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MODELLING OF THE IN-HUMAN HOST AND IN MOSQUITO DYNAMICS OF PARASITE

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Abstract. Malaria is one of infectious diseases that kill a large number of people worldwide, mostly in sub-Saharan Africa. Recently, mathematical models on the in-human host dynamics of malaria has increasingly attracted researchers' interests. This study proposed a mathematical model to describe in-human host and in-mosquito dynamics of malaria. The expression of the basic reproduction number, $\mathscr{R}_0$ of this model is established. Sensitivity analysis of $\mathscr{R}_0$ with respect to each of the parameters is carried out in model validation. Effects of parameters of $\mathscr{R}_0$ was discussed to determine their implications in the control of malaria infection. Infection rate of red blood cells (RBCs) by merozoites, the death rate of merozoites, number of merozoites released per rupturing schizont were found to be crucial parameters in control strategies. Moreover, a number of merozoites released per rupturing schizont and the proportion of merozoites that proceed with asexual replication are the most sensitive parameters. However, numerical simulations show the latter is biologically impractical since a reduction in its magnitude reduces the number of merozoites and at the same time increases the number of gametocytes. Despite having lower sensitivity index compared to the death rate of merozoites, death rate of schizonts have a greater impact on malaria control than that of merozoites.

Keywords: malaria parasite; in-host and in-mosquito dynamics; reproduction number; sensitivity analysis.

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1. Introduction

Despite being both preventable and curable, the impact of malaria on both public health and economic growth worldwide is still high [1]. Children under the age of five years and pregnant women are the most affected groups, and incidence is highest in sub-Saharan Africa. For instance, in 2012, malaria killed almost one child below age o five years in every minute worldwide [2] and global expenditure on malaria control increased from an estimated US$ 960 million to US$ 2.5 billion at annual rate of 4% between 2005 and 2014 [3].

In vertebrate hosts, malaria infection is caused by parasites of more than one hundred species of *Plasmodium*, but only four of these: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malariae* infect humans. Among them, *P.falciparum* is the most pathogenic to humans, especially in Africa. The infection due *P.falciparum* can develop quickly and produce several life-threatening complications such as miscariage, fluid in the lungs, kidney failure, abnormal liver function, anemia, low blood sugar. However, with immediate and effective treatement, it is always curable [3]-[4].

Between human hosts, malaria parasites are transmitted by bites of infected female mosquitoes. Malaria parasite has a complex and multi-stage life cycle in which parasite goes through over a dozen of discernible stages of development as it moves from the mosquito vector to the human host and back again [5]. A simple way to conceptulize this cycle is consider it as set of three sub-cycles: the *exo-erythrocytic* cycle, the *erythrocytic* cycle and the *sporogonic* cycle (See Figure 1). The first two cycles take place in human and the latter occurs in mosquito. In mosquitoes, malaria parasites undergo sexual reproduction by merging the parasites sexual cells (macrogametes and microgametes) while in human, the parasite undergo asexual reproduction (by cell division), initially in hepatocyte liver cells (HLCs) and then, repeatedly, in red blood cells (RBCs).

The exo-erythrocytic cycle starts when the infected mosquito injects *sporozoites*, infectious form of parasites, into human host's skin during its blood meal. Within 15-30 minutes sporozoites travel to the liver through some defensive hepatic macrophages (Kupffer cells) which are impermeable to drugs [6]. The number of sporozoites injected is independent of sporozoites number within mosquito's salivary gland, and in most case less than twenty five sporozoites

are injected per bite [7]. In the liver, sporozoites infect the HCLs where they undergo asexual (mitotic) replication and mature to *schizonts*. After 5-16 days matured liver schizonts rupture and release thousands of *merozoites*, invasive form of malaria parasites, into the blood stream.

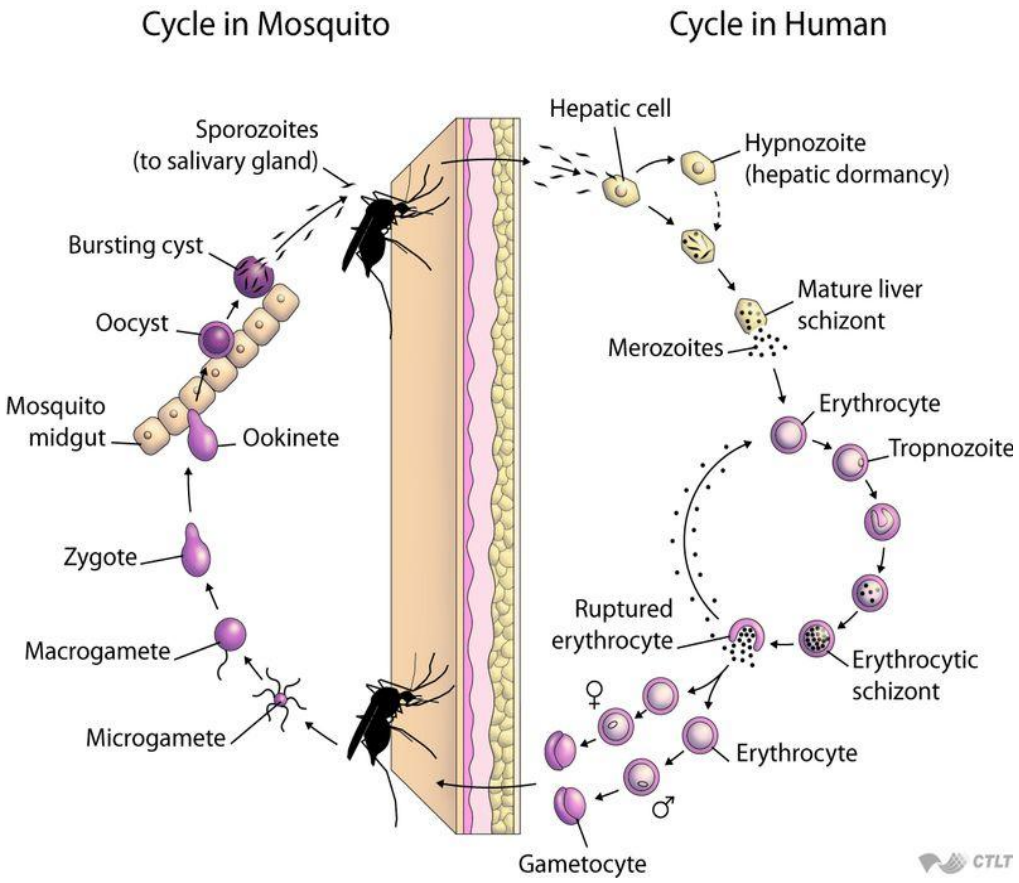


FIGURE 1. Malaria Life Cycle: [8]

The erythrocytic cycle starts when the released merozoites recognize and invade RBCs. After 48 hours, merozoites starts another mitotic replication in RBCs which is quicker and less prolific compared to that in the liver [9]. In RBCs they develop into mature schizonts through ring and trophozoite stages, which finally rupture and release an average of 16 new merozoites per infected RBCs [10] that re-invade other healthy RBCs. In each replication cycle, merozoites develop into one of two ways, either as *asexuals*, which go on to produce other new merozoites, or *sexually*, as gametocytes, which is form of parasite responsible for transmission to mosquito

[11]. Although, the reason to why some merozoites switch to gametocytes is not understood, but it occurs at or before the merozoites stage [12].

