Journal of Computer Science & Computational Mathematics,, Volume 10, Issue 4, December 2020
DOI: 10.20967/jcscm.2020.04.002

Sensitivity Analysis of an Untreated Liver-Stage Malaria

T. S. Faniran[1*], A. O. Falade[2], J. Ogunsanwo[1]

[1]Department of Computer and Physical Sciences, Lead City University, Ibadan, Nigeria
[2]Department of Mathematics, African Institute for Mathematical Sciences, Mbour, Senegal
[*]Corresponding author email: tayefaniran@yahoo.com

***Abstract*:** Malaria is a life-threatening disease caused by Plasmodium falciparum that are transmitted to people through the bite of infected female Anopheles mosquitoes. Liver-stage treatment is the removal of dormant sporozoites from the liver by adhering to prophylactic measures. Several malaria control measures have been recommended by World Health Organization (WHO), but this is threatened by untreated liver-stage infection, which the existing literature did not consider. A new system of differential equations that capture untreated liver-stage infection is formulated to describe the dynamics of malaria transmission between two interacting populations. Hospitalized infectious human is also incorporated in the model. The existence of solutions is established and the basic reproduction number, R_o, is calculated. Local stability of disease-free and endemic equilibrium solution are established. Suitable Lyapunov function is constructed to analyze the global dynamics of the system. Moreover, sensitivity analysis of the model parameters is carried out. The sensitivity analysis reveals the important parameters needed to propose intervention strategies.

***Keywords*:** Malaria, prophylactic measures, Lyapunov function, sensitivity analysis.

1. Introduction

Malaria is caused by protozoan parasites of the genius Plasmodium parasites. The parasites are spread to people through the bites of infected female Anopheles mosquitoes. There are five plasmodium parasite species that cause malaria in humans, and two of these species-P.falciparum and P.vivax, pose the greatest threat. Malaria is endemic to tropical areas where the climatic and weather conditions allow continuous breeding of the mosquito. Malaria is one of the most important parasitic and infectious diseases especially in tropical and subtropical areas. Malaria, affecting mainly children and pregnant women is one of the greatest menaces in our society in terms of morbidity and mortality and the occurrence of malaria in our part of the world correlates with poverty and ignorance [1]. In 2017, there were estimated 219 million cases of malaria in 87 countries and the estimated number of malaria deaths stood at 435000 in the same year [2].

The amount of time between the mosquito bite and the appearance of symptoms varies depending on the strain of parasite involved. The incubation period is usually between eight to twelve days of falciparum malaria, but it can be as long as a month for the other types. Symptoms of malaria include fatigue, severe headache, nausea, and fever. In many cases, this cycle of fever occurs every other day and may last between a week and a month. Those with the chronic form of malaria may have a relapse as long as fifty years after the initial infection ([3, 4]). Malaria falciparum is a medical emergency that should be treated in the hospital. The type of drug, method of administration and length of the treatment depend on the level of sickness of the patient. The treatment malaria is usually artemicinin-based combination therapies (ACTs) ([3, 5]).

Mathematical models have been used before in the study of transmission dynamics and spread of malaria. See ([2, 6–17]) and the references therein. Budhwar et al. [9] presented a mathematical model of malaria incorporating infective immigrants in the human population. They calculated the basic reproduction number, R_o, using the next generation matrix method. Moreover, they discussed about the stability of the equilibrium points. They used the Lyapunov function to show the global stability of the equilibrium points. Bakare et al [17] developed a population level mathematical model for human-mosquito interactions with multiple interventions towards the elimination of plasmodium falciparum malaria in Nigeria. They carried out sensitivity analysis on the model. They applied intervention, which focused on mosquito biting rate and the human recovery rate to reduce the spread of malaria in low and high transmission regions in Nigeria. Olaniyi et al [7] formulated a malaria model with naturally acquired translent immunity in the presence of protected travellers. They established the qualitative analysis of their model, which reveals the existence of backward bifurcation. Their analytical results further reveals that increased fraction of protected travellers is shown to reduce the basic reproduction significantly. Furthermore, they employed optimal control theory to analyse the non-autonomous model, which takes into account four control variables. They illustrated the effects of combining at least any three of the control variables on the malaria dynamics. Lastly, they carried out cost-effectiveness analysis which shows that the combination of the optimal use of personal protection using insecticides, mosquito reduction effort using indoor residual spray and prophylaxis are the most cost-effective strategy of all the various combination of the control that are considered in their work. In another development, Kotou et al.[18] analysed a mathematical model of malaria transmission, taking into account the immature stages of the vectors. They applied Lyapunov Principle to study the stability

