Journal of Advances in Mathematics and Computer Science

30(4): 1-21, 2019; Article no.JAMCS.46649
ISSN: 2456-9968
(Past name: British Journal of Mathematics & Computer Science, Past ISSN: 2231-0851)

Analysis of an Age-Structured Malaria Model Incorporating Infants and Pregnant Women

George Theodore Azu-Tungmah[1*], Francis T. Oduro[1] and Gabriel A. Okyere[1]

[1]Department of Mathematics, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana.

Authors' contributions

This work was carried out in collaboration between all authors. Author GTAT designed the study, performed the analysis, wrote the protocol and it was supervised by authors FTO and GAO. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMCS/2019/46649
Editor(s):
(1) Dr. Nurhan Cucer, Department of Medical Biology, Erciyes University, Turkey.
(2) Dr. Metin Basarir, Professor, Department of Mathematics, Sakarya University, Turkey.
Reviewers:
(1) Aliyu Bhar Kisabo, Nigeria.
(2) Abboubakar Hamadjam, University of Ngaoundere, Cameroon.
Complete Peer review History: http://www.sdiarticle3.com/review-history/46649

Original Research Article

Received: 26 October 2018
Accepted: 18 January 2019
Published: 30 January 2019

Abstract

A new dynamic model for the malaria disease has been developed for areas where the whole populace is at risk and exposure to the malaria infection is continuous throughout the year. In this model, the two vulnerable groups that is, infectious people those under 5years and pregnant women have been given separate compartments. The model has two equilibria, that is, disease-free and endemic equilibrium points. The basic reproduction number (R_0) for the model has been derived using the next-generation matrix approach. The local stability of two equilibria is investigated using matrix elementary row operations. However, global stability of disease-free equilibrium is investigated using theorem by Castillo-Chavez et.al (2002) and that of the endemic equilibrium is also investigated using Lyapunov's function. It is proven that disease-free equilibrium is locally asymptotically stable if $R_0 < 1$ and the endemic equilibrium exists if $R_0 > 1$. The endemic equilibrium is locally asymptotically stable when $A_3A_5\Phi_I > \phi\Phi_P^2\mu_H$ and $E_{17}E_{19} > E_{16}E_{20}$. Sensitivity analysis has proved that malaria can be controlled or eliminated if the following parameters such as biting rates, recruitment rate and density-dependent natural mortality rate for mosquitoes and clinical recovery rates for humans are controlled.

**Corresponding author: E-mail: gazutungmah@yahoo.com;*

Keywords: *Basic reproduction number; disease-free equilibrium point; endemic equilibrium point; biting rates; recruitment rate; density-dependent natural mortality rate; clinical recovery rate.*

1 Introduction

Malaria is a life-threatening disease widely found in tropical and subtropical regions, especially in Africa, Asia, Latin America, the Middle East and some parts of Europe [1,2,3,4,5]. More than two hundred million people suffer the malaria disease yearly, and more than four hundred thousand die from it. Nearly 70 percent of malaria deaths are in children under five [6]. According to the World Health Organization (WHO), the African Region continues to bear 90% of malaria cases and 91% of malaria deaths worldwide [7]. Nigeria, the most populous country in Africa, accounted for 27% of malaria cases and 24% of malaria deaths globally in 2016 [7]. Bill Gates, a leading funder of antimalaria efforts, has said that the cost of controlling malaria "endlessly" is not financially sustainable, therefore he is calling for eradication instead. However, eradicating malaria by 2040 would cost between $90 billion and $120 billion, according to the Gates Foundation [6]. Malaria cost can be measured in lives lost, the time spent ill with the fever, and at the macroeconomic level, national malaria burden reduces economic development [8]. In this article, humans under 5years are known as Infants.

2 Malaria

Malaria is caused by parasites of the species Plasmodium [9,1,4,10]. Four species of the parasite that produce human malaria disease are Plasmodium falciparum (also called malignant tertian malaria), Plasmodium vivax (also called tertian malaria), Plasmodium malariae (also called quartan malaria) and Plasmodium ovale [11,8,12,13]. Plasmodium falciparum is the most common form of the malaria parasite in sub-Saharan Africa, is responsible for the most deaths worldwide; Plasmodium vivax is the most common malaria parasite outside of sub-Saharan Africa. The parasites are transmitted to humans through the bites of infected female Anopheles mosquitos (vectors) [1,6,14,4,5]. After entering a human, the parasites travel through the infected person's blood to the liver, where they grow, multiply, and then spread throughout the body's red blood cells, destroying them in the process. When the parasites are fully developed into infectious forms(gametocytes), then they are transmitted to a new mosquito that bites the infectious person. After approximately 10 to 15 days when the infectious mosquito takes her next blood meal, the parasites are matured in the mosquito to infect a new person. After a human gets bitten the symptoms appear in about 9 to 14 days [1]. The most common symptoms are a headache, fever, and vomiting [15]. If the infected human does not get antimalarial drugs the infection can progress and become life-threatening [1]. Humans with weaker immune systems, particularly children under five, are the most vulnerable. Pregnant women are also at high risk for becoming sick and passing the disease to the fetus (the parasites take hold in the nonimmune placenta), and malaria contracted during pregnancy is thought to contribute to low birth weights that result in a hundred thousand infant deaths each year [6,7].

3 Previous Work

The mathematical modeling of malaria began in 1911 with Sir Ronald Ross [9,1,8,16,10,17], who was awarded the Nobel prize for his work. Ross's model was two-dimensional with one variable representing humans and the other representing mosquitoes [18]. Major extension of the Ross model was formulated by George Macdonald in 1957 by adding Exposed compartment to the mosquito population. This was followed by Anderson and May in 1991, they also added Exposed compartment to the human population [19]. Further work was done by Dietz, Molineux, and Thomas by proposing acquired immunity to the human population. Further work on acquired immunity in malaria was conducted by Aron and Bailey [20]. Aron and May, Koella and Nedelman, also did good work on mathematical modelling of malaria. Some recent papers in malaria included environmental effects and resistance to antimalarial drugs [20]. Ngwa and Shu and Ngwa proposed an ordinary differential equation (ODE) compartmental for the transmission of malaria with a susceptible-exposed-infectious-recovered-susceptible (SEIRS) pattern for humans and susceptible-exposed-

infectious (SEI) pattern for mosquitoes. In a Ph.D. dissertation, Chitnis analysed a similar model for malaria transmission [21]. In 2012, Addawe and Lope proposed an Age-structured malaria transmission model in an article [22]. In another Ph.D. dissertation by Mwamtobe in 2014, proposed that a future work in malaria which will include the vulnerable groups, that is, children under the age of five years and pregnant women could shed more light on which intervention strategy to prioritize to the specific groups [18]. Therefore, in this paper, we extend the Ross model to include compartments for children under five years and pregnant women.

4 Model Description and Formulation

A Flow Chart (Fig. 1) is a new Flow Chart describing the transmission dynamics of Plasmodium falciparum malaria disease in its endemic areas of the word, where the whole populace is at risk. It is similar to the Flow Chart (Fig. 1) in the article 'Analysis of age-structured malaria transmission model' by Addawe and Lope [22]. However, in Fig. 1 in this article, an infectious compartment for pregnant women has been added to study the effect of the disease during pregnancy. There is no recovered compartment in Fig. 1 as it is in Addawe and Lope's model since people who recover completely from the malaria infection through clinical treatment do not have any long-lasting immunity, unlike the HIV disease. It is assumed that each infectious person fully recovers after a one-time period. Therefore, the model in this paper is based on the susceptible-infectives (SIS) models of infectious disease epidemiology. Parameters of the model (1) will be estimated from clinical Malaria data.

The Fig. 1 entails humans and only adult female Anopheles mosquitoes and divides each population into smaller groups called compartments depending on their infectious status of the malaria parasite. And for humans, age and pregnancy have been factored into the compartmental divisions. The human population is partitioned into four compartments: susceptible (S_H), infectious under 5years (I_I), infectious over 5years (I_A) and infectious pregnant women (I_P), since the data for these compartments are always available at the health directorates of the various malaria endemic countries. The susceptible (S_H) are both immune and non-immune individuals with gametocyte free status and are susceptible to the malaria disease. Gametocytes are one of the developmental stages of the Plasmodium falciparum malaria parasite that can infect the female Anopheles mosquito when it takes a blood meal from an infectious person, therefore only people with gametocytes in their blood can transmit the malaria parasite to mosquitoes. In this article, it is assumed that a clinically treated person is someone with gametocyte free status (that is, the gametocytes have been cleared from the person's blood system by antimalarial drugs). Malaria immune people are individuals who have developed partial immunity to the malaria disease due to many years of repeated infections; the immunity is fractional in light of the fact that nobody is completely immune to the disease [2,17]. The immunity can be lost through interruption of exposure, that is, if an immune person migrates to a non- endemic malaria region where the exposure to the disease is not available, then he or she automatically loses their immunity. The immunity can be restored through numerous years of repeated infections, therefore a person living in malaria endemic area cannot lose his or her immunity as long as they continue to stay in the area and the exposure to the disease continues. The advantage of those with malaria immunity is that frequency of the malaria infections is delayed, which could delay the frequency of malaria infections in the adults [23].

