estimated that MDA with ivermectin will reduce malaria prevalence and incidence, hence it is highly recommended in areas where the transmission of malaria is highly persistent with existing interventions not sufficient and also in those areas tending towards elimination [7].

The aim of our current study is to formulate an optimal control mathematical model using multiple control tools that include the use of IVM on livestock (cattle) and human populations, ITNs and treatment of infective humans to study the transmission and control of malaria. Specifically, three controls (ivermectin administration, long-lasting insecticidal nets (LLINs) and the treatment of infective humans) are implemented under four combinations as strategies with comparison carried out. The method of optimal analysis adopted here is the Pontryagin's Maximum Principle [14] which was used to find the necessary optimality conditions. This principle has been applied in several other studies [15–19] on the transmission dynamics and control of malaria.

2. Model formulation

In this section, we present the formulated malaria model consisting of a nonlinear system of ordinary differential equations representing the human and mosquito population to study the transmission and control of malaria. The human and mosquito populations are divided into three compartments each given as Susceptible (S_h), Exposed/Latent (L_h), Infectious (I_h) compartments for the human population and Susceptible (S_v), Exposed/Latent (L_v), Infectious (I_v) compartments for the mosquito population. We assumed that the mosquito population consists of only the female Anopheles mosquito. In addition, there is no immunity and so the proportion of treated humans become susceptible again. The model parameters and description are represented on Table 1 and the model equations are given as follows:

$$\begin{aligned}
\frac{dS_h}{dt} &= \lambda_h + (v+\sigma u_2)I_h - \frac{(1-u_1)abqI_vS_h}{N_h} - \mu_h S_h \\
\frac{dL_h}{dt} &= \frac{(1-u_1)abqI_vS_h}{N_h} - (\mu_h+\theta)L_h \\
\frac{dI_h}{dt} &= \theta L_h - (v+\sigma u_2+\delta+\mu_h)I_h \\
\frac{dS_v}{dt} &= \lambda_v - \frac{(1-u_1)kbqI_hS_v}{N_h} - (\tau u_3+\mu_v)S_v \\
\frac{dL_v}{dt} &= \frac{(1-u_1)kbqI_hS_v}{N_h} - (\omega+\tau u_3+\mu_v)L_v \\
\frac{dI_v}{dt} &= \omega L_v - (\tau u_3+\mu_v)I_v,
\end{aligned} \tag{1}$$

where $\tau = bcm(S_h^0 + A_l)$ accounts for a reduction in the vector population as a result of bites on a proportion of the initial susceptible human (S_h^0) population and available cattle (A_l) population both having ivermectin in their blood at the level of killing mosquito with m as a modification parameter. The rate of the reduction also depends on the mosquito biting and contact rates, b and c respectively. Among other parameters, the force of infection from vectors to humans and vice versa each depends on the term, q which represents the proportion of feeds taken on humans (human blood index - HBI) with cattle availability (see Ref. [9]). It is assumed here that only susceptible humans partake in the ivermectin treatment as a control strategy. Furthermore, u_1, u_2 and u_3 are the control parameters for the use of ITNs, treatment of infectious human and the ivermectin administration respectively.

3. Model analysis

From equation (1), we have that

$$\begin{aligned}
\frac{dN_h}{dt} &= \lambda_h - \mu_h N_h - \delta I_h \\
\frac{dN_v}{dt} &= \lambda_v - (\tau u_3+\mu_h)N_v.
\end{aligned} \tag{2}$$

The initial value of the individual in each compartment is given as:

$$S_h(0) = S_h^0 \geq 0, L_h(0) = L_h^0 \geq 0, I_h(0) = I_h^0 \geq 0,$$

$$S_v(0) = S_v^0 \geq 0, L_v(0) = L_v^0 \geq 0, I_v(0) = I_v^0 \geq 0. \tag{3}$$

Given equation (3), then for all time ($t > 0$),

$$S_h(t) \geq 0, L_h(t) \geq 0, I_h(t) \geq 0, S_v(t) \geq 0, L_v(t) \geq 0, I_v(t) \geq 0.$$

Also, from equation (2) we have that

$$\limsup N_h \leqslant \frac{\lambda_h}{\mu_h},$$

and

$$\limsup N_v \leq \frac{\lambda_v}{(\tau u_3+\mu_v)}.$$

And so the feasible region of biological interest is given as:

$$\Omega = \Omega_h \times \Omega_v \subset \mathfrak{R}_+^3 \times \mathfrak{R}_+^3,$$

where

$$\Omega_h = \left\{(S_h, L_h, I_h) \in \mathfrak{R}_+^3 : S_h + L_h + I_h = N_h \leqslant \frac{\lambda_h}{\mu_h}\right\},$$

and

$$\Omega_v = \left\{(S_v, L_v, I_v) \in \mathfrak{R}_+^3 : S_v + L_v + I_v = N_v \leqslant \frac{\lambda_v}{A_1}\right\}.$$

Ω is positively invariant with respect to system in equation (1). It implies that for all time, $t \geq 0$ all feasible solutions of the equation (1) remain positive and are attracted in the region. Therefore, apart from the malaria model being biologically meaningful, it is also mathematically well-posed in that domain

3.1. The basic reproduction number, R_0

The malaria model of system in equation (1) has two steady states, namely disease free equilibrium (DFE) and endemic equilibrium. The DFE is given as:

$$E_0 = \left\{S_h^0, L_h^0, I_h^0, S_v^0, L_v^0, I_v^0\right\} = \left\{\frac{\lambda_h}{\mu_h}, 0, 0, \frac{\lambda_v}{A_1}, 0, 0\right\}. \tag{4}$$

Applying the next generation matrix method, the basic reproduction number is obtained as

$$R_0 = \sqrt{\frac{(1-u_1)^2ab^2kq^2\omega\theta\lambda_h\lambda_v}{\mu_h N_h^2 A_1^2(\mu_h+\theta)(A_1+\omega)(\sigma u_2+\delta+v+\mu_h)}}. \tag{5}$$

This threshold parameter is used for the stability analysis of the model at the equilibrium points. We investigate the local stability of the disease-free equilibrium using the theorem below.

3.2. Local stability analysis of the disease-free equilibrium

Theorem 1 The disease-free equilibrium point for the malaria model of equation (1) is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

Proof The Jacobian matrix (J_{E_0}) evaluated at the DFE point equation (4) is given as:

$$J_{E_0} = \begin{pmatrix} -\mu_h & 0 & (v+\sigma u_2) & 0 & 0 & \frac{-M_1 J_1 \lambda_h}{\mu_h} \\ 0 & -A_4 & 0 & 0 & 0 & \frac{-M_1 J_1 \lambda_h}{\mu_h} \\ 0 & \theta & -A_3 & 0 & 0 & 0 \\ 0 & 0 & \frac{-M_1 J_1 \lambda_v}{A_1} & -A_1 & 0 & 0 \\ 0 & 0 & \frac{M_1 J_1 \lambda_v}{A_1} & 0 & -A_2 & 0 \\ 0 & 0 & 0 & 0 & \omega & -A_1, \end{pmatrix}, \quad (6)$$

where $M_1 = (1-u_1)$, $A_2 = (\tau u_3+\omega+\mu_v)$, $A_3 = (\delta+v+\mu_h+\sigma u_2)$, $A_4 = (\mu_h+\theta)$, $J_1 = \frac{abq}{A_1}$, $J_2 = \frac{kbq}{A_1}$.

The solutions of the characteristics equation $|J_{E_0} - \lambda I| = 0$ are the eigenvalues of the Jacobian matrix in equation (6) with the eigenvalues $-\mu_h$ and $-A_1$ extracted from the columns containing only the diagonal elements. The remaining 4 eigenvalues are obtained from the matrix in equation (6) as

$$\begin{vmatrix} -\mu_h & 0 & 0 & \frac{M_1 J_1 \lambda_h}{\mu_h} \\ \theta & -A_4 & 0 & 0 \\ 0 & \frac{M_1 J_2 \lambda_v}{A_1} & -A_2 & 0 \\ 0 & 0 & \omega & -A_1 \end{vmatrix} = 0. \quad (7)$$

Solving equation (7) gives

$$(\lambda + A_1)(\lambda + A_2)(\lambda + A_3)(\lambda + A_4) - K = 0,$$

where

$$K = \frac{M_1^2 J_1 J_2 \omega \lambda_h \theta \lambda_v}{\mu_h N_h^2 A_1}.$$

By expansion, we obtain the characteristics polynomial

$$\lambda^4 + \lambda^3 B_1 + \lambda^2 B_2 + \lambda^1 B_3 + B_4, \quad (8)$$

where $B_1 = A_1 + A_2 + A_3 + A_4$, $B_2 = A_4(A_1 + A_2 + A_3) + A_3(A_1+A_2)+A_2A_1$, $B_3 = A_4A_3A_2+A_4A_3A_1+A_4A_2A_1+A_3A_2A_1$, $B_4 = A_4A_3A_2A_1 - K$. Expressing B_4 in terms of R_0, yields

$$B_4 = A_4A_3A_2A_1(1 - R_0). \quad (9)$$

To prove that the roots of the polynomial equation (8) all have negative real parts, we employ the Routh-Hurwitz criterion [20] which provides necessary and sufficient conditions for all the roots of the characteristics polynomial with real coefficients to lie in the left half of the complex plane.