of equilibrium points. They determined the basic reproduction number using next generation matrix and investigated its implication for malaria management. They showed that the mosquito population disappears if the threshold dynamics quantities are less than unity. But if they are greater than unity, mosquito population persists and malaria also. They finally carried out numerical simulations to support their mathematical results.Okuneye et al. [19] developed a weather-driven malaria transmission model considering temperature-dependent Anopheles Plasmodium gonotrophic and sporogonic cycles. They explored the effect of incorporating diurnal temperature variations upon transmission. Analysis of their model showed that the non-trivial disease-free equilibrium is locally asymptotically stable when $R_0 < 1$. They carried out numerical simulations of their model, which suggested a non-linear hyperbolic relationship between the reproduction number and clinical malaria burden. They finally concluded that including the stages of the Anopheles gonotrophic cycle is minimal important while modeling the stages of plasmodium sporogonic cycle. Wedajo et al. [20] presented a deterministic mathematical model for the spread of malaria in human and mosquito population where treatment compartment is incorporated. Formular for the basic reproduction number, R_0, is established. They established the stability analysis of the disease-free equilibrium using Routh-Hurwitz stability criteria. Finally, they supported their analytical work with numerical simulations.

This article presents a mathematical model of malaria incorporating untreated liver-stage human compartment into the human population. This is a crucial stage where attention should be more focused because the untreated liver-stage human cannot yet infect a susceptible mosquito. Therefore, eradication of malaria at this stage prevents the occurrence of symptomatic stage of the infection. Consequently, we investigate the impact of untreated liver-stage humans on transmission dynamic of malaria. Theoretically, we give conditions for the existence of solution and analyze stability of disease-free equilibrium solution of the model. Moreover, sensitivity analysis of the model is also carried out.

This paper is organised as follows: in section 2, the variables and parameters are defined and the model is formulated. In section 3, the existence of solution of the model equations as well as basic reproduction number is established. In section 4, stability analysis is carried out. In section 5, sensitivity analysis of the model results are presented and in section 6, discussion and conclusion are made.

2. Model Formulation

In this section, a mathematical model for the transmission dynamics of malaria with untreated liver-stage humans, is formulated. A compartmental model is used in which individuals move between susceptible, untreated liver-stage, infectious, hospitalized and recovered classes in the human population and between susceptible, exposed and infectious classes in the mosquito vector population respectively.

The interaction of humans and infected mosquitoes is denoted by $\beta_1\beta_2 S_H I_V$ while $\beta_1\theta S_V I_H$ denotes the rate at which the susceptible mosquitoes are infected by infectious human hosts. We let $\varepsilon\beta_1\beta_2 S_H I_V$ be the fraction of the liver-stage humans who are not treated and $(1-\varepsilon)\beta_1\beta_2 S_H I_V$ be the remaining fraction of liver-stage humans who are treated. α is the progression rate of untreated liver-stage humans to infectious human compartment.

Definitions of Variables

$S_H(t)$: The number of susceptible human hosts at time t

$L_{UH}(t)$: The number of untreated liver-stage human hosts at time t

$I_H(t)$: The number of infectious human hosts at time t

$I_P(t)$: The number of hospitalized human hosts at time t

$R_H(t)$: The number of recovered human hosts at time t

$S_V(t)$: The number of susceptible mosquito vectors at time t

$E_V(t)$: The number of exposed mosquito vector at time t

$I_V(t)$: The number of infectious mosquito vectors at time t

2.1 Assumptions of the Model

The following assumptions were made in order to formulate the equations of the model:

(a) Fraction of liver-stage humans who are not treated progress to infectious human compartment

(b) All newborns are susceptible to infection

(c) Infectious humans progress to recovered human compartment when treated

(d) Infectious humans only recover from malaria through treatment

(e) Fraction of liver-stage humans who are treated progress to recovered human compartment.

(f) Total human population is not constant

(g) Infectious humans are hospitalized at the rate κ

Table 1. Summary of the parameters

Parameter	Meaning	Value	Reference
μ_h	Natural human death rate of human	$(0.0000548/\text{day})^{-1}$	[7]
ε	Fraction of untreated liver-stage humans who are not treated	0.5 day^{-1}	[Assumed]
Λ_h	Recruitment rate of humans	0.00011	[21]
β_1	Average daily biting rate by a single mosquito	0.00008 day^{-1}	Assumed
β_2	Probability that a bite infects a susceptible mosquito	0.3day^{-1}	[7]
ρ_1	Recovery rate of infectious humans	0.0022 day^{-1}	[22]
ρ_2	Recovery rate of hospitalized humans	0.0022 day^{-1}	[22]
δ_1	Malaria induced-death rate for I_H	0.333 day^{-1}	[18]
δ_2	Malaria induced-death rate for I_P	0.333 day^{-1}	[18]
κ	Hospitalization rate	0.05	Assumed
Λ_v	Recruitment rate of mosquitoes	0.071 day^{-1}	[21]
μ_v	Natural death rate of mosquito vector	0.00004 day^{-1}	[8]
θ	Probability that a susceptible mosquito becomes infected	0.0083 day^{-1}	[23]
β_3	Progression rate from E_V to I_V	$\frac{1}{18}$	[24]
α	Progression rate from E_H to I_H	$\frac{1}{17}$	[24]