The sporogonic cycle starts when a blood feeding-mosquito takes its meal and ingests gametocytes which then transform into gametes within the mosquito's midgut. The number of gametocytes ingested by mosquito per bite depends on gametocytes load in bloodstream [7]. The male and female gametes fuse and form a mobile fertilized zygote called ookinete that develops into oocyst. Finally, oocysts grow, rupture, and release sporozoites that migrate to the mosquito's salivary glands, ready for transmission to a new host.

Mathematical models have been a useful tool to study the dynamics of infectious diseases because in most cases real experiments are either impossible, unethical or expensive [13]. Undestanding the complexity of this life cycle, where parasite develops through various stages with unique shape and structure each, suggests the use of mathematical models to increase insight on the disease dynamics and improve the likelihood of developing new safe and effective control strategies to rid us of malaria [14]-[15].

Several studies on mathematical modelling of *in vivo* dynamics of malaria parasites have been done. Among the earliest models used to discuss *in vivo* dynamics of malaria was the model introduced by Anderson and others in 1989 as described by Chiyaka *et. al* [9] and Iggidr *et. al* [16], where interaction between unifected RBCs, infected RBCs, and free merozoites was discussed. The extension of this model was done by many other authors to include immune effectors. [See [4], [6], [17] and the references therein]. Further extension of the model was done by Chiyaka *et. al* [9] to include the antibodies and treatment.

All of these studies discussed the erythrocytic dynamics of malaria parasites. To best the knowledge of the authors, exo-erythrocytic and sprogonic dynamics have not yet covered in the study of mathematical modelling for dynamics of malaria parasites. Moreover, Prudêncio [18] argued that liver stage has greatest and most under-exploited potential for intervention, despite being the most understudied stage of malaria parasite. In this study, we formulated and analyzed a basic mathematical model that include all phases of malaria parasite's life cycle, in which the sporozoites-HLCs and merozoites-RBCs interaction assumed to be the mass action.

2. Model Formulation

The model has two settings, within the human host and within the mosquito. Within the human host, the cells are divided into two sub-populations namely, the hepatocytes liver cells (HLCs) and the red blood cells (RBCs). HLCs are divided into uninfected HLCs, H, early infected HLCs, I_h and matured infected HLCs (Liver-Schizonts), T_h. The RBCs are divided into uninfected RBCs, R, early infected RBCs, I_r, matured infected RBCs (Blood-Schizonts), T_r, which develop to either asexual form called merozoites, M or sexual form called gametocytes, G_b. Within the vector, when the mosquito bites the infected human it takes in gametocytes, which develops into mature sexual cells called gametes, G_m. The female and male gametes fuse and develop to Oocysts, C and finally ruptures and form sporozoites, S_m.

An infected mosquito bites uninfected human host and injects the sporozoites, S_h, into the liver at constant rate $ab\nu$, where a is number of mosquito bites per individual, b is number of sporozoites injected per bite and ν is probability that a mosquito bite is infective to human. In the liver, S_h attack the healthy HLCs, H at a rate $\beta_1 S_h H$, and multiply asexually in liver cells to generate infected HLCs I_h, which progress to liver-chizont, T_h at the rate, $\alpha_1 T_h$. Over time, T_h rupture to release merozoites, M at the rate $\delta_1 T_h$. Merozoites enter the bloodstream and attack uninfected RBCs, R, at the rate $\beta_2 RM$, and multiply again to generate infected RBCs, I_r. The I_r develop to blood-schizont, T_r at a rate $\alpha_2 I_r$. The T_r rupture to release r_2 new merozoites per cell at a rate, $\delta_2 T_r$. Some of these relesead merozoites continue with asexual multiplication to produce other merozoites, at $p\delta_2 T_r$ and invade new RBCs. Some of them switch to gametocytes, G_b (sexual form) at a rate $(1-p)\delta_2 T_2$.

An uninfected mosquito bites an infected human and ingests the gametocytes G_b, which develop further into mature sexual cells called gametes G_m, at the rate $\rho q \omega G_b$, where ρ is number of bites a mosquito made during its lifetime, ω is number of gametocytes ingested per bite and q is probability that a mosquito bite is infective to mosquito while G_b is number of gametocytes in blood stream. In the mosquito's midgut the microgametes fuse with macrogametes, to develop into Oocysts C, at a rate, $\alpha_3 G_m$. Then, C, ruptures to release sporozoites S_m at a rate, $\delta_3 C$ which migrates to salivary glands ready for infection to the new host.

H and I_h die at rates, μ_h and μ_{ih} respectively, while T_h dies at a rate μ_{th}. Similary, R and I_r die at rates μ_r and μ_{ir} respectively while T_r dies at a rate μ_{tr}. The death rates of S_h and S_m are μ_{sh} and μ_{sm} respectively, and that of M is, μ_m. The HLCs and RBCs are recruited from bone marrow at rates Λ_h and Λ_r respectively. In the development of this model, we make the following assumptions:

i). The HLCs are regenerated by constant rate from bone marrow stem cells and die naturally.

ii). The RBCs are released from bone marrow at a constant rate and die naturally.

iii). HLCs and RBCs are infected at a rate proportional to their density.

iv). Mosquito-human infection is independent of sporozoites load in salivary gland, while human-mosquito infection depends on gametocytes load in blood stream [7].

v). The infected cells die faster than uninfected ones.

vi). The injected sporozoites and the released merozoites either die or successfully infect the HLCs and RBCs respectively.

vii). The ingested gametocytes either die or macrogametes and microgametes successfully fuse.

viii). Constant proportion of asexual parasites converts to gametocytes within each cycle.

ix). The cycle starts when the infected mosquito bites the human.

x). Bite of an infected mosquito onto an infected host is neglected.

xi). Survival of mosquito depends on human blood for developing their eggs.

Based on the dynamics and assumptions described above, the proposed model for the in-human host and in-mosquito dynamics of malaria parasites is as shown in Figure 2.

