Stability Analysis and Optimal Control ofEndemic Malaria DiseaseTransmission modelwith Cost-Effective Strategies

Dereje Gutema Edossa[1*], Alemu Geleta Wedajo[2],Purnachandra Rao Koya[3]
Wollega University, Department of Mathematics ,Nekemte, Ethiopia

ABSTRACT

In this study, a non-linear system of ordinary differential equation model that describes the dynamics of malaria disease transmission is formulated and analyzed. Conditions are derived from the existence of disease-free and endemic equilibria. The basic reproduction number R_0 of the model is obtained, and we investigated that it is the threshold parameter between the extinction and persistence of the disease.If R_0 is less than unity, then the disease-free equilibrium point is both locally and globally asymptotically stable resulting in the disease removing out of the host populations. The disease can persist whenever R_0 is greater than unity and the conditions for the existence of both forward and backward bifurcation at R_0 is equal to unity are derived.Sensitivity analysis is also performed and the important parameter that derive the disease dynamics is identified. Furthermore, optimal combinations of time dependent control measures are incorporated to the model, and we derived the necessary conditions of optimal control using Pontryagins's maximum principal theory. Numerical simulations were conducted using MATLAB to confirm our analytical results. Our findings were that, malaria may be controlled by reducing the requirement rate of mosquito populations andthe use of a combination of vaccination, insecticide treated net ITN, indoor residual spray IRS and active treatment or strategy **d**can also help to reduce the number populations with malaria symptoms to zero and the spread of the disease dynamics.

Keywords: Disease-free equilibrium, Endemic equilibrium,Basic reproductionnumber,asymptoticallystable, Bifurcation, Optimal control

1. INTRODUCTION

Malaria is aninfectious parasitic disease and transmitted to the human body through the bites of infected female Anopheles' mosquitoes [1]. The burden of malaria disease affects thecommunity socioeconomic in many ways. Some of these are fertility, population growth, saving and investment, worker productivity, absenteeism, premature mortality and medical costs [2]. In areas where malaria is highly endemic, young children bears a larger burden in terms of the disease morbidity and mortality and affects fetal development during early stage of pregnancy in women due to loss of immunity.Malaria is still treating a serious challenge to the global world population.According to 2020 World Health Organization (WHO) report, 241 million cases and 627 thousand deaths from malaria globally and the estimate number of children under 5 years of age deaths caused by malaria only in Africa is 80% [3].

Mathematical modeling has become an important tool in understanding the complex dynamics of disease transmission and in decision making processes regarding intervention programs for disease control. Concerning malaria disease, Ross

(1911) developed the first mathematical model. He focused his study on mosquito control and showed that for the disease to be eliminated the mosquito population should be brought below a certain threshold [4]. Later the idea of Ross is extended by Macdonaldto account for super infection [5]. Ngwa, G. A. Shu, W.S., A mathematical model for endemic malaria with variable human and mosquito population [6].Alemu G. W., Boka K. B., P.R. Koya derived and analyzed deterministic model for the inclusion of infected immigrants on the spread and dynamics of malaria transmission [7] ,Other studies are carried out by using optimal control theory.Okosun *et al*. derived and analyzed a malaria disease transmission mathematical model that includes treatment and vaccination with waning immunity and applied optimal control to study theimpact of a possible vaccination with treatment strategies in controlling the spread of malaria [8],Chernet T. D., and Gemechis F. D., derived and analyzed 'Modeling and optimal control analysis of transmission dynamics of COVID-19'[9],K. O. Okosun and O. D. MakindeModelling the impact of drug resistance in malaria transmission and its optimal control analysis [10] , E. Bonyah, M.A. Khan,K.O. Okosun, J.F. Gómez-Aguilar present ''Modeling the effects of heavy alcohol consumption on the transmission dynamics of gonorrhea with optimal [11].Khan,M.A.;Ali,K; Bonyah,E; Okosun,K.O.;Islam,S.; Khan,A., formulate Mathematical modeling and stability analysis of Wilit Disease with optimal control [12],Makinde and Okosun, wereapplied optimal control to study the impact of chemo-therapyon malaria disease with infective immigrants.[13],K.O.Okosun, O.Rachid, and N. Marcus, applied optimal control strategies and cost-effectiveness analysis of a malaria model [14]. Temesgen D. K, O. D. Makinde & Legesse L.O. derived and analyzedOptimal Control and Cost Effectiveness Analysis of SIRS Malaria Disease Model with Temperature Variability [15].

In this paper, we study SITS-SI and SIRS-SI endemic malaria transmission model with standard incidence law that was presented by [10]. Furthermore, we modified the model [6] by omitting the incubating class from the system and incorporate four-time dependent control measures and the class infective in treatment individuals. The purpose of this study is

(i) to investigate the stability for both disease-free equilibrium and endemic equilibrium
(ii) to study the important parameters in the transmission of malaria disease
(iii) to developeffective ways for controlling the malaria disease
(iv) to explore the best strategy in terms of reducing the number of malaria infectious populations,costminimization and their associated effectiveness

2. Model Description and Formulation

The populations are subdivided into compartments according to the individual's disease status. The human populations are divided in to four sub class namely, SusceptibleS_h,infected I_h, Infective in treatment T_h , and Recovered R_h . Similarly, the mosquito populations are divided in to Susceptible S_v , and Infected I_v .The total population sizes at time t, for humans are denoted and defied by $N_h(t) = S_h(t) + I_h(t) + T_h(t) + R_h(t)$ and $N_v(t) = S_v(t) + I_v(t)$respectively.Note that,$S_h = S_h(t)$,$I_h = I_h(t)$,$T_h = T_h(t)$,$R_h = R_h(t)$,$S_v = S_v(t)$,$I_v = I_v(t)$ and $N_h = N_h(t)$.

The recruitment into the susceptible human populations $S_h$is assumed to be at constant rate $\Lambda_h$and corresponds to birth or immigration. The susceptible human populations either die from natural causes at a rate of μ_h or move to infected class$I_h$by acquiring malaria through contact with infected mosquitoes $I_v$with respective rate of force of infection $\lambda_h = \phi\omega\beta_h \frac{I_v}{N_h}$where, β_h is the rate of probability of human getting infected, ϕ is the mosquito contact rate with human and ω is mosquito biting rate. Infected humans I_h individuals are also either die from natural causes and due to disease death with respective rates μ_h and δ_h respectively or move to infective in treatmentT_h compartment and recovered class R_h

with temporary immunity with respective rates $\gamma(1-\pi_1)$and $\gamma\pi_1$ respectively. Infective in treatmentT_h individuals are individuals with malaria disease that are getting treated under the control. They also either die from natural causes and dueto disease death with respective rates μ_h and δ_h respectively or move to the susceptible class with fraction of ε due to the administered drug kills off the parasites. These infected individuals progress to partially immune group (recovered class), either partiallyimmune group losses immunity and becomes again move to susceptible class with respective rateθor die from natural death at a rate μ_h .Susceptible mosquitoes $S_v$are recruited at the rate Λ_v. They either die due to natural death at a rate of μ_v or move to Infected class $I_v$by acquiring malaria through contact with both infected humans $I_h$and a partially immune group humans R_h with respective rate of force of infection $\lambda_v = \phi\omega\beta_v\left(\frac{I_h+\sigma_h R_h}{N_h}\right)$where, β_v is the Probability of a mosquito getting infected and σ_h is the modification parameter. Infected mosquitoes $I_v$are die because of natural and disease induced death with respective rates μ_v and δ_v respectively.

Diagrammatically, we represent the flow of both the human and mosquito populations from one class to the other asfollows

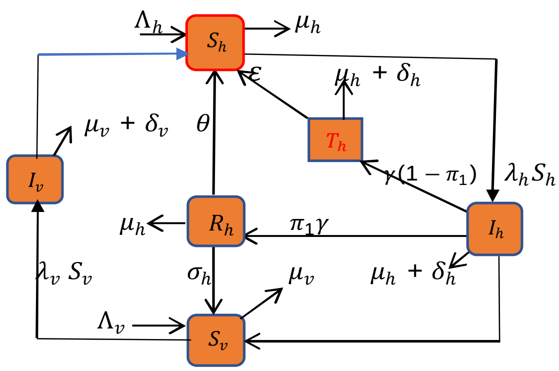


Figure 1 Flow diagram for the Transmission of Endemic malaria model

$$\begin{cases} \frac{dS_h}{dt} = \Lambda_h + \varepsilon T_h + \theta R_h - (\lambda_h + \mu_h)S_h \\ \frac{dI_h}{dt} = \lambda_h S_h - (\mu_h + \delta_h + \gamma)I_h \\ \frac{dT_h}{dt} = (1-\pi_1)\gamma I_h - (\delta_h + \mu_h + \varepsilon)T_h \quad (1) \\ \frac{dR_h}{dt} = \pi_1\gamma I_h - (\theta + \mu_h)R_h \\ \frac{dS_v}{dt} = \Lambda_v - (\lambda_v + \mu_v)S_v \\ \frac{dI_v}{dt} = \lambda_v S_v - (\mu_v + \delta_v)I_v \end{cases}$$

With,

$$S_h(0) = S_{0h}, I_h(0) = I_{0h}, T_h(0) = T_{0h}, R_h(0) = R_{0h}, S_v(0) = S_{0v}, \; I_v(0) = I_{0v} \quad (2)$$

and

with some of the following additional assumptions

(i) The susceptible class in both the human and mosquito populations enter into the infective classes by adequate contact with infectious populations not infective in treatment.

(ii) infective individuals in treatment are not infectious to the susceptible populations

(iii) Those infective humans recovered from the disease due to natural immunity and enter intoapartially immune group

(iv) Those infective individuals in treatment recovered from the disease due to the administered drug killed off the parasites

(v) one part of the recovered class again becomes susceptible to the disease

(vi) No recovered compartment formosquitoes.

3. Basic Property of the Model

3.1 Positivity of the Model

Theorem 1 Every solution of (1) with initial conditions (2) exists in the interval $[0, \infty)$ and $S_h(t) > 0, I_h(t) > 0, T_h(t) > 0, R_h(t) > 0$, $S_v(t) > 0$ and $I_v(t) > 0$ for all $t \geq 0$.

Proof. To show positivity of solutions, it is enough to show that each of the trajectories of system (1) is non-negative for all $t \geq 0$.

Sincethe right-hand side of system(1) is completely continuous and locally Lipschitzian on C, the solution$\left(S_h(t),\ I_h(t),\ T_h(t), R_h(t), S_v(t),\ I_v(t)\right)$ofsystem (1) with initial conditionEquation (2) exists and unique on $[0,\ k)$ where $0 < k < +\infty$.