The dynamics of the transmission is represented by the following system of ordinary differential equations:

$$\frac{dS_H}{dt} = \Lambda_h - \beta_1\beta_2 S_H I_V - \mu_h S_H, \tag{1}$$
$$\frac{dL_{UH}}{dt} = \varepsilon\beta_1\beta_2 S_H I_V - (\alpha+\mu_h)L_{UH}, \tag{2}$$
$$\frac{dI_H}{dt} = \alpha L_{UH} - (\rho_1+\kappa+\delta_1+\mu_h)I_H, \tag{3}$$
$$\frac{dI_P}{dt} = \kappa I_H - (\rho_2+\delta_2+\mu_h)I_P, \tag{4}$$
$$\frac{dR_H}{dt} = \rho_1 I_H + \rho_2 I_P - \mu_h R_H, \tag{5}$$
$$\frac{dS_V}{dt} = \Lambda_v - \beta_1\theta S_V I_H - \mu_v S_V, \tag{6}$$
$$\frac{dE_V}{dt} = \beta_1\theta S_V I_H - (\beta_2+\mu_v)E_V, \tag{7}$$
$$\frac{dI_V}{dt} = \beta_2 E_V - \mu_v I_V. \tag{8}$$

With initial conditions

$$S(0) = S_o > 0,\ L_{UH}(0) = L^0_{UH}(0) > 0,$$
$$I_H(0) = I^o_H(0) > 0,\ I_P(0) = I^o_P(0) > 0,$$
$$R_H(0) = R^o_H > 0,\ S_V(0) = S^o_V > 0,$$
$$S_V(0) = S^o_V > 0,\ I_V(0) = I^o_V > 0$$

2.2 Basic Properties of the Model

For the malaria model to be epidemiologically meaningful, it is important to prove that all state variables are non-negative at all times. That is, solutions of the model Eq. (1)-Eq. (8) with non-negative initial conditions or data, remain non-negative for all time $t > 0$.

Theorem 1: Let the initial data be $(S_H(0), L_{UH}(0), I_H0, I_P(0), R_H(0), S_V(0), E_V(0), I_V(0)) \in \Gamma$, then the solution set $S_H(t)$, $L_{UH}(t)$, $I_H(t)$, $I_P(t)$, $R_H(t)$, $S_V(t)$, $E_V(t)$, $I_V(t)$ of the model Eq. (1)-Eq. (8) is positive for all $t > 0$.

Proof: The first equation of the model Eq. (1)-Eq. (8) gives

$$\frac{dS_H}{dt} + \beta_1\beta_2 S_H I_V + \mu_h S_H \geq 0$$
$$\frac{d}{dt}[S_H exp^{\int_0^t \beta_1\beta_2(s)ds + \mu_h t}] \geq 0$$

This implies that

$$S_H \geq S_H(0) exp^{-(\int_0^t \beta_1\beta_2(s)ds + \mu_h t)} > 0, \text{ for all } t > 0$$

The same argument can be used to prove that the remaining state variables, $L_{UH}; I_H; I_P; R_H; S_V; E_V; I_V$ are non-negative for all time $t > 0$. □

Eq. (1)-Eq. (3) are independent of the states I_P and R_H and after decoupling the equations for I_P and R_H from the model, we have the remaining equations of the model below

$$\frac{dS_H}{dt} = \Lambda_h - \beta_1\beta_2 S_H I_V - \mu_h S_H, \tag{9}$$
$$\frac{dL_{UH}}{dt} = \varepsilon\beta_1\beta_2 S_H I_V - (\alpha+\mu_h)L_{UH}, \tag{10}$$
$$\frac{dI_H}{dt} = \alpha L_{UH} - (\rho_1+\kappa+\delta_1+\mu_h)I_H, \tag{11}$$
$$\frac{dS_V}{dt} = \Lambda_v - \beta_1\theta S_V - \mu_v S_V, \tag{12}$$
$$\frac{dE_V}{dt} = \beta_1\theta S_V I_H - (\beta_2+\mu_v)E_V, \tag{13}$$
$$\frac{dI_V}{dt} = \beta_2 E_V - \mu_v I_V. \tag{14}$$