Newborns have malaria immunity up to the first 3–6 months of their lives due to passive transfer of maternal antibodies through the placenta. After these months, they are vulnerable to clinical malaria episodes until they develop their own immunity [20,17]. People enter the human population through the susceptible (S_H) compartment at per capita recruitment rate (Z_H). When the malaria infection begins in humans, the individuals under 5years move to I_I compartment, over 5years who are not pregnant move to I_A compartment and pregnant women move to I_P compartment. Those in infectious compartments I_I and I_A and I_P are clinically treated (that is, gametocytes are completely cleared) at the rates Λ_I, Λ_A and Λ_P respectively, before they return to S_H compartment for re-infection. Also, the infectious individuals can exit the human population through disease-induced deaths at the rates $(\boldsymbol{\pi_I})$, $(\boldsymbol{\pi_A})$ and $(\boldsymbol{\pi_P})$ respectively**.** The infectious under 5years can join the infectious over 5years at the rate (ϕ) when they attain aged 5 and

also infectious over 5years can join the infectious pregnant women compartment at the rate (Ω) when the become pregnant. It is assumed that infectious pregnant women cannot join the infectious over 5years compartment since most infectious pregnant women are clinically treated before they give birth. Humans can also exit their population through density-dependent mortality rate (μ_H) in each compartment.

The mosquito populace is divided into two compartments namely: susceptible (S_M) and infectious (I_M) . The adult female Anopheles mosquito becomes infectious when it bites gametocyte carriers (that is, infectious humans) and ingests the gametocytes. The mosquito in the S_M compartment becomes infectious and moves to the I_M compartment only when the malaria parasites becomes mature and moves to the mosquito's salivary glands and remains in the infectious status for life. The mosquito exits its population through density-dependent mortality at the rate (μ_M) or mortality due to insecticides but cannot die directly from the malaria parasite infection [9]. Female mosquitoes enter their population through the susceptible compartment at per capita recruitment rate (Z_M) . It is assumed that there is no immigration of infectious individuals in the human population.

The Flow Chart for malaria transmission dynamics is given below as Fig. 1.

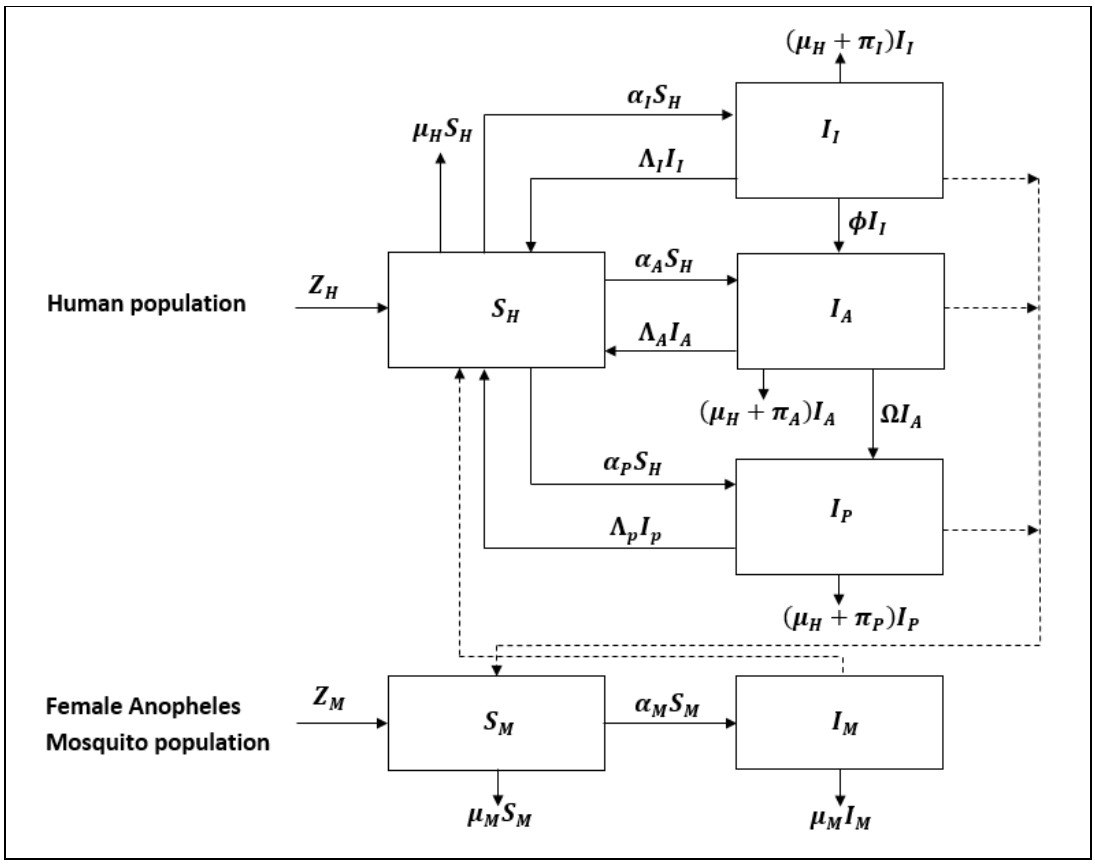

Fig. 1. Flow chart for the malaria transmission dynamics

The flow chart demonstrates the interactions between human and mosquito populations and the movement of individuals from one compartment to another. The solid arrows show progression of individuals from one compartment to another and the dotted arrows show how the humans and mosquitoes interact and infect each other. Susceptible humans in S_H get infected when infectious mosquitoes from I_M bite them. They then

progress to I_I , I_A and I_P when they are infectious. Humans in I_I , I_A and I_P move to S_H compartment for re-infection after clinical treatment. Susceptible mosquitoes in S_M get infected when they bite humans in I_I , I_A and I_P compartments and then move to I_M when they are infectious. Mosquitoes remain in I_M until they die through density-dependent mortality or insecticide. Humans exit their population through density-dependent mortality and disease-induced mortality. Mosquitoes enter their population at per capita recruitment rate and Humans enter through birth or immigration.

Detailed description of the symbols in Fig. 1 is given in Table 1 and Table 2.

Table 1. The state variables for the model 1

State variables	Description
$S_H(t)$	Number of susceptible humans at time t .
$I_I(t)$	Number of infectious infants at time t.
$I_A(t)$	Number of infectious adults at time t.
$I_P(t)$	Number of infectious pregnant women at time t.
$S_M(t)$	Number of susceptible mosquitoes at time t.
$I_M(t)$	Number of infectious mosquitoes at time t .
$N_H(t)$	Total human population at time t .
$N_M(t)$	Total mosquito population at time t .

Table 2. The parameters for the model 1

Parameter	Description
Z_H	Recruitment for the human population. Dimension: Humans × Time^{-1}
Z_M	Recruitment rate for mosquitoes. Dimensions: Time^{-1}
μ_H	Density-dependent natural mortality rate for humans. Dimensions: Time^{-1}
μ_M	Density-dependent natural mortality rate for adult female Anopheles mosquitoes. Dimensions: Time^{-1}
π_I	Per capita disease-induced mortality rate for people under 5 years. Dimensions: Time^{-1}
π_A	Per capita disease-induced mortality rate for people over 5 years Dimensions: Time^{-1}
π_P	Per capita disease-induced mortality rate for pregnant women Dimensions: Time^{-1}
Λ_I	Clinical recovery rate for people under 5 years. Dimensions: Time^{-1}
Λ_A	Clinical recovery rate for people over 5 years. Dimensions: Time^{-1}
Λ_P	Clinical recovery rate for the pregnant women. Dimensions: Time^{-1}
Φ_I	Number of bites on people under 5 years per female mosquito per unit time. Dimensions: Time^{-1}
Φ_A	Number of bites on people over 5 years per female mosquito per unit time. Dimensions: Time^{-1}
Φ_P	Number of bites on pregnant women per female mosquito per unit time. Dimensions: Time^{-1}
θ_{MH}	Fraction of bites that successfully infect humans
θ_{HM}	Fraction of bites that successfully infect mosquitoes.
ϕ	Rate of progression from I_I to I_A compartment. Dimensions: Humans × Time^{-1}
Ω	Rate of progression from I_A to I_P compartment. Dimensions: Humans × Time^{-1}

Putting the assumptions and the ideas together, the malaria model is given by a system of six (6) differential equations as stated in (1) below.

$$\left.\begin{aligned}
\frac{dS_H}{dt} &= \mathrm{Z}_H + \Lambda_I I_I + \Lambda_A I_A + \Lambda_P I_P - \alpha_I S_H - \alpha_A S_H - \alpha_P S_H - \mu_H S_H \\
\frac{dI_I}{dt} &= \alpha_I S_H - \Lambda_I I_I - (\mu_H + \pi_I) I_I - \phi I_I \\
\frac{dI_A}{dt} &= \alpha_A S_H + \phi I_I - (\mu_H + \pi_A) I_A - \Lambda_A I_A - \Omega I_A \\
\frac{dI_P}{dt} &= \alpha_P S_H + \Omega I_A - (\mu_H + \pi_P) I_P - \Lambda_P I_P \\
\frac{dS_M}{dt} &= \mathrm{Z}_M - \alpha_M S_M - \mu_M S_M \\
\frac{dI_M}{dt} &= \alpha_M S_M - \mu_M I_M
\end{aligned}\right\} \quad (1)$$

Applying the definitions of the force of infections as stated in the model of Addawe and Lope [22] the force of infections for infants, adults and pregnant women are

$$\alpha_I = \frac{\Phi_I \theta_{MH} I_M{}'}{N_H}, \quad \alpha_A = \frac{\Phi_A \theta_{MH} I_M}{N_H} \text{ and } \alpha_P = \frac{\Phi_P \theta_{MH} I_M}{N_H}. \quad (2)$$