It follows from the first ofsystem (1) that, the differential inequality describing the evolution of the susceptible human population over time t is given by

$$\frac{dS_h}{dt} \geq \Lambda_h - \left(\phi\omega\beta_h \left(\frac{I_v}{N_h}\right)(t) + \mu_h\right) S_h(t)$$

$$\frac{d}{dt}\left[S_h(t) exp\left\{\mu_h t + \int_0^t \phi\omega\beta_h \left(\frac{I_v}{N_h}\right)(s)\, ds\right\}\right] \geq \Lambda_h exp\left\{\mu_h t + \int_0^t \phi\omega\beta_h \left(\frac{I_v}{N_h}\right)(s)\, ds\right\}$$

Hence,

$$S_h(t) exp\left\{\mu_h t + \int_0^t \phi\omega\beta_h \left(\frac{I_v}{N_h}\right)(s)\, ds\right\} - S_{0h} \geq \int_{\tilde{t}}^t \Lambda_h exp\left\{\mu_h t + \int_0^t \phi\omega\beta_h \left(\frac{I_v}{N_h}\right)(\psi) d\psi\right\} dt$$

Thus,

$$S_h(t) \geq S_{0h} exp\left[-\left\{\mu_h t + \int_0^t \phi\omega\beta_h \left(\frac{I_v}{N_h}\right)(S_h)\, ds\right\}\right] + exp\left[-\left\{\mu_h t + \int_0^t \phi\omega\beta_h \left(\frac{I_v}{N_h}\right)(s)\, ds\right\}\right]$$
$$\times \int_0^t \Lambda_h exp\left\{\mu_h t + \int_0^t \phi\omega\beta_h \left(\frac{I_v}{N_h}\right)(\psi) d\psi\right\} dt > 0.$$

From the second of system(1) we have,

$\frac{dI_h}{dt} \geq -(\mu_h + \delta_h + \gamma) I_h(t)$is equivalent to $I_h(t) \geq exp[-(\mu_h + \delta_h + \gamma)t] > 0.$

From the third of system(1) we have,

$\frac{dT_h}{dt} \geq -(\mu_h + \delta_h + \epsilon) I_h(t)$ is equivalent to $T_h(t) \geq exp[-(\mu_h + \delta_h + \varepsilon)t] > 0.$

From the fourth of system(1) we have,

$\frac{dR_h}{dt} \geq -(\mu_h + \theta) I_h(t)$ is equivalent to $R_h(t) \geq exp[-(\mu_h + \theta)t] > 0.$

From the fifth of system(1) we have,

$$\frac{dS_v}{dt} \geq \Lambda_v - \left(\int_0^t \phi\omega\beta_v \left(\frac{I_h + \sigma_h R_h}{N_h}\right)(t) + \mu_v\right) S_v$$

$$\frac{d}{dt}\left[S_v(t) exp\left\{\mu_v t + \int_0^t \phi\omega\beta_v \left(\frac{I_h + \sigma_h R_h}{N_h}\right)(s)\, ds\right\}\right] \geq \Lambda_v exp\left\{\mu_h t + \int_0^t \phi\omega\beta_v \left(\frac{I_h + \sigma_h R_h}{N_h}\right)(s)\, ds\right\}$$

Hence,

$$S_v(t) exp\left\{\mu_v t + \int_0^t \phi\omega\beta_v \left(\frac{I_h + \sigma_h R_h}{N_h}\right)(s)\, ds\right\} - S_{0v} \geq \int_{\tilde{t}}^t \Lambda_v exp\left\{\mu_v t + \int_0^t \phi\omega\beta_v \left(\frac{I_h + \sigma_h R_h}{N_h}\right)(\psi) d\psi\right\} dt$$

Thus,

$$S_v(t) \geq S_{0h} exp\left[-\left\{\mu_v t + \int_0^t \phi\omega\beta_v \left(\frac{I_h + \sigma_h R_h}{N_h}\right)(s)\, ds\right\}\right] + exp\left[-\left\{\mu_v t + \int_0^t \phi\omega\beta_h \left(\frac{I_h + \sigma_h R_h}{N_h}\right)(s)\, ds\right\}\right]$$
$$\times \int_0^t \Lambda_v exp\left\{\mu_v t + \int_0^t \phi\omega\beta_v \left(\frac{I_h + \sigma_h R_h}{N_h}\right)(\psi) d\psi\right\} dt > 0.$$

From the sixth of system (1) we have,

$\frac{dI_v}{dt} \geq -(\mu_v + \delta_v)I_v(t)$ is equivalent to $I_v(t) \geq exp[-(\mu_v + \delta_v)t] > 0$.

Therefore; we can see that $S_h(t) > 0$, $I_h(t) > 0$, $T_h(t) > 0$, $R_h(t) > 0$, $S_v(t) > 0$, $I_v(t) > 0$ for all $t \geq 0$.

3.2 Invariant Region

Theorem 2 The feasible region Γ defined by

$\Gamma = \{\Gamma_h \times \Gamma_v\} \subset \{\mathbb{R}_+^4 \times \mathbb{R}_+^2\}$ where, $\Gamma_h = \left\{(S_h, \quad I_h, \quad T_h, \quad R_h) \in \mathbb{R}_+^4 : N_h \leq \frac{\Lambda_h}{\mu_h}\right\}$ and $\Gamma_v = \left\{(S_v, \quad I_v,) \in \mathbb{R}_+^2 : N_v \leq \frac{\Lambda_v}{\mu_v}\right\}$, with initial conditions $S_h(0) = S_{0h}$, $I_h(0) = I_{0h}$, $T_h(0) = T_{0h}$, $R_h(0) = R_{0h}$, $S_v(0) = S_{0v}$, $I_v(0) = I_{0v}$, is bounded.

Proof: Let $N_h(t) = S_h(t) + I_h(t) + T_h(t) + R_h(t)$ and $N_v(t) = S_v(t) + I_v(t)$

The feasible region of both the human and mosquito populations are determined by the feasible region of $N_h(t)$ and $N_v(t)$ respectively as follows

The feasible region of $N_h(t)$: Total sum of human compartments of system (1) leads to

$\frac{dN_h}{dt} = \Lambda_h - \mu_h N_h(t) - \delta_h(I_h(t) + T_h(t))$ which is equivalent to

$\frac{dN_h}{dt} \leq \Lambda_h - \mu_h N_h(t)$ if and only if

$$\frac{dN_h}{dt} + \mu_h N_h(t) \leq \Lambda_h$$

The resulting differential inequality can be solved by separation of variables to give,

$$\int \frac{d}{dt}(N_h e^{\mu_h t}) \leq \int \Lambda_h e^{\mu_h t}$$

Taking the initial conditions $t = 0$ and denoting $N_h(0)$ by N_{0h}, then the complete solution $N_h(t) \leq \frac{\Lambda_h}{\mu_h} + \left(N_{0h} - \frac{\Lambda_h}{\mu_h}\right)e^{-\mu_h t}$.

As $t \to \infty$,$0 < N_h \leq \frac{\Lambda_h}{\mu_h}$.So if $N_{0h} \leq \frac{\Lambda_h}{\mu_h}$, then $\lim_{t\to\infty} N_h(t) \leq \frac{\Lambda_h}{\mu_h}$ .This means that $\frac{\Lambda_h}{\mu_h}$ is upper bound of N_h.On the other hand if $N_{0h} > \frac{\Lambda_h}{\mu_h}$,then $N_h(t)$ will decrease to $\frac{\Lambda_h}{\mu_h}$Thus $N_{0h} \leq N_h(t) \leq \frac{\Lambda_h}{\mu_h}$. Therefore; the total human population is bounded.

The feasibleregion of $N_v(t)$: total sum of mosquito compartments of the system of equations (1) leads to $\frac{dN_v}{dt} = \Lambda_v - \mu_v N_v - \delta_v I_v$

$$\frac{dN_v}{dt} \leq \Lambda_v - \mu_v N_v(t)$$

$$\frac{dN_v}{dt} + \mu_v N_v(t) \leq \Lambda_v$$

The resulting differential inequality can be solved by separation of variables to give,

$$\int \frac{d}{dt}(N_v e^{\mu_v t}) \leq \int \Lambda_v e^{\mu_v t}$$

Taking the initial conditions $t = 0$ and denoting $N_v(0)$ by N_{0v}, then the complete solution

$N_v(t) \leq \frac{\Lambda_v}{\mu_v} + \left(N_{0v} - \frac{\Lambda_v}{\mu_v}\right) exp(-\mu_v t)$.

As $t \to \infty$,$0 < N_v \leq \frac{\Lambda_v}{\mu_v}$ .So if $N_{0v} \leq \frac{\Lambda_v}{\mu_v}$, then $\lim_{t\to\infty} N_v(t) \leq \frac{\Lambda_v}{\mu_v}$ .This means that $\frac{\Lambda_v}{\mu_v}$ is upper bound of N_v.On the other hand if $N_{0v} > \frac{\Lambda_v}{\mu_v}$,then $N_v(t)$ will decrease to $\frac{\Lambda_v}{\mu_v}$ .Thus $N_{0v} \leq N_v(t) \leq \frac{\Lambda_v}{\mu_v}$.

Therefore; the total mosquito population is bounded.

Thus, the solutions of the model variables representing human populations $\{(S_h, \quad I_h, \quad T_h, \quad R_h)\}$ are confined in the feasible region $\Gamma_h = \left\{(S_h(t), \quad I_h(t), \quad T_h(t), \quad R_h(t)) \in \mathbb{R}_+^4 : N_h \leq \frac{\Lambda_h}{\mu_h}\right\}$. Similarly, the solutions of the model variables representing mosquito populations$\{(S_v, \quad I_v)\}$ are confined in the feasible region $\Gamma_v = \left\{(S_v, \quad I_v) \epsilon \mathbb{R}_+^2 : N_v \leq \frac{\Lambda_v}{\mu_v}\right\}$ .This shows that the feasible region of the system(1) is bounded and is given by $\Gamma = \{S_h(t), \quad I_h(t), \quad T_h(t), \quad R_h(t), \quad S_v(t), \quad I_v(t)\} \in \mathbb{R}_+^6$or equivalent to $\Gamma = \{\Gamma_h \times \Gamma_v\} \subset \{\mathbb{R}_+^4 \times \mathbb{R}_+^2\}$.

Thus, in Γ the system(1) is well-posed epidemiologically and mathematically. Hence, it is sufficient to study the dynamics of the model in Γ.

4. Disease-free Equilibrium and Basic Reproduction Number, Disease-free Stability

The disease-free equilibrium point of the model is its steady state solutions without infection or disease.

Consider the disease free-equilibrium point denoted and given by:

$E_0 = (S_h^0 \quad I_h^0 \quad T_h^0 \quad R_h^0 \quad S_v^0 \quad I_v^0)$where,$S_h^0, I_h^0, T^0, R_h^0, S_v^0$ and I_v^0 are the components of E_0 and$I_h^0 = T_h^0 = R_h^0 = I_v^0 = 0$ and the non-infectious are obtained by setting$\frac{dS_h}{dt} = \frac{dV_s}{dt} = \frac{dS_v}{dt} = 0$ for the malaria modelsystem(1) and after computing the resultant gives $S_h^0 = \frac{\Lambda_h}{\mu_h}$and $S_v^0 = \frac{\Lambda_v}{\mu_v}$.