Theorem 2 By the Routh-Hurwitz criteria, let

$$P(\lambda) = \lambda^n + \lambda^{n-1} B_1 + \lambda^{n-2} B_2 + ... + \lambda^1 B_{n-1} + B_n \quad (10)$$

be a polynomial of degree n where the coefficients $B_{i's}$ are real constants with $i = 1, 2, 3, \ldots$. Based on its coefficients, we define the n Hurwitz matrices as follows:

$$H_1 = (B_1), H_2 = \begin{pmatrix} B_1 & 1 \\ B_3 & B_2 \end{pmatrix}, H_3 = \begin{pmatrix} B_1 & 1 & 0 \\ B_3 & B_2 & B_1 \\ B_5 & B_4 & B_3 \end{pmatrix},$$

$$H_4 = \begin{pmatrix} B_1 & 1 & 0 & \cdots & 0 \\ B_3 & B_2 & B_1 & \cdots & 0 \\ \vdots & \vdots & \vdots & \cdots & \vdots \\ 0 & 0 & 0 & \cdots & B_n \end{pmatrix},$$

where $B_j = 0$ if $j > n$. All the roots of the polynomial in equation (10) have negative real parts or are negative if and only if all the determinants of the Hurwitz matrices are positive. That is, iff $\det(H_j) > 0$, $j = 1, 2, 3, ..., n$.

Proof Equation (8) is a fourth order polynomial and so, the Routh Hurwitz criteria are as follows: $(B_1B_2B_3B_4) > 0, \det(H_1) = B_1 > 0, \det(H_2) = B_1B_2 > 0,$

$$\det(H_3) = B_1B_2B_3 - B_3^2 =$$
$$(A_1^3A_2^2A_3 + A_1^3A_2^2A_4 + A_1^3A_3^2A_2 + 3A_1^3A_2A_3A_4 + A_1^3A_4^2A_2 +$$
$$A_1^3A_3^2A_4 + A_1^3A_4^2A_3 + A_2^3A_1^2A_3 + A_2^3A_1^2A_4 + 6A_1^2A_2^2A_3A_4 +$$
$$2A_1^2A_2^2A_3^2 + 2A_1^2A_2^2A_4^2 + A_3^3A_1^2A_2 + 6A_1^2A_2A_3^2A_4 + A_4^3A_1^2A_2$$
$$+ 6A_1^2A_2A_3A_4^2 + A_3^3A_1^2A_4 + 2A_1^2A_3^2A_4^2 + A_4^3A_1^2A_3 + A_3^3A_2^2A_1 +$$
$$3A_1A_2^3A_3A_4 + A_2^3A_4^2A_1 + A_3^3A_2^2A_1 + 6A_1A_2^2A_3^2A_4 + 6A_1A_2^2A_3A_4^2 +$$
$$A_4^3A_2^2A_1 + 3A_1A_2A_3^3A_4 + 6A_1A_2A_3^2A_4^2 + 3A_1A_2A_3A_4^3 + A_3^3A_4^2A_1 +$$
$$A_4^3A_3^2A_1 + A_2^3A_3^2A_4 + A_2^3A_4^2A_3 + A_3^3A_2^2A_4 + 2A_2^2A_3^2A_4^2 +$$
$$A_4^3A_2^2A_3 + A_3^3A_4^2A_2 + A_4^3A_3^2A_2) > 0,$$

$$\det(H_4) = B_1B_2B_3B_4 - B_1^2B_4^2 - B_3^2B_4 = A_4A_3A_2A_1(1 - R_0)$$
$$(A_1^3A_2A_3A_4R_0 + 2A_1^2A_2^2A_3A_4R_0 + 2A_1^2A_2A_3A_4^2R_0 + A_1A_2^3A_3A_4R_0 +$$
$$2A_1A_2^2A_3^2A_4R_0 + 2A_1A_2^2A_3A_4^2R_0 + A_1A_2A_3^2A_4R_0 + 2A_1A_2A_3^2A_4^2R_0 +$$
$$A_1A_2A_3A_4^3R_0 + A_1^3A_2^2A_3 + A_1^3A_2^2A_4 + 2A_1^2A_2^2A_3^2 + 4A_1^2A_2^2A_3A_4 +$$
$$2A_1^2A_2^2A_4^2 + A_3^3A_1^2A_2 + 4A_1^2A_2A_3^2A_4 + 4A_1^2A_2A_3A_4^2 + A_4^3A_2^2A_1 +$$
$$A_3^3A_1^2A_4 + 2A_1^2A_2^2A_4^2 + A_4^3A_1^2A_3 + A_2^3A_3^2A_1 + 2A_1A_2^3A_3A_4 + A_2^3A_4^2A_1$$
$$+ A_3^3A_2^2A_1 + 4A_1A_2^2A_3^2A_4 + 4A_1A_2^2A_3A_4^2 + A_4^3A_2^2A_1 + 2A_1A_2A_3^3A_4 +$$
$$4A_1A_2A_3^2A_4^2 + 2A_1A_2A_3A_4^3 + A_3^3A_4^2A_1 + A_4^3A_3^2A_1 + A_2^3A_3^2A_4 +$$
$$A_2^3A_4^2A_3 + A_3^3A_2^2A_4 + 2A_2^2A_3^2A_4^2 + A_4^3A_2^2A_3 + A_3^3A_4^2A_2 + A_4^3A_3^2A_2).$$

Now, $B_4 > 0$ provided $R_0 < 1$ and so $\det(H_4) > 0$. With this, we have that for $R_0 < 1$, all the determinants of the Hurwitz matrices are positive, which implies that all the eigenvalues of the Jacobian matrix equation (7) have negative real parts under such circumstance. Hence the disease free equilibrium point is locally asymptotically stable whenever $R_0 < 1$. The epidemiological implication of this situation is that the disease can be controlled in the population. On the other hand, whenever $R_0 > 1$, then the coefficient $B_4 < 0$ (negative) which differs in sign from all the other coefficients. This means that not all the roots of the polynomials will have negative real parts and hence the disease free equilibrium is locally asymptotically unstable for $R_0 > 1$. Also, the epidemiological implication of such situation is that the disease will persist in the population.

3.3. Global stability of the disease-free equilibrium

For the global stability, define the Lyapunov function

$$F_L = n_1L_h + n_2I_h + n_3L_v + n_4I_v.$$

Therefore,

$$\frac{dF_L}{dt} = n_1\frac{dL_h}{dt} + n_2\frac{dI_h}{dt} + n_3\frac{dL_v}{dt} + n_4\frac{dI_v}{dt}$$

$$= n_1[M_1J_1I_vS_h - A_4L_h] + n_2[\theta L_h - A_3I_h] + n_3[M_1J_2I_hS_v - A_2L_v] + n_4[\omega L_v - A_1I_v]. \quad (11)$$

Now choosing

$$n_1 = \frac{\theta}{mu_hA_4A_3A_1^2A_2}, n_2 = \frac{1}{mu_hA_3A_1^2A_2}, n_3 = \frac{1}{\lambda_vJ_2}, n_4 = 1. \quad (12)$$

By equating the right hand side of the system of equation (1) to zero and representing the state variables in terms of I_v , we obtain

$$L_h = \frac{M_1J_1I_vS_h}{A_4}, I_h = \frac{M_1J_1\theta I_vS_h}{A_4A_3}, L_v = \frac{M_1^2J_1J_2\theta S_hS_vI_v}{A_4A_3A_2}. \quad (13)$$

Substituting equations (12) & (13) into equation (11) and simplifying yields $\frac{dF_L}{dt} \leq A_1(R_0^2 - 1)I_v$. Now, $\frac{dF_L}{dt} < 0$ provided $R_0 < 1$. On the other hand, $\frac{dF_L}{dt} = 0 \iff R_0 = 1$ or $I_v = 0$. Since $I_v \to 0$ as $t \to \infty$, then $t \to \infty$. Therefore the largest positively invariant set in

$$\left\{S_h^0, L_h^0, I_h^0, S_v^0, L_v^0, I_v^0\right\} = \left\{\frac{\lambda_h}{\mu_h}, 0, 0, \frac{\lambda_v}{A_1}, 0, 0\right\},$$

when $R_0 < 1$ is the singleton E_0. Hence by LaSalle's invariance principle [21], it follows that all trajectories starting in Ω approach E_0 as $t \to \infty$. That is, the DFE, E_0 is globally asymptotically stable in Ω if $R_0 < 1$, hence the proof.