The force of infection for mosquitoes is

$$\alpha_M = \frac{(\Phi_I I_I + \Phi_A I_A + \Phi_P I_P)\theta_{HM}}{N_H}. \quad (3)$$

Substituting (2) and (3) into (1), leads to (4).

$$\left.\begin{aligned}
\frac{dS_H}{dt} &= \mathrm{Z}_H + \Lambda_I I_I + \Lambda_A I_A + \Lambda_P I_P - \frac{(\Phi_I + \Phi_A + \Phi_P)\theta_{MH} I_M S_H}{N_H} - \mu_H S_H \\
\frac{dI_I}{dt} &= \frac{\Phi_I \theta_{MH} I_M S_H}{N_H} - (\mu_H + \pi_I + \Lambda_I + \phi) I_I \\
\frac{dI_A}{dt} &= \frac{\Phi_A \theta_{MH} I_M S_H}{N_H} + \phi I_I - (\mu_H + \pi_A + \Lambda_A + \Omega) I_A \\
\frac{dI_P}{dt} &= \frac{\Phi_P \theta_{MH} I_M S_H}{N_H} + \Omega I_A - (\mu_H + \pi_P + \Lambda_P) I_P \\
\frac{dS_M}{dt} &= \mathrm{Z}_M - \frac{(\Phi_I I_I + \Phi_A I_A + \Phi_P I_P)\theta_{HM} S_M}{N_H} - \mu_M S_M \\
\frac{dI_M}{dt} &= \frac{(\Phi_I I_I + \Phi_A I_A + \Phi_P I_P)\theta_{HM} S_M}{N_H} - \mu_M I_M
\end{aligned}\right\} \quad (4)$$

where the initial values are $S_H(0) = S_{H0} \geq 0$, $I_I(0) = I_{I0} \geq 0$, $I_A(0) = I_{A0} \geq 0$, $I_P(0) = I_{P0} \geq 0$, $S_M(0) = S_{M0} \geq 0$ and $I_M(0) = I_{M0} \geq 0$

5 Invariant Region

The invariant region is a region where solutions of the model (4) exist biologically.

Biological entities cannot be negative, therefore all the solutions of the model (4) are positive for all time $t \geq 0$. [14]

The total population sizes N_H and N_M can be defined by $N_H = S_H + I_I + I_A + I_P$ and $N_M = S_M + I_M$.

In absence of the malaria disease, the differential equation for N_H is given as

$$\frac{dN_H}{dt} \leq Z_H - \mu_H N_H \tag{5}$$

The differential equation for N_M is also given as

$$\frac{dN_M}{dt} < Z_M - \mu_M N_M \tag{6}$$

Lemma 1. The model (4) has feasible solutions which are contained in the proper subset

$$\Psi = \Psi_H \times \Psi_M .$$

Proof

Let $(S_H, I_I, I_A, I_P, S_M, I_M) \in R_+^6$ be any solution of the system with non-negative initial conditions. Using (5)

$$\frac{dN_H}{dt} \leq Z_H - \mu_H N_H \implies \int d(N_H e^{\mu_H}) \leq Z_H \int e^{\mu_H t}\, dt$$

$$N_H \leq \frac{Z_H}{\mu_H} + \left(N_{H0} - \frac{Z_H}{\mu_H}\right) e^{-\mu_H t} \tag{7}$$

Therefore, as $t \longrightarrow \infty$, the human population N_H approaches $\frac{Z_H}{\mu_H}$ and it follows that

$$\lim_{t \to \infty} \sup N_H(t) \leq \frac{Z_H}{\mu_H} \quad \text{and} \quad \lim_{t \to \infty} \sup N_M(t) \leq \frac{Z_M}{\mu_M} .$$

Therefore, the feasible solution set for the model (4) is given by

$$\Psi = \left\{ \begin{array}{c} (S_H, I_I, I_A, I_P, S_M, I_M) \in R_+^6 : (S_H, S_M) > 0 \\ \\ (I_I, I_A, I_P, I_M) \geq 0 ;\ S_H + I_I + I_A + I_P \leq \frac{Z_H}{\mu_H} ;\ S_M + I_M \leq \frac{Z_M}{\mu_M} \end{array} \right\}$$

6 Positivity of State Variables

Lemma 2. Let the initial data be

$$\{ (S_H(0), S_M(0)) > 0 , (I_I(0), I_A(0), I_P(0), I_M(0)) \geq 0 \} \in \Psi .$$

Then the solution set $\{S_H, I_I, I_A, I_P, S_M, I_M\}(t)$ of the system (4) is positive for all $t > 0$.

Proof

From the first equation in the model (1),

$$\frac{dS_H}{dt} = Z_H + \Lambda_I I_I + \Lambda_A I_A + \Lambda_P I_P - (\alpha_I + \alpha_A + \alpha_P + \mu_H)S_H$$

$$\geq -(\alpha_I + \alpha_A + \alpha_P + \mu_H)S_H \implies \frac{dS_H}{dt} \geq -(\alpha_I + \alpha_A + \alpha_P + \mu_H)S_H$$

Therefore $S_H \geq S_H(0)e^{-(\alpha_I+\alpha_A+\alpha_P+\mu_H)t}$

Similarly, it can be proved that the remaining equations of the model (1) are also true for

all $t > 0$, because $e^{\beta} > 0$ for all $\beta \in R$.

7 Disease-Free Equilibrium Point

Definition 1 A disease-free equilibrium point (DFE) is a steady state solution of the model for which there is no malaria disease in the population.

Lemma 3 For all DFE points on $\Psi \cap R_+^6$, $I_I = I_A = I_P = I_M = 0$

Proof

We need to show that for an equilibrium point in Ψ, if any one of the classes is zero, all the rest are also equal to zero. We first define the conditions [21]:

N1 : $I_I = 0$

N2 : $I_A = 0$

N3 : $I_P = 0$

N4 : $I_M = 0$

N5 : N1, N2 and N3

We show by setting the right-hand side of (4) equal to 0, that if any one of the above statements is true, all the others are true. For $\frac{dI_I}{dt} = 0$, $(N1)$ is true if and only if $(N4)$ is true. Similarly, if for $\frac{dI_A}{dt} = 0$, $(N2)$ is true if and only if $(N1)$ and $(N4)$ are true. Thus, from $\frac{dI_P}{dt} = 0$, we can see that if $(N3)$ is true, then $(N2)$ and $(N4)$ are true. Finally, for $\frac{dI_M}{dt} = 0$, $(N4)$ is true if and only if $(N5)$ is true.

Theorem 1. The malaria model (4) has exactly one DFE point in $\Psi \cap R_+^6$ which is represented by

$$E_0 = \left(\frac{Z_H}{\mu_H}, 0, 0, 0, \frac{Z_M}{\mu_M}, 0 \right)$$

Proof

We know from lemma 3 that on $\Psi \cap R_+^6$, $I_I = I_A = I_P = I_M = 0$.

For $I_I = I_A = I_P = I_M = 0$, from (4 . 4a) $S_H = \frac{\Lambda_H}{\mu_H}$ *and* when $(N5)$ is true, then from (4 . 4e) , $S_M = \frac{\Lambda_M}{\mu_M}$.

This completes the proof that E_0 is unique in Ψ .

8 The Basic Reproduction Number R_0

The basic reproduction number R_0 , is defined as the expected number of secondary infection cases produced by a single infectious individual in a completely susceptible population. The next generation method is used to derived the basic reproduction number [22,24].

The basic reproduction number is

$$R_0 = \sqrt{\frac{\theta_{HM}\theta_{MH}\mu_H\Lambda_M\left(\phi\Omega\Phi_I\Phi_p + A_1\Omega\Phi_A\Phi_p + A_3\phi\Phi_I\Phi_A + A_2A_3\Phi_I^2 + A_1A_3\Phi_A^2 + A_1A_2\Phi_P^2\right)}{A_1A_2A_3\mu_M^2\Lambda_H}}$$

Theorem 2

i. If $R_0 < 1$, then the disease-free equilibrium point (DFE) for the model (4 . 4) is locally asymptotically stable (LAS).
ii. If $R_0 > 1$, then the disease-free equilibrium point is unstable and the endemic equilibrium point is locally asymptotically stable (LAS).

Proof:

At the disease-free equilibrium $\left(\frac{\Lambda_H}{\mu_H}, 0, 0, 0, \frac{\Lambda_M}{\mu_M}, 0\right)$, the Jacobian matrix is given by

$$J = \begin{bmatrix} -A_1 & 0 & 0 & 0 & \Phi_I\theta_{MH} \\ \phi & -A_2 & 0 & 0 & \Phi_A\theta_{MH} \\ 0 & \Omega & -A_3 & 0 & \Phi_p\theta_{MH} \\ -\frac{\Phi_I\theta_{HM}\mu_H\Lambda_M}{\mu_M\Lambda_H} & -\frac{\Phi_A\theta_{HM}\mu_H\Lambda_M}{\mu_M\Lambda_H} & -\frac{\Phi_p\theta_{HM}\mu_H\Lambda_M}{\mu_M\Lambda_H} & -\mu_M & 0 \\ \frac{\Phi_I\theta_{HM}\mu_H\Lambda_M}{\mu_M\Lambda_H} & \frac{\Phi_A\theta_{HM}\mu_H\Lambda_M}{\mu_M\Lambda_H} & \frac{\Phi_p\theta_{HM}\mu_H\Lambda_M}{\mu_M\Lambda_H} & 0 & -\mu_M \end{bmatrix} \quad (8)$$

where $A_1 = (\mu_H + \pi_I + \Lambda_I + \phi)$, $A_2 = (\mu_H + \pi_A + \Lambda_A + \Omega)$ and $A_3 = (\mu_H + \pi_P + \Lambda_P)$

Since the fourth column contains only the diagonal term, this diagonal term forms one eigenvalue of the Jacobian matrix: $\lambda_5 = -\mu_M$.