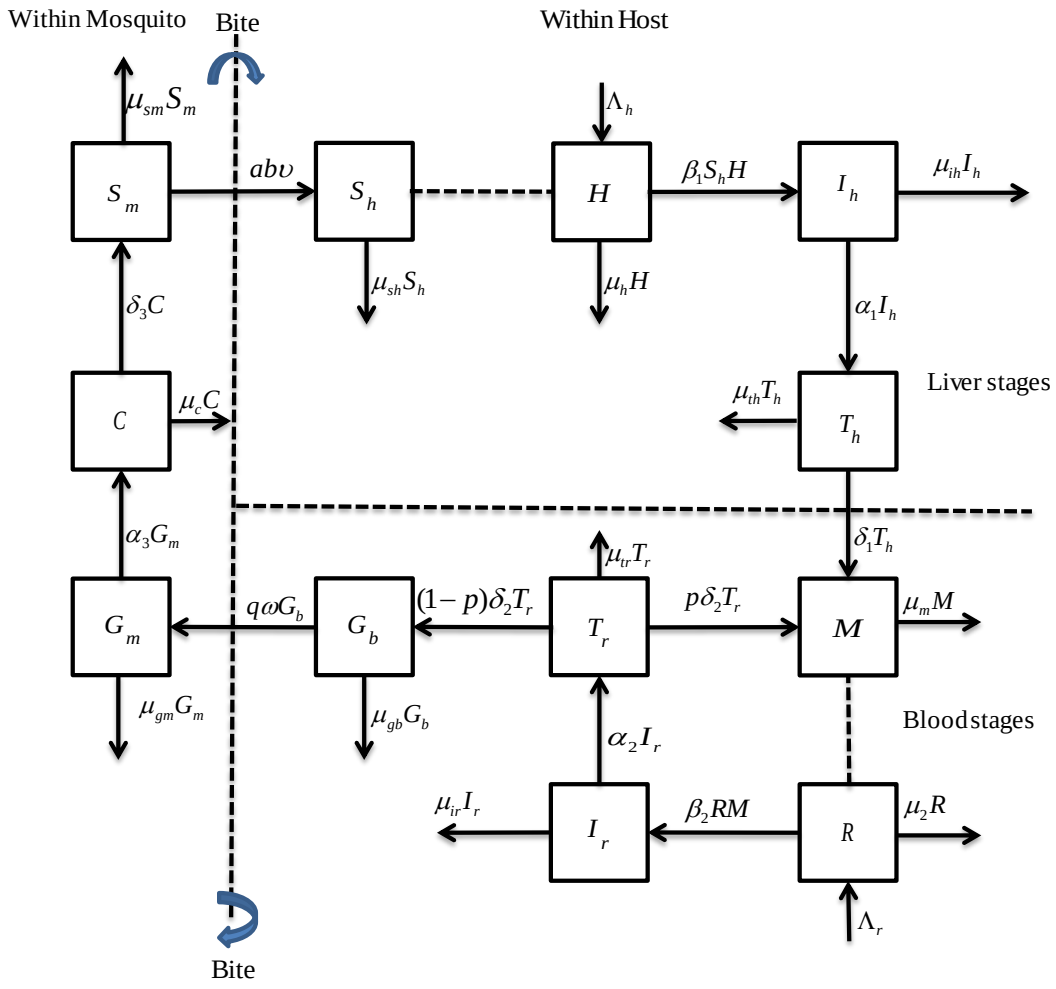


FIGURE 2. Model compartmental diagram for the in-human host and in-mosquito dynamics of malaria parasite

The variables and parameters are described in Table 1 and Table 2, respectively.

TABLE 1. List of state variables

Variable	**Descrption**
S_h :	number of sporozoites in human
H :	number of uninfected HLCs
I_h :	number of infected HLCs
T_h :	number of liver schizonts
T_r :	number of blood schizonts
M :	number of merozoites
R :	number of uninfected RBCs
I_r :	number of infected RBCs
G_b :	number of gametocytes
G_m :	number of gametes
C :	number of Oocysts
S_m :	number of sporozoites in mosquito

Based on the variables and parameters which are respectively described in Table 1 and Table 2, and the assumptions stated above, the in-human host and in-mosquito dynamics of malaria, captured in Figure 1, are governed by the following system of ordinary differential equations.

$$\text{(1a)}\quad \frac{\mathrm{d}H}{dt} = \Lambda_h - \beta_1 S_h H - \mu_h H$$

$$\text{(1b)}\quad \frac{\mathrm{d}I_h}{dt} = \beta_1 S_h H - \alpha_1 I_h - \mu_{ih} I_h$$

$$\text{(1c)}\quad \frac{\mathrm{d}T_h}{dt} = \alpha_1 I_h - \delta_1 T_h - \mu_{th} T_h$$

$$\text{(1d)}\quad \frac{\mathrm{d}M}{dt} = r_1 \delta_1 T_h + p r_2 \delta_2 T_r - \beta_2 R M - \mu_m M$$

$$\text{(1e)}\quad \frac{\mathrm{d}R}{dt} = \Lambda_r - \beta_2 R M - \mu_r R$$

$$\text{(1f)}\quad \frac{\mathrm{d}I_r}{dt} = \beta_2 R M - \alpha_2 I_r - \mu_{ir} I_r$$

$$\text{(1g)}\quad \frac{\mathrm{d}T_r}{dt} = \alpha_2 I_r - \delta_2 T_r - \mu_{tr} T_r$$

$$\text{(1h)}\quad \frac{\mathrm{d}G_b}{dt} = (1-p) r_2 \delta_2 T_r - q\omega G_b - \mu_{gb} G_b$$

$$\text{(1i)}\quad \frac{\mathrm{d}G_m}{dt} = \rho q \omega G_b - \alpha_3 G_m - \mu_{gm} G_m$$

$$\text{(1j)}\quad \frac{\mathrm{d}C}{dt} = \alpha_3 G_m - \delta_3 C - \mu_c C$$

$$\text{(1k)}\quad \frac{\mathrm{d}S_m}{dt} = r_3 \delta_3 C - a\nu S_m - \mu_{sm} S_m$$

$$\text{(1l)}\quad \frac{\mathrm{d}S_h}{dt} = ab\nu - \beta_1 S_h H - \mu_{sh} S_h$$

3. Analysis of the Model

In this section, the invariant region, the positivity of solutions and existence of malaria free equilibrium of model system (1a)-(1l) are studied. The invariant region describes the region in which the solutions of the system are biologically feasible whereas positivity describes non negativity of the solutions of the system.

3.1 Invariant Region

Using equations (1a)-(1c) we define the function

$$N_h(t) = H(t) + I_h(t) + T_h(t)$$

to be the total population of liver cells which implies

$$\frac{dN_h}{dt} = \Lambda_h - \mu_h H - \mu_{ih} I_h - (\mu_{th} + \delta_1) T_h$$

Hence,

$$\frac{dN_h}{dt} \leq \Lambda_h - \mu_1 N_h, \tag{2}$$

where,

$$\mu_1 = \min\{\mu_h,\ \mu_{th} + \delta_1\}.$$

Since one of the model assumption guarantees that $\mu_h < \mu_{ih}$. Using Birkhoff and Rota's theorem on differential inequalities on solving (2) and applying initial conditions, we get

$$N_h(t) \leq \frac{\Lambda_h}{\mu_1} + \left(N_h(0) - \frac{\Lambda_h}{\mu_1}\right) e^{-\mu_1 t} \tag{3}$$

Case 1: When $N_h(0) - \dfrac{\Lambda_h}{\mu_1} > 0$,
The largest value of RHS of inequality (3) occurs at $t = 0$, and that value is $N_h(0)$.
Hence,

$$N_h(t) \leq N_h(0),\ \ \forall t. \tag{4}$$

Case 2: When $N_h(0) - \dfrac{\Lambda_h}{\mu_1} < 0$,
The value of $\left(N_h(0) - \dfrac{\Lambda_h}{\mu_1}\right) e^{-\mu_1 t}$ is negative and it approaches 0 as $t \to \infty$.
Therefore, the largest value that the RHS of inequality (3) is $\dfrac{\Lambda_h}{\mu_1}$, $\ \forall t$.
Thus,

$$N_h(t) \leq \frac{\Lambda_h}{\mu_1} \tag{5}$$

Hence from (4) and (5), we conclude that

$$N_h(t) \leq \max\left\{N_h(0),\ \frac{\Lambda_h}{\mu_1}\right\},$$

for all values of t and whatever value of $N_h(0)$.