2.3 Basic Reproduction Number

The computation of the basic reproduction number R_0 is needed in order to assess the global stability of disease-free equilibrium. This is obtained by expressing Eq. (1)-Eq. (8) as the difference between the rate of new infection in each infected compartment F and the rate of transfer between each

infected compartment G. Hence, we have

$$\begin{bmatrix} \frac{dL_{UH}}{dt} \\ \frac{dI_H}{dt} \\ \frac{dE_V}{dt} \\ \frac{dI_V}{dt} \end{bmatrix} = F - G$$

$$= \begin{bmatrix} \varepsilon\beta_1\beta_2 S_H I_V \\ 0 \\ \beta_1\theta S_V I_H \\ 0 \end{bmatrix} - \begin{bmatrix} m_1 L_{UH} \\ -\alpha L_{UH} + m_2 I_H \\ (\beta_3+\mu_v)E_V \\ -\beta_3 E_V + \mu_v I_V \end{bmatrix}$$

The Jacobian matrices J_F and J_G of F and G are found about E_0.

$$S = J_F J_G^{-1}$$

$$= \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{\beta_1\theta\Lambda_v}{\mu_v(\beta_3+\mu_v)} & \frac{\beta_1\theta\Lambda_v\beta_3}{\mu_v^2(\beta_3+\mu_v)} \\ 0 & 0 & 0 & 0 \\ \frac{\varepsilon\beta_1\beta_2\Lambda_h}{\mu_h m_1} & \frac{\varepsilon\beta_1\beta_2\Lambda_h\alpha}{\mu_h m_1 m_2} & 0 & 0 \end{bmatrix}$$

R_0 is the maximum eigenvalue of S given as

$$R_0 = \sqrt{\frac{\beta_1^2\beta_2\Lambda_h\theta\beta_3\Lambda_v\alpha\varepsilon}{m_1 m_2\mu_h\mu_v^2(\beta_3+\mu_v)}}$$

where

$$m_1 = \alpha + \mu_h$$
$$m_2 = \rho_1 = \kappa + \delta_1 + \mu_h$$

and

$$m_3 = \rho_2 + \delta_2 + \mu_h$$

3. Stability Analysis

The stability analyses of both the disease-free and endemic equilibrium points are investigated in what follows

3.1 Global Stability of the disease-free equilibrium

Theorem 2: The disease-free equilibrium E_0 of the model is globally asymptotically stable in Γ if $R_0 < 1$ and unstable if $R_0 > 1$.

Proof: Consider the Lyapunov function $L = \frac{\alpha}{m_1 m_2}L_{UH} + \frac{1}{m_2}I_H + \frac{\mu_v R_0}{\beta_1\theta\Lambda_v}E_V + \frac{\mu_v(\beta_3+\mu_v)R_0}{\beta_1\theta\beta_3\Lambda_v}I_V$. Its time derivative is

$$\begin{aligned}\dot{L} =& \frac{\alpha}{m_1 m_2}(\varepsilon\beta_1\beta_2 S_H I_V - m_1 L_{UH}) + \frac{1}{m_2}(\alpha L_{UH} - m_2 I_H) \\ &+ \frac{\mu_v R_0}{\beta_1\theta\Lambda_v}(\beta_1\theta S_V I_H - (\beta_3+\mu_v)E_V) \\ &+ \frac{\mu_v(\beta_3+\mu_v)R_0}{\beta_1\theta\beta_3\Lambda_v}(\beta_3 E_V - \mu_v I_V) \\ \dot{L} =& \frac{\beta_1\alpha\varepsilon\rho S_H I_V}{r_1 r_2} - C_H - \frac{\mu_v R_c S_V C_H}{\omega_v} - \frac{\mu_v^2(\beta_2+\mu_v)R_c I_V}{\alpha\eta\beta_2\omega_v} \\ \dot{L} =& \left[\frac{\alpha\varepsilon\beta_1\beta_2 S_H}{m_1 m_2} - \frac{\mu_v^2(\beta_3+\mu_v)R_0}{\beta_1\theta\beta_3\Lambda_v}\right]I_V + \left(\frac{\mu_v R_0 S_V}{\Lambda_v} - 1\right)I_H \\ \leq& \left[\sqrt{\frac{\alpha\varepsilon\beta_2\lambda_h\mu_v^2(\beta_3+\mu_v)}{m_1 m_2\theta\beta_3\Lambda_v}}(R_0-1)\right]I_V + (R_0-1)I_H \\ \leq& \left[\sqrt{\frac{\alpha\varepsilon\beta_2\Lambda_h\mu_v^2(\beta_3+\mu_v)}{m_1 m_2\theta\beta_3\Lambda_v}}.I_V + I_H\right](R_0-1)\end{aligned}$$