3.4. Existence of endemic equilibrium points

By equating the right hand side of the malaria model of system in equation (1) to zero and solving simultaneously, we obtain the following

$$L_v^* = \frac{M_1kbqI_h^*\lambda_v}{(A_1+\omega)(M_1kbqI_h^* + N_hA_1)}, S_v^* = \frac{\lambda_vN_h}{M_1kbqI_h^* + N_hA_1},$$
$$L_h^* = \frac{(r+\delta+\mu_h)I_h^*}{\theta}, I_v^* = \frac{M_1wkbq\lambda_vI_h^*}{A_1(A_1+\omega)(M_1kbqI_h^* + N_hA_1)},$$
$$S_h^* = \frac{\lambda_h(M_1abqI_h^* + M_2N_h}{\mu_hN_hA_1R_0^2},$$

where $M_2 = (v + \sigma u_2)$. It follows that the endemic equilibrium is either given as $I_h^* = 0$ which corresponds to the DFE or in form of the polynomial

$$AI_h^{*2} + BI_h^* + C = 0, \quad (14)$$

where

$$A = M_1^2A_1N_hwk^2b^2q^2\mu_h\lambda_h + M_1^2A_1^2N_hk^2b^2q^2\mu_h\lambda_h + M_1^3wak^2b^3q^3\lambda_v\lambda_h + M_1M_2A_1^2N_h^2Kbq\mu_hw - M_1M_2N_h^2Kbq\mu_hR_0^2, \quad (15)$$

$$B = M_1^2A_1N_hawkb^2q^2\lambda_v\lambda_h + 2M_1A_1^3N_h^2kbq\mu_h\lambda_h + 2M_1A_1^2N_h^2wk^2bq\mu_h\lambda_h - M_2A_1^3N_h^3\mu_hwR_0^2 - A_1^4N_h^3\mu_hR_0^2 - M_1A_1^3N_h^2\lambda_hkbq\mu_hR_0^2 - M_1A_1^2N_h^2\lambda_hwkbq\mu_hR_0^2, \quad (16)$$

and

$$C = (A_1^4N_h^3\mu_h\lambda_h + A_1^3N_h^3\mu_hw)(1 - R_0^2). \quad (17)$$

Considering the quadratic equation (14), the possibility of multiple endemic equilibrium can be analysed whenever $R_0 < 1$. Note that the coefficients A and B and the constant term, C of the quadratic equation (14) as represented in equations (15) - (17) are positive whenever $R_0 < 1$, hence the following results:

Theorem 3 The malaria model has

1. One unique endemic equilibrium if $C < 0$ iff $R_0 > 1$.
2. One unique endemic equilibrium if $B < 0$ and $C = 0$ or $B^2 - 4AC = 0$.
3. Two unique endemic equilibrium if $B < 0$, $C > 0$ and $B^2 - 4AC > 0$.

3.5. Bifurcation analysis

The possibility of the existence of backward bifurcation, a phenomena that makes the control of any disease to be more difficult is investigated using the Centre Manifold theory as described by Castilo-Chavez and Song [22]. Let f_k be the k^{th} component of equation (1) with

$$a_1 = \frac{v}{2}D_{xx}f(0,0)w^2 = \frac{1}{2}\sum_{i,j,k=1}^{n} v_iw_jw_k\frac{\partial^2 f_i}{\partial x_j\partial x_k}(0,0), \quad (18)$$

$$b_1 = vD_{xa}f(0,0)w = \sum_{i,j,k=1}^{n} v_iw_j\frac{\partial^2 f_i}{\partial x_j\partial a}(0,0). \quad (19)$$

To proceed with the application of the Centre Manifold Theorem on the system in equation (1), we consider the following change of variables for convenience. Let

$$x_1 = S_h, x_2 = L_h, x_3 = I_h, x_4 = S_v, x_5 = L_v, x_6 = I_v,$$

so that $N_h = x_1 + x_2 + x_3$ and $N_v = x_4 + x_5 + x_6$. The vector representation of the system is given by

$$\begin{aligned}
\frac{dx_1}{dt} &= f_1 = \lambda_h + M_2I_h - \frac{M_1abqI_vS_h}{N_h} - \mu_hS_h,\\
\frac{dx_2}{dt} &= f_1 = \frac{(M_1abqI_vS_h}{N_h} - (\mu_h+\theta)L_h,\\
\frac{dx_3}{dt} &= f_1 = \theta L_h - (M_2+\delta+\mu_h)I_h,\\
\frac{dx_4}{dt} &= f_1 = \lambda_v - \frac{M_1kbqI_hS_v}{N_h} - (\tau u_3+\mu_v)S_v,\\
\frac{dx_5}{dt} &= f_1 = \frac{M_1kbqI_hS_v}{N_h} - (\omega+\tau u_3+\mu_v)L_v,\\
\frac{dx_6}{dt} &= f_1 = \omega L_v - (\tau u_3+\mu_v)I_v,
\end{aligned} \quad (20)$$

where M_1, M_2 and A_1 are as previously defined. Taking $N_h = \frac{\lambda_h}{\mu_h}$ and choosing 'a' as the bifurcation parameter with $a = a^*$, from equation (5) at $R_0 = 1$ we obtain the bifurcation parameter

$$a^* = \frac{A_1^2\lambda_h(\mu_h+\theta)(A_1+\omega)(M_2+\delta+\mu_h)}{M_1^2b^2kq^2w\theta\mu_h\lambda_v}. \tag{21}$$

Linearizing equation (19) at the DFE point, and considering equation (20) we obtain the Jacobian matrix given as

$$J_{(E_0,a^*)} = \begin{pmatrix} -\mu_h & 0 & M_2 & 0 & 0 & -k_1 \\ 0 & -A_4 & 0 & 0 & 0 & k_1 \\ 0 & \theta & -A_3 & 0 & 0 & 0 \\ 0 & 0 & -k_2 & -A_1 & 0 & 0 \\ 0 & 0 & k_2 & 0 & -A_2 & 0 \\ 0 & 0 & 0 & 0 & \omega & -A_1 \end{pmatrix}, \tag{22}$$

where $k_1 = \frac{M_1a_*bq\lambda_h}{\mu_hN_h}, k_2 = \frac{M_1kbq\lambda_v}{A_1N_h}$.

One of the eigenvalues of the matrix (22) is a simple zero and all others have negative real parts which allows for the application of the Centre Manifold theorem. And so to obtain the right eigenvector, w from the matrix (22), we have that

$$\begin{aligned} -\mu_hw_1 + M_2w_3 - k_1w_6 &= 0, \\ -A_4w_2 + k_1w_6 &= 0, \\ \theta w_3 + A_3w_3 &= 0, \\ -k_2w_3 - A_1w_4 &= 0, \\ k_2w_3 - A_2w_5 &= 0, \\ \omega w_5 - A_1w_6 &= 0. \end{aligned} \tag{23}$$

Solving the equation (23), we have the following:

$$\begin{aligned} w_1 &= \left(\frac{M_2\theta}{k_2\mu_h} - \frac{k_1\omega k_2\theta}{\mu_hA_1A_2A_3}\right)w_2 \\ w_2 &= \left(\frac{k_1\omega k_2\theta}{A_1A_2A_3A_4}\right)w_2 \\ w_3 &= \frac{\theta}{A_3}w_2 \\ w_4 &= -\frac{k_2\theta}{A_1A_3}w_2 \\ w_5 &= -\frac{k_2\theta}{A_2A_3}w_2 \\ w_6 &= -\frac{\omega k_2\theta}{A_1A_2A_3}w_2. \end{aligned} \tag{24}$$

Similarly, the matrix for the left eigenvector v which corresponds to the zero eigenvalue, $vD_xf(0,0) = 0$ when $R_0 = 1$ is given as:

$$J_{E_0,a^*} = \begin{pmatrix} -\mu_h & 0 & 0 & 0 & 0 & 0 \\ 0 & -A_4 & \theta & 0 & 0 & 0 \\ M_2 & 0 & -A_3 & -k_2 & k_2 & 0 \\ 0 & 0 & 0 & -A_1 & 0 & 0 \\ 0 & 0 & 0 & 0 & -A_2 & \omega \\ -k_1 & k_1 & 0 & 0 & 0 & -A_1 \end{pmatrix}. \tag{25}$$