In similar approach, we have the following results:

From equations (1e)-(1g) we define the function

$$N_r = R + I_r + T_r$$

as the total population of RBCs which implies that

$$\frac{\mathrm{d}N_r}{dt} = \Lambda_r - \mu_r R - \mu_{ir} I_r - (\mu_{tr} + \delta_2) T_r$$

hence

$$\frac{\mathrm{d}N_r}{dt} \leq \Lambda_r - \mu_2 N_r \tag{6}$$

where $\mu_2 = \min\{\mu_r,\ \mu_{tr} + \delta_2\}$

so, we obtain

$$N_r(t) = R(t) + I_r(t) + T_r \leq \max\left\{N_r(0),\ \frac{\Lambda_r}{\mu_2}\right\} \tag{7}$$

From equation (1h) and using the fact $T_r \leq \dfrac{\Lambda_r}{\mu_2}$ from (7), we have

$$G_b(t) \leq \max\left\{G_b(0),\ \frac{(1-p) r_2 \delta_2}{\mu_{gb}} \frac{\Lambda_r}{\mu_2}\right\} \tag{8}$$

Using equations (1i) and (1j) we define

$$N_m(t) = G_m(t) + C(t)$$

as total the population of parasites in mosquito's midgut which implies that

$$\frac{\mathrm{d}N_m}{dt} \leq q\rho\omega G_b - \mu_3 N_m \tag{9}$$

where $\mu_3 = \min\{\mu_{gm}, \mu_c\}$, hence by (8) and (9) we obtain

$$N_m(t) \leq \max\left\{N_m(0),\ \frac{q\rho\omega}{\mu_3}\left[\frac{(1-p) r_2 \delta_2}{\mu_{gb}} \frac{\Lambda_r}{\mu_2}\right]\right\}$$

Lastly, using equations (1d), (1k) and (1l) respectively, we obtain

$$M(t) \leq \max\left\{M(0),\ \frac{1}{\mu_m}\left[r_1 \delta_1 \frac{\Lambda_h}{\mu_1} + p r_2 \delta_2 \frac{\Lambda_r}{\mu_2}\right]\right\},$$

$$S_m(t) \leq \max\left\{S_m(0),\ \frac{r_3 \delta_3}{\mu_{sm}} \frac{q\rho\omega}{\mu_3}\left[(1-p) r_2 \delta_2 \frac{\Lambda_r}{\mu_2}\right]\right\}$$

and

$$S_h(t) \leq \max\left\{S_h(0),\ \frac{ab\nu}{\mu_{sh}}\right\}$$

Therefore, the positively invariant region for the model (1a)-(1l) is

$$\begin{aligned}\Omega = \Bigg\{ &(H,I_h,T_h,M,R,I_r,T_r,G_b,G_m,C,S_m,S_h) \in \mathbb{R}_+^{12} : N_h(t) \leq \max\left\{N_h(0),\ \frac{\Lambda_h}{\mu_1}\right\},\\ &N_r(t) \leq \max\left\{N_r(0),\ \frac{\Lambda_r}{\mu_2}\right\},\ M(t) \leq \max\left\{M(0),\ \frac{1}{\mu_m}\left[r_1\delta_1\frac{\Lambda_h}{\mu_1} + pr_2\delta_2\frac{\Lambda_r}{\mu_2}\right]\right\},\\ &G_b(t) \leq \max\left\{G_b(0),\ (1-p)r_2\delta_2\frac{\Lambda_r}{\mu_2}\right\},\ N_m(t) \leq \max\left\{N_m(0),\ \frac{q\rho\omega}{\mu_3}\left[(1-p)r_2\delta_2\frac{\Lambda_r}{\mu_2}\right]\right\},\\ &S_m \leq \max\left\{S_m(0),\ \frac{r_3\delta_3}{\mu_{sm}}\frac{q\rho\omega}{\mu_3}\left[(1-p)r_2\delta_2\frac{\Lambda_r}{\mu_2}\right]\right\},\ S_h(t) \leq \max\left\{S_h(0),\ \frac{ab\nu}{\mu_{sh}}\right\}\Bigg\}\end{aligned}$$

3.2 Positivity of the Solutions

Since the model (1a)-(1l) governs the population of cells and parasites within and in-mosquito cells, then we need to show that solutions of the system (1a)-(1l) with positive initial conditions remain positive for all $t > 0$. That is, we need to prove that all the state variables are nonnegative. This is done by proving the following lemma.

Lemma 3.1. *Let the initial conditions for the model (1a)-(1l) be*

$$(H(0),I_h(0),T_h(0),M(0),R(0),I_r(0),T_r(0),G_b(0),G_m(0),C(0),S_m(0),S_h(0)) > 0,$$

then the solution

$$(H(t),I_h(t),T_h(t),M(t),R(t),I_r(t),T_r(t),G_b(t),G_m(t),C(t),S_m(t),S_h(t))$$

of the model (1a)-(1l) is non-negative for all values of $t > 0$.

Proof. From equation (1a), we have

$$\frac{\mathrm{d}H}{dt} = \Lambda_h - \beta_1 S_h H - \mu_h H \geq -(\beta_1 S_h + \mu_h)H$$

which yields to

$$H(t) \geq H(0)\exp(-\int_0^t \beta_1 S(z)dz + \mu_h t) > 0$$

since $H(0) > 0$, and from equation (1b), we have

$$\frac{\mathrm{d}I_h}{dt} = \beta_1 S_h H - \alpha_1 I_h - \mu_{ih} I_h \geq -(\alpha_1 + \mu_{ih}) I_h$$

gives

$$I_h(t) \geq I_h(0) \exp(-(\alpha_1 + \mu_{ih})t) > 0$$

since $I_h(0) > 0$.

Using the equations (1c)-(1l), other variables can similarly shown that they are non-negative. This completes the proof. Therefore the solution of the model (1a)-(1l) is non-negative for all values of $t > 0$.

3.3 Existence of Malaria Free Equilibrium

Malaria-free equilibrium (MFE) is the state where there is no infection. MFE of the system (1a)-(1l) is obtained by setting right hand side of the model equations equal to zero and solving for variables provided all infectious state variables assume the value of zero.

Let

$$E^0 = (H^0, I_h^0, T_h^0, M^0, R^0, I_r^0, T_r^0, G_b^0, G_m^0, C^0, S_m^0, S_h^0)$$

be the MFE of the system (1a)-(1l), then in absence of infection,

$$I_h^0 = T_h^0 = M^0 = I_r^0 = T_r^0 = G_b^0 = G_m^0 = C^0 = S_m^0 = S_h^0 = 0.$$

Using equations (1a) and (1e), we obtain

$$H^0 = \frac{\Lambda_h}{\mu_h} \quad \text{and} \quad R^0 = \frac{\Lambda_r}{\mu_r}$$

Therefore the MFE is

$$E^0 = \left(\frac{\Lambda_h}{\mu_h}, 0, 0, 0, \frac{\Lambda_r}{\mu_r}, 0, 0, 0, 0, 0, 0, 0, 0\right)$$

3.4 Basic Reproduction Number, $\mathscr{R}_0$

Guardiola and Vecchio [19] defined the intra-host reproduction number as number of newly infected cells produced by a single infected cell during its infectious lifetime.

