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Stability and Time-Scale Analysis of Malaria Transmission in Human-Mosquito Population

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Abstract: More realistic human-mosquito mathematical model in which re-infected asymptomatic humans are considered is presented. The Next Generation Matrix technique is used to construct epidemiological threshold known as the reproduction number. Locally and globally asymptotically stable disease-free equilibrium conditions for the model are established. Possible time-scale of events for model transition from non-endemic to endemic is analyzed. Results show that the buildup of the latent asymptomatic humans at steady state is the main dynamics of malaria in the endemic region.

Keywords: Malaria Transmission, Stability Analysis, Mathematical Modeling

1. Introduction

Malaria is one of the most serious health problems in the world. In 2015, the World health organization reported that 1.2 billion people worldwide were at high risk of malaria with 214 million cases and 438,000 deaths [1]. Typical indicators of malaria infections range from cyclical fevers to coma and death. The period of cyclical fever lasts several days with symptoms such as vague, anemia, blood stools, convulsion, myalgia, diarrhea, nausea, and vomiting very common [2]. During this period, a high probability of deaths and abortions have been observed among children under five years of age and pregnant women, respectively, in the endemic regions [2, 3]. Sub-Saharan Africa carries a disproportionately high rate of malaria cases (88%) and deaths (90%). Therefore, more insight and better intervention programs needed to be established to control and possibly eradicate the disease.

The etiological agent of malaria is a eukaryotic protozoan parasite of the genus Plasmodium belonging to the apicomplexan family. Parasites are transmitted to humans by Anopheles mosquitos' bites. The parasite life cycle is divided into two parts: one is within the host (human) body while the other is within the vector (mosquito) body as shown in Fig 1.

The struggle to combat malaria has been focused on reducing 1) high density of Anopheles mosquitoes, 2) high density of human infections, and 3) large rate of transmission of malaria parasite between humans and mosquitoes. Methods such as pesticide spraying, use of bed nets, mosquito-repellents have been used to reduce the high density of mosquitoes and the large rate of malaria parasite transmission between humans and mosquitoes in endemic regions. In addition, drugs such as Chloroquine, Quinuine, Primaquine, and combinations of Sulfadoxine and Pyrimethamine have been effectively used to treat the infectious population [7]. Despite these adequate antimalarial treatments, it remains one of the commonest disease in Sub-Saharan Africa [8, 9].

The complexity of malaria and the tendency for its patients to become resistant to malaria drugs make it very challenging to control or eradicate the disease. Mono-therapies have been identified as one of the main contributors to drug resistance, thus, making many malaria patients temporarily asymptomatic parasite carriage [10, 11]. The issue of asymptomatic parasite carriage is crucial in the transmission of malaria. Ogutu et al. reported that a large proportion of P. falciparum infections are asymptomatic with microscopy-detection level as high as 39 percent on children under 10 years old in endemic regions. Based on their findings they hypothesized without testing that a significant reduction of the malaria parasite pool could be obtained through the treatment of the asymptomatic class in endemic population [12].