Hence, excluding this column and its corresponding row, the remaining 4 eigenvalues can be obtained using the following matrix:

$$\text{If } Z = \begin{bmatrix} -\mathrm{A}_1 & 0 & 0 & \Phi_I\theta_{MH} \\ \phi & -\mathrm{A}_2 & 0 & \Phi_A\theta_{MH} \\ 0 & \Omega & -\mathrm{A}_3 & \Phi_p\theta_{MH} \\ \dfrac{\Phi_I\theta_{HM}\mu_H\mathrm{Z}_M}{\mu_M\mathrm{Z}_H} & \dfrac{\Phi_A\theta_{HM}\mu_H\mathrm{Z}_M}{\mu_M\mathrm{Z}_H} & \dfrac{\Phi_p\theta_{HM}\mu_H\mathrm{Z}_M}{\mu_M\mathrm{Z}_H} & -\mu_M \end{bmatrix} \quad (9)$$

Theorem 3

If Z is a square matrix, then $\det(Z) = \det(Z^T)$.

Lemma 3

A $k \times k$ matrix Z and its transpose Z^T have the same eigenvalues.

Now applying theorem 3 and lemma 3 to (9), we can compute its eigenvalues. We have the transpose of the matrix (9) as Z^T .

$$\text{Hence } Z^T = \begin{bmatrix} -\mathrm{A}_1 & \phi & 0 & \dfrac{\Phi_I\theta_{HM}\mu_H\mathrm{Z}_M}{\mu_M\mathrm{Z}_H} \\ 0 & -\mathrm{A}_2 & \Omega & \dfrac{\Phi_A\theta_{HM}\mu_H\mathrm{Z}_M}{\mu_M\mathrm{Z}_H} \\ 0 & 0 & -\mathrm{A}_3 & \dfrac{\Phi_p\theta_{HM}\mu_H\mathrm{Z}_M}{\mu_M\mathrm{Z}_H} \\ \Phi_I\theta_{MH} & \Phi_A\theta_{MH} & \Phi_p\theta_{MH} & -\mu_M \end{bmatrix}$$

Using matrix elementary row operations on Z^T, leads to the matrix below

$$Z^T = \begin{bmatrix} -\mathrm{A}_1 & \phi & 0 & \dfrac{\Phi_I\theta_{HM}\mu_H\mathrm{Z}_M}{\mu_M\mathrm{Z}_H} \\ 0 & -\mathrm{A}_2 & \Omega & \dfrac{\Phi_A\theta_{HM}\mu_H\mathrm{Z}_M}{\mu_M\mathrm{Z}_H} \\ 0 & 0 & -\mathrm{A}_3 & \dfrac{\Phi_p\theta_{HM}\mu_H\mathrm{Z}_M}{\mu_M\mathrm{Z}_H} \\ 0 & 0 & 0 & A_4 \end{bmatrix}$$

where $\mathrm{A}_4 = -\mathrm{A}_1\mathrm{A}_2\mathrm{A}_3\mu_M[1 - R_0^2]$

Therefore, the eigenvalues are $\lambda_1 = -\mathrm{A}_1 < 0$, $\lambda_2 = -\mathrm{A}_2 < 0$, $\lambda_3 = -\mathrm{A}_3 < 0$

and $\lambda_4 = \mathrm{A}_4 = -\mathrm{A}_1\mathrm{A}_2\mathrm{A}_3\mu_M[1 - R_0^2]$

Hence $\lambda_4 < 0$ if $R_0 < 1$, this implies that all the eigenvalues of the Jacobian matrix have negative real parts. Therefore, the disease-free equilibrium (E_0) is locally asymptotically stable when $R_0 < 1$.

9 Global Asymptotic Stability of Disease-Free Equilibrium (E_0)

The global asymptotic stability (GAS) of the disease-free equilibrium will be investigated using a theorem by Castillo -Chavez et al.

Let begin by dividing the model (4) into two submodels, that is,

$$\left.\begin{aligned} \frac{dT_1}{dt} &= W_1(\,T_1\,,\;T_2\,) \\ \frac{dT_2}{dt} &= W_2(\,T_1\,,\;T_2\,)\;,\; W_2(\,T_1\,,\;0\,)=0 \end{aligned}\right\} \quad \text{where } T_1 \in R_+^2\;,\; T_2 \in R_+^4\;. \qquad (10)$$

where $T_1 = (\,S_H\;,\;S_M\,)$ denotes uninfected population and $T_2 = (\,I_I\;,\;I_A\,,I_P\;,\;I_M\,)$ denotes the infectious population.

The conditions in (11) must be met to guarantee a global asymptotic stability:

$$\left.\begin{aligned} &\frac{dT_1}{dt} = W_1(\,T_1\,,\;0\,),\; T_1^* \text{ is globally asymptotically stable (GAS)} \\ &\mathrm{W_2}(\,\mathrm{T_1}\,,\;\mathrm{T_2}\,) = \mathrm{HY} - \bar{W}_2(\,\mathrm{T_1}\,,\;\mathrm{T_2}\,)\;,\; \bar{W}_2(\,\mathrm{T_1}\,,\;\mathrm{T_2}\,) > 0 \text{ for } (\,\mathrm{T_1}\,,\;\mathrm{T_2}\,) \in \Psi \end{aligned}\right\} \qquad (11)$$

where $H = D_{\mathrm{T_2}}\, W_2(\,T_1^*\,,\;0\,)$ is an M −matrix (the off-diagonal elements of H are non-negative) and Ψ is the region where the model makes biological sense. If the model (10) satisfies the conditions of (11) then the theorem below holds

Theorem 4.

The fixed point $\mathrm{E_0} = (\,T_1^*\;,\;0\,)$ is a globally asymptotically stable (GAS) equilibrium of the (10) provided $\mathrm{R_0} < 1$ and the assumptions in (11) are satisfied.

Proof

Then the two vector-valued functions are

$$W_1(\,T_1\,,\;T_2\,) = \left[\begin{array}{c} \mathrm{Z}_H + \Lambda_I I_I + \Lambda_A I_A + \Lambda_P I_P - \dfrac{(\Phi_I + \Phi_A + \Phi_P)\theta_{MH} I_M S_H}{N_H} - \mu_H S_H \\ ,\; \mathrm{Z}_M - \dfrac{(\Phi_I I_I + \Phi_A I_A + \Phi_P I_P)\theta_{HM} S_M}{N_H} - \mu_M S_M \end{array}\right]^T$$

$$W_2(\,T_1\,,\;T_2\,) = \left.\left[\begin{array}{c} \dfrac{\Phi_I \theta_{MH} I_M S_H}{N_H} - (\mu_H + \pi_I + \Lambda_I + \phi) I_I\;, \\ \dfrac{\Phi_A \theta_{MH} I_M S_H}{N_H} + \phi I_I - (\mu_H + \pi_A + \Lambda_A + \Omega) I_A\;, \\ \dfrac{\Phi_P \theta_{MH} I_M S_H}{N_H} + \Omega I_A - (\mu_H + \pi_P + \Lambda_P) I_P\;, \\ \dfrac{(\Phi_I I_I + \Phi_A I_A + \Phi_P I_P)\theta_{HM} S_M}{N_H} - \mu_M\, I_M \end{array}\right]^T\right\}$$

where T denotes the transpose. Now consider the reduced model: $\frac{dT_1}{dt} = W_1(\,T_1\,,\;0\,)$ is given by

$$\left.\begin{aligned} \frac{dS_H}{dt} &= \mathrm{Z}_H - \mu_H S_H \\ \frac{dS_M}{dt} &= \mathrm{Z}_M - \mu_M S_M \end{aligned}\right\} \qquad (12)$$

and $T_1^* = \left(\frac{\Lambda_H}{\mu_H} , \frac{\Lambda_M}{\mu_M} \right)$ is a global asymptotically stable equilibrium point for

the reduced model $\frac{dT_1}{dt} = W_1(T_1 , 0)$. To see this, (12) is solved by integration

$$\frac{dS_H}{dt} = \Lambda_H - \mu_H S_H \Longrightarrow \int d[S_H e^{\mu_H t}] = \int \Lambda_H e^{\mu_H t} dt \Longrightarrow S_H = \frac{\Lambda_H}{\mu_H} + \left(S_H(0) - \frac{\Lambda_H}{\mu_H} \right) e^{-\mu_H t}$$

Similarly , $\frac{dS_M}{dt} = \Lambda_M - \mu_M S_M \Longrightarrow S_M = \frac{\Lambda_M}{\mu_M} + \left(S_M(0) - \frac{\Lambda_M}{\mu_M} \right) e^{-\mu_M t}$

Therefore $S_H = \frac{\Lambda_H}{\mu_H} + \left(S_H(0) - \frac{\Lambda_H}{\mu_H} \right) e^{-\mu_H t}$ approaches $\frac{\Lambda_H}{\mu_H}$ $as\ t \longrightarrow \infty$ and

$S_M = \frac{\Lambda_M}{\mu_M} + \left(S_M(0) - \frac{\Lambda_M}{\mu_M} \right) e^{-\mu_M t}$ also approaches $\frac{\Lambda_M}{\mu_M}$ $as\ t \longrightarrow \infty$

This asymptotic dynamics is independent of initial conditions in Ψ . Hence, the convergence of solutions of (12) is global in in Ψ .