From equation (25), we obtain

$$\begin{aligned} -\mu_hv_1 &= 0, \\ A_4v_2 + \theta v_3 &= 0, \\ M_2v_1 + A_3v_3 - k_2v_4 + k_2v_5 &= 0, \\ -A_1v_4 &= 0, \\ k_2v_5 + \omega v_6 &= 0, \\ -k_1v_1 + k_2v_2 - A_1v_6 &= 0. \end{aligned} \tag{26}$$

Solving equation (26) yields the left eigenvector, v as

$$\begin{aligned} v_1 &= 0, v_4 = 0, \\ v_2 &= \left(\frac{k_1\omega k_2\theta}{c}\right)v_2, \\ v_3 &= \frac{\omega k_1k_2}{A_1A_2A_3}v_2, \\ v_5 &= \frac{\omega k_1}{A_2A_1}v_2, \\ v_6 &= \frac{k_1}{A_1}v_2. \end{aligned} \tag{27}$$

To examine the sign of a_0 in equation (27), the non-zero second partial derivatives obtained from equation (19) are as follows:

$$\begin{aligned} \frac{\partial^2f_2}{\partial x_1\partial x_6} &= \frac{\partial^2f_2}{\partial x_6\partial x_1} = \frac{M_1abq}{N_h}, \\ \frac{\partial^2f_5}{\partial x_3\partial x_4} &= \frac{\partial^2f_5}{\partial x_4\partial x_3} = \frac{M_1kbq}{N_h}. \end{aligned}$$

Now, from equation (17), for $v_k \neq 0$ we obtain

$$\begin{aligned} a_0 &= v_2w_1w_6\frac{M_1abq\mu_h}{\lambda_h} + v_5w_3w_4\frac{M_1kbq\mu_h}{\lambda_h} \\ &= v_2w_2^2\frac{M_1kbq\omega\theta^2}{A_1^2A_2^2A_3^2\lambda_h}[\chi_1 - \chi_2], \end{aligned} \tag{28}$$

where $\chi_1 = A_1A_2A_3M_2a, \chi_2 = k_1k_2(\omega a + k\mu_hA_2)$.

It therefore follows from equation (28) that $a_0 > 0$ provided $\chi_1 > \chi_1$ and $a_0 < 0$ for $\chi_1 < \chi_1$.

Similarly for b_0, the required non-zero second partial derivatives at the DFE based on equation (18) are

$$\frac{\partial^2f_2}{\partial x_a\partial x_6} = \frac{\partial^2f_2}{\partial x_6\partial x_a} = \frac{M_1bqx_1}{N_h} = M_1bq.$$

And so, $b_0 = 2v_2w_6M_1bq = \frac{M_1bq\theta\omega k_2}{A_1A_2A_3} > 0$.

Since the coefficient of b_0 is always positive, therefore we conclude with the following results as established in (Castillo Chavez & Song [22]):

Theorem 4

The malaria model in equation (1) exhibits the phenomenon of backward bifurcation at $R_0 = 1$ whenever $a_0 > 0$ and $b_0 > 0$. On the other hand, whenever $a_0 < 0$ and $b_0 > 0$, then the model in equation (1) exhibits a forward bifurcation at $R_0 = 1$.

3.6. Sensitivity analysis

Applying the method of normalized forward sensitivity index (see Ref. [23]) on the basic reproduction number, the sensitivity indices of the parameters in the expression of equation (5) were estimated as represented in Table 1.

The positive indices on Table 1 indicate that an increase in any of such parameter value will result in an increase of the value of R_0 and vice versa while the negative indices imply that increase in such parameter values will result to a decrease in the value of R_0 and vice versa. The parameters with the most impact on R_0 are the mosquito biting rate and the parameter that controls livestock availability. Followed by mosquito mortality rate and the rate at which the mosquitoes are killed due to ivermectin consumption during bloodmeal. These parameters project the importance of vector reduction and reducing the bites on human which both the livestock availability and treating them with ivermectin takes care off. Thus handling one of the gaps from the conventional control methods.

4. Optimal control analysis

To have an idea on the optimal level of efforts that would be required to achieve maximum success for any intervention programme that is aimed at controlling malaria disease at minimal cost, an optimal control analysis is carried out. To begin with, we modified the system of equations (1) by considering time dependent controls $u_1(t)$ (use of mosquito treated bed nets), $u_2(t)$ (the treatment of infectious humans) and $u_3(t)$ (the use of ivermectin drug).The goal is to minimize the number of infected humans so as to curtail the spread of the disease through the given controls of the study while keeping the costs of these control as low as possible based on a defined objective functional that includes relative costs associated with each control. The modified model is as follows:

$$\begin{aligned}
\frac{dS_h}{dt} &= \lambda_h + (v + \sigma u_2(t))I_h - \frac{(1-u_1(t)abqI_vS_h}{N_h} - \mu_h S_h \\
\frac{dL_h}{dt} &= \frac{(1-u_1(t)abqI_vS_h}{N_h} - (\mu_h + \theta)L_h \\
\frac{dI_h}{dt} &= \theta L_h - (v + \sigma u_2(t) + \delta + \mu_h)I_h \\
\frac{dS_v}{dt} &= \lambda_v - \frac{(1-u_1(t)kbqI_hS_v}{N_h} - (\tau u_3(t) + \mu_v)S_v \\
\frac{dL_v}{dt} &= \frac{(1-u_1(t)kbqI_hS_v}{N_h} - (\omega + \tau u_3(t) + \mu_v)L_v \\
\frac{dI_v}{dt} &= \omega L_v - (\tau u_3(t) + \mu_v)I_v.
\end{aligned} \tag{29}$$

Given the time dependent control functions, $u_i(t)$ for $i = 1, 2, 3, ...$ which are bounded, Lebesque integrable functions. $u_1(t)$ and $u_3(t)$ model the effort geared towards bringing down the mosquito population to zero if possible by killing the adult mosquitoes seeking for blood meal while $u_2(t)$ models the efforts required for the treatment of infectious humans with the WHO recommended antimalarial drugs. Here, σ and τ each represents the efficacy of the antimalarial drug and the effect of ivermectin drug respectively, with the assumption that $0 \le u_1(t) \le 1$, $0 \le u_2(t) \le 1$ and $0 \le u_3(t) \le 1$. Consider the objective functional J defined over a feasible set of controls and given as

$$J(u_1, u_2, u_3) = \int_0^{t_f} [PI_h + Qu_1^2 + Ru_2^2 + Su_3^2]dt, \tag{30}$$

where P, Q, R, S are the desired positive weights on the benefits of the disease control. PI_h is the cost (social cost) associated with malaria infection and Qu_1^2, Ru_2^2, Su_3^2 each represents the relative cost weights of bed net usage, infectious human treatment and the ivermectin administration respectively, while t_f is the expected final time for implementing the controls. As regards the epidemiological cost of controlling diseases, the choice of a quadratic cost on the controls is in line with what is applicable in other literature (see Refs. [16, 28–31]) and this is based on the assumption that no linear relationships exist between the coverage of these control measures and their corresponding costs. Here, we seek an optimal control $u^* = (u_i^*), i = 1, 2, 3$, which minimizes the objective function, J such that

$$J(u^*) = \min J(u_1, u_2, u_3) | u_i \in W,$$

where

$$W = \{u_i(t) : 0 \le u_i(t) \le 1,$$

is Lebesque measurable with $0 \le u_i(t) \le 1$, $i = 1, 2, 3$ for $t \in [0, t_f]\}$ is the control set. In optimization problems, there exists a principle that provides suitable conditions with differential equations as constraints. It is known as the Pontryagin's Maximum Principle [14] which provides the necessary conditions that an optimal control must satisfy and this principle works in such a way that equations (29) and (30) are transformed into a problem of point-wise minimization of the Hamiltonian (H_C) with respect to and The Hamiltonian formed from the objective function in equation (30) subject to the model equation (29) is given as:

$$\begin{aligned}
H_C = {} & [PI_h + Qu_1^2 + Ru_2^2 + Su_3^2]dt \\
& + \lambda_{Sh}\left[\lambda_h + (v + \sigma u_2(t))I_h - \frac{(1-u_1(t)abqI_vS_h}{N_h} - \mu_h S_h\right] \\
& + \lambda_{Lh}\left[\frac{(1-u_1(t)abqI_vS_h}{N_h} - (\mu_h + \theta)L_h\right] \\
& + \lambda_{Ih}\left[\theta L_h - (v + \sigma u_2(t) + \delta + \mu_h)I_h\right] \\
& + \lambda_{Sv}\left[\lambda_v - \frac{(1-u_1(t)kbqI_hS_v}{N_h} - (\tau u_3(t) + \mu_v)S_v\right] \\
& + \lambda_{Lv}\left[\frac{(1-u_1(t)kbqI_hS_v}{N_h} - (\omega + \tau u_3(t) + \mu_v)L_v\right] \\
& + \lambda_{Iv}\left[\omega L_v - (\tau u_3(t) + \mu_v)I_v\right].
\end{aligned} \tag{31}$$

where λ_{Sh}, λ_{Lh}, λ_{Ih}, λ_{Sv}, λ_{Lv} and λ_{Iv} are the adjoint or co-state variables. The proof of the existence of an optimal control given in Ref. [32] is valid here. Implying that the control set W is closed and convex and the convexity of the integrand of the objective functional in equation (30) with respect to W. In addition to these, the a priori boundedness of the state solutions,

Table 1: Descriptions, values, references and sensitivity indices of the parameters of R_0.