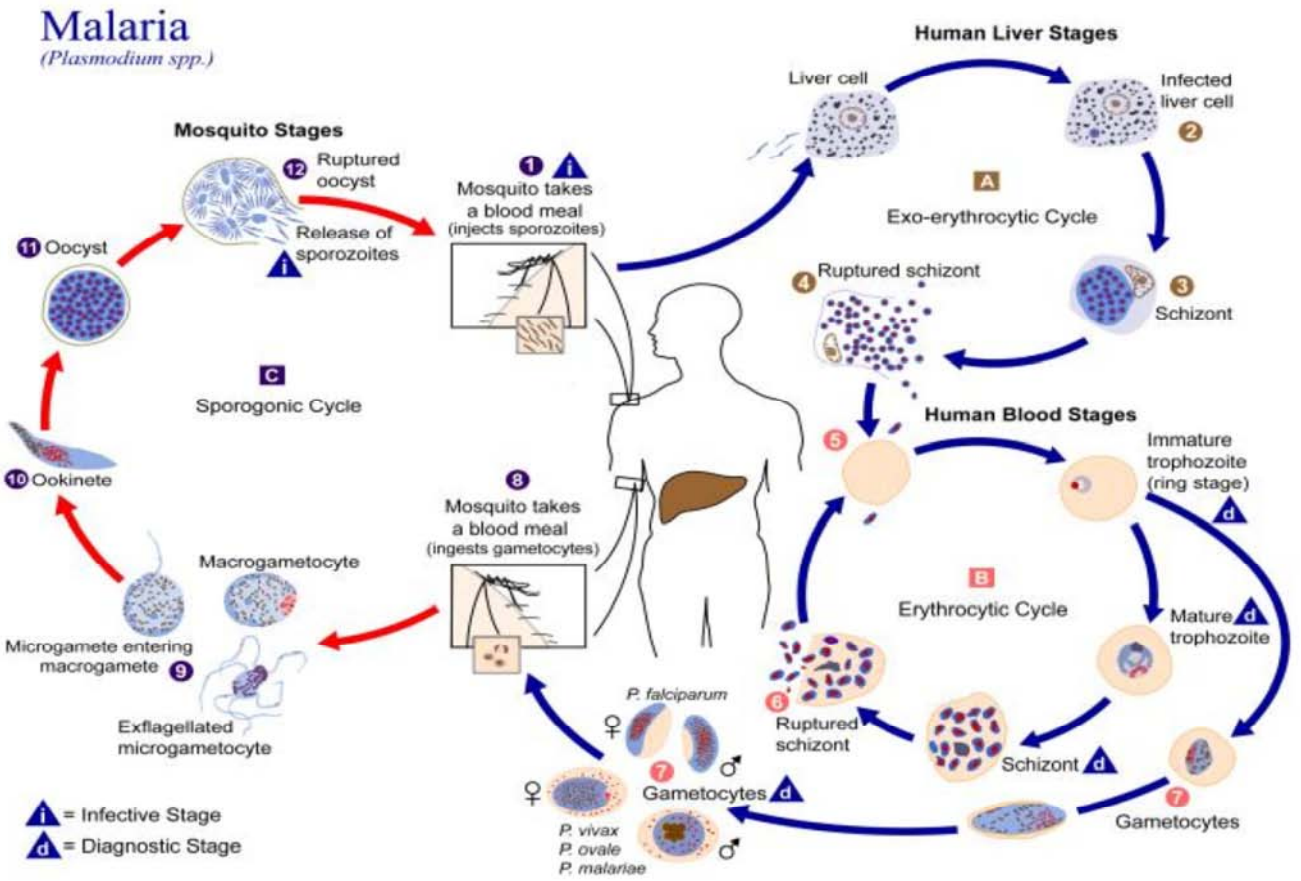

Fig. 1. *Human infection starts from a blood meal of an infectious female mosquito. The parasites enter the bloodstream of the human though mosquito bites migrate to the liver. Within minutes after entering in the human body, it infect hepatocytes, and multiply asexually and asymptomatically for a period of 5-30 [4, 5]. These merozoites rupture their host cells undetectably by wrapping themselves in the membrane of infected liver cells and then escape into the bloodstream to infect red blood cells. Within the red blood cells, a proportion of parasites keep multiplying asexually and periodically break out of infected old red blood cells to invade fresh red blood cells. Such amplification cycles may cause the symptom of waves of fever. The rest parasites follow sexual maturation and produce male (micro-) and female (macro-) gametocytes which may be taken up by bites of female mosquitoes. When an uninfected female mosquito bites infectious human, it ingests the human's blood cells with gametocytes. In the mosquito gut, exflagellated micro-gametocytes enter macro-gametocytes after released from the human's red blood cells, and further form diploid zygotes, which develop into active ookinetes. Ookinetes burrow into the mosquito midgut and become oocysts. The growth and division of each oocyst produces thousands of active haploid forms called sporozoites. After 8 - 15 days, the oocyst bursts and releases sporozoites into the body cavity of the mosquito, from where sporozoites travel to and invade the mosquito salivary glands. Then the malaria parasites once more undergoes a cycle of human infection when the mosquito takes a blood meal from another human [6].*

In this paper, we derive a mathematical model to elucidate the risks of partial immunity caused by mono-therapies or inadequate clearance of malaria patients in endemic regions. The patients who have recovered from the worst malaria symptoms, the partially immune humans (asymptomatic) and the re-infected asymptomatic incubating class, could still transmit the disease and therefore included in our model. The Next Generation Matrix method is used to construct the threshold parameter R_0. The model is then analyzed to adduce a sufficient condition that the disease free state is locally and globally asymptotically stable if $R_0 < 1$ and unstable for $R_0 > 1$. Finally, a time scale analysis is conducted to demonstrate the existence of the endemic state and to provide more insight into malaria transmission.

The organization of this paper is as follows: Model formulation is developed in section 2. Existence and stability analysis for equilibrium state in section 3. Time scale analysis in section 4 and the conclusion in section 5.

2. Model Formulation

2.1. Variables Description

A population of humans in a region is susceptible to malaria infection if the environmental conditions in that region favor the breeding of the anopheles mosquitos. Once an infectious female anopheles mosquito injects malaria parasites into a human at the site of bite, these parasites undergo developmental stages within the host. These stages partition the host into a waiting state to disease manifestation, or disease state or non-disease state in the presence of the parasites. In order to set the necessary mathematical framework, we divide the human population into classes of susceptible (S_h), latent (L_h), latent asymptomatic (L_A), symptomatic (I_s) and asymptomatic (A) carriers. Also,

mosquito population is subdivided into susceptible (T_m), latent (L_m) and infectious (I_m) classes. Detailed state variables are given in Table 1 and the movement between compartments summarized in Fig 2.