Therefore, $\dot{L} \leq 0$ for $R_0 \leq 1$ for $\dot{L} = 0$ if and only if $R_0 = 1$ or $I_H = 0$, $I_P = 0$ and $I_V = 0$. Consequently, the largest compact invariant set in $\{(S_H, L_{UH}, I_H, I_P, R_H, S_V, E_V, I_V) \in \Gamma : \dot{L} = 0\}$ is the E_0 and by Lyapunov-Lasalle's invariance principle, the disease-free equilibrium point is globally asymptotically stable in Γ if $R_0 \leq 1$ and this completes the proof.

The epidemiological implication of the above theorem is that malaria can be eradicated irrespective of the initial sizes of the sub-population of the model.

3.2 Global Stability of Endemic Equilibrium Point

The endemic equilibrium solution at steady state is $E_1 = (S_H^*, L_{UH}^*, I_H^*, S_V^*, E_V^*, I_V^*)$, where

$$S_H^* = \frac{\Lambda_h}{H_T^* + \mu_h}$$
$$L_{UH}^* = \frac{\varepsilon H_T^*\Lambda_h}{m_1(H_T^* + \mu_h)}$$
$$I_H^* = \frac{\alpha\varepsilon H_T^*\Lambda_h}{m_1 m_2(H_T^* + \mu_h)}$$
$$S_V^* = \frac{\Lambda_v}{G_T^* + \mu_v}$$
$$E_V^* = \frac{G_T^*\Lambda_v}{(\beta_3+\mu_v)(G_T^* + \mu_v)}$$
$$I_V^* = \frac{\beta_3 G_T^*\Lambda_v}{\mu_v(\beta_3+\mu_v)(G_T^* + \mu_v)}$$

where the forces of infection for humans and mosquitoes at equilibrium state are

$$H_T^* = \beta_1\beta_2 I_V^*$$

and

$$G_T^* = \beta_1\theta I_H^*$$

Substituting I_V^*, G_T^*, I_H^* and H_T^* in $H_T^* = \beta_1\beta_2 I_V^*$ gives the following linear equation:

$$X_1 H_T^* + X_2 = 0 \tag{15}$$

where

$$X_1 = \beta_1\theta\alpha\varepsilon\Lambda_v\mu_h + m_1 m_2\mu_h\mu_v$$

and

$$X_2 = (m_1 m_2\mu_h\mu_v)\mu_h(1-R_0^2)$$

From Eq. (15), $H_T^* = \dfrac{-X_2}{X_1} \leq 0$ if $X_2 \geq 0$ at $R_0 \leq 1$, and no endemic equilibrium exists. On the other hand, $H_T^* = \dfrac{-X_2}{X_1} > 0$ if $X_2 < 0$ at $R_0 > 1$. Hence, an endemic equilibrium exists only at $R_0 > 1$. □

The theorem below summarizes the above result.

Theorem 3: The model Eq. (1)-Eq. (8) has a unique endemic equilibrium whenever $R_0 > 1$, and no endemic equilibrium otherwise.

We establish the global stability of the endemic equilibrium solutions of the model Eq. (1)-Eq. (8), for the case $\varepsilon = 1$, hereunder.

Theorem 4: The unique endemic equilibrium E_1, is globally asymptotically stable whenever $R_0 > 1$.

Proof: We make use of Goh-Volterra type Lyapunov function [25].

Given the following equations which are satisfied by the endemic equilibrium point E_1:

$$\Lambda_h = \beta_1\beta_2 S_H^* I_V^* + \mu_h S_H^*, \tag{16}$$
$$\beta_1\beta_2 S_H^* I_V^* = m_1 L_{UH}^*, \tag{17}$$
$$\alpha L_{UH}^* = m_2 I_H^*, \tag{18}$$
$$\Lambda_v = \beta_1\theta S_V^* I_H^* + \mu_v S_V^*, \tag{19}$$
$$\beta_1\theta S_V^* I_H^* = m_3 E_V^*, \tag{20}$$
$$\beta_3 E_V^* = \mu_v I_V^*. \tag{21}$$