Hence;

$$E_0 = \begin{pmatrix} \frac{\Lambda_h}{\mu_h} & 0 & 0 & 0 & \frac{\Lambda_v}{\mu_v} & 0 \end{pmatrix} \quad (3)$$

The basic reproduction number denoted by R_0 is the average number of secondary infectious infected by an infective individual during his or her whole course of disease [16]. We use the next generation matrix method by van den Driessche and Watmough [17] to derive the basic reproduction number $R_0$of system(1).The infectious compartment of modesystem (1) are,I_h,R_h, and I_v. To apply the method [17], let the system (1) be rearranged by beginning with the infected classes as follows:

Let$X = (I_h \quad T_h \quad I_v \quad S_h \quad R_h \quad S_v)^T$

$$F(X_i) = \begin{pmatrix} \frac{\phi\omega\beta_h I_v}{N_h} S_h \\ 0 \\ 0 \\ \frac{\phi\omega\beta_v(I_h+\sigma_h R_h)}{N_h} S_v \end{pmatrix} \quad \text{and} \quad V(X_i) = \begin{pmatrix} (\mu_h + \delta_h + \gamma)I_h \\ (\mu_h + \delta_h + \varepsilon)T_h - \gamma(1-\pi_1)I_h \\ (\mu_h + \theta)R_h - \gamma\pi_1 I_h \\ (\mu_v + \delta_v)I_v \end{pmatrix}$$

The new infection matrix F and the transition matrix V are given, respectively, by

$$F = \frac{\partial F(X_i)}{\partial X_i}(E_0) = \begin{pmatrix} 0 & 0 & 0 & \phi\omega\beta_h \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ \frac{\phi\omega\beta_v\Lambda_v\mu_h}{\Lambda_h\mu_v} & 0 & \frac{\sigma_h\phi\omega\beta_v\Lambda_v\mu_h}{\Lambda_h\mu_v} & 0 \end{pmatrix} \quad \text{and} \quad V = \frac{\partial V(X_i)}{\partial X_i}(E_0) = \begin{pmatrix} J_1 & 0 & 0 & 0 \\ -\gamma(1-\pi_1) & J_2 & 0 & 0 \\ -\gamma\pi_1 & 0 & J_3 & 0 \\ 0 & 0 & 0 & J_4 \end{pmatrix}$$

Where, $J_1 = \mu_h + \delta_h + \gamma$,$J_2 = \mu_h + \delta_h + \varepsilon$, $J_3 = \theta + \mu_h$, $J_4 = \mu_v + \delta_v$

$$FV^{-1} = \begin{pmatrix} 0 & 0 & 0 & \frac{\phi\omega\beta_h}{(\mu_v+\delta_v)} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ \frac{\phi\omega\beta_v\mu_h\Lambda_v(J_3+\sigma\gamma\pi_1)}{J_1 J_3\Lambda_h\mu_v} & 0 & \frac{\sigma_h\phi\omega\beta_v\Lambda_v\mu_h}{J_3\Lambda_h\mu_v} & 0 \end{pmatrix} \text{and}$$

The basic reproduction number ofsystem (1) is the dominant eigen value of the next generation matrix FV^{-1} which is given by

$$R_0 = \sqrt{\frac{\phi^2\omega^2\beta_h\beta_v\mu_h\Lambda_v((J_3+\sigma_h\gamma\pi_1))}{\Lambda_h\mu_v J_1 J_3 J_4}} \quad (4)$$

4.1 Local Stability of Disease-Free Equilibrium Point

Theorem3 The disease-free equilibrium point $E_0$of system (1) is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

Proof:

The local stability of the system is determined by the signs of the eigenvalues and it is further proved by linearizing to obtain its Jacobian at disease-free steady-state points so that

The Jacobian matrix of system (1) at disease free equilibrium point E_0 defined and given by

$$J(E_0) = \begin{pmatrix} -\mu_h & 0 & \varepsilon & \theta & 0 & -J_{16} \\ 0 & -J_1 & 0 & 0 & 0 & J_{26} \\ 0 & \gamma(1-\pi_1) & -J_2 & 0 & 0 & 0 \\ 0 & \gamma\pi_1 & 0 & -J_3 & 0 & 0 \\ 0 & -J_{52} & 0 & -J_{54} & -\mu_v & 0 \\ 0 & J_{62} & 0 & J_{64} & 0 & -J_4 \end{pmatrix} \quad (5)$$

Where, $J_3 = \theta + \mu_h, J_{16} = J_{26} = \phi\omega\beta_h$, $J_{52} = J_{62} = \frac{\phi\omega\beta_v\mu_h\Lambda_v}{\Lambda_h\mu_v}, J_{54} = J_{64} = \frac{\sigma_h\phi\omega\beta_v\mu_h\Lambda_v}{\Lambda_h\mu_v}$

$Det(J(E_0) - \lambda I) = 0$ if and only if $\lambda_1 = -\mu_h < 0, \lambda_2 = -\mu_v < 0, \lambda_3 = -J_2 < 0$, and

$a_0\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0$ (6)

Where,

$a_0 = 1,$

$a_1 = J_1 + J_3 + J_4$ (7)

$a_2 = J_4(J_1 + J_3) + J_1J_3 - J_{26}\, J_{52}$ and

$$a_3 = (1 - R_0^2)J_1J_3J_4$$

By the principle of Ruth-Hurwitz criteria [18], equation(6) has negative real eigenvalues if and only if $a_1 > 0, a_3 > 0$ and $a_1a_2 > a_3$. Clearly, we see that, $a_1 > 0$ because of it is the sum of positive variables, but $a_3 > 0$ if and only if $1 - R_0^2 > 0$ which is equivalent to $R_0 < 0$ and hence, all eigenvalues of the determinant of equation(5) will have negative real eigenvalues. Therefore; the disease-free equilibrium point E_0 is locally asymptotically stable.

5. Existence of Endemic Equilibrium and Bifurcation

Let $E^* = (S_h^* \quad I_h^* \quad T_h^* \quad R_h^* \quad S_v^* \quad I_v^*)$ be a non-trivial endemic equilibrium point of equation(1),that is, all components of E_* are positive.

If we set (1) to zero we get the following

$$S_h^* = \frac{J_1J_2J_3\Lambda_h}{J_1J_2J_3\mu_h + \left(\mu_h K + J_3\delta_h\left(J_2 + \gamma(1-\pi_1)\right)\right)\lambda_h^*} \;,\; I_h^* = \frac{\lambda_h^* S_h^*}{J_1} \;,\; T_h^* = \frac{\gamma(1-\pi_1)\lambda_h^* S_h^*}{J_1J_2} \;,\; R_h^* = \frac{\pi_1\gamma\lambda_h^* S_h^*}{J_1J_3}$$

$$S_v^* = \frac{\Lambda_v}{\mu_v + \lambda_v^*} \;,\; I_v^* = \frac{\Lambda_v\lambda_v^*}{(\mu_v + \lambda_v^*)J_4} \;, \quad (8)$$

$\lambda_h^* = \phi\omega\beta_h \frac{I_v^*}{N_h^*}$(9)

$\lambda_v^* = \phi\omega\beta_v \frac{(I_h^* + \sigma_h R_h^*)}{N_h^*}$(10)

Where, $N_h^* = S_h^* + I_h^* + T_h^* + R_h^*$ and substituting (9) in to (11) we get

$\lambda_v^* = \frac{\phi\omega\beta_v J_2(J_3 + \sigma_h\gamma\pi_1)\lambda_h^*}{J_1J_3(J_1J_2J_3 + K\lambda_h^*)}$(11)

Again substituting (9) and (12) respectively in to (10) we get

$\lambda_h^*(a_0(\lambda_h^*)^2 + b_0\lambda_h^* + c_0) = 0$(12)

$$a_0 = \Lambda_h J_2 J_1^2 J_3^2 K(K\mu_v + \phi\omega\beta_v(J_3 + \sigma_h\gamma\pi_1)J_2)$$

$b_0 = J_1^2J_2^2J_3^3\phi\omega\beta_v(J_3 + \sigma_h\gamma\pi_1)\left(J_1J_3J_4 - \delta_h\phi\omega\beta_v\left(J_2 + \gamma(1-\pi)\right)\right) + J_1^4J_2^3J_3^4J_4\mu_v\Lambda_h\left((1 - R_0^2) + K\right)$ and

$c_0 = J_1^4J_2^3J_3^4J_4\mu_v\Lambda_h(1 - R_0^2)$(13)

Where, R_0 is the basic reproduction number, $K = J_2J_3 + \gamma(\pi_1J_2 + (1-\pi)J_3)$ equation(12) admits a trivial solution $\lambda_h^* = 0$ which corresponds to the disease-free equilibrium point (DFEP). Now we assume $\lambda_h^* \neq 0$ the existence of endemic equilibria is regulated by the quadratic equation $a_0(\lambda_h^*)^2 + b_0\lambda_h^* + c_0 = 0$. The coefficient a_0 in equation(13)is always positive and c_0 is positive if $R_0 < 1$ and negative if $R_0 > 1$. So, the sign of b_0 and $c_0$will decide about the positivesolution of equation(12). For the case when $R_0 > 1$, two solutions can be obtained for equation(12), that are positive and negative. For the case when considering c_0= 0 if and only if $R_0 = 1$, then a solution of the form $\lambda_h^* = \frac{-b_0}{a_0}$ exists when$b_0 < 0$ .It follows that the number of endemic equilibria of system(1) is depend on the coefficient a_0, b_0 and c_0 as follows:

Theorem 4 The system (1) has

(i) a unique endemic equilibrium if $c_0 < 0$ if and only if $R_0 > 1$.

(ii) a unique endemic equilibrium if $b_0 < 0$and $c_0 = 0$or($b_0 < 0$, $c_0 > 0$ and $b_0^2 - 4a_0c_0 = 0$).

(iii) Two endemic equilibria if $c_0 > 0$ and $b_0 < 0$ and $b_0^2 - 4a_0c_0 > 0$.

(iv) otherwise, no endemic equilibrium.'

Condition (iii) of theorem 4, indicate the occurrence of multiple endemic equilibria for $R_0 < 1$.From epidemiological perspective this implies that the elimination of the disease in the population is no longer guaranteed by the condition $R_0 < 1$.

Here also, if we put for the value of$\Lambda_h = 100$, $\theta = 0.03$,$\delta_h = 0.068$,$\mu_v = 0.1429$, $\gamma = 0.98$, $\pi_1 = 0.9$, $\varepsilon = 0.9$ and use table 2 for the other parameters values , the two roots are presented graphically as shown in figure 2. Where, the green line represents stable equilibrium and the red line represents unstable equilibrium.

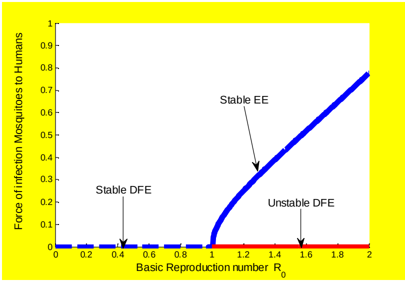


Figure 2: When we plot the basic reproduction number R_0 versus the force of infection mosquitoes to humans, we note stable disease free region when $\lambda_h^* = 0$ and when $R_0 = 1$, the force of infection mosquitoes to humans starts to increase in stable endemic region where we note that the disease start to spread again and hence, forward bifurcation.

5.1 Existence of Back ward Bifurcation

To show the existence of bifurcation of system (1) , we employ the method developed in Gumel and Song, 2008; Castillo-Chavez and Song, 2004 [19 - 21].We also assume as a summary that the normal form representing the dynamics of the system on the Centre manifold theory as summary it is given by $\dot{\mu} = a\mu^2 + b\xi\mu$, where,

$$a = \frac{v}{2}.D_{xx}f(x_0,0)w^2 = \frac{1}{2}\sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \eth x_j}(x_0,0) \neq 0 \text{for j =1,2…,n} \quad (14)$$

$$b = V.D_{x\xi}f(x_0,0)w = \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \eth\xi}(x_0,0) \neq 0 \text{ for i =1,2…,n} (15)$$

Where,

ξdenotes a bifurcation parameter to be chosen, f_ks Denote the right hand side of (1),

$x$denotes the state vector, $x_0$denotes the disease-free equilibriumE_0,$D_x$denotes the differential operator with respect to$x$,

D_ξ denotes the differential operator with respect toξ , and

w ,$v$denotes the right and left eigenvectors respectively corresponding to the null eigenvalue of the Jacobian matrix of system (1), evaluated at x_0 for $\xi = 0$.