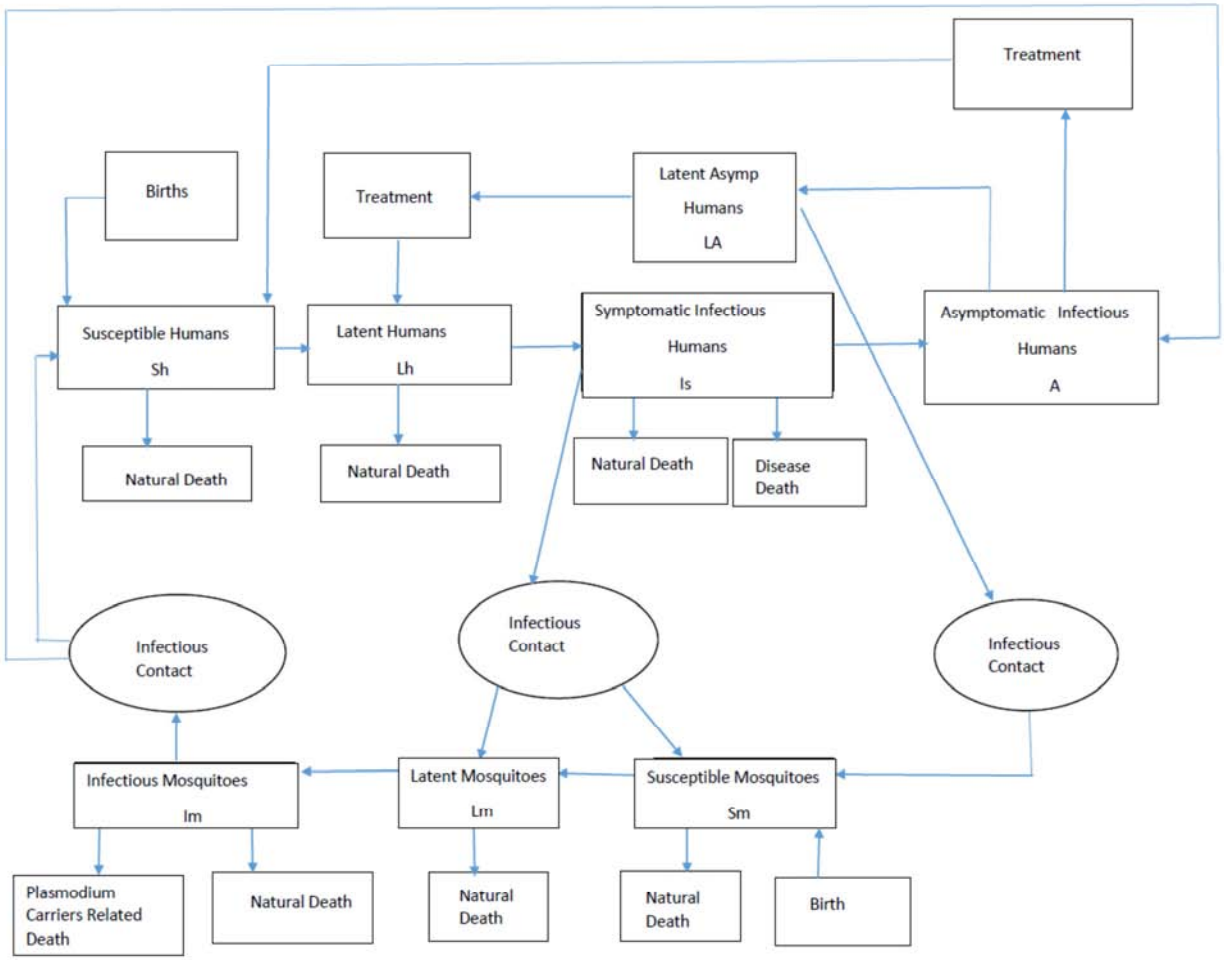

Fig. 2. *Compartmental model depicting human-mosquito malaria parasite interactions. The rectangles indicate state variables and actions within humans and mosquitoes, while the circles depict actions between species.*

Table 1. *Description of State Variables.*

N	Total human population
S_h	Susceptible human population, who initially do not have malaria parasites but have natural non-specific immunity,
L_h	Incubating human population who have received infectious bites and are within the laver and early erythrocyte stage infection.
L_A	Number of latent asymptomatic infectious humans in the erythrocyte stage that have developed both disease symptoms and gametocytes.
I_s	Number of symptomatic infectious humans who require treatment since they know that they are infected.
A	Number of asymptomatic infectious humans who no longer have symptoms of the disease that warrant medical attention but are still infectious to mosquitoes.
T_m	Total female anopheles (mosquitoes) population.
S_m	Number of susceptible mosquitoes.
L_m	Number of incubating (latent) mosquitoes.
I_m	Number of infectious mosquitoes.