Parameter	Description	Parameter Value	Reference	Sensitivity Index
q	Proportion of vector bloodmeals on humans	0.485	[9]	+1
b	Mosquito Biting rate	0.5	[19]	+1
τ	Effect of ivermectin	0.02-0.5	Estimated	-0.660256
μ_v	Mosquito natural death	0.05	[9]	-0.660256
k	Probability of mosquito being infected by an infectious human	0.09	[19]	+0.5
a	Probability of human being infected by an infectious mosquito	0.3	[19]	+0.5
λ_h	Human birth rate	0.00011	[19]	-0.5
λ_v	Mosquito birth rate	0.071	[19]	+0.5
μ_h	Human natural death rate	0.0000548	[24]	+0.4998879
σ	Treatment efficacy	0.01-0.7	[25]	-0.478810
ω	Mosquito Progression rate from Latent to Infectious state	0.056	[26]	+0.3205128
δ	Disease induced death rate	0.0003454	[27]	-0.0008559
θ	Human Progression rate from Latent to Infectious state	0.058824	[24]	+0.0004654

and the Lipschitz property of the state system with respect to the state variables S_h^*, L_h^*, I_h^*, S_v^*, L_v^*, I_v^* also satisfies the necessary conditions for the existence of an optimal control. To obtain the optimal solution, following the Pontryagin's Maximum Principle with the existence result for the optimal control from Ref. [32], we obtain the following theorem.

Theorem 5 Let (u_1^*, u_2^*, u_3^*) be an optimal control and be the optimal state solutions of the corresponding state system in equation (29) which minimizes the objective functional, $J(u_1, u_2, u_3)$ over W. Then there exists co-state variables λ_{Sh}^*, λ_{Lh}^*, λ_{Ih}^*, λ_{Sv}^*, λ_{Lv}^* and λ_{Iv}^* that satisfy the following system of equations:

$$\begin{aligned}
\frac{\lambda_{Sh}}{dt} &= (\lambda_{Sh} - \lambda_{Lh})\left[\frac{(1-u_1(t))abqI_v}{N_h}\left(1 - \frac{S_h}{N_h}\right)\right] \\
&\quad + \mu_h\lambda_{Sh} - \frac{(1-u_1(t))kbqI_hS_v}{N_h^2}(\lambda_{Sv} - \lambda_{Lv}), \\
\frac{\lambda_{Lh}}{dt} &= (\lambda_{Lh} - \lambda_{Sh})\left[\frac{(1-u_1(t))abqI_vS_h}{N_h^2}\right] - \theta\lambda_{Ih} \\
&\quad + (\mu_h + \theta)\lambda_{Lh} - \frac{(1-u_1(t))kbqI_hS_v}{N_h^2}(\lambda_{Sv} - \lambda_{Lv}), \\
\frac{\lambda_{Ih}}{dt} &= -P - (\lambda_{Sh} - \lambda_{Lh})\left[\frac{(1-u_1(t))abqI_vS_h}{N_h^2}\right] \\
&\quad - (r + \sigma u_2(t))\lambda_{Sh} + (r + \sigma u_2(t) + \delta + \mu_h)\lambda_{Ih} \\
&\quad + (\lambda_{Sh} - \lambda_{Lh})\left[\frac{(1-u_1(t))kbqS_v}{N_h}\left(1 - \frac{I_h}{N_h}\right)\right], \\
\frac{\lambda_{Sv}}{dt} &= (\lambda_{Sv} - \lambda_{Lv})\left[\frac{(1-u_1(t))kbqI_h}{N_h}\right] + (\tau u_3(t) + \mu_v)\lambda_{Sv}, \\
\frac{\lambda_{Lv}}{dt} &= (\tau u_3(t) + \omega + \mu_v)\lambda_{Lv} - \omega\lambda_{Iv}, \\
\frac{\lambda_{Iv}}{dt} &= (\tau u_3(t) + \mu_v)\lambda_{Iv} + (\lambda_{Sh} - \lambda_{Lh})\left[\frac{(1-u_1(t))abqI_vS_h}{N_h}\right].
\end{aligned} \tag{32}$$

and transversality conditions $\lambda_{Sh}(t_f) = \lambda_{Lh}(t_f) = \lambda_{Ih}(t_f) = \lambda_{Sv}(t_f) = \lambda_{Lv}(t_f) = \lambda_{Iv}(t_f) = 0$, whereby the controls u_1^*, u_2^*, u_3^* satisfy the optimality conditions

$$\begin{aligned}
u_1^* &= \max\left\{0, \min\left(1, \frac{abqI_v^*(\lambda_{Lh} - \lambda_{Sh})S_h^* + kbqI_h^*(\lambda_{Lv} - \lambda_{Sv})S_v^*}{2QN_h}\right)\right\}, \\
u_2^* &= \max\left\{0, \min\left(1, \frac{\sigma(\lambda_{Ih} - \lambda_{Sh})I_h^*}{2R}\right)\right\}, \\
u_3^* &= \max\left\{0, \min\left(1, \frac{\tau(S_v^*\lambda_{Sv} + L_v^*\lambda_{Lv} + I_v^*\lambda_{Iv})}{2S}\right)\right\}.
\end{aligned} \tag{33}$$

Proof Differentiating the Hamiltonian function with respect to each state variable and evaluating at the optimal control, we obtain the differential equations that governs the adjoint variable with the adjoint system as

$$\begin{aligned}
\frac{\lambda_{Sh}}{dt} &= -\frac{\partial H_C}{\partial S_h} = (\lambda_{Sh} - \lambda_{Lh})\left[\frac{(1-u_1(t))abqI_v}{N_h}\left(1 - \frac{S_h}{N_h}\right)\right], \\
&\quad + \mu_h\lambda_{Sh} - \frac{(1-u_1(t))kbqI_hS_v}{N_h^2}(\lambda_{Sv} - \lambda_{Lv}), \\
\frac{\lambda_{Lh}}{dt} &= -\frac{\partial H_C}{\partial S_h} = (\lambda_{Lh} - \lambda_{Sh})\left[\frac{(1-u_1(t))abqI_vS_h}{N_h^2}\right] - \theta\lambda_{Ih} \\
&\quad + (\mu_h + \theta)\lambda_{Lh} - \frac{(1-u_1(t))kbqI_hS_v}{N_h^2}(\lambda_{Sv} - \lambda_{Lv}), \\
\frac{\lambda_{Ih}}{dt} &= -\frac{\partial H_C}{\partial S_h} = -P - (\lambda_{Sh} - \lambda_{Lh})\left[\frac{(1-u_1(t))abqI_vS_h}{N_h^2}\right] \\
&\quad - (r + \sigma u_2(t))\lambda_{Sh} + (r + \sigma u_2(t) + \delta + \mu_h)\lambda_{Ih} \\
&\quad + (\lambda_{Sh} - \lambda_{Lh})\left[\frac{(1-u_1(t))kbqS_v}{N_h}\left(1 - \frac{I_h}{N_h}\right)\right], \\
\frac{\lambda_{Sv}}{dt} &= -\frac{\partial H_C}{\partial S_h} = (\lambda_{Sv} - \lambda_{Lv})\left[\frac{(1-u_1(t))kbqI_h}{N_h}\right] + (\tau u_3(t) + \mu_v)\lambda_{Sv}, \\
\frac{\lambda_{Lv}}{dt} &= -\frac{\partial H_C}{\partial S_h} = (\tau u_3(t) + \omega + \mu_v)\lambda_{Lv} - \omega\lambda_{Iv} \\
\frac{\lambda_{Iv}}{dt} &= -\frac{\partial H_C}{\partial S_h} = (\lambda_{Sh} - \lambda_{Lh})\left[\frac{(1-u_1(t))abqI_vS_h}{N_h}\right] \\
&\quad + (\tau u_3(t) + \mu_v)\lambda_{Iv},
\end{aligned} \tag{34}$$

with transversality conditions

$$\lambda_{Sh}(t_f) = \lambda_{Lh}(t_f) = \lambda_{Ih}(t_f) = \lambda_{Sv}(t_f) = \lambda_{Lv}(t_f) = \lambda_{Iv}(t_f) = 0. \tag{35}$$