We used the next generation matrix technique by Van den Driessche and Watmough [19] to compute $\mathscr{R}_0$, which is given by the dominant eigenvalue of

$$\left[\frac{\partial \mathscr{F}_i}{\partial x_i}(E^0)\right]\left[\frac{\partial \mathscr{V}_i}{\partial x_i}(E^0)\right]^{-1}$$

where $\mathscr{F}_i$ be the rate of appearance of new infection in compartment i,

$\mathscr{V}_i^+$ be the rate of transfer of individuals into compartment i by all other means,

$\mathscr{V}_i^-$ be the rate of transfer of individuals out of compartment i by all other means and

$\mathscr{V}_i = \mathscr{V}_i^+ - \mathscr{V}_i^-$.

From system of equations (1a)-(1j), the matrices F and V are

$$F = \left.\frac{\partial \mathscr{F}_i}{\partial x_j}\right|_{E^0} = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \beta_1\frac{\Lambda_h}{\mu_h} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \beta_2\frac{\Lambda_r}{\mu_r} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \rho q \omega & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix} \tag{10}$$

and

$$V = \left.\frac{\partial \mathcal{Y}_i}{\partial x_j}\right|_{E^0} = \begin{pmatrix} v_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -\alpha_1 & v_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & v_3 & v_4 & 0 & v_5 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & v_6 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -\alpha_2 & v_7 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & v_8 & v_9 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \alpha_3 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -\alpha_3 & v_{10} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & v_{11} & v_{12} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & v_{13} \end{pmatrix} \tag{11}$$

where

$$\begin{aligned} v_1 =& \alpha_1 + \mu_{ih},\ v_2 = \delta_1 + \mu_{th}, v_3 = -r_1\delta_1,\ v_4 = \beta_2\frac{\Lambda_r}{\mu_r} + \mu_m, v_5 = -pr_2\delta_2, \\ v_6 =& \alpha_2 + \mu_{ir},\ v_7 = \delta_2 + \mu_{tr},\ v_8 = -(1-p)r_2\delta_2,\ v_9 = q\omega + \mu_{gb}, \\ v_{10} =& \delta_3 + \mu_c,\ v_{11} = -r_3\delta_3,\ v_{12} = a\nu + \mu_{sm} \text{ and } v_{13} = \beta_1\frac{\Lambda_h}{\mu_h} + \mu_{sh} \end{aligned} \tag{12}$$

Then we compute the inverse, V^{-1}, of V from (11), and we obtain

$$V^{-1} = \begin{pmatrix} \frac{1}{v_1} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{\alpha_1}{v_2 v_1} & \frac{1}{v_2} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{v_3\alpha_1}{v_4 v_2 v_1} & \frac{v_3}{v_4 v_2} & \frac{1}{v_4} & \frac{v_5\alpha_2}{v_7 v_6 v_4} & \frac{v_5}{v_7 v_4} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{1}{v_6} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{\alpha_2}{v_7 v_6} & \frac{1}{v_7} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{\alpha_2 v_8}{v_9 v_7 v_6} & \frac{v_8}{v_9 v_7} & \frac{1}{v_9} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \frac{1}{\alpha_3} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \frac{1}{v_{10}} & \frac{1}{v_{10}} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \frac{v_{11}}{v_{10} v_{12}} & \frac{v_{11}}{v_{12} v_{10}} & \frac{1}{v_{12}} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{1}{v_{13}} \end{pmatrix} \tag{13}$$

Hence, from (10) and (13), we have

$$FV^{-1} = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & A_1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ A_2 & A_3 & A_4 & A_5 & A_6 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & A_7 & A_8 & A_9 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix} \tag{14}$$

where,

$$\begin{aligned} A_1 &= \frac{\beta_1 \Lambda_h}{v_{13}\mu_h},\ A_2 = \frac{\beta_2 \alpha_1 v_3 \Lambda_r}{v_4 v_2 v_1 \mu_r},\ A_3 = \frac{\beta_2 v_3 \Lambda_r}{v_4 v_2 \mu_r},\ A_4 = \frac{\beta_2 \Lambda_r}{v_4 \mu_r},\ A_5 = \frac{\beta_2 \Lambda_r v_5 \alpha_2}{v_7 v_6 v_4 \mu_r} \\ A_6 &= \frac{\beta_2 v_5 \Lambda_r}{v_7 v_4 \mu_r},\ A_6 = \frac{\beta_2 v_5 \Lambda_r}{v_7 v_4 \mu_r},\ A_7 = \frac{\rho q \omega v_8 \alpha_2}{v_9 v_7 v_6},\ A_8 = \frac{\rho q \omega v_8}{v_9 v_7},\ A_9 = \frac{\rho q \omega}{v_9} \end{aligned} \tag{15}$$

From (14), the only nonzero eigenvalue is A_5. Therefore the dominant eigenvalue is

$$\lambda = A_5 = \frac{\beta_2 \Lambda_r v_5 \alpha_2}{v_7 v_6 v_4 \mu_r}.$$

Hence,

$$\mathscr{R}_0 = \frac{\beta_2 \Lambda_r v_5 \alpha_2}{v_7 v_6 v_4 \mu_r} \tag{16}$$

Substituting the values of $v_4,\ v_5,\ v_6,$ and v_7 from equation (12) into equation (16) we get

$$\mathscr{R}_0 = \frac{\beta_2 \Lambda_r}{\beta_2 \Lambda_r + \mu_m \mu_r} . \frac{\alpha_2}{(\alpha_2 + \mu_{ir})} . \frac{p r_2 \delta_2}{(\delta_2 + \mu_{tr})}$$

which can be expressed as

$$\mathscr{R}_0 = \left[\frac{\beta_2 r_0}{(\beta_2 r_0 + \mu_m)}\right] \left[\frac{\alpha_2}{(\alpha_2 + \mu_{ir})}\right] \left[\frac{1}{(\delta_2 + \mu_{tr})}\right] p r_2 \delta_2 \tag{17}$$

where $r_0 = \dfrac{\Lambda_r}{\mu_r}$ is value of R at MFE.

The term $\frac{\beta_2 r_0}{\beta_2 r_0 + \mu_m}$ in equation (17) is the proportion of RBCs that is infected by a merozite introduced into entirely susceptile RBC population before it dies, while the term $\frac{\alpha_2}{\alpha_2 + \mu_{ir}}$ represents the proportion of infected RBCs that progress to schizonts, the term $\frac{1}{\delta_2 + \mu_{tr}}$ is the mean period spent by the blood-schizont before they rupture, and the term $pr_2\delta_2$ is number of relesead merozoites that proceeds to asexuals replication in each erythrocytic cycle.

4. Sensitivity Analysis of $\mathscr{R}_0$

Sensitivity analysis, also known as *what-if analysis* is a technique used to determine how do variations on input parameters affect the anticipated model outputs [21]. The main reason for why we need sensitivity analysis is that, it helps the modeller (researcher) to identify the parameters that need the most numerical attention and highlight which parameters should be targeted in planning and developing management strategies [13].