Consider the following Goh-Volterra Lyapunov function

$$\begin{aligned} V = &\left(S_H - S_H^* - S_H^*\ln\frac{S_H}{S_H^*}\right) \\ &+ \left(L_{UH} - L_{UH}^* - L_{UH}^*\ln\frac{L_{UH}}{L_{UH}^*}\right) \\ &+ a\left(I_H - I_H^* - I_H^*\ln\frac{I_H}{I_H^*}\right) \\ &+ \left(S_V - S_V^* - S_V^*\ln\frac{S_V}{S_V^*}\right) \\ &+ \left(E_V - E_V^* - E_V^*\ln\frac{E_V}{E_V^*}\right) \\ &+ b\left(I_V - I_V^* - I_V^*\ln\frac{I_V}{I_V^*}\right) \end{aligned}$$

where $a = \dfrac{\beta_1\theta S_V^*}{m_2}$ and $b = \dfrac{\beta_1\beta_2 S_H^*}{\mu_v}$ with the Lyapunov time derivative obtained as

$$\begin{aligned} \dot{V} = &\left(1-\frac{S_H^*}{S_H}\right)S_H' + \left(1-\frac{L_{UH}^*}{L_{UH}}\right)L_{UH}' + a\left(1-\frac{I_H^*}{I_H}\right)I_H' \\ &+ \left(1-\frac{S_V^*}{S_V}\right)S_V' + \left(1-\frac{E_V^*}{E_V}\right)E_V' + b\left(1-\frac{I_V^*}{I_V}\right)I_V' \\ \dot{V} = &\left(1-\frac{S_H^*}{S_H}\right)(\Lambda_h - \beta_1\beta_2 S_H I_V - \mu_h S_H) \\ &+ \left(1-\frac{L_{UH}^*}{L_{UH}}\right)(\beta_1\beta_2 S_H I_V - m_1 L_{UH}) \\ &+ a\left(1-\frac{I_H^*}{I_H}\right)(\alpha L_{UH} - m_2 I_H) \\ &+ \left(1-\frac{S_V^*}{S_V}\right)(\Lambda_v - \beta_1\theta S_H I_V - \mu_v S_V) \\ &+ \left(1-\frac{E_V^*}{E_V}\right)(\beta_1\theta S_V I_H - m_3 E_V) \\ &+ b\left(1-\frac{I_V^*}{I_V}\right)(\beta_3 E_V - \mu_v I_V) \end{aligned}$$

Using Eq. (16), we have

$$\begin{aligned} \dot{V} = &\left(1-\frac{S_H^*}{S_H}\right)(\beta_1\beta_2 S_H^* I_V^* + \mu_h S_H^* - \beta_1\beta_2 S_H I_V \\ &- \mu_h S_H) + \left(1-\frac{L_{UH}^*}{L_{UH}}\right)(\beta_1\beta_2 S_H I_V - m_1 L_{UH}) \\ &+ a\left(1-\frac{I_H^*}{I_H}\right)(\alpha L_{UH} - m_2 I_H) \\ &+ \left(1-\frac{S_V^*}{S_V}\right)(\Lambda_v - \beta_1\theta S_H I_V - \mu_v S_V) \\ &+ \left(1-\frac{E_V^*}{E_V}\right)(\beta_1\theta S_V I_H - m_3 E_V) \\ &+ b\left(1-\frac{I_V^*}{I_V}\right)(\beta_3 E_V - \mu_v I_V) \end{aligned}$$

Ignoring some terms and further simplification gives

$$\begin{aligned} \dot{V} = &\beta_1\beta_2 S_H^* I_V^* + m_1 L_{UH}^* + m_3 E_V^* + a m_2 I_H^* \\ &+ b\mu_v I_V^* - \frac{\beta_1\beta_2 (S_H^*)^2 I_V^*}{S_H} \\ &- \frac{\beta_1\beta_2 I_V S_H L_{UH}^*}{L_{UH}} - \frac{\beta_1\theta (S_V^*)^2 I_H^*}{S_V} \\ &- \frac{a\alpha L_{UH} I_H^*}{I_H} - \frac{\beta_1\theta S_V I_H E_V^*}{E_V} \\ &- \frac{b\beta_3 E_V I_V^*}{I_V} + 2\mu_h S_H^* - \frac{\mu_h (S_H^*)^2}{S_H} \\ &- \mu_h S_H - \frac{\mu_v (S_V^*)^2}{S_V} - \mu_v S_V + 2\mu_v S_V^* + \beta_1\theta S_V^* I_H^* \end{aligned}$$