Clarify L_A is the individuals in the A class being bitten by infectious mosquitoes. Since they carry both gametocytes and asexual parasites, loss of immunity may cause their immediate transition into the I_s class instead of the S_h class. Also, a mosquito is in the L_m class as soon as it ingest gametocytes from an infectious human but before the sporazoites migrate to the salivary gland. Finally, the L_A, I_s, and A classes are infectious to the S_m class while the I_m class infects S_h and A classes.

2.2. Model Assumptions

1) Malaria is transmitted when a susceptible human is bitten by an infected anopheline mosquito and each mosquito has the same biting behavior.

2) The rate at which a susceptible individual becomes infected is a function of contact rate with infective mosquitoes and the level of host susceptibility.

3) Mosquito biting vectors are equally susceptible and

human infectiousness to mosquitoes is determined mainly by the gametocyte density or the density of infection in the human host.

4) The recruitment of human into the susceptible population occurs at a constant per capita birth rate λ_h and apart from asymptomatic individual, no human in the latent and symptomatic infectious classes would be affected by a bite from an infectious mosquito.

5) Plasmodium parasite reduces the life span of infectious mosquitoes.

6) We focus on an endemic area and year time scale, where the total population change is negligible in the absence of the disease

7) We consider a small perturbation of the disease free-state and assume that growth and decay is faster than population change.

2.3. Model Description

The susceptible humans get infected at rate $\beta_h e I_m S_h / N$ where eI_m is the rate at which infected mosquitoes bite, e is a constant value of the biting rate per human per unit time, S_h / N is the probability that the human bitten is susceptible, and β_h is the number of human infections per bite. Similarly, the rate of infection of an asymptomatic individual is $\beta_h e I_m A / N$. The rate at which uninfected mosquitoes obtain the plasmodium parasite from human carriers is $\left(e\beta_s I_s + \beta_a A + \beta_a L_A\right)\frac{S_m}{N}$ where β_a is the probability that a bite from a susceptible mosquito on an asymptomatic infectious human transfers the infection to the mosquito, and β_s is the probability that a susceptible mosquito gets infected after biting a symptomatic infectious human.

Susceptible mosquitoes are recruited into the mosquito population through a constant birth rate λ_m. Applying assumption 4, there will be a total of eT_m bites by mosquitoes on humans. However, only S_h / N of these bites will be made on susceptible humans. The proportion that a bite is made by an infectious mosquito is I_m / T_m. Since β_h assumes that not all bites by an infectious mosquito on a susceptible human can lead to infection, the parameter $\beta_h \in [0,1]$ is the proportion of bites by an infectious mosquito that leads to infection. Here $\beta_h = 1$ implies all bites transmit the disease. The cross infection rate $\beta_h e I_m / N$ between the human and mosquito population depends on the average number of mosquito bites per unit time and the transmission probability of the human population.

Based on assumption 4, the individuals in the L_h class are already in the process of transition into the I_s class and are entitled to treatment. Thus, the incubating humans become infectious after a mean latency time $1/\eta_h$. All humans who die naturally have a per capita rate of $1/\mu_h$, while some individuals in the I_s class die at rate $\alpha_h I_s$ from the disease. In addition, those who survives receive treatment and are either recover with complete clearance to join the susceptible class at a rate $r_s I_s$ (treatment period 14-days), or only recover from symptoms (after a 3-day monotherapy) without parasite clearance to join the A class at a rate $r_a I_s$. The post symptomatic class A still can carry merozoites and produce gametocytes. So, they can infect biting mosquitoes. [22] have shown that a human can be in this state for several weeks or months and hence can play an important role in sustaining the epidemic. Thus, we consider a putative treatment which removes individual from A and L_A classes into S_h and L_h, respectively, with the effect of the treatment parameter being $\psi\theta_h$, where ψ are those being treated.