Next $W_2(\Lambda_1 , \Lambda_2) = H Y - \bar{W}_2(\Lambda_1 , \Lambda_2)$, $\bar{W}_2(\Lambda_1 , \Lambda_2) > 0$ for $(\Lambda_1 , \Lambda_2) \in \Psi$, where

$$H = D_{\Lambda_2} W_2(T_1^* , 0) = \begin{pmatrix} -A_1 & 0 & 0 & 0 \\ \phi & -A_2 & 0 & 0 \\ 0 & \Omega & -A_3 & 0 \\ 0 & 0 & 0 & -\mu_M \end{pmatrix} \text{ and}$$

$$\bar{W}_2(\Lambda_1 , \Lambda_2) = \begin{pmatrix} \Phi_I \theta_{MH} I_M \left(1 - \frac{S_H}{N_H} \right) \\ \Phi_A \theta_{MH} I_M \left(1 - \frac{S_H}{N_H} \right) \\ \Phi_p \theta_{MH} I_M \left(1 - \frac{S_H}{N_H} \right) \\ (\Phi_I I_I + \Phi_A I_A + \Phi_P I_P) \theta_{HM} \left(\frac{\mu_H \Lambda_M}{\mu_M \Lambda_H} - \frac{S_M}{N_H} \right) \end{pmatrix}$$

The matrix H is an M -matrix since all its off-diagonal elements are non-negative, but to establish the result of global stability of E_0 , there is the need to prove that

$\bar{W}_2(\Lambda_1 , \Lambda_2) \geq 0$, but it can be seen that $\bar{W}_2(\Lambda_1 , \Lambda_2) \geq 0$, since $S_H = N_H$ at the disease-free equilibrium point and $\frac{\mu_H \Lambda_M}{\mu_M \Lambda_H} \geq \frac{S_M}{N_H}$. Therefore, the disease-free equilibrium point may be globally asymptotically stable if $R_0 \leq 1$.

10 Endemic Equilibrium and Its Stability

The endemic equilibrium point is steady state solution where the disease is present in the population. The endemic equilibrium point is given by

$E_* = (S_H^* , I_I^* , I_A^* , I_P^* , S_M^* , I_M^*)$, which leads to theorem 5.

Theorem 5

The malaria model (4) has a unique endemic equilibrium (E_*) in Ψ if $R_0 > 1$.

Proof

To derive E_*, model (4) is solved by equating it to zero. The procedure for obtaining the expression E_* is given below. The model (4) is set to zero,

$$\left.\begin{aligned}
\frac{dS_H}{dt} &= \mathrm{Z}_H + \Lambda_I I_I + \Lambda_A I_A + \Lambda_P I_P - \frac{(\Phi_I + \Phi_A + \Phi_P)\theta_{MH} I_M S_H}{N_H} - \mu_H S_H = 0 \\
\frac{dI_I}{dt} &= \frac{\Phi_I \theta_{MH} I_M S_H}{N_H} - (\mu_H + \pi_I + \Lambda_I + \phi) I_I = 0 \\
\frac{dI_A}{dt} &= \frac{\Phi_A \theta_{MH} I_M S_H}{N_H} + \phi I_I - (\mu_H + \pi_A + \Lambda_A + \Omega) I_A = 0 \\
\frac{dI_P}{dt} &= \frac{\Phi_P \theta_{MH} I_M S_H}{N_H} + \Omega I_A - (\mu_H + \pi_P + \Lambda_P) I_P = 0 \\
\frac{dS_M}{dt} &= \mathrm{Z}_M - \frac{(\Phi_I I_I + \Phi_A I_A + \Phi_P I_P)\theta_{HM} S_M}{N_H} - \mu_M S_M = 0 \\
\frac{dI_M}{dt} &= \frac{(\Phi_I I_I + \Phi_A I_A + \Phi_P I_P)\theta_{HM} S_M}{N_H} - \mu_M I_M = 0
\end{aligned}\right\} \quad (13)$$

Let $\mathrm{A}_1 = (\mu_H + \pi_I + \Lambda_I + \phi)$, $\mathrm{A}_2 = (\mu_H + \pi_A + \Lambda_A + \Omega)$, $\mathrm{A}_3 = (\mu_H + \pi_P + \Lambda_P)$

It is assumed that the initial conditions are such that the total population size is at equilibrium,

$$\left.\begin{aligned}
S_H + I_I + I_A + I_P &= N_H = N_H^* = \frac{Z_H}{\mu_H} \\
\mathrm{Z}_H + \Lambda_I I_I^* + \Lambda_A I_A^* + \Lambda_P I_P^* - \frac{(\Phi_I + \Phi_A + \Phi_P)\mu_H \theta_{MH} I_M^* S_H^*}{Z_H} - \mu_H S_H &= 0 \\
\frac{\mu_H \Phi_I \theta_{MH} I_M^* S_H^*}{Z_H} - \mathrm{A}_1 I_I^* &= 0 \\
\frac{\mu_H \Phi_A \theta_{MH} I_M^* S_H^*}{Z_H} + \phi I_I^* - \mathrm{A}_2 I_A^* &= 0 \\
\frac{\mu_H \Phi_P \theta_{MH} I_M^* S_H^*}{Z_H} + \Omega I_A^* - \mathrm{A}_3 I_P^* &= 0 \\
\mathrm{Z}_M - \frac{(\Phi_I I_I^* + \Phi_A I_A^* + \Phi_P I_P^*)\mu_H \theta_{HM} S_M^*}{Z_H} - \mu_M S_M^* &= 0 \\
\frac{(\Phi_I I_I^* + \Phi_A I_A^* + \Phi_P I_P^*)\mu_H \theta_{HM} S_M^*}{Z_H} - \mu_M I_M^* &= 0
\end{aligned}\right\} \quad (13)$$

Solving for the state variables from (13), we have:

The endemic equilibrium point is given by

$$E_* = (\ S_H^* \ , \ I_I^* \ , \ I_A^* \ , \ I_P^* \ , \ S_M^* \ , \ I_M^* \ )$$

where

$$S_H^* = \frac{Z_H(R_0^2\mu_M Z_H + A_5 Z_M \theta_{MH})}{R_0^2\mu_H(A_5\theta_{MH}Z_M + \mu_M Z_H)}$$
$$I_I^* = \frac{\Phi_I \theta_{MH} Z_H Z_M (R_0^2 - 1)}{A_1 R_0^2 (A_5\theta_{MH}Z_M + \mu_M Z_H)}$$
$$I_A^* = \frac{\theta_{MH} Z_H Z_M (A_1\Phi_A + \phi\Phi_I)(R_0^2 - 1)}{A_1 A_2 R_0^2 (A_5\theta_{MH}Z_M + \mu_M Z_H)}$$
$$I_P^* = \frac{\theta_{MH} Z_H Z_M (A_1 A_2 \Phi_P + A_1\Phi_A\Omega + \Omega\phi\Phi_I)(R_0^2 - 1)}{A_1 A_2 A_3 R_0^2 (A_5\theta_{MH}Z_M + \mu_M Z_H)}$$
$$S_M^* = \frac{Z_M(A_5\theta_{MH}Z_M + \mu_M Z_H)}{\mu_M(R_0^2\mu_M Z_H + A_5 Z_M\theta_{MH})}$$
$$I_M^* = \frac{Z_H Z_M (R_0^2 - 1)}{R_0^2\mu_M Z_H + A_5 Z_M \theta_{MH}}$$

It is clear that if $R_0 > 1$, then there exists a unique endemic equilibrium point.

Theorem 6

The model (4) is locally asymptotically stable at the endemic equilibrium point (E_*) if all the eigenvalues of the Jacobian matrix at (E_*) have negative real parts when $R_0 > 1$.