Replacing a and b by their values and exploiting Eq. (16)-

Eq. (21) gives

$$a\alpha = \frac{\beta_1 \theta I_H^* S_V^*}{L_{UH}^*} \tag{22}$$

$$b\beta_3 = \frac{\beta_1 \beta_2 S_H^* I_V^*}{E_V^*} \tag{23}$$

Using Eq. (16)-Eq. (21) and Eq. (22)-Eq. (23), we have

$$\begin{aligned}
\dot{V} =& \mu_h S_H^* \left(2 - \frac{S_H^*}{S_H} - \frac{S_H}{S_H^*}\right) + 3\beta_1\beta_2 S_H^* I_V^* \\
& - \frac{\beta_1\beta_2 (S_H^*)^2 I_V^*}{S_H} - \frac{\beta_1\beta_2 S_H I_V L_{UH}^*}{L_{UH}} \\
& - \frac{\beta_1 \theta S_V^* L_{UH} (I_H^*)^2}{I_H L_{UH}^*} + \mu_v S_V^* (2 - \frac{S_V^*}{S_V} - \frac{S_V}{S_V^*}) \\
& + 3\beta_1 \theta S_V^* I_H^* - \frac{\beta_1 \theta (S_V^*)^2 I_H^*}{S_V} - \frac{\beta_1 \theta I_H S_V E_V^*}{E_V} \\
& - \frac{\beta_1 \beta_2 (I_V^*)^2 E_V S_H^*}{E_V^* I_V} \\
& \left(3 - \frac{S_H^*}{S_H} - \frac{S_H E_H^* I_H}{S_H^* E_H I_H^*} - \frac{E_H I_H^*}{E_H^* I_H}\right) \\
\dot{V} =& \mu_h S_H^* \left(2 - \frac{S_H^*}{S_H} - \frac{S_H}{S_H^*}\right) + \mu_v S_V^* \left(2 - \frac{S_V^*}{S_V} - \frac{S_V}{S_V^*}\right) \\
& + \beta_1\beta_2 I_V^* S_H^* \\
& \left(3 - \frac{S_H^*}{S_H} - \frac{S_H I_V L_{UH}^*}{S_H^* I_V^* L_{UH}} - \frac{\theta S_V^* L_{UH} (I_H^*)^2}{L_{UH}^* I_H \beta_2 I_V^* S_H^*}\right) \\
& + \beta_1 \theta S_V^* I_H^* \left(3 - \frac{S_V^*}{S_V} - \frac{I_H S_V E_V^*}{S_V^* I_H^* E_V} - \frac{\beta_2 (I_V^*)^2 E_V S_H^*}{E_V^* I_V \theta S_V^* I_H^*}\right)
\end{aligned}$$

Using arithmetic-geometric means inequality, i.e., $n - (a_1 + a_2 + ... + a_n) \leq 0$, where $a_1.a_2...a_n = 1$ and $a_1, a_2, ..., a_n > 0$, it follows that $\dot{V} \leq 0$ with $V = 0$ if and only if $S_H = S_H^*$, $L_{UH} = L_{UH}^*$, $I_H = I_H^*$, $S_V = S_V^*$, $E_V = E_V^*$, $I_V = I_V^*$.

Hence, the largest compact invariant subset of the set where $\dot{V} = 0$ is

$$(S_H, L_{UH}, I_H, S_V, E_V, I_V^*) = (S_H^*, L_{UH}^*, I_H^*, S_V^*, E_V^*, I_V^*)$$

and by classical stability theorem of Lyapunov and LaSalle's Invariance Principle, it follows that every solution in Γ approaches E_1 for $R_0 > 1$ as $t \to \infty$.

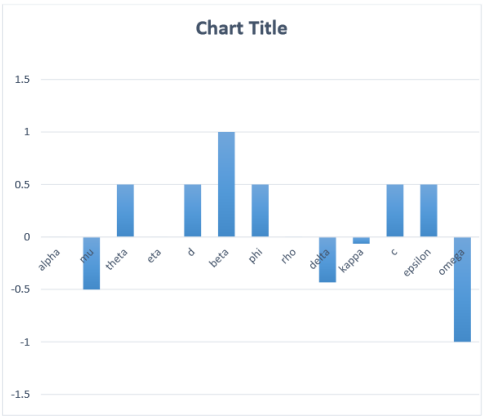
The epidemiological implication of the above result is that malaria will establish itself whenever $R_0 > 1$, in the population.

□

4. Sensitivity Analysis

In this section, a sensitivity analysis of parameters of the model system Eq. (1)-Eq. (6) is carried out so as to determine the relative importance of model parameters on the disease infection. The rationale is to consider and to manage several factors responsible for malaria infections.

Sensitivity indices are computed numerically to find out parameters that have reasonable impact on basic reproduction



number R_0 and which of the parameters is most sensitive which can help in combating the disease.

The analysis is conducted on all parameters which account for disease dynamics using [22] approach. Sensitivity indices is computed on the R_0, which measures initial disease infection and allows us to measure relative change in a state variable when a variable changes.

The normalized forward sensitivity index of a variable to a parameter is the ratio of the relative change in the variable to the relative change in the parameter. When the variable is a differentiable function of the parameter, the sensitivity index may be alternatively defined using partial derivatives.