By solving the equations

$$\frac{\partial H_C}{\partial u_1} = 0, \ \frac{\partial H_C}{\partial u_2} = 0, \ \frac{\partial H_C}{\partial u_3} = 0,$$

on the interior of the control sets, that is $0 \leq u_1(t) \leq 1$, $0 \leq u_2(t) \leq 1$ and $0 \leq u_3(t) \leq 1$, we have

$$\begin{aligned}
\frac{\partial H_C}{\partial u_1} &= 2Qu_1^* + \frac{abqI_v^*(\lambda_{Sh} - \lambda_{Lh})S_h^*}{N_h} + \frac{kbqI_h^*(\lambda_{Sv} - \lambda_{Lv})S_v^*}{N_h} = 0,\\
\frac{\partial H_C}{\partial u_2} &= 2Ru_2^* + \sigma I_h^*(\lambda_{Sh} - \lambda_{Lh}) = 0,\\
\frac{\partial H_C}{\partial u_3} &= 2Su_3^* - \tau(S_h^*\lambda_{Sh} + L_h^*\lambda_{Lh} + I_h^*\lambda_{Ih}) = 0.
\end{aligned}$$

It then follows that

$$\begin{aligned}
u_1^* &= \frac{abqI_v^*(\lambda_{Lh} - \lambda_{Sh})S_h^* + kbqI_h^*(\lambda_{Lv} - \lambda_{Sv})S_v^*}{2QN_h}\\
u_2^* &= \frac{\sigma(\lambda_{Lh} - \lambda_{Sh})I_h^*}{2R}\\
u_3^* &= \frac{\tau(S_h^*\lambda_{Sh} + L_h^*\lambda_{Lh} + I_h^*\lambda_{Ih})}{2S},
\end{aligned}$$

with the optimality conditions given as

$$\begin{aligned}
u_1^* &= \max\{0\,, \\
&\quad \min\left(1, \frac{abqI_v^*(\lambda_{Lh} - \lambda_{Sh})S_h^* + kbqI_h^*(\lambda_{Lv} - \lambda_{Sv})S_v^*}{2QN_h}\right)\Bigg\},\\
u_2^* &= \max\left\{0, \min\left(1, \frac{\sigma(\lambda_{Ih} - \lambda_{Sh})I_h^*}{2R}\right)\right\},\\
u_3^* &= \max\left\{0, \min\left(1, \frac{\tau(S_v^*\lambda_{Sv} + L_v^*\lambda_{Lv} + I_v^*\lambda_{Iv})}{2S}\right)\right\}.
\end{aligned}$$

5. Numerical results and discussion

Our focus in this section is basically to obtain an optimal result numerically for the malaria model for some combinations of the control strategies under consideration. This we achieved by solving the optimality system consisting of six ODE's each for the state in equation (29) and adjoint equations (32) using an iterative scheme adopted from Ref. [33] and also applied in several other studies such as Refs. [15, 30, 34]. The process begins by solving the state equations (26) forward in time over a simulated time using the fourth order Runge-Kutta scheme with an initial guess for the controls. Next is to solve the adjoint equations backward in time applying the backward fourth order Runge-Kutta scheme which uses the current iterations solution of the state equations. The choice of this scheme is because of the transversality conditions. The controls are then updated using a convex combination of the current and previous control by entering the new values of the state and adjoint equations into the characterization of the optimal control. This procedure is repeated until the values of the unknowns are sufficiently close to the corresponding ones at the previous iteration (verifying convergence) after which the iteration stops and output the current values as the required solutions.

Considering the three malaria control tools, we formed four different strategies (S1 - S4) based on a combination of any two and all three tools. These are Strategy S1 which is a combination of the use of treated bed net and treatment of infective individuals (i.e. $u_1 \neq 0$ and $u_2 \neq 0$, with $u_3 = 0$), Strategy S2 which combines the use of treated bed net and ivermectin usage (i.e. $u_1 \neq 0$ and $u_3 \neq 0$, with $u_2 = 0$), Strategy S3 consisting of the treatment of infective individuals and ivermectin usage (i.e. $u_2 \neq 0$ and $u_3 \neq 0$, with $u_1 = 0$) and Strategy S4, a combination of all three controls (i.e $u_1 \neq 0$, $u_2 \neq 0$ and $u_3 \neq 0$).

Numerically, we explored the optimal control of malaria based on the impact of each of the strategies S1 - S4 on both the human and mosquito populations using the following initial conditions $S_h(0) = 700$, $L_h(0) = 100$, $I_h(0) = 0$, $S_v(0) = 5000$, $L_v(0) = 300$, $I_v(0) = 30$ and the parameter values of Table 1 with which the basic reproduction number obtained with controls at zero level is $R_0 = 5.3362$. Since the cost associated with u_2 includes the cost of antimalarial drugs, medical examinations and hospitalization [30], it is assumed that the weight constant R associated with u_2 is greater than Q and S each associated with controls u_1 and u_3. And so the values chosen for these weight constants are $P = 0.8$, $Q = 0.25$, $R = 0.6$ and $S = 0.1$.

*Strategy **S1**: Optimal use of treated bed net (u_1) and treatment of infectious human (u_2)*

In this scenario, by setting the control on the use of ivermectin to zero, we applied the control on the use of treated bed nets (u_1) and the treatment of infectious individuals (u_1) to optimize the objective function, J while the control on the use of ivermectin is set to zero. The results on Figure 1 a and b shows very drastic reduction in the infectious human population as compared to that of the infectious mosquito population which makes it not so effective for malaria elimination. In Figure 1c, the control profile for the optimal use of ITNs (u_1) is shown to be at upper bound for 61 days followed by a drastic drop to its lower bound at the final time interval. Similarly, the optimal treatment of infective human (u_2) is shown to maintain an upper bound for 54 days after which it gradually declines to 64% at day $t = 78$ but then followed an increasing trend slightly for about 27 days before dropping gradually to its lower bound at the final time.

*Strategy **S2**: optimal use of treated bed net (u_1) and Ivermectin usage (u_3)*

The control on the use of treated bed nets (u_1) and the administration of ivermectin to livestock and human (u_1) are used to optimize the objective function, J while the control on the treatment of infective individuals is set to zero. The result on Figure 2b shows that the strategy has very strong effect on the mosquito population with the potential of bringing it to zero

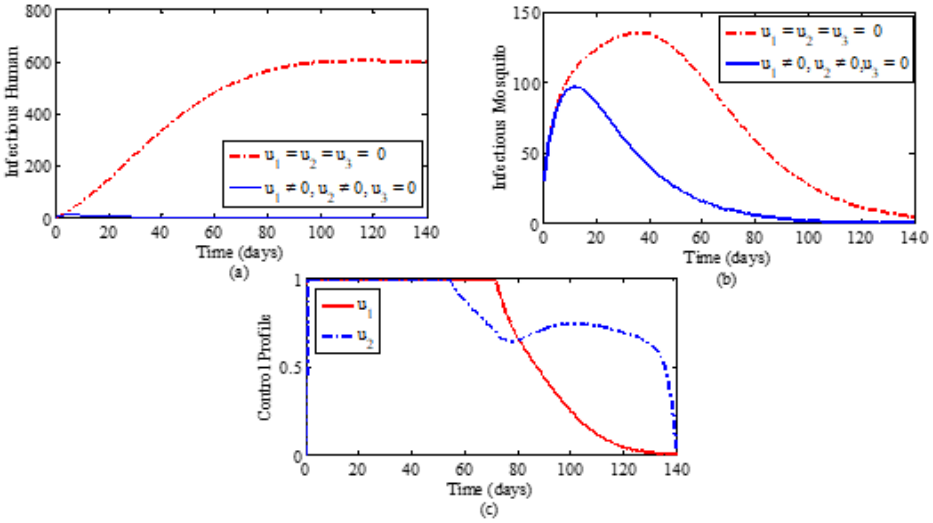

Figure 1: The impact of the optimal use of treated bed net (u_1) and treatment of infectious individuals (u_2) on (a) infective human and (b) infective mosquito, with the corresponding control profile (c).