Proof

At the endemic equilibrium point, the Jacob matrix (4) is given as:

$$J(E_*) = \begin{bmatrix} -E_1 & \Lambda_I & \Lambda_A & \Lambda_P & 0 & -E_2 \\ E_3 & -A_1 & 0 & 0 & 0 & E_4 \\ E_5 & \phi & -A_2 & 0 & 0 & E_6 \\ E_7 & 0 & \Omega & -A_3 & 0 & E_8 \\ 0 & -E_9 & -E_{10} & -E_{11} & -E_{12} & 0 \\ 0 & E_9 & E_{10} & E_{11} & E_{13} & -\mu_M \end{bmatrix} \quad (14)$$

where $E_1 = (\Pi_I + \Pi_A + \Pi_P)I_M^* + \mu_H$, $E_2 = (\Pi_I + \Pi_A + \Pi_P)S_H^*$, $E_3 = \Pi_I I_M^*$, $E_4 = \Pi_I S_H^*$, $E_5 = \Pi_A I_M^*$, $E_6 = \Pi_A S_H^*$, $E_7 = \Pi_P I_M^*$, $E_8 = \Pi_P S_H^*$, $E_9 = \Sigma_I S_M^*$, $E_{10} = \Sigma_A S_M^*$ $E_{11} = \Sigma_P S_M^*$, $E_{12} = E_{13} + \mu_M$, $E_{13} = \Sigma_I I_I^* + \Sigma_A I_A^* + \Sigma_P I_P^*$

Applying matrix elementary row operations to (14), gives (15)

$$J(E_*) = \begin{bmatrix} -E_1 & \Lambda_I & \Lambda_A & \Lambda_P & 0 & -E_2 \\ 0 & -A_1 E_7 & -\Omega E_3 & A_3 E_3 & 0 & 0 \\ 0 & 0 & -E_{21} & -E_{22} & -E_{23} & \mu_M E_{14} \\ 0 & 0 & 0 & -E_{26} & -E_{27} & \mu_M E_{14} \\ 0 & 0 & 0 & 0 & -E_{28} & -E_{29} \\ 0 & 0 & 0 & 0 & 0 & -E_{30} \end{bmatrix} \quad (15)$$

where $E_{14} = \phi E_3 + A_1 E_5$, $E_{15} = \Omega E_5 + A_2 E_7$, $E_{16} = E_9 E_{15} + \phi E_7 E_{10}$, $E_{17} = \frac{(R_0^2\mu_M Z_H A_3\Phi_I + Z_M\theta_{MH}(A_3A_5\Phi_I - \phi\Phi_P^2\mu_H)(R_0^2 - 1))\Phi_A\theta_{MH}\theta_{HM}\mu_H^2 I_M^* S_M}{(R_0^2\mu_M Z_H + A_5 Z_M\theta_{MH})Z_H^2}$

$E_{17} > 0$ if $A_3A_5\Phi_I > \phi\Phi_P^2\mu_H$

$$, \ E_{18} = \phi\, E_7 E_{12} \ , \ E_{19} = \Omega E_5 E_{14} + \mathrm{A}_1\mathrm{A}_2 E_5 E_7 \ , \ E_{20} = \mathrm{A}_3\, E_5 E_{14} \ ,$$
$$E_{21} = \mathrm{A}_2 E_3 E_9 + E_{10} E_{14} \ \ E_{22} = \ E_{11} E_{14} \ , \ E_{23} = \ E_{13} E_{14} \ ,$$
$$E_{24} = E_{17} E_{19} - E_{16} E_{20} > 0 \ \text{ if } \ E_{17} E_{19} > E_{16} E_{20}$$
$$E_{25} = E_{18} E_{19} \ , \ E_{25} = E_{18} E_{19} \ , \ E_{26} = E_{19} E_{22} + \mathrm{E}_{20} E_{21} \ , \ E_{27} = E_{19} E_{23}$$
$$E_{28} = E_{25} E_{26} + E_{24} E_{27} \ , \ E_{29} = \mu_M E_{14} E_{24} \ , \ E_{30} = \mu_M (E_{28} + E_{29})$$

The eigenvalues of the Jacobian matrix (15) are the solutions of the characteristic equation

$$|J - \lambda \mathrm{I}| = 0$$

$$\begin{vmatrix} -(E_1+\lambda) & \Lambda_I & \Lambda_A & \Lambda_P & 0 & -E_2 \\ 0 & -(\mathrm{A}_1 E_7 + \lambda) & -\Omega E_3 & \mathrm{A}_3 E_3 & 0 & 0 \\ 0 & 0 & -(E_{21}+\lambda) & -E_{22} & -E_{23} & \mu_M E_{14} \\ 0 & 0 & 0 & -(E_{26}+\lambda) & -E_{27} & \mu_M E_{14} \\ 0 & 0 & 0 & 0 & -(E_{28}+\lambda) & -E_{29} \\ 0 & 0 & 0 & 0 & 0 & -(E_{30}+\lambda) \end{vmatrix} = 0$$

$$\Longrightarrow (E_1+\lambda)(\mathrm{A}_1 E_7 + \lambda)(E_{21}+\lambda)(E_{26}+\lambda)(E_{28}+\lambda)(E_{30}+\lambda) = 0$$
$$E_1 + \lambda_1 = 0 \Longrightarrow \lambda_1 = -E_1$$
$$\mathrm{A}_1 E_7 + \lambda_2 = 0 \ \Longrightarrow \lambda_2 = -\mathrm{A}_1 E_7$$
$$E_{21} + \lambda_3 = 0 \Longrightarrow \lambda_3 = -E_{21}$$
$$E_{26} + \lambda_4 = 0 \Longrightarrow \lambda_4 = -E_{26}$$
$$E_{28} + \lambda_5 = 0 \ \Longrightarrow \ \lambda_5 = -E_{28}$$
$$E_{30} + \lambda_6 = 0 \Longrightarrow \lambda_6 = -E_{30}$$

All the eigenvalues of the Jacobian matrix $\mathrm{J}(E_*)$ are negatives if $\mathrm{A}_3\mathrm{A}_5\Phi_I > \phi\Phi_P^2\mu_H$ and $E_{17}E_{19} > E_{16}E_{20}$ are true. Hence, it can be concluded that the endemic equilibrium E_* of the model (4) is locally asymptotically stable if $R_0 > 1$.

This concludes the proof.

Theorem 7

If $R_0 > 1$ the endemic equilibrium point E_* of model (4) is globally asymptotically stable in the interior of Ψ .

Proof

The global stability of the endemic equilibrium can be determined by constructing a a common quadratic Lyapunov function $L(t)$ of the form

$$V(S_H, I_I, I_A, I_P, \ S_M, I_M) = \frac{1}{2}[(S_H - S_H^*) + (I_I - I_I^*) + (I_A - I_A^*) + (I_P - I_P^*)]^2 + \frac{1}{2}[(S_M - S_M^*) + (I_M - I_M^*)]^2 \quad (16)$$

Therefore $\dfrac{\partial V}{\partial t} = -[\mu_H D_7^2 + \mu_M D_8^2] \leq 0$

where $D_1 = S_H - S_H^*$, $D_2 = I_I - I_I^*$, $D_3 = I_A - I_A^*$, $D_4 = I_P - I_P^*$, $D_5 = S_M - S_M^*$, $D_6 = I_M - I_M^*$, $\mu_1 = (\mu_H + \pi_I)$, $\mu_2 = (\mu_H + \pi_A)$, $\mu_3 = (\mu_H + \pi_p)$, $D_7 = D_1 + D_2 + D_3 + D_4$ and $D_8 = D_5 + D_6$

It can be seen that $\frac{\partial V}{\partial t} = 0$ if and only if $S_H = S_H^*$, $I_I = I_I^*$, $I_A = I_A^*$, $I_P = I_P^*$, $S_M = S_M^*$ and $I_M = I_M^*$. This leads to theorem 8.

Theorem 8

If a function $V(t)$ is positive definite on the entire state space and has the additional property that $|V(t)| \longrightarrow \infty$ as $\|t\| \longrightarrow \infty$, and if its derivative V is negative definite on the entire state space, then the equilibrium point at the origin is globally asymptotically stable.

Therefore, $\frac{dV}{dt} \leq 0$ and by the LaSalle's Extension (LaSalle's 1976), it implies that the omega limit set of each solution lies in an invariant set contained in Ψ. The only invariant set contained in Ψ is the singleton E_*. This shows that each solution which intersects $\mathbb{R}_+^6$ limits to the endemic equilibrium and that trivial equilibrium is globally asymptotically stable in the invariant feasible region. This completes the proof.

The clinical data in Table 3 was used to determine the parameter values in model (4) [25].

Table 3. Data values for the state variables of the model 4

Years	S_H	I_I	I_A	I_P	S_M	I_M
2000	15,475,505	1,303,685	2,045,843	102,834	246,498,646,800	2,061,060,114,000
2001	16,248,546	1,316,724	1,728,120	80,036	224,544,432,000	1,877,493,360,000
2002	16,645,417	966,923	2,173,970	85,192	231,627,669,000	1,936,718,745,000
2003	16,748,794	1,421,148	2,131,748	82,055	261,177,701,400	2,183,796,747,000
2004	17,419,477	1,289,874	2,126,159	78,008	251,116,727,400	2,099,673,477,000
2005	17,584,872	900,000	3,175,705	95,337	299,026,198,800	2,500,261,074,000
2006	18,086,432	946,946	2,914,402	99,862	284,758,194,000	2,377,379,370,000
2007	18,086,432	1,239,374	4,145,311	100,068	393,182,164,200	3,287,531,541,000
2008	17,784,946	1,363,920	3,845,506	121,548	380,631,543,600	3,182,591,478,000
2009	16,629,384	1,875,338	5,067,370	141,068	505,781,606,400	4,229,014,272,000
2010	16,172,616	2,223,194	5,768,026	153,894	581,561,139,600	4,862,633,058,000
2011	15,210,099	2,747,162	6,774,978	196,261	693,893,831,400	5,801,885,397,000
2012	14,904,333	3,095,178	7,342,778	202,271	759,712,207,800	6,352,215,519,000
2013	15,107,273	3,311,214	7,528,239	217,04	789,481,009,800	6,601,122,729,000
2014	19,609,450	2,454,620	4,562,437	160,093	512,448,510,000	4,284,758,550,000
2015	23,549,481	1,244,974	2,501,649	112,898	275,569,799,400	2,304,135,032,000
2016	23,464,661	1,463,608	2,947,607	134,403	324,557,125,200	2,713,733,946,000

11 Sensitivity Analysis

Sensitivity analysis tells us which parameters have a high impact on the basic reproduction number (R_0) and should be targeted by intervention strategies. Sensitivity index also measures the relative change in a variable when a parameter change [1]. The normalized forward sensitivity index of a variable with respect to a parameter is the ratio of the relative change in the variable to the relative change in the parameter. When the variable is a differentiable function of the parameter, then the sensitivity index could be defined using partial derivatives.