In this study we computed the normalized sensitivity index $\Omega_{p_i}^{\mathscr{R}_0}$ of the basic reproduction number $\mathscr{R}_0$ using method described by Chitnis *et al.* [22] and Cariboni *et al.* [21] , where partial derivatives of $\mathscr{R}_0$ with respect to each of its input parameter, p_i were obtained using the formula

$$\Omega_{p_i}^{\mathscr{R}_0} = \frac{\partial \mathscr{R}_0}{\partial p_i} \times \frac{p_i}{\mathscr{R}_0} \tag{18}$$

Substituting values of parameters given in Table 2 in equation (18) we obtained the sensitivity indices of $\mathscr{R}_0$ which have been presented in the Table 3.

TABLE 2. Parameter estimates for the model (1a)-(1l)

Parameter	Description	Value	Reference
a :	probability that a bite infects human	0.75	[23]-[24]
b :	number of mosquito bites per individual	$15day^{-1}$	Estimated
v :	number of sporozoites injected per bite	$10-20$	[25]
β_1 :	infection rate of HLCs by sporozoites	$0.001\ \mu lcell^{-1}day^{-1}$	Estimated
r_1 :	number of merozoites per liver schizont	10000	[26]
α_1 :	progression rate of infected HLCs to schizonts	$0.125\ day^{-1}$	Estimated
δ_1 :	rupture rate of liver schizonts	$0.0975\ day^{-1}$	Estimated
Λ_h :	the recruitmet rate of HLCs	$3000\ cellsday^{-1}\mu l^{-1}$	Estimated
μ_h :	natural death rate of uninfected HLCs	$0.94\ day^{-1}$	Estimated
μ_{ih} :	death rate of infected HLCs	$0.95\ day^{-1}$	Estimated
μ_{th} :	death rate of liver-schizonts	$0.029\ day^{-1}$	Estimated
β_2 :	infection rate of RBCs by merozoites	$2\times10^{-6}\ \mu lcell^{-1}day^{-1}$	Estimated
δ_2 :	rupture rate of blood schizonts	$0.115\ day^{-1}$	Estimated
α_2 :	progression rate of infected RBCs to schizonts	$0.145\ day^{-1}$	Estimated
r_2 :	number of merozoites per blood schizont	16	[4],[6]
q :	probability that a bite is infectious to mosquito	0.09	[27]
ω :	number of gametocytes ingested per bite	10	Estimated
ρ :	number of bites made by mosquito in its lifetime	3	Estimated
Λ_r :	the recruitmet rate of RBCs	$4.15\times10^4\ cells\mu l^{-1}day^{-1}$	[17]
μ_r :	natural death rate of uninfected RBCs	$0.02\ day^{-1}$	[6]
μ_{ir} :	total death rate of infected RBCs	$0.025\ day^{-1}$	[28]
μ_{tr} :	death rate of blood-schizonts	$0.185\ day^{-1}$	Estimated
μ_m :	death rate of merozoites	$48\ day^{-1}$	[17],[28]
μ_{gb} :	death rate of gametocytes in bloodstream	$6.25\times10^{-5}day^{-1}$	Estimated
δ_3 :	rupture rate of Oocysts	$0.05\ day^{-1}$	Estimated
r_3 :	number of sporozoites per Oocyst	1000	[25]
α_3 :	progresion rate of gametes to Oocysts	$0.07\ day^{-1}$	Estimated
μ_{gm} :	death rate of gametes in mosquito's midgut	$0.052\ day^{-1}$	Estimated
μ_c :	death rate of Oocysts	$0.024\ day^{-1}$	Estimated
μ_{sm} :	death rate of sporozoites in mosqouito	$40\ day^{-1}$	Estimated
μ_{sh} :	death rate of sporozoites in human liver	$1.2\times10^{-11}\ day^{-1}$	Estimated
p :	proportion of asexual that differentiate to merozoites	0.926	Estimated

TABLE 3. Sensitivity indices of R_0

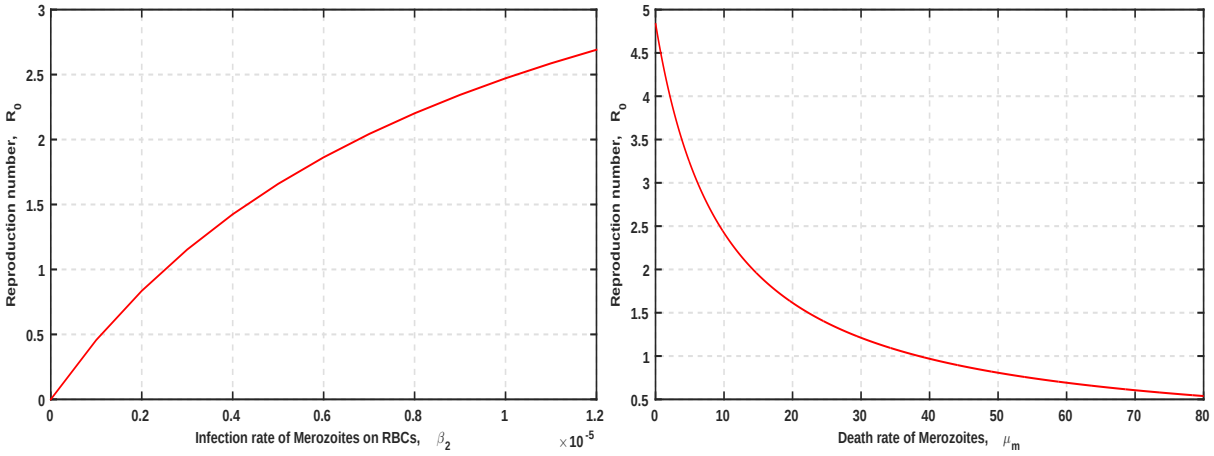
Parameter, p_i	Sensitivity index, $\Omega_{p_i}^{R_0}$
r_2	$+1.00000$
p	$+0.99999$
r_0	$+0.97959$
β_2	$+0.97959$
μ_m	-0.97959
μ_{tr}	-0.61667
δ_2	$+0.61667$
μ_{ir}	-0.14706
α_2	$+0.14706$

From Table 3, it is found that the number of merozoites released per ruptured schizont r_2, is the most sensitivity parameter of the model ($\Omega_{r_2}^{\mathscr{R}_0} = 1.00000$), followed by proportion of released merozoites that proceed with asexual replication, p, with $\Omega_p^{\mathscr{R}_0} = +0.99999$, indicating that these parameters have a greatest effect on model outcomes. For example, an increase of 10% on r_2, will also cause the same effect (increase) of 10% on $\mathscr{R}_0$ and vice versa.

Parameters with next highest sensitivity index are initial suspectible population of RBCs, r_0, infection rate of RBCs by merozoites, β_2 and death rate of merozoites, μ_m. All these have the same magnitude of sensitivity indices, but r_0 and β_2 are positive while μ_m is negative. That is, an increase (a decrease) of 10% on r_0 or β_2 will results an increase (a decrease) of 9.7959% on $\mathscr{R}_0$, while with similar increase (decrease) on μ_m, $\mathscr{R}_0$ decreases (increases) by 9.7959%. These are followed by death rate of blood-schizonts, μ_{tr} and rupture rate of blood-schizonts to release merozoite, δ_2, with the same index in magnitude but different signs, implying that increasing μ_{tr} will cause a decrease on $\mathscr{R}_0$, though the increase in δ_2 will cause an increase in $\mathscr{R}_0$. The death rate of infected RBCs, μ_{ir} and progression rate of infected RBCs to schizonts α_2 are parameters having the least impact on $\mathscr{R}_0$.