Thus, the system of equations for the human compartments are,

$$\frac{dS_h}{dt} = \lambda_h N + r_s I_s + l_a A - \beta_h e \frac{I_m}{N} S_h - \mu_h S_h + \psi\theta_h A, \quad (1)$$

$$\frac{dL_h}{dt} = \beta_h e \frac{I_m}{N} S_h - \eta_h L_h - \mu_h L_h + \psi\theta_h L_A, \quad (2)$$

$$\frac{dL_A}{dt} = \beta_h e \frac{I_m}{N} A - \eta_h L_A - \mu_h L_A - \psi\theta_h L_A, \quad (3)$$

$$\frac{dI_s}{dt} = \eta_h L_h + \eta_h L_A - \alpha_h I_S - r_S I_S - r_a I_S - \mu_h I_S, \quad (4)$$

$$\frac{dA}{dt} = r_a I_S - \beta_h e \frac{I_m}{N} A - l_a A - \mu_h A - \psi\theta_h A, \quad (5)$$

where the total human population is $\frac{dN}{dt} = \lambda_h N - \alpha_h I_S - \mu_h N.$

Similarly, the susceptible mosquitoes get infected through infectious human contact at a rate $e\left(\beta_a I_S + \beta_a A + \beta_a L_A\right)\frac{S_m}{N}$ and proceed to the incubating class. Applying assumption 6, we state that mosquitoes in the incubating class die naturally at a rate $\mu_m L_m$ and the rest get infected at a rate $\eta_m L_m$ to join the infectious class which they remain until their death either normally, or are killed by the parasites at rate $\alpha_m I_m$. Thus, the system of equations for the mosquito classes are

$$\frac{dS_m}{dt} = \lambda_m I_m - \beta_S e \frac{I_S}{N} S_m - \beta_a e \frac{A}{N} S_m - \beta_a e \frac{L_A}{N} S_m - \mu_m S_m, \quad (6)$$

$$\frac{dL_m}{dt} = \beta_S e \frac{I_S}{N} S_m + \beta_a e \frac{A}{N} S_m + \beta_a e \frac{L_A}{N} S_m - \eta_m L_m - \mu_m L_m, \quad (7)$$

$$\frac{dI_m}{dt} = \eta_m L_m - \alpha_m I_m - \mu_m I_m, \quad (8)$$

with the total mosquito population as $\frac{dT_m}{dt} = \lambda_m T_m - \alpha_m I_m - \mu_m T_m.$ Here, the initial conditions for

humans-mosquitoes are $t=0$, $N=N_0$, $T_m=T_{m_0}$ and their parameter values defined in Table 2.

2.4. Model Parameterization

Table 2. *Model Parameterization.*

Parameter	Description	Value	Source
λ_h	Per capita human birth rate	0.000104/ day	[13]
l_a	Rate of immunity loss by asymptomatic infectious humans	0.006061/day	[14]
e	Average number of bites each mosquito gives to human per unit time	0.44/day	[15]
β_h	Probability that a bite by an infectious mosquito infects a susceptible human.	0.086	[16]
μ_h	Per capita human death rate.	0.0000356/day	[13]
η_h	Transition rate of incubating humans into symptomatic infectious per unit time.	0.067013/day	[17], [18]
α_h	Per capita death rate of humans due to disease influence.	0.0006061/day	
r_s	Drug recovery rate of symptomatic infectious humans per unit time	value 0.07/day	[19]
r_a	Transmission rate of symptomatic infectious humans to asymptomatic infectious class per unit time.	0.33/ day	[19]
λ_m	Per capita mosquito birth rate.	0.13/day	[20]
η_m	Transition rate of incubating mosquitoes into infectious class per unit time.	0.0830/day	[21]
β_s	Susceptible mosquito gets infected after biting a symptomatic infectious human.	0.1	
β_a	The probability that a bite by a susceptible mosquito on an asymptomatic infectious human transfers the infection to the mosquito.	0.53	
α_m	Per capita death rate of mosquitoes due to gametocyte carriage per unit time.	0.03152 /day	
θ_h	Recovery rate of asymptomatic infectious humans due to treatment per unit time.		
ψ	Fraction of post malaria treatment.		

Introduce new variables as follows,

$$S_h^*=\frac{S_h}{N},\ \mathrm{L}_h^*=\frac{L_h}{N},\ L_A^*=\frac{L_A}{N},\ I_S^*=\frac{I_s}{N},\ A^*=\frac{A}{N},\ S_m^*=\frac{S_m}{T_m},\ L_m^*=\frac{L_m}{T_m},\ I_m^*=\frac{I_m}{T_m},$$

such that $S_h^*+L_h^*+L_A^*+I_s^*+A^*=1$ and $I_s^*+L_m^*+I_m^*=1$, we define the dimensionless parameters (stated below) with their values defined in Table 3

$$\beta=\frac{\beta_h e T_m(0)}{l_a N(0)},\quad b=\frac{\beta_s e}{l_a},\quad d=\frac{\beta_a e}{l_a},\quad \eta=\frac{\eta_h}{l_a},\quad \mu=\frac{\mu_h}{l_a},\quad \lambda=\frac{\lambda_h}{l_a},\quad \alpha=\frac{\alpha_h}{l_a}$$
$$\gamma=\frac{r_s}{l_a},\qquad \rho=\frac{r_a}{l_a},\qquad \theta=\frac{\psi\theta_h}{l_a},\quad f=\frac{\eta_m}{l_a},\quad q=\frac{\lambda_m}{l_a},\quad g=\frac{\mu_m}{l_a},\quad h=\frac{\alpha_m}{l_a}.$$