To analyze the bifurcation of system(1), let we choose the rate of transmission of infection from an infectious mosquito to a susceptible human β_h as the bifurcation parameter. We observe that $R_0 = 1$ is equivalent to:

$$\beta_h = \beta_h^* = \frac{\Lambda_h \mu_v J_1 J_3 J_4}{\phi^2 \omega^2 \beta_v \mu_h \Lambda_v (\sigma_h \gamma \pi + J_3)}. \quad (16)$$

and the linearized Jacobian matrix evaluated at E_0 and β_h^* is denoted and given by

$$J(E_0) = \begin{pmatrix} -\mu_h & 0 & \varepsilon & \theta & 0 & -J_{16}^* \\ 0 & -J_1 & 0 & 0 & 0 & J_{26}^* \\ 0 & \gamma(1-\pi_1) & -J_2 & 0 & 0 & 0 \\ 0 & \gamma\pi_1 & 0 & -J_3 & 0 & 0 \\ 0 & -J_{52} & 0 & -J_{54} & -\mu_v & 0 \\ 0 & J_{62} & 0 & J_{64} & 0 & -J_4 \end{pmatrix} (17)$$

Where, $J_3 = \theta + \mu_h$, $J_{16}^* = J_{16}^* = \phi\omega\beta_h^*$, $J_{52} = J_{62} = \frac{\phi\omega\beta_v \mu_h \Lambda_v}{\Lambda_h \mu_v}$, $J_{54} = J_{64} = \frac{\sigma_h \phi\omega\beta_v \mu_h \Lambda_v}{\Lambda_h \mu_v}$

$Det(J(E_0) - \lambda I) = 0$ if and only if $\lambda_1 = -\mu_h < 0, \lambda_2 = -\mu_v < 0, \lambda_3 = -J_2 < 0$, and

$$\lambda(g_0\lambda^3 + g_1\lambda^2 + g_2\lambda + g_3) = 0 \quad (18)$$

Where,

$g_0 = 1$,

$g_1 = J_1 + J_3 + J_4$

$g_2 = J_4(J_1 + J_3) + J_1 J_3 - J_{26} J_{52}$ and

$g_3 = (1 - R_0^2) J_1 J_3 J_4$ (19)

If we also substitute 1(one) for R_0 in to equation (18), then system(1) will have a simple zero eigenvalue and the other eigenvalues have negative real parts. Therefore; the disease-free equilibrium point E_0 is a non- hyperbolic. To compute the coefficients equation(14) and equation(15), we determine the right and left eigenvectors corresponding to the zero eigenvalue. Thus, the components of the right eigenvectors denoted by w_i, for $i = 1, \ldots, 6$ are given by

$$\begin{cases} -\mu_h w_1 + \varepsilon w_3 + \theta w_4 - J_{16}^* w_6 = 0 \\ -J_1 w_2 + J_{26}^* w_6 = 0 \\ \gamma(1-\pi_1) w_2 - J_2 w_3 = 0 \\ \gamma\pi w_2 - J_3 w_4 = 0 \\ -J_{52}(w_2 + w_4) - \mu_v w_5 = 0 \\ J_{52}(w_2 + w_4) - J_4 w_6 = 0 \end{cases} \quad (20)$$

Where, $J_{16}^* = J_{26}^* = \phi\omega\beta_h^*$, $J_{52}^* = \frac{\phi\omega\beta_v \mu_h \Lambda_v}{\Lambda_h \mu_v}$,

$$w_1 = \frac{J_{26}^* \gamma(\pi_1 J_2 \theta + \sigma_h (1-\pi_1) J_3) - J_{16}^* J_1 J_2 J_3}{\mu_h J_1 J_2 J_3} w_6, \; w_2 = \frac{J_{26}^*}{J_1} w_6, \; w_3 = \frac{\gamma(1-\pi_1) J_{26}^*}{J_1 J_2} w_6,$$

$$w_4 = \frac{\pi_1 \gamma J_{26}^*}{J_1 J_3} w_6, \; w_5 = -\frac{J_{26}^* J_{52}(J_3 + \sigma_h \gamma \pi_1)}{J_1 J_3 \mu_v} w_6, \text{ and } w_6 = w_6 > 0 \quad (21)$$

and

The components of the left eigenvectors denoted by v_i, for $i = 1, \ldots, 6$ are given by

$$\begin{cases} -\mu_h v_1 = 0 \\ -J_1 v_2 + \gamma(1-\pi_1) v_3 + \pi_1 \gamma v_4 - J_{52}(v_5 - v_6) = 0 \\ \alpha v_1 - J_2 v_3 = 0 \\ \theta v_1 - J_3 v_4 - \sigma_h J_{54}(v_5 - v_6) = 0 \\ -\mu_v v_5 = 0 \\ -J_{16}^* v_1 + J_{26}^* v_2 - J_4 v_6 = 0 \end{cases} \quad (22)$$

$$v_1 = v_3 = v_5 = 0, \; v_2 = \frac{J_{52}(J_3 + \sigma_h \gamma \pi_1)}{J_1 J_3} v_6, \; v_4 = \frac{\sigma_h J_{52}}{J_3} v_6, \text{ and } v_6 = v_6 > 0, \quad (23)$$

Let we also make the following change of state variables $S_h = x_1, I_h = x_2, T_h = x_3, R_h = x_4, S_v = x_5, I_v = x_6$ and using the vector notation $x = (x_1, \ x_2, x_3, \ x_4, \ x_5, \ x_6,)^T$.The system system(1) can thenbe written in the form $\frac{dx}{dt} = F(x)$were, $F = (f_1, \ f_2, f_3, \ f_4, \ f_5, \ f_6,)^T$ as shown below

$$\begin{cases} \frac{dx_1}{dt} = f_1 = \Lambda_h + \varepsilon x_3 + \theta x_4 - \left(\phi\omega\beta_h^* \frac{x_6}{x_1 + x_2 + x_3 + x_4} + \mu_h\right) x_1 \\ \frac{dx_2}{dt} = f_2 = \phi\omega\beta_h^* \left(\frac{x_6}{x_1 + x_2 + x_3 + x_4}\right) x_1 - (\mu_h + \delta_h + \gamma) x_2 \\ \frac{dx_3}{dt} = f_3 = \gamma(1 - \pi_1) x_2 - (\delta_h + \mu_h + \varepsilon) x_3 \\ \frac{dx_4}{dt} = f_4 = \gamma\pi_1 x_2 - (\theta + \mu_h) x_4 \\ \frac{dx_5}{dt} = f_5 = \Lambda_v - \left(\phi\omega\beta_v \frac{x_2 + \sigma_h x_4}{x_1 + x_2 + x_3 + x_4} + \mu_v\right) x_5 \\ \frac{dx_6}{dt} = f_6 = \left(\phi\omega\beta_v \frac{x_2 + \sigma_h x_4}{x_1 + x_2 + x_3 + x_4}\right) x_5 - (\mu_v + \delta_v) x_{76} \end{cases} \quad (24)$$

$\frac{\partial^2 f_2}{\partial I_v \eth I_h}(x_0, 0) = \frac{\partial^2 f_2}{\partial I_v \eth T_h}(x_0, 0) = \frac{\partial^2 f_2}{\partial I_v \eth R_h}(x_0, 0) = -\frac{\phi\omega\beta_h^*}{S_h^0}, \frac{\partial^2 f_6}{\partial I_h^2}(x_0, 0) = -\frac{2\phi\omega\beta_v S_v^0}{(S_h^0)^2}, \frac{\partial^2 f_6}{\partial R_h^2}(x_0, 0) = -\frac{2\sigma\phi\omega\beta_v S_v^0}{(S_h^0)^2}$

$, \frac{\partial^2 f_6}{\partial I_h \eth S_h}(x_0, 0) = \frac{\partial^2 f_6}{\partial I_h \eth T_h}(x_0, 0) = -\frac{\phi\omega\beta_v S_v^0}{(S_h^0)^2}, \frac{\partial^2 f_6}{\partial I_h \eth S_v}(x_0, 0) = \frac{\phi\omega\beta_v}{S_h^0}, \frac{\partial^2 f_6}{\partial R_h \eth I_h}(x_0, 0) = -\frac{\phi\omega\beta_v S_v^0}{(S_h^0)^2}(1 + \sigma_h)$

$\frac{\partial^2 f_6}{\partial R_h \eth S_h}(x_0, 0) = \frac{\partial^2 f_6}{\partial R_h \eth T_h}(x_0, 0) = -\frac{\sigma\phi\omega\beta_v S_v^0}{(S_h^0)^2}$(25)

$\frac{\partial^2 f_2}{\partial I_v \eth \beta_h^*}(x_0, 0) = \phi\omega$ (26)

Thus,

$a = v_2 w_2 w_6 \frac{\partial^2 f_2}{\partial I_v \eth I_h}(x_0, 0) + v_2 w_3 w_6 \frac{\partial^2 f_2}{\partial I_v \eth T_h}(x_0, 0) + v_2 w_4 w_6 \frac{\partial^2 f_2}{\partial I_v \eth R_h}(x_0, 0) + v_6 w_2^2 \frac{\partial^2 f_6}{\partial I_h^2}(x_0, 0) + v_6 w_4^2 \frac{\partial^2 f_6}{\partial R_h^2}(x_0, 0) +$

$w_1 v_6 \left(w_2 \frac{\partial^2 f_6}{\partial I_h \eth S_h}(x_0, 0) + w_4 \frac{\partial^2 f_6}{\partial R_h \eth S_h}(x_0, 0)\right) + w_3 v_6 \left(w_2 \frac{\partial^2 f_6}{\partial I_h \eth T_h}(x_0, 0) + w_4 \frac{\partial^2 f_6}{\partial R_h \eth T_h}(x_0, 0)\right) + w_5 v_6 \left(w_2 \frac{\partial^2 f_6}{\partial I_h \eth S_v}(x_0, 0) +\right.$

$\left. w_4 \frac{\partial^2 f_6}{\partial R_h \eth S_v}(x_0, 0)\right) + v_6 w_2 w_4 \frac{\partial^2 f_6}{\partial I_h \eth R_h}(x_0, 0) + v_6 w_2 w_4 \frac{\partial^2 f_6}{\partial R_h \eth I_h}(x_0, 0)$(27) and

$b = v_2 w_6 \frac{\partial^2 f_2}{\partial I_v \eth \beta_h^*}(x_0, 0)$ (28)

After substitutingequation (21),equation (23) and equation(25) respectively in to equation(27), then the coefficient a in terms of w_6 and $v_6$is given by

$a = \frac{\Lambda_v \mu_h^2 \phi^3 \omega^3 {\beta_h^*}^2 \beta_v}{\mu_v(\mu_h + \delta_h + \alpha)\Lambda_h^2(\theta + \mu_h)^2(\mu_h + \delta_h + \gamma)^2} v_6 w_6^2 \Delta_0$(29)

Where,

$$\Delta_0 = \frac{(J_3 + \sigma_h \gamma \pi_1) J_1 J_2 J_3}{\mu_h} - 2 J_3 (1 - \pi)\gamma + J_2 \left(\left(1 + J_3 + \mu_v \mu_h \pi\gamma\right) J_3 + \gamma\pi_1\left((1 + \sigma_h^2 \gamma\pi_1) + (\sigma_h + 1)\right)\right) - (J_3 + \sigma_h \gamma\pi_1)\left(\frac{\mu_h J_2 \phi\omega\beta_v + \gamma(\theta\pi J_2 + \alpha(1 - \pi) J_3)\mu_v}{\mu_v \mu_h}\right)$$

Similarly, after substituting equation(21), equation(23) and equation(26) respectively in to equation(28), then the coefficient b in terms of w_6 and $v_6$is given by

$b = \frac{\phi^2 \omega^2 \beta_v (J_3 + \sigma_h \gamma\pi_1) S_v^0}{J_1 J_3 S_h^0} w_6 v_6 > 0$ (30)

Clearly, the coefficient b is positive since all the parameters are non-negative. Thus, the local dynamics of the system (1) around E_0, for $\beta_h = \beta_h^*$ is depends on the sign of the coefficient a.Similar to theorem [22] we also establishthe following theorem.

Theorem 5 The system (1) will undergo backward bifurcation at $R_0 = 1$ if the coefficient a is positive($\Delta_0 > 0$)otherwise it will exhibit a forward bifurcation if a is negative ($\Delta_0 < 0$).