$\mathscr{R}_0$ increases (decreases) as parameters with positives indices increases (decreases) and decreases (increases) as parameters with negative indices increases (decreases). In order for malaria infection to be eradicated, we need to reduce the value of $\mathscr{R}_0$ to be less than unity. Therefore, we can lower the value of $\mathscr{R}_0$ by reducing the values of r_2, p, r_0, β_2, δ_2 and α_2 or

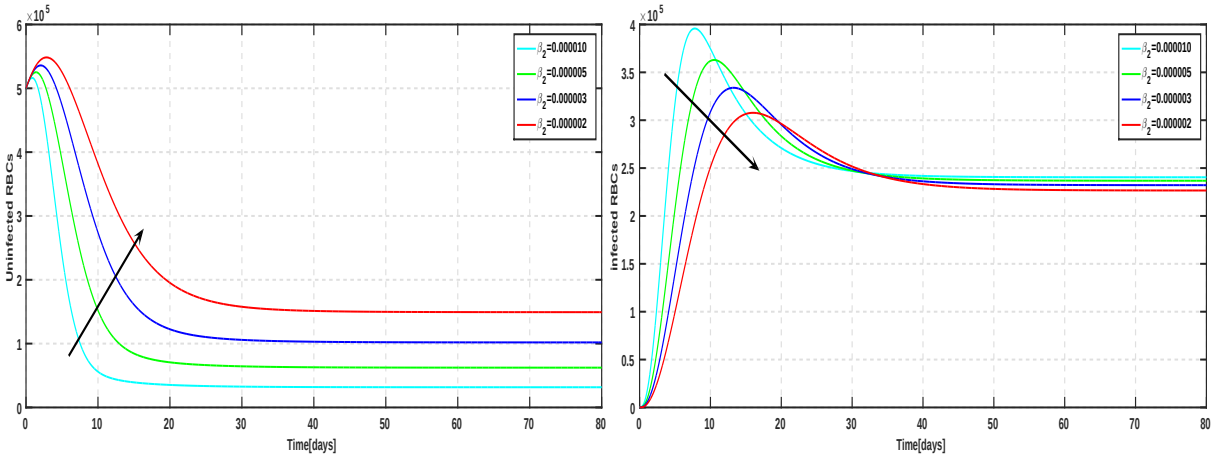
by increasing the values of μ_m, μ_{tr} and μ_{ir}. Figure 3 illustrates the effect of varitions of some parameters on reproduction numbers.



(A) Effect of β_2, on $\mathscr{R}_0$ (B) Effect of μ_m, on $\mathscr{R}_0$

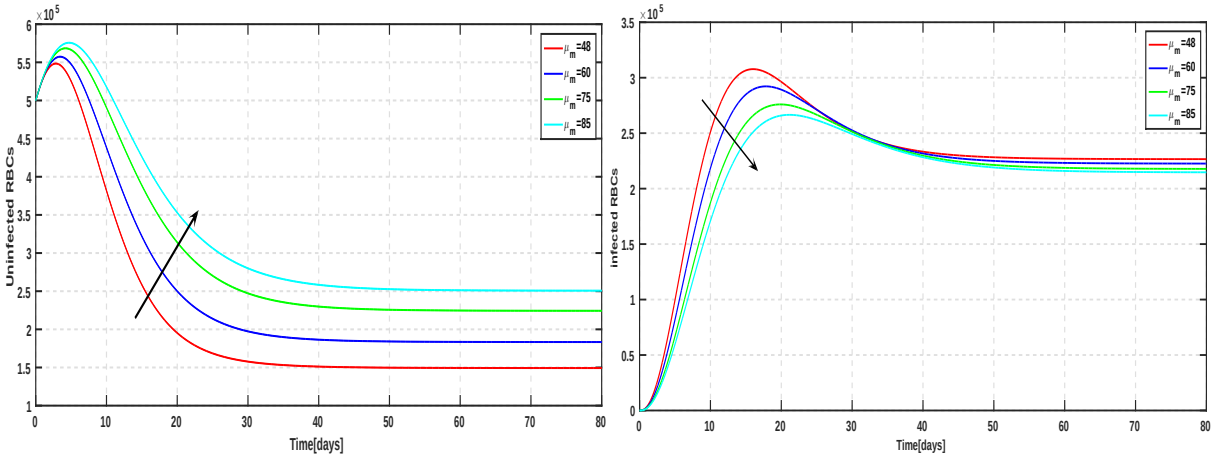
FIGURE 3. Effect of infection rate of RBCs by merozoites, β_2 and death rate of merozoites μ_m, on basic reproduction number, $\mathscr{R}_0$

To control the malaria infection in nonimmune host we need to have a stable malaria free equilibrium, which is achieved when $\mathscr{R}_0 < 1$. Now, we have to find out which parameters of $\mathscr{R}_0$ can lead us to this condition. Using information in the Table 3 and expression of $\mathscr{R}_0$ in equation (16), we can infer the following: lessening a number of merozoites released, r_2, and infection rate of merozoites on RBCs, β_2 or rising the death rate of merozoites, μ_m will lessen $\mathscr{R}_0$. This conforms with the findings of Dube *et al.* [6]. A reduction of infection rate and rise on death rate of merozoites certainly reduce the number of succesful conctacts between merozoites and uninfected RBCs and hence reduces number of infected RBCs and increases number of uninfected , as indicated in Figures 4 and 5.



(A) Effect of decreasing β_2 on uninfected RBCs (B) Effect of decreasing β_2 on infected RBCs

FIGURE 4. Effect of decreasing infection rate of merozoites on number of uninfected RBCs and infected RBCs. Arrows are in direction of decreasing β_2



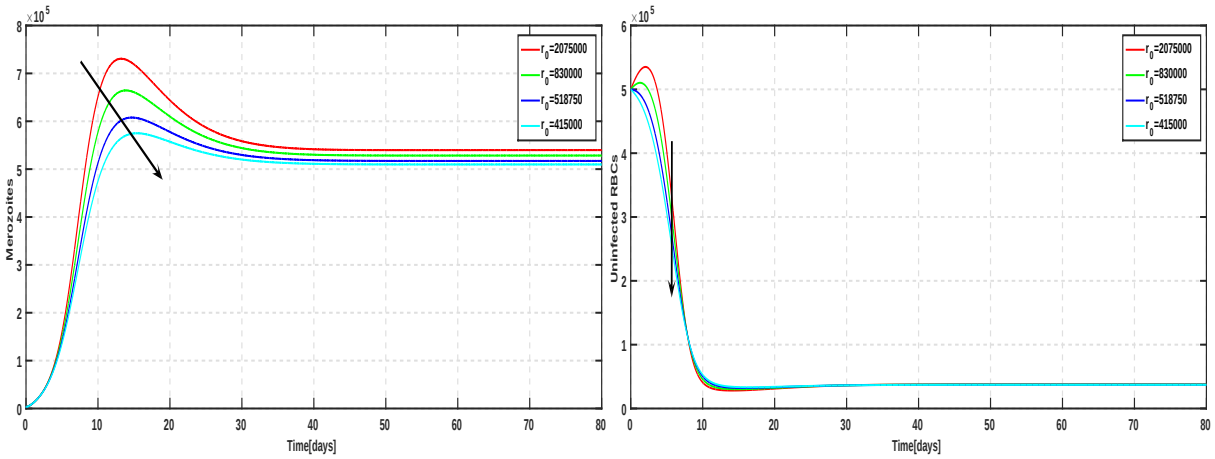
(A) Effect of increasing μ_m on uninfected RBCs (B) Effect of increasing μ_m on infected RBCs