Based on assumption 6, we scale the time with asymptomatic susceptible transmission parameter l_a, and rewrite $t=t^*/l_a^*$ where $t^*=1$ is about 165 days, (Since time scale for asymptomatic clearance is approximately 6 months). So, rescaling initial humans and mosquitoes populations, we have, respectively, $N=N(0)N^*$ and $T_m=T_m(0)T_m^*$. Consequently, the dimensionless model equations (1)-(8) becomes:

$$\frac{dS_h}{dt}=\lambda+\gamma I_S+A-\beta I_m S_h\frac{T_m}{N}-\lambda S_h+\alpha S_h I_S+\theta A \tag{9}$$

$$\frac{dl_h}{dt}=\beta I_m S_h\frac{T_m}{N}-\eta L_h-\lambda L_h+\alpha L_h I_S+\theta L_A \tag{10}$$

$$\frac{dL_A}{dt}=\beta I_m A\frac{T_m}{N}-\eta L_A-\lambda L_A+\alpha L_A I_S-\theta L_A \tag{11}$$

$$\frac{dI_s}{dt}=\eta L_h+\eta L_A-(\alpha+\gamma+\rho+\lambda)I_S+\alpha I_S^2 \tag{12}$$

$$\frac{dA}{dt}=\rho I_S-(1+\beta I_m\frac{T_m}{N}+\lambda-\alpha I_S+\theta)A \tag{13}$$

$$\frac{dS_m}{dt}=q(1-S_m)-bI_S S_m-dAS_m-dL_A S_m+hI_m S_m \tag{14}$$

$$\frac{dL_m}{dt}=bI_S S_m+dAS_m+dL_A S_m-(f+g)L_m+hI_m L_m \tag{15}$$

$$\frac{dI_m}{dt}=fL_m-(h+q)I_m+hI_m^2 \tag{16}$$

$$\frac{dN}{dt}=-\alpha I_S N+(\lambda-\mu)N \tag{17}$$

$$\frac{dT_m}{dt} = -hI_m T_m + (q-g)T_m \tag{18}$$

Table 3. *Dimensionless parameters and their values.*

Dimensional	Dimensionless	Value	Value in ε
$\beta_h e T_m(0)/l_a N(0)$	β	62.43	$O(\varepsilon^{-2})$
η_h/l_a	η	11.1	ε^{-1}
μ_h/l_a	μ	0.0056	$O(\varepsilon^{2})$
$\beta_s e/l_a$	b	7.2	$O(\varepsilon^{-1})$
$\beta_a e/l_a$	d	38.2	$O(\varepsilon^{-1})$
λ_h/l_a	λ	0.017	$O(\varepsilon^{-1})$
α_h/l_a	α	0.01	$O(\varepsilon^{2})$
r_s/l_a	γ	11.5	$O(\varepsilon^{-1})$
r_a/l_a	ρ	54.45	$O(\varepsilon^{-2})$
$\psi\theta_h/l_a$	θ		
η_m/l_a	f	14	$O(\varepsilon^{-1})$
λ_m/l_a	q	21.45	$O(\varepsilon^{-1})$
μ_m/l_a	g	20.62	$O(\varepsilon^{-1})$
α_m/l_a	h	1.45	O(1)

By definition, ε is the ratio of the proportion of time for the latency period (η_h) compared to the mean asymptomatic state timescale (l_a). For $\varepsilon \ll 1$, it means that asymptomatic humans remain infectious for a longer time compared to the latency period of humans.

3. Existence and Stability of Equilibrium Analysis

The points at which the differential equations (9)-(18) equal to zero are referred to as equilibrium points or steady-state solutions. As shown in Annan and Fisher (2013), [23], it is important to note that there is no trivial equilibrium points as long as S_h and S_m are not zero. The implication is that $(S_h, L_h, L_A, I_s, A, T_m, S_m, L_m, I_m) \neq (0,0,0,0,0,0,0,0,0)$ and the population is not extinct.