6 Global Stability

6.1 Global Stability of Disease-Free Equilibrium Point

To investigate theglobal stabilityof the disease-free equilibrium point E_0,weconsiderthe Lyapunov function [23].So that $L = J_4(J_3 + \sigma_h\gamma\pi_1)I_h + J_1J_4R_h + \phi\omega\beta_h(J_3 + \sigma_h\gamma\pi_1)I_v$. Then

$$\frac{dL}{dt} = J_4(J_3 + \sigma_h\gamma\pi_1)\frac{dI_h}{dt} + J_1J_4\frac{dR_h}{dt} + \phi\omega\beta_h(J_3 + \sigma_h\gamma\pi_1)\frac{dI_v}{dt} \quad (31)$$

After substituting $\frac{dI_h}{dt}$, $\frac{dR_h}{dt}$ and $\frac{dI_v}{dt}$ from system(1) and simplifying it , then we get

$$\frac{dL}{dt} = \phi^2\omega^2\beta_h\beta_v(J_3 + \sigma_h\gamma\pi_1)\frac{(I_h + \sigma_h R_h)}{N_h}S_v - J_1J_3J_4(I_h + \sigma_h R_h). \quad (32)$$

Since $\frac{dS_h}{dt} \le \frac{\Lambda_h}{\mu_h} = S_h^0 = N_h^0$,$\frac{dS_v}{dt} \le \frac{\Lambda_v}{\mu_v} = S_v^0$equation (32) is equivalent to

$$\frac{dL}{dt} = \frac{\phi^2\omega^2\beta_h\beta_v(\sigma_h\gamma\pi_1 + J_3)\Lambda_v\mu_h}{(1-\varphi)\Lambda_h\mu_v}(I_h + \sigma_h R_h) - J_1J_3J_4(I_h + \sigma R_h) \quad (33)$$

Since $R_0^2 = \frac{\phi^2\omega^2\beta_h\beta_v\mu_h\Lambda_v\mu_h(J_3 + \sigma_h\gamma\pi_1)}{\Lambda_h\mu_v J_1J_3J_4}$,equation(34) is also equivalent to

$$\frac{dL}{dt} = (R_0^2 - 1)J_1J_3J_4(I_h + \sigma_h R_h) \quad (34)$$

So,$\frac{dL}{dt} \le 0$ if $(R_0^2 - 1) \le 0$ which leads to $R_0 \le 1$.$\frac{dL}{dt} = 0$ if and only if $I_h = R_h = 0$ or $R_0^2 = 1$.

Therefore; by Lasalle's invariant principle [24], every solution to equations of the modelsystem(1) with initial conditions inΓ approaches to the disease-free equilibrium point E_0 at time t leads infinity whenever, $R_0 \le 1$.Hence,we establish the following theorem

Theorem 6 The disease-free equilibrium point $E_0$of system(1) is globally asymptotically stable if $R_0 \le 1$ and unstable if $R_0 > 1$.

The epidemiological implication of theorem 6 is that the elimination of the malaria disease is possible regardless of initial condition equation(2) of the sub-population of the modelsystem(1) whenever $R_0 \le 1$.

7. Sensitivity Analysis

The use of sensitivity analysis enables us to identify the model parameters that have great influence on the basic reproduction number R_0.The method developed by Chitnis *et al* [25, 26] is used to compute the sensitivity index of each parameterthat has relation with basic reproduction number R_0.The sensitivity indices of each parameter that have great influence on the basic reproduction number R_0 is computed as follows:

Let p be a parameter in R_0 , then the sensitivity of p is given by $\Upsilon_p^{R_0} = \frac{\partial R_0}{\partial p} \times \frac{p}{R_0}$.

Table 1: Table for summary of sensitivity analysis

Symbol	Description	Sensitivity indices
Λ_h	Humans recruitments either due to birth or immigration	-0.0021
μ_h	Human natural death rate	+0.0002
Λ_v	Mosquitoes recruitments due to birth	+0.5000
μ_v	Mosquito natural death rate	-0.0042
ϕ	Mosquito contact rate with human	+1.0000
ω	Mosquito biting rate	+1.0000
γ	Per capita rate of recovery from malaria	-0.0002
θ	Per capita rate of human immunity loss	-0.0017
σ_h	Modification parameter	+0.00000039659
δ_h	Humans death rate due to malaria disease	-0.0019
δ_v	Mosquitoes death rate due to malaria disease	-0.0001

β_h	the rate of transmission of infection from an infectious mosquito to a susceptible human	+0.5000
β_v	the rate of transmission of infection from an infectious human to a susceptible mosquito	+0.5000

Parameters (ϕ , ω, β_h , Λ_v , σ_h ,$\mu_h$and β_v) have direct relations with R_0 hence if their magnitude is increased ,then they can expand the disease but parameters (δ_h ,δ_v ,μ_v,γ,θ and Λ_h) have inverse relations with R_0 hence if their magnitude is increased, then they can reduce the burden of the disease in the community.

8. Analysis of the Model with Optimal Control

In this section, we consider model system (1) and incorporate optimal combinations of time dependent control measures namely, (i) prevention measure vaccination $u_1(t) = u_1$ for the purpose of immunization of an individual to infection who are requited to the susceptible human populations due to birth or immigration ,(ii) the use of insecticide treated bed net (ITN) $u_2(t) = u_2$as preventive measure i.e., to reduce the number of bites from mosquitoes as they physically provide a barrier between the infectious mosquitoes and the susceptible humans, and also to reduce the population of the mosquitoes by killing them after they land on the treated net. (iii) treatment with drugs $u_3(t) = u_3$, treating individuals who developed symptoms of the disease, and (iv) the use of indoor residual spray (IRS), $u_4(t) = u_4$as preventive measure i.e., insecticide spray on the breeding site of mosquitoes reduces the number of mosquito populations by killing these rest indoors after feeding. The controls are practiced on time interval $[t_0 , t_f]$, where t_0 and t_f are initial and final time respectively. After incorporating the above controls in to the basic modelsystem(1) we get the following modified state equations:

$$\begin{cases} \frac{dS_h}{dt} = (1-u_1)\Lambda_h + (\varepsilon + (1-\tau u_3))T_h + \theta R_h - ((1-u_2)\lambda_h + \mu_h)S_h \\ \frac{dI_h}{dt} = (1-u_2)\lambda_h S_h - (\mu_h + \delta_h + \gamma + \tau u_3)I_h \\ \frac{dT_h}{dt} = \gamma(1-\pi_1)I_h - (\delta_h + \mu_h + \varepsilon + (1-\tau u_3))T_h \\ \frac{dR_h}{dt} = (\pi_1\gamma + \tau u_3)I_h - (\theta + \mu_h)R_h \\ \frac{dS_v}{dt} = \Lambda_v - ((1-u_2)\lambda_v + \mu_v + \delta u_2 + \beta u_4)S_v \\ \frac{dI_v}{dt} = (1-u_2)\lambda_v S_v - (\mu_v + \delta_v + \delta u_2 + \beta u_4)I_v \end{cases} \quad \mathbf{(35)}$$

Here the following objective function J is used to minimize the number of infected and infective in treatment human populations and total mosquito populations while keeping the costs of applying the controls u_1,u_2, $u_3$and $u_4$as low as possible.

The form of the objective function is defined based on the approach [27,28].It is also denoted and defined by

$$J = min \int_0^{t_f} \left(B_1 I_h + B_2 T_h + B_3 I_v + \frac{1}{2}\sum_1^4 n_i u_i^2\right) dt \quad (36)$$

Where, i =1,2,3,4 ,B_1 , B_2, and $B_3$and n_1,n_2 ,n_3 and ,n_4 are coefficients associated to the state variable and controls respectively. Following the approach [27 ,28], the cost of the controls have been chosen quadratic. Thus, the goal is to find, an optimal control quadruple, u_1^* , u_2^*, $u_3^*$and u_4^* such that

$$J(u_1^* , u_2^*, u_3^*, u_4^*) = min\{J(u_1, u_2, u_3, u_4): u_1, u_2, u_3, u_4 \epsilon U\} \quad (37)$$

Where,$\Phi = \{u_1(t) \quad u_2(t) \quad u_3(t) \quad u_4(t) \quad : 0 \le u_i < 1, i = 1,2,\ldots,4, 0 \le t \le t_f\}$ is the control set.The Pontryagins's MaximumPrinciple [29] converts the system equation(35) with equation(36) and equation(37) into a problem of minimizing pointwise the Hamiltonian H with respect to u_1,u_2, $u_3$and u_4

$$H = (S_h, I_h, T_h, R_h, S_v I_v, t) = L(I_h, T_h, I_v, u_1, u_2, u_3, u_4, t) + \lambda_1 \frac{dS_h}{dt} + \lambda_2 \frac{dI_h}{dt} + \lambda_3 \frac{dT_h}{dt} + \lambda_4 \frac{dR_h}{dt} + \lambda_5 \frac{dS_v}{dt} + \lambda_6 \frac{dI_v}{dt} \quad (38)$$

Where, $L(I_h, T_h, I_v, u_1, u_2, u_3, u_4, t) = B_1 I_h + B_2 T_h + B_3 I_v + \frac{1}{2}\sum_1^4 n_i u_i^2$ for i=1,2,3,4

and λ_i, for i= 1,2,3,4,5,6 are adjoint variables. Using the exitance result for the optimal control [29], we established the following theorem as

Thereom7 There exists a set of an optimal control $u_i^* = (u_1^*, u_2^*, u_3^*, u_4^*)$and corresponding state solution, S_h^*, I_h^*, T_h^* R_h^* S_v^* and I_v^* that minimizes $J(u_1, u_2, u_3, u_4)$ over Φsubject to equation(35).Further , there exists adjoint functions $\lambda_1(t), \ldots, \lambda_6(t)$, and $u_1(t), \ldots u_4(t)$ satisfying

$$\begin{cases} \frac{d\lambda_1}{dt} = \mu_h\lambda_1 + (1-u_2)\lambda_h(\lambda_1-\lambda_2) \\ \frac{d\lambda_2}{dt} = -B_1 + (\mu_h+\delta_h)\lambda_2 + \gamma(\lambda_2-\lambda_3-\lambda_4) + \tau u_3(\lambda_2-\lambda_4) + \frac{(1-u_2)\phi\omega\beta_v}{N_h}S_v\left(1-\frac{I_h}{N_h}\right)(\lambda_5-\lambda_6) \\ \frac{d\lambda_3}{dt} = -B_2 + (\mu_h+\delta_h)\lambda_3 + \left(\varepsilon + (1-\tau u_3)\right)(\lambda_3-\lambda_1) \\ \frac{d\lambda_4}{dt} = \mu_h\lambda_4 + \theta(\lambda_4-\lambda_1) + \frac{(1-u_2)\phi\omega\beta_v}{N_h}S_v\left(1-\frac{\sigma_h R_h}{N_h}\right)(\lambda_5-\lambda_6) \\ \frac{d\lambda_5}{dt} = (1-u_2)\lambda_v(\lambda_5-\lambda_6) + (\mu_v+\delta u_2+\beta u_4)\lambda_5 \\ \frac{d\lambda_6}{dt} = -B_3 + (1-u_2)\frac{\phi\omega\beta_h S_h}{N_h}(\lambda_1-\lambda_2) + (\mu_v+\delta_v+\delta u_2+\beta u_4)\lambda_6 \end{cases} \quad (39)$$

with transversality conditions

$\lambda_i(t_f) = 0$ for $i =$ 1,2,3,4,5, (40)

Further, the optimal controls u_1^* , u_2^*, u_3^* and u_4^* are given by

$$u_1^* = min\left\{max\left(0, \frac{\Lambda_h(\lambda_1-\lambda_4)}{n_1}\right), 1\right\}$$

$$u_2^* = min\left\{max\left(0, \frac{\lambda_h(\lambda_2-\lambda_1)S_h+\lambda_v(\lambda_5-\lambda_6)S_v+\delta(S_v\lambda_5+I_v\lambda_6)}{n_2}\right), 1\right\} \quad (41)$$

$$u_3^* = min\left\{max\left(0, \frac{\tau(\lambda_2-\lambda_4)I_h+\tau(\lambda_1-\lambda_3)T_h}{n_3}\right), 1\right\}$$

$$u_4^* = min\left\{max\left(0, \frac{\beta(S_v\lambda_5+I_v\lambda_6)}{n_4}\right), 1\right\}$$

Proof:

The existence of the optimal control follows from Fleming and Rischel [30] due to convexity of the integrand objective functional J in equation(36) with respect to u_i , $i = 1,2,3,4$over the convex and closed control set Φ and the system equation(35) satisfies the and Lipchitz property with respect to state variables since the state solutions are bounded. The differential equation(39) governing the adjoint variables $\lambda_1, \lambda_2, \ldots, \lambda_6$ are obtained by partial differentiation of the Hamiltonian H given by (38) with respect to the corresponding state variables that is,$\frac{d\lambda_1}{dt} = -\frac{\partial H}{\partial S_h}, \frac{d\lambda_2}{dt} = -\frac{\partial H}{\partial I_{hs}}, \frac{d\lambda_3}{dt} = -\frac{\partial H}{\partial I_{hr}}, \frac{d\lambda_4}{dt} = -\frac{\partial H}{\partial T_h}, \frac{d\lambda_5}{dt} = -\frac{\partial H}{\partial R_h}, \frac{d\lambda_6}{dt} = -\frac{\partial H}{\partial S_v}$ with terminal conditionsequation(40).The characterization of optimal control given by equation(41) is obtained by partial derivative of the Hamiltonian H equation(38) with respect to each control u_i and solving$\frac{\partial H}{\partial u_i} = 0$,for $i = 1,2,3,4$.