FIGURE 5. Effect of increasing death rate of merozoites on densities of uninfected RBCs and infected RBCs. Arrows are in direction of increasing μ_m

We examine the effect of infection rate of merozoites to RBCs on the dynamics of malaria transmission using the following values of the infection rate: 0.000010, 0.000005, 0.000003, 0.000002. Their corresponding values of the reproduction number were 2.47, 1.66, 1.15, 0.84

respectively. These results are illustrated in Figure 4, which confirm that, decreasing infection rate has the effect of reducing $\mathscr{R}_0$ (number of newly infected RBCs) and then reduce the infection of malaria parasites to RBCs.

Also, reducing the initial population of RBCs, r_0, reduces $\mathscr{R}_0$. This can either be done by reducing recruitment rate, Λ_r or increasing the death rate μ_r of uninfected RBCs. However, this is may be biologically impractical because it may cause the catastrophic anemia [29]. This is indicated in Figure 6, where Figure 6A indicates that the decrease in r_0 reduces number of merozoites in bloodstream but also number of uninfected RBCs decreases as indicated in Figure 6B.

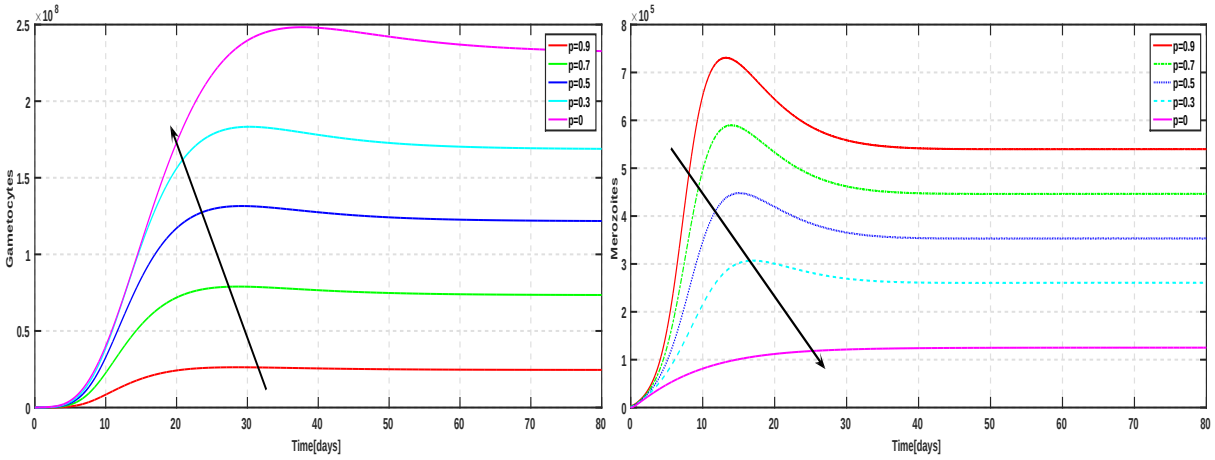


(A) Effect of decreasing r_0 on merozoites (B) Effect of decreasing r_0 on uninfected RBCs

FIGURE 6. Effect of decreasing r_0 on densities of uninfected merozoites and uninfected RBCs. Arrows are in direction of decreasing r_0. Values of r_0 are calculated using a fixed value of $\Lambda_r = 41500$, and different values of $\mu_r = 0.02, 0.05, 0.08$ and 0.10

Moreover, the same goal of reducing $\mathscr{R}_0$ can be achieved by a decrease in proportion of merozoites that proceeds with asexual replication, rupture rate of blood-schizonts, progression rate of infected RBCs to schizonts, and an increase in death rates of blood-schizonts and infected RBCs. Decreasing the proportion p, of merozoites that proceeds to asexuals, despite its effect on decreasing number asexuals merozoites (see Figure 7B) is still impractical because doing

so will cause rise on number of merozoites that switch to gametocytes as shown in Figure 7A, consequently increase the probability of human-mosquito infection and persistence of disease.



(A) Effect of p on gametocytes (B) Effect of p on merozoites

FIGURE 7. Effect of reducing p on merozoites and gametocytes. Arrows are in direction of decreasing p. Values of p used are $p = 0.9,\ 0.7,\ 0.5,\ 0.3,\ 0$.

However, the impact of progression rate of infected RBCs to schizonts and death rate of infected RBCs is insignificant compared to others, because a change of 10% on these parameters will cause a change of about 1.4% on $\mathscr{R}_0$, while same change on the remaining paramenters will cause a change of at least 6.17% on $\mathscr{R}_0$.

Therefore, any biological means that will enhance the decrease of infection rate of RBCs by merozoites and number of merozoites per rupturing schizonts and/or increase the death rates of schizonts and merozoites will be of great importance on eradiction or control of malaria. These mechanism could be medication or vaccination to boost the immunity system.

5. Discussions and Conclusions

A mathematical model for in-human host and in-mosquito dynamics of malaria parasites was developed and analyzed. The model involved three main phases in life cycle of malaria parasites. We considered four, five and three compartments in the liver, blood and mosquito stages respectively.

In analysis of the model, we included the determination of invariant region and positivity of the solutions which found to be mathematically and biologically well-posed. Malaria-free equilibrium (MFE) for the model was obtained. The threshold parameter, $\mathscr{R}_0$, called basic reproduction number was obtained and depends only on parameters in erythrocytic phase.

To prove the analytical solutions obtained on sensitivity indices, we carried some numerical simulations. The effects of varying the sensitive parameters on the basic reproduction number were examined, to determine their implications in the control of malaria infection (see Figures 3, 4 and 7). The infection rate of RBCs by merozoites, death rate of merozoites, number of merozoites released are found be vital parameters in control of malaria infection. Despite having lower sensitivity index compared to death rate of merozoites, death rate of schizonts have greater impact on malaria control than that of merozoites. This is because each matured schizont bursts and releases an average of 8-32 merozoites [30]. In addition to that, increasing the death rate of schizonts will automatically reduce the number of contact between RBCs and merozoites, hence reduces the number of infected RBCs. Therefore, the planned intervetions should aim at increasing the death of schizonts (liver or blood stage) to lower the total number of merozoites.

This work provides a basic model for studying the in-human host and in-mosquito vector dynamics of malaria parasite. At this time where malaria eradication is on world agenda, this work may be used as starting point to examine how and which are new control strategies of malaria can be established to overcome the disease. We propose that subsequent future work should be on determination of conditions for existence of malaria-infection equilibrium and where stability of equilibra would be discussed.

Conflict of Interests

The authors declare that there is no conflict of interests.

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