Definition 2

The normalized forward sensitivity index of R_0 , that depends differentiably on a parameter p , is defined by [1,11]

$$\xi_p^{R_0} = \frac{\partial R_0}{\partial P} \times \frac{P}{R_0}$$

Computation of the sensitivity index of the basic reproduction number R_0 with respect to each parameter is given Table 4 for the model.

Table 4. Sensitivity analysis values

Parameter	Value	Sensitivity index
Z_H	414521	−0.43575
Z_M	134267979835	0.47706
μ_H	0.016	0.44885
μ_M	0.058176	−0.83339
π_I	0.020605	−0.00891
π_A	0.19113	−0.21104
π_P	0.49273	−0.00025
Λ_I	0.11855	−0.04825
Λ_A	0.14348	−0.16136
Λ_P	0.14154	−0.00025
θ_{MH}	0.00016937	0.47712
θ_{HM}	0.00454	0.47712
Φ_I	0.33575	0.18607
Φ_A	0.98982	0.83034
Φ_P	0.012704	0.0000054
ϕ	0.10743	0.00569
Ω	0.016744	−0.0198

The most positive parameter is the biting rate (Φ_A) for the people above 5 years and this is followed by fractions of bites that successfully infect humans and mosquitoes (θ_{MH} and θ_{HM}) . Also, these are followed by the recruitment rate for mosquitoes (Z_M) Therefore, decreasing these four parameters will decrease the basic reproduction number and will have a great impact on the elimination of malaria. Since the three biting rates are all positive, then decreasing them is the surest way to malaria elimination. Since the three clinical recovery rates are all negatives, therefore increasing them will lead to a decrease in R_0 . Increasing the density-dependent natural mortality rate for adult female Anopheles mosquitoes will lead to a decrease in R_0 , that is, reducing the lifespan of mosquitoes may assist in the elimination of malaria. Therefore, from the sensitivity analysis, we have to control the following parameters in order to eliminate malaria or bring it under control:

- biting rates,
- recruitment rate for mosquitoes,
- density-dependent natural mortality rate for mosquitoes and
- clinical recovery rates.

The red lines in the Figs. 1, 2, 3 and 4 show the current state of the malaria disease using the clinical data in Table 3. The yellow and green lines show either the first and second increments of the parameters or the first and second reductions of the parameters respectively. The yellow and green lines in Fig. 1 show the impact of reducing the biting rate of mosquitoes. Therefore, reducing biting rates through the Insecticide Treated Nets (ITNs) is one of the key strategies to consider in fighting the malaria menace. Fig. 2 shows the impact of reducing the recruitment rate of the mosquito population through the ITN, clearing the breeding grounds for mosquitoes and spraying the larvae sites of mosquitoes.

We also have Fig. 3 which shows the impact of increasing the natural death rate of mosquitoes through the Indoor Residual Spraying (IRS), Mass Spraying and the ITN. And finally, we have Fig. 4 which shows the impact of increasing the clinical recovery rate of humans through Improved Antimalarial drugs. That is if Antimalarial drug producers can develop new drugs such that the number of days it takes to recover from malaria infection is reduced to the shortest possible minimum will also assist in malaria elimination quickly,

because the longer the parasite stays in the human, the more that person spreads the parasite to mosquitoes. Therefore, the key parameters to consider in the elimination of the malaria disease are biting rates of mosquitoes, the recruitment rate of mosquitoes, the natural death rate of mosquitoes and clinical recovery rates of humans.