9. Numerical simulation

In this section, numerical simulations are performed to confirm with our analytical results stated in the proof of theorem 3,4,5,6 and the optimality system which is characterized by the state systemequation(35) and the adjoint system equation(39) was solved numerically by applying Runge Kutta fourth order schemes of the approach [31]. The implimentation of the scheme was done using MATLAB packege.

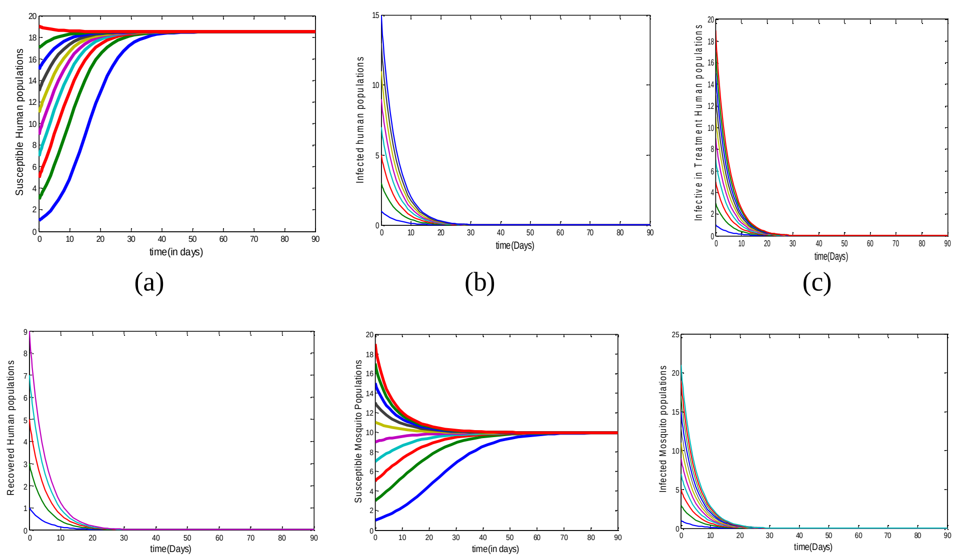
Tables2 : Table for parameter values

Parameter	Value	Source
β_h	0.8333	[32]
Λ_h	0.00099	[32]
ε	(0, 1)	Assumed
μ_h	0.00005447	[33]
δ_h	0.0500	[34]

Parameter	Value	Source
θ	0.01672	[26]
τ	0.5000	Assumed
ω	0.2000	[35]
ϕ	0.6000	[36]
β_v	0.4800	[26]
Λ_v	50.00	Assumed
μ_v	0.0714	[26]
γ	0.005	[37]
δ_v	0.0100	[37]
σ_h	0.1000	[38]
β	0.2500	Assumed
δ	0.2500	Assumed
π_1	0.0230	Assumed

Initial values that we used for simulation of the optimal control are: $S_h(0)$ = 800,$I_h(0)$= 60,$T_h(0)$ = 10, $R_h(0)$=10, $S_v(0)$ = 5000,and $I_v(0)$ = 100. And. Due to the lack of the available literatures and data, as an example, we assumed cost of weight factor of controls are n_1 =,n_2 = n_3 = n_4 = 4.

First we considered the stability analysis in case when R_0 = 0.8274039204 < 1.Using parameter values given in Table2 and replacing value of Λ_v in the table 2 by Λ_v = 0.71and for different initial conditions, the dynamics of the model equation(1) is presented in figures 3(a)-(f) .These figures show that only the susceptible human(S_h^0 = 18.1751422802) and mosquito(S_v^0 = 9.943977591) populations exists and the infective in treatment class, recovered class, infected human and mosquito populations ($I_h^0 = T_h^0 = R_h^0 = I_v^0 = 0$) that is, tends to the disease free equilibrium(E_0) as time t tends to infinity. This numerical result supports the result stated in theorem3 i.e., the disease free equilibrium is locally asymptotical stable if R_0 < 1.

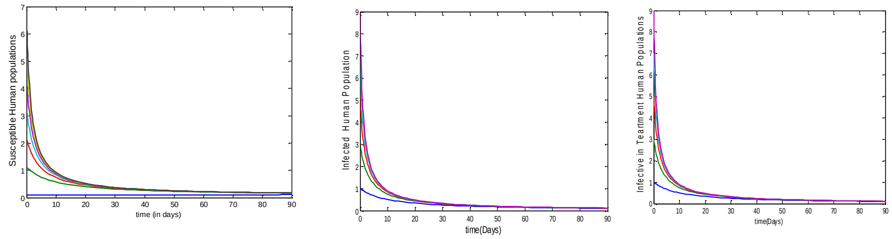


(a) (b) (c)

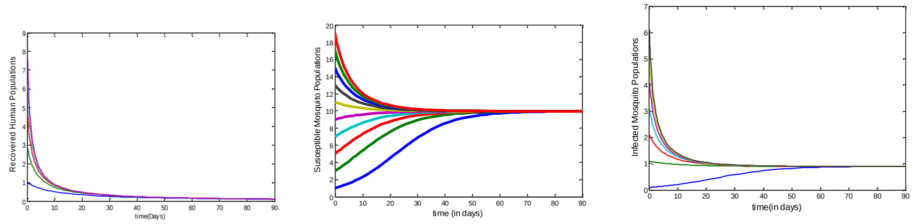
(d) (e) (f)

Figure 3 Time series plots Susceptible humans,((a) Infected humans,(b),Infective in Treatment humans(c),Recovered humans (d)Susceptible mosquitoes,(e) and (f) Infected mosquitoes for R_0 = 0.8274039204 < 1with various initial conditions

Second,we considered the stability analysis in case when R_0 = 6.9434194577 > 1 using the parameter values given in Table2 and for different initial conditions, the dynamics of the model system(1) is presented in figures 4(a)-(f). These figures show that, susceptible humans, infected humans, infective intreatment humans, recoveredhumans, susceptible and infected mosquito populations exists S_h^* = 0.96988308, I_h^* = 0.0160824661, T_h^* = 0.00000567. I_v^* = 0.9003 R_h^* = 0.000000407, S_v^* = 9.9513) that is the population tends to endemic equilibrium E^* when R_0 > 1. This shows that the endemic equilibrium E^* is locally asymptotically stable if R_0 > 1, which is also supports our analytical results stated in theorem4.



(a) (b) (c)



(d) (e) (f)

Figure4 Time series plots Susceptible humans,((a) Infected humans,(b), Infective in Treatment humans (c), Recovered humans (d) Susceptible mosquitoes,(e) and (f) Infected mosquitoes for R_0 = 6.9434194577 > 1with various initial conditions.

Third for the modelsystem(1), we proposed optimal combinations of the aforementioned control strategies as alternative choose to minimize the spread of endemic malaria disease dynamics. So as to do this, we introduced different optimal combination strategies in our model and numerically compare their effects on malaria infeected populatons.Thus,the proposed optimal combinations and numerical result analysis for R_0 = 6.9434194577 > 1are as follows

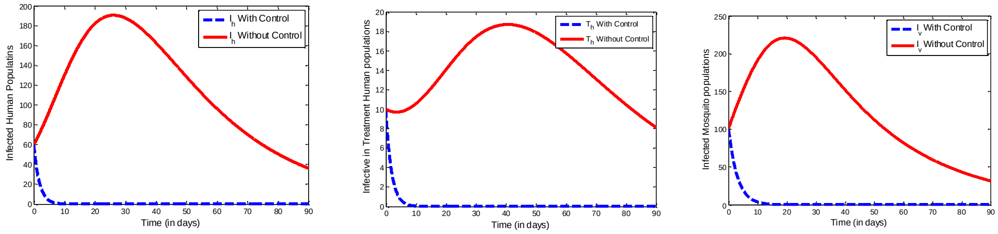
9.1 Strategy $\boldsymbol{a}$: Combination of use of insecticide treated net ITN and treatment of infective individuals

9.2 Strategy $\boldsymbol{b}$: Combination of use of vaccination, insecticide treated net ITN and treatment of infective individuals

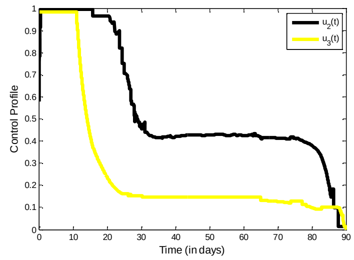
9.3 Strategy $\boldsymbol{c}$: Combinations of use of insecticide treated nets ITN, indoor residual spray IRS for vector control and treatment of infective individuals

9.4 Strategy $\boldsymbol{d}$: Combinations of use of vaccination, insecticide treated nets ITN and indoor residual spray IRS and treatment of infective individuals

Strategy $\boldsymbol{a}$: *Control withthe preventive of insecticide treated net ITN and indoor residual spray IRS,* $(u_2 \neq 0, u_3 \neq 0)$. In this strategy, we compare the strategya situation where no control ($u_1 = 0$, $u_2 = 0, u_3 = 0, u_4 = 0$) was used with the application of strategy$a$. It can be seen from the figures 5a,5b and 5c that there is a significant decrease in the number of infected and infective in treatment human populations and infected mosquito populations compared to the strategy with no control at a given time respectively. With the application of strategy$a$, I_h , T_h and I_v in between time t = 8, 8, and 11 days respectively will be eliminated from the system. The control profile shown in figure 5d shows that, control u_2 is at 60% initially and increased up to the maximum of 100% before steadily decline to the lower bound within 90 days while control u_3 is at the maximum of 100% initially before dropping gradually to the lower bound within 90 days. This suggests that, a high effort is required for the use of medical treatmentu_3 and there is a low effort for the uses of insecticide treated net $u_2$under this strategy.