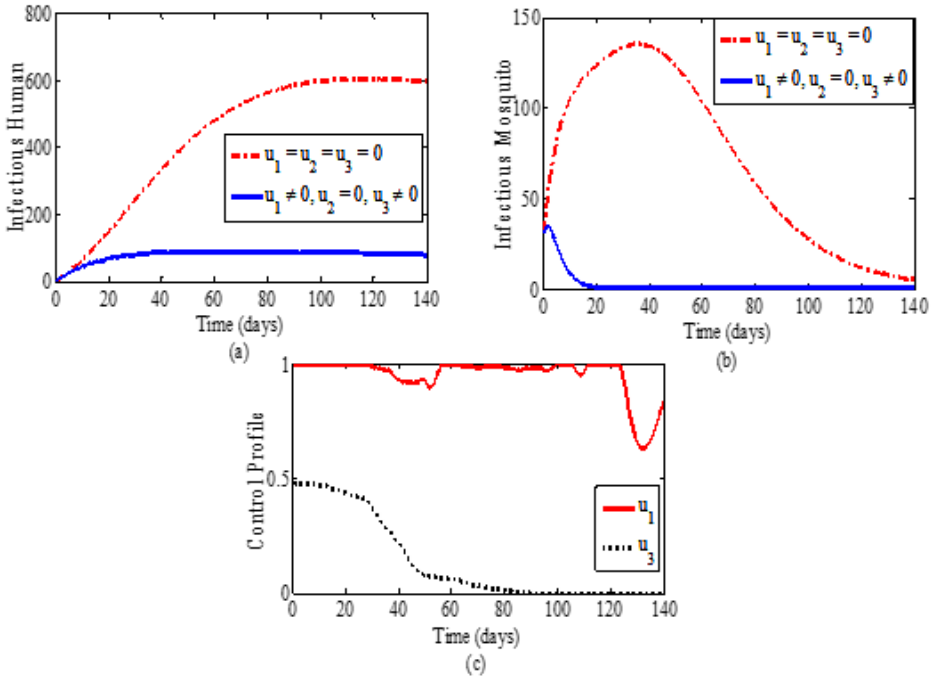

Figure 2: The impact of the optimal use of treated bed net (u_1) and ivermectin (u_3) on (a) infective human and (b) infective mosquito, with the control profile (c).

level. As for the infectious human population (Figure 2a), although there is a huge drop in the total infectious population with this strategy as compared to the case of zero control, nevertheless the population remained almost at an equilibrium even to the final time and so not feasible for the disease elimination [17]. The control profiles of Figure 2c shows that a maximum coverage (100%) of the optimal use of treated bed net for protection (u_1) is maintained for 27 days then dropped gradually to about 90% at time $t = 52$ day after which it continued on the average with 100% coverage to time $t = 123$ day. This was followed by a drastic decline in the control effort to 63% within a period of 9 days and then rose gradually to a coverage of 84% at the final time of the intervention. On the other hand, for the optimal administration of ivermectin drug (u_3) as a means of reducing the mosquito population through bite of humans having the drug concentration in the blood, it started with a 48% coverage and maintained a slow decline to the lower bound after 133 days.

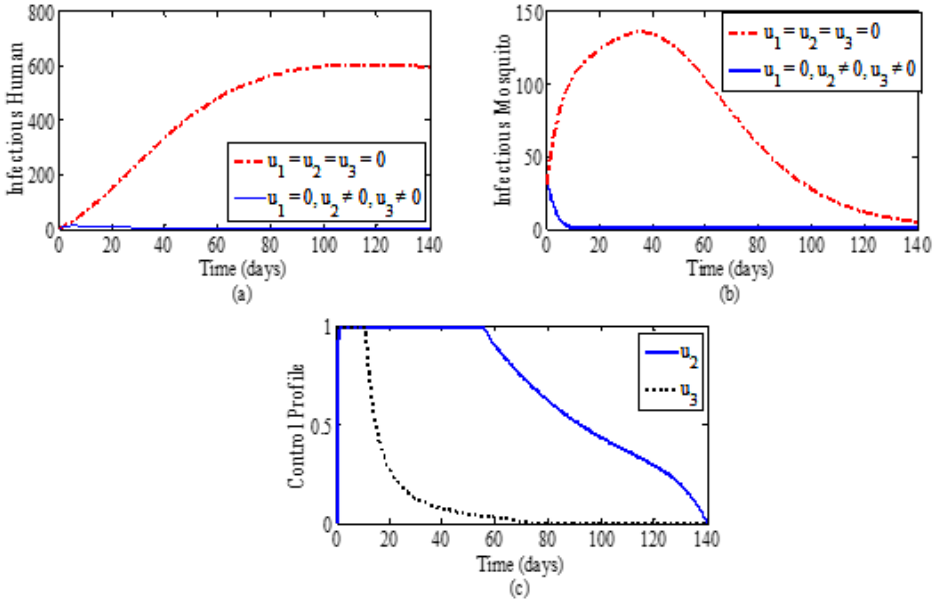

Figure 3: The optimal treatment of (a) infective individuals (u_2) and ivermectin usage (u_3) on infective human and (b) infective mosquito with the control profile (c).

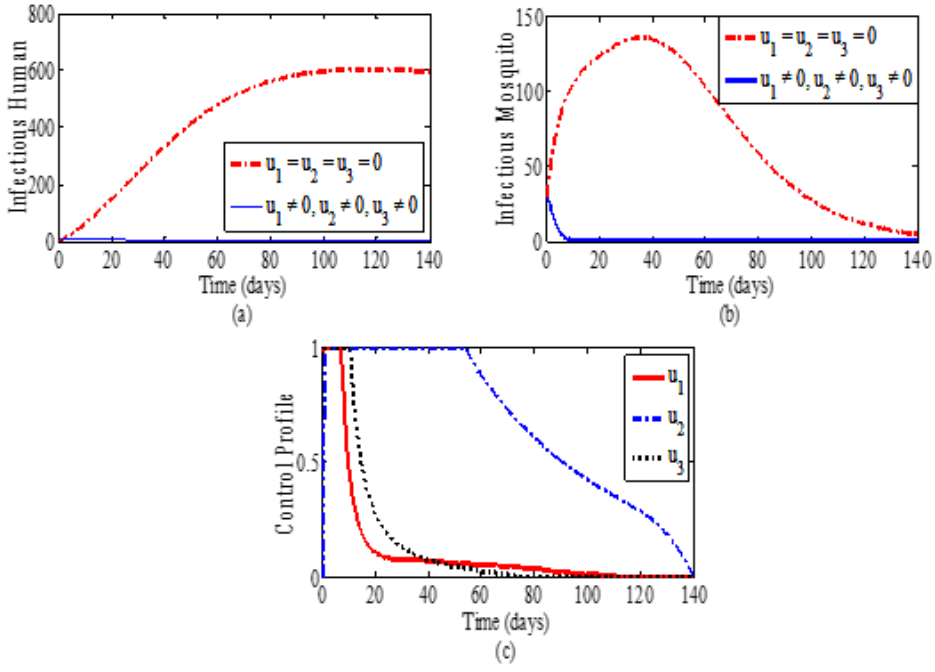

Figure 4: The impact of the optimal use of treated bed nets (u_1), treatment of infective individuals (u_2) and ivermectin usage (u_3) on (a) infective iuman and (b) infective mosquito with the control profile (c).