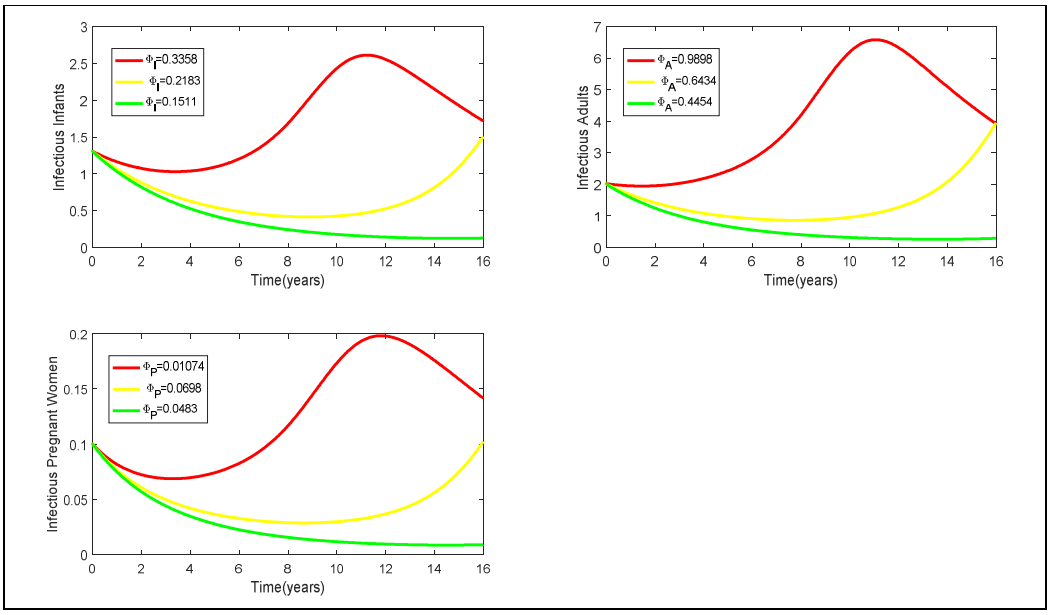

Fig. 1. The impact of reducing the biting rates

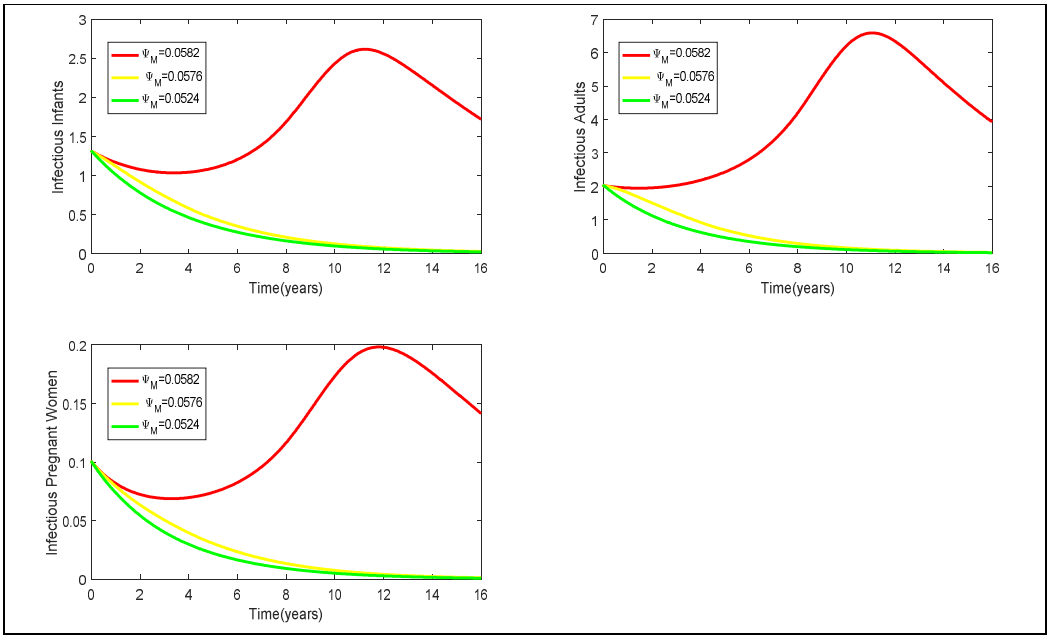

Fig. 2. The impact of reducing the recruitment rate of mosquitoes

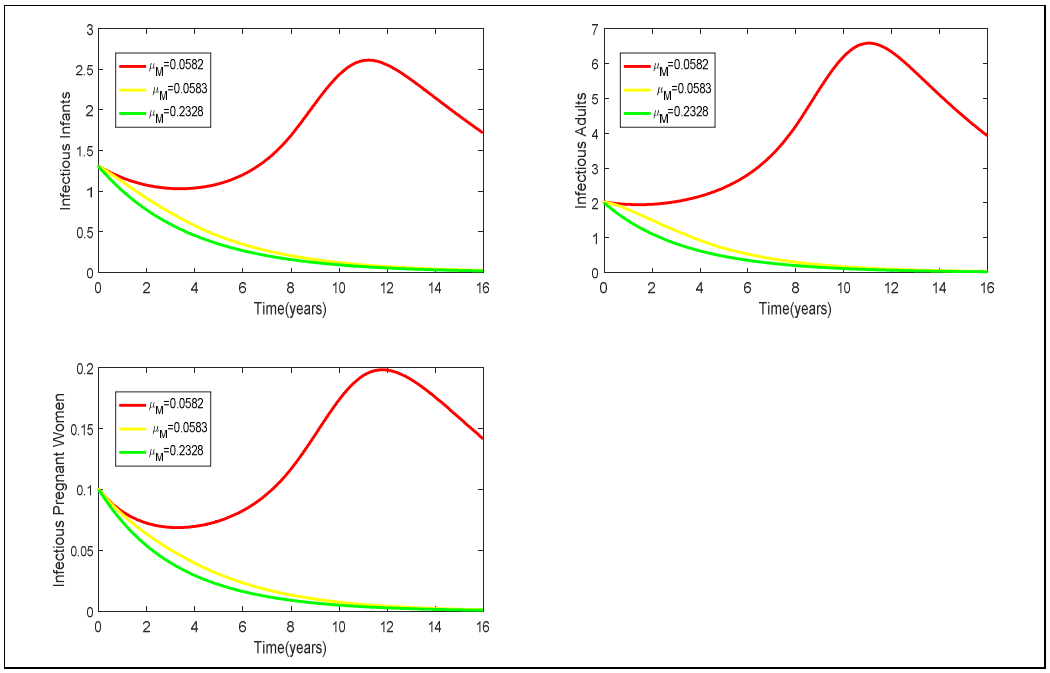

Fig. 3. The impact of increasing the death rate for mosquitoes

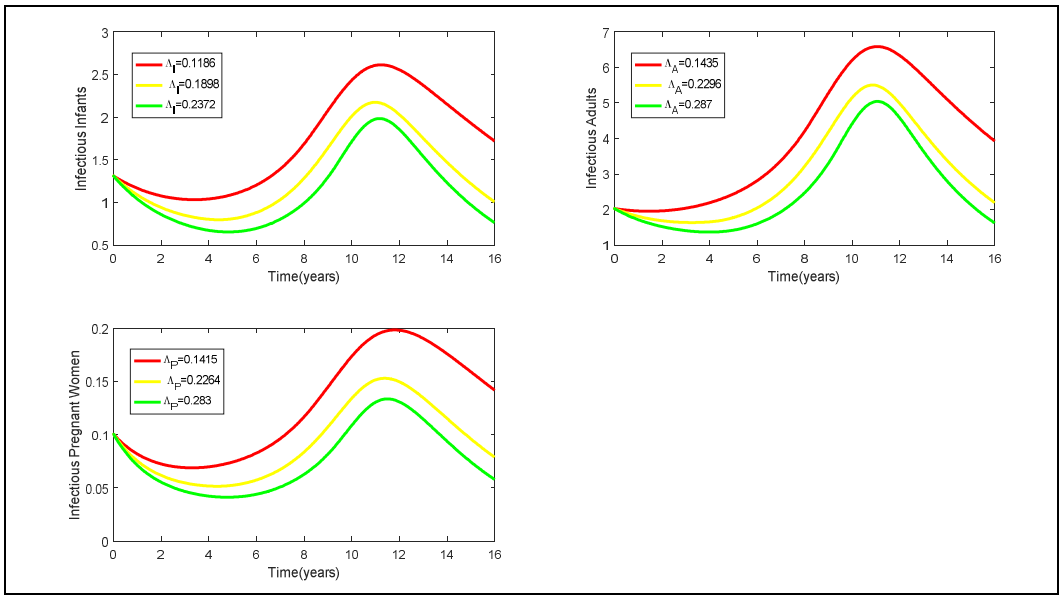

Fig. 4. The impact of increasing the clinical recovery rates for humans

12 Conclusion

It can be seen that either reducing the recruitment rate for mosquitoes in Fig. 2 or increasing the density-dependent natural mortality rate for mosquitoes in Fig. 3 or both are key parameters to consider in the

elimination of the disease. The biting rate for the over 5years population is highest among the three biting rates since most of the over 5years population do not even sleep under the insecticide-treated bed net (ITNs). One striking revelation is the high disease-induced death rate for infectious pregnant women, which means infectious pregnant women can easily lose their lives and that of the unborn babies if they do not seek treatment when they exhibit any symptoms of Malaria infection.

Competing Interests

Authors have declared that no competing interests exist.

References

[1] Johansson P, Leander J. Mathematical modelling of malaria. Chalmers University of Technology, Gothenburg; 2010.

[2] Tumwiine J, Mugisha JYT, Luboobi LS. On oscillatory pattern of malaria dynamics in a population with temporary immunity. Computational and Mathematical Methods in Medicine. 2007;8(3). September 2007, 191–203. Taylor & Francis Group. http://www.tandf.co.uk/journals, DOI: 10.1080/17486700701529002.

[3] Mwamtobe PMM. MSc Thesis-r Modelling the effects of multi-intervention campaigns for the Malaria Epidemic in Malawi.2University of Dares Salaam; 2010.

[4] Understanding Malaria, Fighting an Ancient Scourge (2007). U.S. Department of Health and Human Services, National Institutes of Health National Institute of Allergy and Infectious Diseases, NIH Publication No. 07-7139, www.niaid.nih.gov.

[5] King JML. MSc Thesis- malaria in the Amazon: An agent-based approach to epidemiological modeling of coupled systems. University of Waterloo, Waterloo, Ontario, Canada; 2009.

[6] Can Malaria Be Eradicated? Council on Foreign Relations; 2016.

[7] World Malaria Day 2018 “Ready to beat malaria” Report.

[8] The National Academies Press. Saving Lives, Buying Time: Economics of Malaria Drugs in an Age of Resistance This PDF is available at http://nap.edu/11017, Sciences Engineering Medicine.

[9] Azu-Tungmah GT. MPhil-Thesis: A mathematical model to control the spread of malaria in Ghana. Department of Mathematics under College of Science, Kwame Nkrumah University of Science and Technology, Kumasi-Ghana; 2012.

[10] Chitnis N. Introduction to mathematical epidemiology. Universität Basel, Mathematisches Institut, Swiss Tropical and Public Health Institute; 2011.

[11] Martcheva M, Hoppensteadt F. India’s approach to eliminating *Plasmodium falciparum* malaria: A modeling perspective. Department of Mathematics, University of Florida, 358 Little Hall, PO Box 118105, Gainesville, FL 32611–8105; 2010.

[12] Pongsumpun P, Mumtong P. Mathematical model for the Incubation of the *Plasmodium vivax* Malaria. Department of Mathematics, Faculty of Science, King Mongkut's institute of Technology Ladkrabang, Chalongkrung road, Ladkrabang, Bangkok 10520, Thailand; 2011.

[13] Aneke SJ, Shonkwiler R. Some mathematical models for malaria. School of Mathematics, Georgia Institute of Technology, Atlanta, GA30332.

[14] Lawi GO, Mugisha JYT, Omolo – Ongati N. Mathematical model for malaria and meningitis co-infection among children. Applied Mathematical Sciences. 2011;5(47):2337–2.

[15] Frequently asked questions for malaria.

[16] Bokil VA. Introduction to the mathematics of infectious diseases. Department of Mathematics, Oregon State University, Corvallis, Oregon.2007 REU Program in Mathematics, Mathematical Epidemiology; 2007.

[17] Ducrot A, Sirima SB, Somé B, Zongo P. A mathematical model for malaria involving differential susceptibility, exposedness and infectivity of human host. Journal of Biological Dynamics. 2009;3(6):574-598. http://dx.doi.org/10.1080/17513750902829393.

[18] Mwamtobe PMM. PhD Thesis- Optimal (Control of) Intervention Strategies for Malaria Epidemic in Karonga District, Malawi. School of Computational and Applied Mathematics, University of the Witwatersrand, Johannesburg, South Africa; 2014.

[19] Mandal S, Sarkar RR, Sinha S. Mathematical models of malaria - A review. Mandal et al. Malaria Journal 2011, 10:202, http://www.malariajournal.com/content/10/1/202. Centre for Cellular and Molecular Biology (CSIR), Uppal Road, Hyderabad 500007, India; 2011.

[20] N. Chitnis, J. M. Cushing and J. M. Hyman (2006): Bifurcation Analysis of a Mathematical Model for Malaria Transmission. 2006 Society for Industrial and Applied Mathematics, Vol. 67, No. 1, pp. 24–45. DOI. 10.1137/050638941

[21] Chitnis NR. PhD-Thesis -Using mathematical models in controlling the spread of malaria, 2005, Graduate College, University of Arizona; 2005.

[22] Addawe JM, Lope JEC. Analysis of aged-structured malaria transmission model. Department of Mathematics and Computer Science, University of the Philippines Baguio; 2012.

[23] Owusu-Agyei S, Smith T, Beck HP, Amengo-Etego L, Felger I. Molecular epidemiology of *Plasmodium falciparum* infections among asymptomatic inhabitants of a holoendemic malarious area in northern Ghana. Navrongo Health Research Centre, Navrongo, Ghana. Tropical Medicine and International Health. 2002;7(5):421-428.

[24] Medlock J. Mathematical analysis of epidemiological models. Computing R_0. Clemson University, Department of Mathematical Sciences; 2010.

[25] Azu-Tungmah GT, Oduro FT, Okyere GA. Estimating the parameters of a disease model from clinical data. Journal of Advanced in Mathematics and Computer Science. 2017;24(3):1-11. Article no. JAMCS.34641.

Peer-review history:
The peer review history for this paper can be accessed here (Please copy paste the total link in your browser address bar)
http://www.sdiarticle3.com/review-history/46649