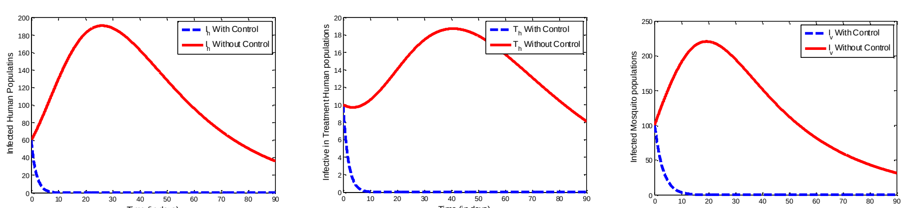
(a) (b) (c)



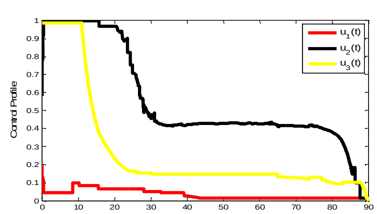
(d)

Figure 5 Simulations of the model Showing the effects of a combination of ITN and treatment

Strategy *b*: *Control withthe preventive of vaccination,insecticide treated net ITN and treatment* ($u_1 \neq 0$, $u_2 \neq 0, u_3 \neq 0$). In this strategy, we compare the strategya situation where no control ($u_1 = 0$, $u_2 = 0, u_3 = 0, u_4 = 0$) was used with the application of strategy$d$. It can be seen from the figures 6a, 6b and 6c that there is a significant decrease in the number of infected and infective in treatment human populations and infected mosquito populations compared to the strategy with no control at a given time respectively. With the application of strategy$b$, I_h ,T_h and I_v in between time $t =$ 8 ,8 and 10days respectively will be eliminated from the system. This result is a bit more promising than strategy a.The control profile shown in figure 6d shows that, control u_2 is at 60% initially and increased up to the maximum of 100% before steadily decline to the lower bound within 90 days while controls u_1 and u_3 are at the maximum of 20% and 100% initially before dropping gradually to the lower bound within 90 days respectively. This suggests that, a high effort is required for the use of medical treatmentu_3 and there is a low effort for the uses of preventive controls vaccination $u_1$and insecticide treated net u_2 under this strategy.



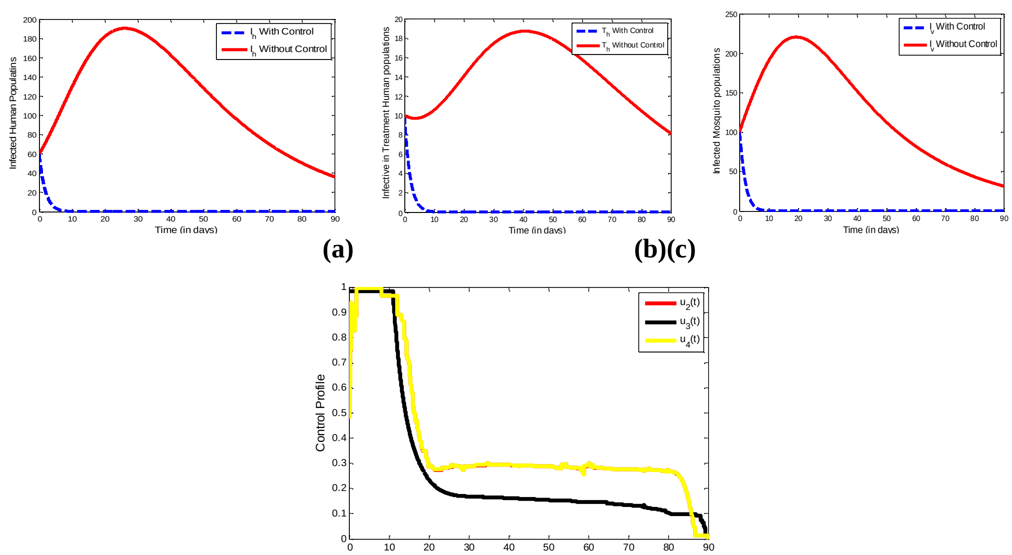
(a) **(b)** **(c)**



(d)

Figure 6 Simulations of the model Showing the effects of a combination of Vaccination , ITN and treatment

Strategy $\boldsymbol{c}$: *Control withthe preventive of insecticide treated net ITN, indoor residual spray IRS, and treatment* ($u_2 \neq 0, u_3 \neq 0, u_4 \neq 0$). In this strategy, we compare the strategya situation where no control ($u_1 = 0$, $u_2 = 0, u_3 = 0, u_4 = 0$) was used with the application of strategy$d$. It can be seen from the figures 7a, 7b and 7f that there is a dramatic decrease in the number of infected and infective in treatment human populations and infected mosquito populations compared to the strategy with no control at a given time respectively. With the application of strategy $\boldsymbol{c}$, I_h , T_h and I_v will be eliminated from the system almost within time $t = 8$, days . This result is a bit more promising than strategy a. The control profile shown in figure 7d shows that, both control u_2 and u_4 are at 60% initially and increased up to the maximum of 100% before steadily decline and converges to the lower bound within 90 days while control u_3 is at the maximum of 100% initially before dropping gradually to the lower bound within 90 days. This suggests that, a high effort is required for the use of medical treatmentu_3 and there is a low effort for the uses of insecticide treated net u_2, and indoor residual spray IRS u_4 under this strategy.

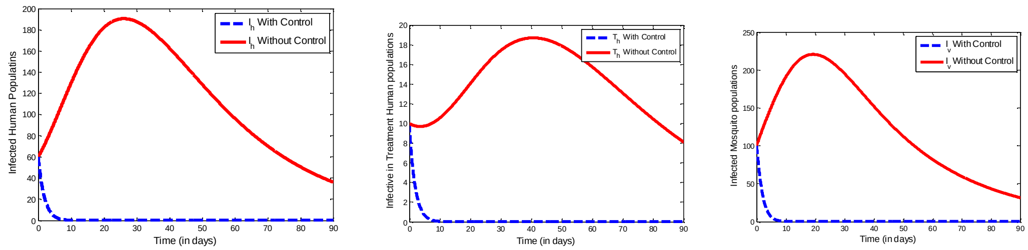


(a) **(b)(c)**

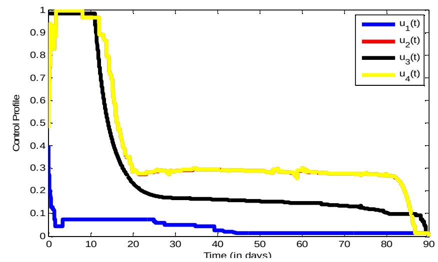
(d)

Figure 7 Simulations of the model Showing the effects of a combination of ITN, treatment and IRS

Strategy $\boldsymbol{d}$: *Control withthe preventive of vaccination,insecticide treated net ITN, indoor residual spray IRS, and treatment* ($u_1 \neq 0$, $u_2 \neq 0, u_3 \neq 0, u_4 \neq 0$). In this strategy, we compare the strategya situation where no control ($u_1 = 0$, $u_2 = 0, u_3 = 0, u_4 = 0$) was used with the application of strategy$d$. It can be seen from the figures 8a,8b and 8c that there is a dramatic decrease in the number of infected and infective in treatment human populations and infected mosquito populations compared to the strategy with no control at a given time respectively. With the application of strategy$d$, I_h , T_h and I_v will be eliminated from the system within time $t = 7$ days. This result is a bit more promising than when strategy$a$except possibly strategies b and c which yield almost the same results. The control profile shown in figure 8d shows that, both control $u_2$and u_4 are at 60% initially and increased up to the maximum of 100% before steadily decline and converges to the lower bound within 90 days while controls u_1 and u_3 are at the maximum of 40% and 100% initially before dropping gradually to the lower bound within 90 days respectively. This suggests that, a high effort is required for the use of medical treatmentu_3 and there is a low effort for the uses of preventive controls vaccination u_1 , insecticide treated net u_2, and indoor residual spray IRS u_4 under this strategy.



(a) (b)(c)



(d)

Figure 8 Simulations of the model Showing the effects of a combination of vaccination, ITN, treatment and IRS

10. Cost Effectiveness Analysis

To analyze the cost-effectiveness of the strategies, we employ the approach of incremental cost-effective ratio (ICER) in [14]. The ICER is used to compare the cost and the health outcomes of two alternative intervention strategies that compete for the same resources.

Based on values of ICER of the strategy k , the alternative that are more expensive and less ineffective are then excluded. This is done after simulating the optimal control model and then ranking strategies in order of increasing effectiveness measured as the total infection averted. We calculate ICER based on strategy $k(k = a, b, cd)$ by using the following formula.

ICER(a)=$\frac{Cost\ of\ intervention(a)-Cost\ \ of\ intervention(b)}{Effect\ of\ intervention(a)-Effect\ of\ intervention(b)}$

The total infection averted by optimal strategy $k$during the time period $t_f$is denoted and defined as

$$TA_k = \frac{B_1 A_{kI_h} + B_3 A_{kT_h} + B_3 A_{kI_v}}{B_1 + B_2 + B_3} \quad (42)$$

Where,

$$A_{kI_h} = t_f I_h(0) - \int_{t_0}^{t_f} I_h^*(t)dt \quad (43)$$

$$A_{kT_h} = t_f T_h(0) - \int_{t_0}^{t_f} T_h^*(t)dt$$

$$A_{kI_v} = t_f I_v(0) - \int_{t_0}^{t_f} I_v^*(t)dt$$

And A_{kI_h} ,A_{kT_h} and A_{kI_v} are the total infected and infective in treatment human populations and infected mosquito populations respectively averted by optimal strategy$k$during the time periodfinal time t_f,I_h^* , T_h^*, and I_v^* are the optimal solution associated with optimal controls $(u_1^*, u_2^*, u_3^*, u_4^*)$system(35) and $I_h(0), T_h(0)$ and $I_v(0)$ are the corresponding initial values. Note that these initial values are obtained as the equilibrium proportion of the system system(35) with no post-exposure intervention ($u_1 = u_2 = u_3 = u_4 = 0$). The total cost associated with a strategy is denoted and given by

$$C_{kT} = \int_{t_0}^{t_f} \left[n_1 u_1^*(t) S_h^*(t) + n_2 u_2^*(t)\left(S_h^*(t) + I_h^*(t) + S_v^*(t) + I_v^*(t)\right) + n_3 u_3^*(t)\left(S_h^*(t) + I_h^*(t) + T_h^*(t)\right) + n_4 u_4^*(t)\left(S_v^*(t) + I_v^*(t)\right)\right] dt \quad (44)$$

Where, n_1 corresponds to the per person unit cost following preventive control of vaccination intervention, n_2 corresponds to the per person unit cost of preventive control of ITN intervention, n_3 corresponds to the per person unit cost of treatment intervention, and n_4 corresponds to the per person unit cost of preventive control of IRS intervention. Parameters values from Table2are used to estimate the total infection averted and total cost presented in table 2.