3.1. Model Linearization and Reproduction Number

We adapt the Next Generation Matrix (NGM) method derived for infection disease models in [23] to determine the basic reproduction number, R_0. The NGM operator approach approximates the number of secondary infections produced by one infected individual and expresses R_0 as the product of the expected duration of the infectious period and the secondary rate infectious. We denote $F\ell$ as the emergence of new infection, $V\ell$ as the transition of the new infections between components, and ℓ as the infection domain. Thus, the linearized system is of the form $\ell' = (F-V)\ell$, where $\ell' = \frac{d\ell}{dt}$ and

$$F = \begin{bmatrix} 0&0&0&0&0&\beta \\ 0&0&0&0&0&0 \\ 0&0&0&0&0&0 \\ 0&0&0&0&0&0 \\ 0&d&b&d&0&0 \\ 0&0&0&0&0&0 \end{bmatrix},\quad V = \begin{pmatrix} a_1&-\theta&0&0&0&0 \\ 0&a_0&0&0&0&0 \\ -\eta&-\eta&a_2&0&0&0 \\ 0&0&-\rho&a_3&0&0 \\ 0&0&0&0&a_4&0 \\ 0&0&0&0&-f&a_5 \end{pmatrix},\quad \ell = \begin{bmatrix} L_h \\ L_A \\ I_s \\ A \\ L_m \\ I_m \end{bmatrix}. \tag{19}$$

Here, the constants $a_i's$ are expressed as:

$$\begin{aligned} a_0 = \eta+\gamma+\theta,\ a_1 = \eta+\gamma,\ a_2 = \alpha+\gamma+\rho+\lambda,\ a_3 \\ = 1+\lambda+\theta,\ a_4 = f+q,\ a_5 = h+q. \end{aligned} \tag{20}$$

Accordingly, computing the non-negative matrix FV^{-1} gives

$$FV^{-1} = \frac{1}{b_0}\begin{pmatrix} 0&0&0&0&\beta b_1&\beta\nu \\ 0&0&0&0&0&0 \\ 0&0&0&0&0&0 \\ 0&0&0&0&0&0 \\ f_1&f_2&f_3&f_4&a_4&0 \\ 0&0&0&0&0&0 \end{pmatrix}, \quad \text{where} \tag{21}$$

$$\begin{aligned} &b_0 = a_0a_1a_2a_3a_4a_5,\ b_1 = fa_0a_1a_2a_3,\ \nu = a_0a_1a_2a_3a_4,\ b_2 = \eta a_0a_3a_4a_5,\ b_3 = \eta\rho a_0a_4a_5, \\ &b_4 = a_1a_2a_3a_4a_5,\ b_5 = \eta a_1a_3a_4a_5,\ b_6 = \eta\rho a_1a_4a_5,\ b_7 = a_0a_1a_3a_4a_5,\ b_8 = \rho a_0a_1a_4a_5, \\ &b_9 = a_0a_1a_2a_4a_5,\ f_1 = bb_2+db_3,\ f_2 = db_4+bb_5+db_6,\ f_3 = bb_7+db_8,\ f_4 = db_9. \end{aligned}$$

Thus, the NGM defined by the product FV^{-1} guarantees a unique dominant positive real eigenvalue of the matrix called the reproduction number, R_0, expressed as

$$R_0 = \frac{\beta(bb_2+db_3)b_1}{b_0^2} = \frac{\beta\eta f(b(1+\lambda+\theta)+\rho d)}{(f+q)(h+q)(\eta+\lambda)(1+\lambda+\theta)(\alpha+\gamma+\rho+\lambda)}. \tag{22}$$

Consider the domain of biological interest for equations (9)-(18) of the form

$$\Omega = \left\{(S_h, L_h, L_A, I_s, A, T_m, S_m, L_m, I_m, \mathrm{N}) \in \mathbb{R}_+^{10} \mid \text{they are} \geq 0 \text{ for all } t > 0\right\}.$$

Then, the disease-free state $(S_h, L_h, L_A, I_s, A, T_m, S_m, L_m, I_m) = (1,0,0,0,0,0,1,0,0)$ is locally and globally asymptotically stable when $R_0 < 1$ and unstable when $R_0 > 1$. Since normally $R_0 \gg 1$ and the ratio of the asymptomatic infectious humans to mosquitoes is significantly large, a possible treatment is to reduce the infectivity of asymptomatic humans, d, and that of symptomatic humans, b by increasing the parameters θ and λ.