Definition 1: The normalized forward sensitivity index of a variable, $u(p)$, that depends differentiably on a parameter, p, is defined as:

$$N_p^u = \frac{\partial u}{\partial p} \times \frac{p}{u} \quad \text{for } u \neq 0$$

Consequently, we derive analytical expression for the sensitivity index of R_0 as

$$N_{p_i}^{R_0} = \frac{\partial R_0}{\partial p_i} \times \frac{p_i}{R_0}$$

where $p_i, i \in \mathbb{N}$ denotes each parameter involved in R_0

$$R_0 = \sqrt{\frac{\beta_1^2 \beta_2 \Lambda_h \theta \beta_3 \Lambda_v \alpha \varepsilon}{m_1 m_2 \mu_h \mu_v^2 (\beta_3 + \mu_v)}}$$

where $m_1 = \alpha + \mu_h$ and

$$m_2 = \rho_1 + \kappa + \delta_1 + \mu_h$$

and parameters values in Table 1. We compute sensitivity index of each parameter with respect to the R_0, for instance:

$$N_{\beta_1}^{R_0} = \frac{\partial R_0}{\partial \beta_1} \times \frac{\beta_1}{R_0} = 1.00000$$

We have Table 2 which summarizes the sensitivity indices on R_0 with respect to parameters i.e

$$N_{\beta_2}^{R_0}, N_{\theta}^{R_0}, N_{\varepsilon}^{R_0}, N_{\rho_1}^{R_0}, N_{\alpha}^{R_0}, N_{\delta_1}^{R_0}, N_{\Lambda_v}^{R_0}, N_{\Lambda_h}^{R_0}, N_{\kappa}^{R_0}, N_{\beta_3}^{R_0}$$

Table 2. Numerical values of sensitivity indices of R_0 with respect to parameter involved .

Parameter symbol	Sensitivity Index
β_1	+1.00000
β_2	+0.50000
θ	+0.50000
ε	+0.50000
α_1	-0.00046
ρ_1	-0.00285
δ_1	-0.43218
κ	-0.06489
Λ_v	+0.50000
μ_v	-1.00035
β_3	0.00035
Λ_h	0.50000

5. Interpretation of sensitivity Indices obtained in Table 2

Sensitivity indices on R_0 with respect to the involved parameters gives insights to the model system proposed. Provided all parameters remain constant, most sensitive parameter is β_1 (Average daily biting rate by a single mosquito) being the highest positive index. The indication is that if β_1 increases, then R_0 increases by 100%. Thus, as R_0 continues to be higher, epidemic of the disease infection tends to occur. In the same vein, sensitivity indices of $\beta_2, \theta, \varepsilon, \Lambda_h$ show direct variation with respect to R_0. Precisely, increase in ε (portion of liver-stage human who are not treated) increases R_0 as well as Λ_v (recruitment rate of mosquitoes). On the other angle, μ_h (Natural birth rate of mosquito vector) has highest negative impact on R_0, followed by δ_1 (Malaria induced-death rate of infectious human compartment), followed by κ (rate of hospitalization) and ρ_1 (recovery rate of infectious human). It implies that increase in these parameters will cause decrease in R_0 drastically and thereby leading to malaria infection going into extinction. These parameters are significant in curtailing the malaria infection. The diagram above also confirms the illustration.

6. Conclusion

A model for the transmission dynamics of malaria that captures untreated hepatic-stage humans, is formulated. The untreated liver-stage human compartment is introduced in order to reduce the ignorance of people to this group (the untreated hepatic-stage humans), as these are the group who progress to become infectious. The disease-free equilibrium of the model is obtained to be both locally and globally stable for $R_o < 1$. It is also shown that the endemic equilibrium solution of the model is locally stable for $R_o > 1$. The result from the sensitivity analysis shows that increasing the value of any of the parameters $\beta_1, \beta_2, m, \theta, \varepsilon, \alpha$ increase the basic reproduction number, R_o, and the magnitude of the infectious individuals in the community. Most importantly, increase in ε, i.e portion of the untreated liver-stage human has positive impact on R_o. Therefore, it is necessary medically to control plasmodium parasite at this stage (liver-stage) before they undergo nuclear division where thousands of them move down to the blood stream of humans as merozoites (blood stage) and after which they become gametocytes as the merozoites mature sexually. This method will help to reduce the occurrence of malaria in a population since the group can be restricted from progressing to become infectious with adherence to prophylactic measure, after being bitten by an infected mosquito. Also increase in education r, on adherence to prophylactic measures reduces the spread of malaria in the population. In view of the above, liver-stage humans should be encouraged to adhere to prophylactic measures, which will help to reduce the spread of malaria in the population.

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