*Strategy **S3**: optimal treatment of infective individuals (u_2) and Ivermectin usage (u_3)*

In this scenario, the control on the treatment of infective humans (u_2) and the administration of ivermectin (u_3) were used to optimise the objective functional, J while the control on ITNs is set to zero. A very interesting result is obtained with this strategy as compared to those of strategies **S1** and **S2** given that its effectiveness is strongly seen on both the infective human and mosquito populations as shown in Figures 3a and b where both populations dropped drastically near zero level within a short period of time. Furthermore, in Figure 3c the control profile for the treatment of infectious humans (u_2) shows 100% coverage for 55 days after which a gradual decrease is noticed to its lower bound at the end of the intervention, while for iver-

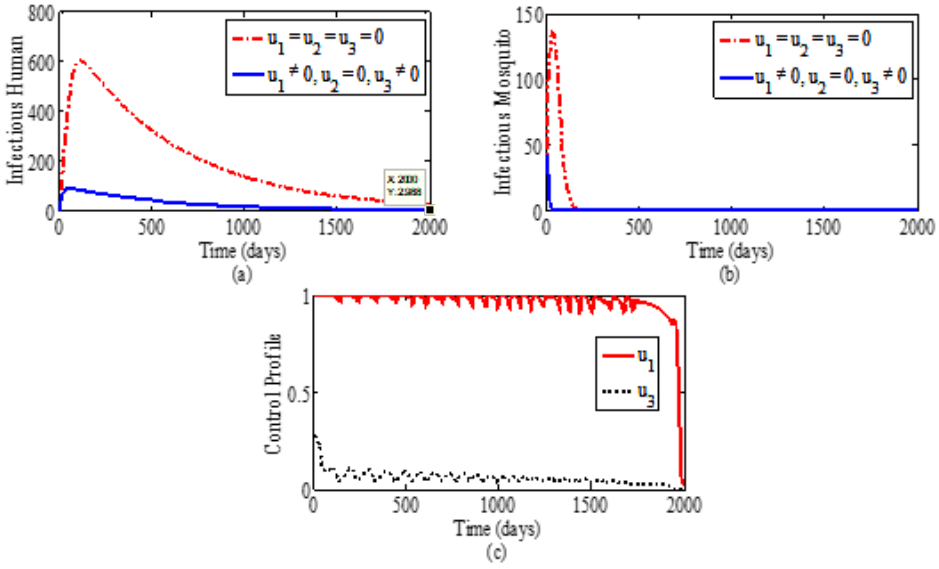

Figure 5: Simulations for strategy S2 with t = 2000 as final implementation time.

mectin administration (u_3), the effort was at upper bound for just 11 days before declining gradually to its lower bound.

*Strategy **S4**: the optimal use of treated bed nets (u_1), treatment of infective individuals (u_2) and Ivermectin usage (u_3)*

With this scenario, all three controls ITNs (u_1), treatment of infective individuals (u_2) and ivermectin usage (u_3) are used to optimize the objective function J. Like the result of strategy **S3**, this strategy has very significant effect on both the infective human and mosquito populations. This strategy shows an optimal use of ITNs (u_1) at maximum coverage for 6 days followed by a drastic drop to day 16 which continues gradually to its lower bound at the final time. Similarly, the control on ivermectin administration (u_3) had a coverage of 100% within the first 10 days of the intervention followed by a drastic decline but not as much as that of control profile after which a very slow decline is maintained to its lower bound at day 134. As for an optimal treatment of infectious humans (u_2), a maximum coverage (100%) is maintained for the first 54 days after which a gradual decrease is noticed till the end of the intervention.

*5.1. A comparison of the control strategies (**S1 - S4**)*

In Table 2, a clear picture on the effectiveness of each of the four control strategies on both the human and mosquito populations based on the level of decline (in percent) of each of the infectious mosquito and infectious human populations projected at 40 days into an intervention is presented. The purpose of this is for easy comparison among the four strategies considered in this study to aid a more accurate recommendation on the best option to be considered for an intervention that would yield desired results within a short time frame given limited available resources and time. The decline is obtained based on the difference between each population with no control and the population with each strategy at that set time using the population with no control at that set time as the baseline.

Both Figures 1 and 2 and Table 2 show a kind of biasedness on the effects of strategies S1 and S2. While the effect of strategy S1 is strong on the infectious human population that of strategy S2 is tilted towards the mosquito population. On the contrary, the effectiveness of strategies S3 and S4 are shown to distribute fairly across both the infectious human and mosquito populations (see Figures 3 and 4, Table 2) as required for successful intervention with the target of elimination. In terms of the level of decline of the populations with each strategy, we have the following: Strategy **S4** ranks first position with the highest decline of the infectious individuals having an average decline of 99.75%. The next is strategy **S3** with an average decline rate of 99.73% while strategy **S2** takes the third position with an average decline rate of 87.13%. The least performed strategy in terms of average decline of the infectious population with time is strategy **S1** with 84.66%. Nonetheless, with strategy **S2**, it would require over two thousand days (> 2000 days) (Figure 5) to bring down the infectious human population to a level obtained just in 98 days with strategy **S1** among the infectious mosquito population. As a result, strategy S1 is more feasible and more promising in the long run than strategy **S2**. It is seen that all the strategies (**S2**, **S3** and **S4**) with ivermectin as a control had the highest decline rate and this control tool basically work on the vector reduction through additional vector mortality with cattle availability thus corresponding to the outcome of the sensitivity analysis for mosquito biting rate and the proportion of blood meal on humans due to ivermectin treated cattle availability. Now, with respect to the human population, those strategies (**S1** and **S4**) where the use of ITN to prevent disease transmission and the treatment of infective humans to reduce transmission from humans to mosquitoes are included, the highest decline of the infective human population is recorded and this is in line with the impact of the mosquito biting rate and treatment efficacy parameters on the basic reproduction number obtained from the sensitivity result.

Table 2: Percentage decline in the infectious human and infectious mosquito populations at day 40 of intervention implementation for each strategy.

Infectious Population	Control Strategies (**S1 - S4**)			
	Strategy **S1**	Strategy **S2**	Strategy **S3**	Strategy **S4**
Human	99.51%	74.26%	99.47%	99.51%
Mosquito	68.81%	99.99%	99.99%	99.99%

6. Conclusion

In this study, we formulated a mathematical model comprising of a system of ordinary differential equations with control tools for malaria transmission and control. The disease free equilibrium was found to be locally and globally asymptotically stable. The endemic equilibrium of the model was also found to be locally asymptotically stable and the possibility of the model exhibits a phenomenon known as bifurcation was explored based on the Centre Manifold theory approach. To ascertain the impact of the model's parameters to malaria incidence through a threshold parameter called the basic reproduction number, a sensitivity analysis was carried out based on the normalized forward sensitivity index method. It was found to be most sensitive to the mosquito biting rate and the proportion of bloodmeal on human with cattle availability with positive index. The implication of such is that reducing the exposure of humans to the mosquito bites by increasing the use of ITNs and also decreasing the proportion of bloodmeal on human host through increasing the availability of cattle, especially in areas where the zoophagic vectors are predominant by any percent has the potential of bringing down malaria transmission by an equal percent and such knowledge is very crucial for achieving elimination. And so reasonable efforts should be channeled towards bringing down the values of these parameters as it will go a long way in minimizing the chances of new malaria cases thereby controlling the disease transmission.

Next on the impact of the model's parameters to the basic reproduction number is the mosquito mortality rate with negative index. The implication such impact is that vector reduction is very crucial towards malaria elimination and this can be greatly achieved using one of the control tools of this study that is ivermectin on livestock and/or human which has dual benefits as it helps to improve the health of the livestock and then their productivity (milk and meat) while being lethal to mosquitoes that ingest blood meal having the drug concentration. We carried out an optimal control analysis and based on the outcome from the numerical simulations we recommend two strategies to be adopted for malaria control. The first of which is the combination of insecticide treated bed net (transmission blocker) for prevention, treatment of infective human that is aimed at clearing the parasite from the human population thereby reducing the transmission probability from human to mosquito and livestock/ivermectin usage which also reduces the disease transmission as it serves as an alternate biting host and then minimizes the disease spread and prevalence through vector reduction. This strategy clearly aligns with the current public health policies of prevention, treatment and reduction of disease transmission as key focus for any disease control and elimination.

Now, in the event of limited resources, the strategy that combines all three control tools may be more expensive. If that be the case our second recommendation is the strategy that combines only the treatment of infective human and ivermectin usage with cattle availability as an alternative intervention to be adopted for malaria control and elimination given that it showed to be also highly effective on both the infective humans and mosquito populations with the potential of contributing significantly to the disease elimination. This strategy also aligns with the current public health policies as it covers treatment of infective human which clears the parasite and so reduce the transmission probability from human to mosquito and then cattle availability helps to reduce the disease transmission by acting as alternative biting host while ivermectin controls the spread of the disease through vector reduction. With the strategies recommended in this study, there is likely double benefits which has to do with the animal health and public health. This is because ivermectin drug is not only lethal to the mosquitoes but also improves the health of the livestock thereby promoting the livestock productivity (milk and meat). Now, the benefit of treating infective human cannot be overemphasized as it improves their health and well-being, minimize malaria related death and reduce the transmission from human to mosquito. This can contribute to achieving the WHO target of 90% reduction of malaria burden as it also minimize malaria transmission across local and international communities.

Malaria being a global threat, and as the benefits of these strategies cut across both public and animal health any of the recommended strategies can be realistically implemented despite the socio-economic constraints in malaria-endemic regions with the support of individuals, non-governmental organizations and global funding. These findings are therefore important to aid malaria elimination stakeholders, national and global malaria control programmes and policymakers to arrive at an objective conclusion when evaluating the consequences of the available strategies required for dealing with the disease.

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