Table 2 Cases Averted and Total Costs

Strategy k	A_{kI_h}	A_{kT_h}	A_{kI_v}	TA_k	$Costs(\$)C_{kT}$
d	5395.293	899.973	8993.5470	5995.5570	494140
c	5395.293	899.973	8993.5560	5995.5610	502060
b	5394.609	899.964	8992.3500	5994.7950	669410
a	5394.618	899.964	8992.3590	5994.8020	669900

Table 3 incorporates ICER, it is presented as follows; first we rearrange control strategies from Table 2 in increasing order of effectiveness (TA_k). Next, we compute incremental effectiveness $\triangle TA_k$and incremental costsΔC_{Tk} .The ICER is calculated by dividing ΔC_{Tk} to $\triangle TA_k$ where $k = a, b, c, d$ and their ICER are as follows

ICER($\boldsymbol{b}$) $= \frac{\Delta C_{Tb}}{\Delta TA_b} = \frac{669410}{5994.7950}$ = 111.6652028968463

ICER($\boldsymbol{a}$) $= \frac{C_{Ta} - C_{Tb}}{TA_a - Tb} = \frac{\Delta C_{Ta}}{\Delta TA_a}$= 70,000

ICER($\boldsymbol{d}$) $= \frac{C_{Td} - C_{Ta}}{TA_d - TA_a} = \frac{\Delta C_{Td}}{\Delta TA_d}$= -23,2794.701986755

ICER($\boldsymbol{c}$) $= \frac{C_{Tc} - C_{Td}}{TA_c - TA_d} = \frac{\Delta C_{Tc}}{\Delta TA_c}$= 1,980,000

Table3 Incremental cost-effectiveness ratios of different optimal control strategies

Strategy k	TA_k	ΔTA_k	$Costs(\$)C_{Tk}$	ΔC_{Tk}	ICER ($\Delta C_{Tk}/\Delta TA_k$)
b	5994.7950	5994.7950	669410	669410	111.6652028968463
a	5994.8020	0.007	669900	490	70,000
d	5995.5570	0.755	494140	-175760	-23,2794.70198675
c	5995.5610	0.004	502060	7920	1,980,000

Table 4 Incremental cost-effectiveness ratios for optimal control strategies a , b and d

Strategy k	TA_k	ΔTA_k	$Costs(\$)C_{Tk}$	ΔC_{Tk}	ICER ($\Delta C_{Tk}/\Delta TA_k$)
b	5994.7950	5994.7950	669410	669410	111.6652028968463
a	5994.8020	0.007	669900	490	70,000
d	5995.5570	0.755	494140	-175760	-23,2794.70198675

Table 5 Incremental cost-effectiveness ratios for optimal control strategies$b$ and d

Strategy k	TA_k	ΔTA_k	$Costs(\$)C_{Tk}$	ΔC_{Tk}	ICER ($\Delta C_{Tk}/\Delta TA_k$)
b	5994.7950	5994.7950	669410	669410	111.6652028968463
d	5995.5570	0.755	494140	-175760	-23,2794.70198675

Finally, the comparison results reveal that strategy $\boldsymbol{d}$ is cheaper than strategy $\boldsymbol{b}$. Therefore, strategy $\boldsymbol{d}$ (the use of vaccination, insecticide treated net ITN, treatment for infected and infective in treatment individuals, and indoor residual spray IRS is the best of all possible strategies due to its more effectiveness and less cost or due to its cost-e□ectiveness and healthy benefits.

11. Discussion and Conclusion

In this study, a non-linear system of ordinary differential equation model that describes the dynamics of malaria disease transmission is formulated and analyzed. Conditions are derived from the existence of disease-free and endemic equilibria. The basic reproduction number R_0 of the model is obtained, and we investigated that it is a threshold parameter between the extinction and persistence of the disease.If R_0 is less than unity, then the disease-free equilibrium point is both locally and globally asymptotically stable resulting in the disease removing out of the host populations. The disease can persist whenever R_0 is greater than unity and the conditions for the existence of both forward and backward bifurcation at R_0 is equal to unity are derived.Sensitivity analysis is also performed and hence, (i) An increase of magnitude of the indices of parameter with positive indicesincreases the magnitude of the associatedbasic reproduction number, (ii) An increase of magnitude of the indices of parameter with negative indices decreases the magnitude of the associated basic reproduction number. Furthermore, optimal combinations of time dependent control measures, namely; vaccination, insecticide treated nets ITN, treatment and indoor residual spray IRS are incorporated to the model.The theory of Pontryagins's maximum principle is used to find the necessary conditions for the optimal control.

Clearly, from the numerical simulations of system (1), the disease-free equilibrium is both locally and globally asymptotically stable whenever the basic reproduction number is less than one andthe endemic equilibrium is unstableif the basic reproduction number is greater than one.We note that in order to reduce the basic reproduction number below one, we need to focused on the reduction of requirement rate of mosquito populations.

The optimality system which is characherized by the state system(35) and the adjoint system(39) was solved numerically by applying Runge Kutta fourth order schemesNumerical simulations results of these show that the use of a combination of vaccination, insecticide treated net ITN, active treatment, and indoor residual spray IRS or strategy **d**perform well for the time period of intervention and it is the most optimal cost-effective strategy. Finally, we note that with the strict application of either one of the incorporated combinations of optimal control strategies, it is possible to reduce the number populations with malaria symptoms to zero in the given time and the spread of the disease dynamics. Further note that, application of optimal control strategy to malaria disease is not only minimize the number populations with malaria symptoms and costs related to infectious and control measures but also minimize the spread of the disease dynamics.

12.Recommendations

Here we recommend tomalaria control policy makers, health care workers and any concerning body can use the incorporated strategy in this paper to reduce the burden of malaria disease in community.

Acknowledgements

This work was supported by Wollega University. The authors would like to thank the editors and reviewers of Asian Research Journal of Mathematics for their suggestions to improve the quality of the manuscript.

Completing Interests

Authors have declared that no completing interest exist

Reference

[1] Meibalan E, Marti M. Biology of malaria transmission. Cold Spring Harb Perspect Med. 2017,7: a025452
[2] Sachs JD., A new Infected global effort to control malaria. *Science*. 2002;298:122 – 124.
[3] World Health Organization. World malaria report 2021.
[4] Ross, R., The Prevention of Malaria, 2nd ed. *Murray London*, 1911.
[5] MacDonald., The analysis of infection rates in diseases in which superinfection occurs. *Trop. Dis. Bull.* 1950;47: 907–915.
[6] Ngwa, G.A., and Shu, W.S.,. A mathematical model for endemic malaria with variable human and mosquito population. *Math. Comput. Model*. 2000;32: 747–763.

[7] A.G.Wedajo, B. K. Bole, P. R. Koya. Analysis of SIR Mathematical Model for Malaria disease with the inclusion of Infected Immigrants. *IOSR Journal of Mathematics (IOSR – JM).* 2018; 14 : 10–21.
[8] Okosun, K.O., Ouifki, R., Marcus, N., Optimal control analysis of a malaria disease transmission model that includes treatment and vaccination with waning immunity. *Biosystems.*2011;106:136–145.
[9] Chernet T. D., and Gemechis F. D., derived and analyzed 'Modeling and optimal control analysis of transmission dynamics of COVID-19: The case of Ethiopia. *Alexandria Engineering Journal.*2021;.60 :719-732.
[10] K. O. Okosun and O. D. MakindeModelling the impact of drug resistance in malaria transmission and its optimal control analysis.*Int. J. Phys. Sci.* 2011;6(28):6479-6487.
[11] E. Bonyah, M.A. Khan, K.O. Okosun, J.F. Gómez-Aguilar derived, Modelling the effects of heavy alcohol consumption on the transmission dynamics of gonorrhea with optimal control. *Mathematical Biosciences.*2019 *;309:*1-11.
[12] Khan,M.A.;Ali,K; Bonyah,E; Okosun,K.O.;Islam,S.; Khan,A., formulate 'Mathematical modeling and stability analysis of Wilit Disease with optimal control'. Scientific Reports.2017;7(1):3115.
[13] Makinde, O.D. and Okosun, K.O., Impact of Chemotherapy on Optimal Control of Malaria Disease with Infected Immigrants, *Biosystems*.2011;104(1): 32-41.
[14] Okosun, Kazeem O. and Rachid, Ouifki and Marcus, Nizar, Optimal Control Strategies and Cost-Effectiveness Analysis of a Malaria Model, *Biosystems*.2013;111(2):83-101.
[15] Temesgen D. K,, O. D.Makinde2 & Legesse L. O. derived and analyzedOptimal Control and Cost Effectiveness Analysis of SIRS Malaria Disease Model with Temperature Variability.*J. Math. Fund. Sci.* 2021;53(1):134-163.
[16] O. Diekmann, J. A. P. Heesterbeek and J. A. J. Metz, on the definition and computation of the basic reproduction ratio in models for infectious diseases in heterogeneous populations, J. *Math. Bio*, 1990;28 :365-382.
[17] P.van den Driessche and J. Watmough, "Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission," *Mathematical Biosciences*. 2002;180: 29–48.
[18] B. K. Sahu, M. M. Gupta and B. Subudhi, Stability analysis of nonlinear systems using Dynamic-Routh's stability criterion: *A new approach*, 2013.
[19] Niger, A. & Gumel, B., Mathematical Analysis of the Role of Repeated Exposure on Malaria Transmission Dynamics, *Differ. Equ. Dyn. Syst.*2008;16: 251-87.
[20] Castillo-Chavez, and B. Song: Dynamical models of tuberculosis and their applications. *Math. Biosci.and Engineering*. 2004 ,1(2):361–404.
[21] Dushoff, J., Huang, W., Castillo-Chavez, C.: Backward bifurcations and catastrophe in simple models of fatal diseases. *J. Math. Biol.*1998;36, : 227–248.
[22] Castillo-Chavez C, Song B. Dynamical models of tuberculosis and their applications. *Math Biosci Eng*.2014; 404:1-361.
[23] Traoré B, Sangaré B, Traoré B. A mathematical model of malaria transmission with structured vector population and seasonality. *Journal of Applied Mathematics.* 2017; 2017(6754097):1-15
[24] J. P. LaSalle, The Stability of Dynamical Systems. *SIAM, Philadelphia, Pa, USA*, 1976.
[25] Guckenheimer, J., Holmes, P.: Nonlinear Oscillations, Dynamical Systems, and Bifurcations of VectorFields, *Applied Mathematical Sciences*, *edn. Springer-Verlag, New*York ,vol. 42(7) 2002.
[26] Chitnis, J. M. Hyman and J. M. Cushing, Determining important parameters in the spread of malaria through the sensitivity analysis of a mathematical model, *Bull. Math. Biol.* 2008;70: 1272–1296.
[27] Sharomi O, Malik T. Optimal control in epidemiology. *Ann Oper Res.*2015; 227: 1-17.
[28] G.T. Tilahun , O.D. Makinde , D. Malonza , Modelling and optimal control of pneumonia disease with cost-effective strategies, J. *Biol. Dyn*. 11 (Sup2) ,2017.
[29] L. S. Pontryagins's, V. G. Boltyanskii, R. V. Gamkrelidze, and E. F. Mishchenko, The Mathematical Theory of Optimal Processes. New York: *Wiley,*1962.
[30] W. H. Fleming and R. W. Rishel, Deterministic and Stochastic Optimal Control, *Springer, New York, NY, USA*, 1975.
[31] S. M. Lenhart and J. T. Workman, Optimal Control Applied to Biological Models*, CRC Press*, 2007
[32] Mukandavire, Z., Gumel, A.B., Garira, W., Tchuenche, J.M., Mathematical analysis of a model for HIV-malaria co-infection. *Math. Biosci. Eng.* ,2009; 6:333–362.
[33] Kenya National Bureau of Statistics. Kenya Population and Housing Census 2009; KNBS, Ministry of Planning, National Development and Vision 2030: Nairobi, Kenya, 2010.
[34] KNBS and ICF Macro. Kenya Demographic and Health Survey, 2008–2009; Kenya National Bureau of Statistics (KNBS) and ICF Macro: Calverton, Maryland, 2010.
[35] Kbenesh B.;Yanzhao C.; Hee-Dae K., Optimal control of vector borne diseases: Treatment and Prevention. Disc. Conti. Dyn. Sys. series B., 2009;11(3):587 – 611.
[36] Nakul C, Cushing JM, Hyman JM., Bifurcation Analysis of a Mathematical model for malaria transmission. *SIAM J. Appl.Math*..2006; 67(1): 24 – 45.
[37] Chiyaka, C.; Tchuenche, J. M.; Garira, W.; Dube, S.; A Mathematical analysis of the effects of control strategies on the transmission dynamics of Malaria. *Applied Mathematics and Computation,* 2008.;195:641–662.
[38] N. Chitnis, J.M. Cushing, J.M. Hyman, Bifurcation analysis of a mathematical model for malaria transmission, *SIAM J. Appl. Math*. 2006.;67:24–45.