3.2. Stability Analysis of Disease-free Equilibrium

We establish the global stability of the disease-free equilibrium in domain Ω by deriving the Jacobian matrix (23) for equations (9)-(16) about the disease-free equilibrium. Here, $a_i^{'}s$ are defined for $0 \leq i \in (\mathbb{Z} \leq 5)$ and $a_6 = \alpha + \gamma$. Thus, the characteristic equation with eigenvalues λ is obtained in equation (24) were,

$$\Pi_1 = a_1 + a_2 + a_3 + a_4 + a_5,$$
$$\Pi_2 = a_1a_2 + a_1a_3 + a_1a_4 + a_1a_5 + a_2a_3 + a_2a_4 + a_2a_5 + a_3a_4 + a_3a_5 + a_4a_5,$$
$$\Pi_3 = a_1a_2a_3 + a_1a_2a_4 + a_1a_2a_5 + a_1a_3a_4 + a_1a_3a_5 + a_1a_4a_5 + a_2a_3a_4 + a_2a_3a_5 + a_2a_4a_5 + a_3a_4a_5,$$

$$\Pi_4 = a_1a_2a_3a_4 + a_1a_2a_3a_5 + a_1a_2a_4a_5 + a_1a_3a_4a_5 + a_2a_3a_4\,\mathrm{a}_5 - bf\beta\eta,$$
$$\Pi_5 = a_1a_2a_3a_4a_5 - f\beta\eta(ba_3 + d\rho).$$

$$J = \begin{bmatrix} -\lambda & 0 & 0 & a_6 & 1+\theta & 0 & 0 & -\beta \\ 0 & -a_1 & \theta & 0 & 0 & 0 & 0 & \beta \\ 0 & 0 & -a_0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \eta & \eta & -a_2 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \rho & -a_3 & 0 & 0 & 0 \\ 0 & 0 & -d & -b & -d & -q & 0 & h \\ 0 & 0 & d & b & d & 0 & -a_4 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & f & -a_5 \end{bmatrix}. \quad (23)$$

$$(\lambda + a_0)(\lambda + q)(\lambda + \lambda)(\lambda^5 + \Pi_1\lambda^4 + \Pi_2\lambda^3 + \Pi_3\lambda^2 + \Pi_4\lambda + \Pi_5) = 0, \quad (24)$$

Lemma 1: The malaria-free equilibrium is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

Proof: Further operation of Π_5 in terms of the reproduction number, R_0, gives

$$R_0 = \frac{f\beta\eta(ba_3 + d\rho)}{a_1a_2a_3a_4a_5}.$$

For $R_0 < 1$, we have $a_1a_2a_3a_4a_5 > f\beta\eta(ba_3 + d\rho)$. So, the coefficients of equation (24) are all positive and non-zero. Therefore applying the Descartes' rule of signs, there are no positive real eigenvalues for equation (24). In addition, using the Routh Hurwitz stability conditions for fifth order polynomial cited in [25], we have $\Pi_1\Pi_2\Pi_3 > \Pi_3^2 + \Pi_1^2\Pi_4 \Rightarrow \xi = \Pi_1\Pi_2\Pi_3 - \Pi_3^2 - \Pi_1^2\Pi_4 > 0$ and $(\Pi_1\Pi_4 - \Pi_5)(\Pi_1\Pi_2\Pi_3 - \Pi_3^2 - \Pi_1^2\Pi_4) > \Pi_5(\Pi_1\Pi_2 - \Pi_3)^2 + \Pi_1\Pi_5^2$, which implies that $\vartheta = (\Pi_1\Pi_4 - \Pi_5)\xi - \Pi_5(\Pi_1\Pi_2 - \Pi_3)^2 - \Pi_1\Pi_5^2 > 0$. In terms of the model parameters, since $a_1a_2a_3a_4a_5 > fd\beta\eta\rho$ and $a_1a_2a_4a_5 > bf\beta\eta$ it follows that $\vartheta > 0$. However, if $R_0 > 1$, $a_1a_2a_3a_4a_5 < f\beta\eta(ba_3 + d\rho)$ where the coefficients Π_1, Π_2, Π_3 are positive and Π_5 is negative. Thus, by the Descartes' rule of signs, there is exactly one sign change in the sequence $1, \Pi_1, \Pi_2, \Pi_3, \Pi_4, \Pi_5$ of coefficients of equation (24). So, there is one eigenvalue with positive real part and the disease-free equilibrium is unstable.

Lemma 2: The malaria-free equilibrium is globally asymptotically stable in Ω if

$$\frac{\beta\eta}{\eta + \lambda} \leq (h + q), \quad \frac{bf}{f + q} \leq \lambda + \gamma, \quad \text{and} \quad \frac{fd}{f + q} \leq \frac{\lambda(\theta + \eta + \lambda)}{\eta + \lambda}. \quad (25)$$

Proof: Consider $\phi = \left\{(S_h, L_A, I_s, A, S_m, L_m, I_m) \in \Omega \mid \mathrm{S}_h, S_m > 0\right\} \to \mathbb{R}$, where

$$\phi = \frac{\eta(1 - S_h) + \lambda(L_A + S_h + A)}{\eta + \lambda} + \frac{f(1 - S_m) + qI_m)}{f + q}. \quad (26)$$

Equation (26) is positive and is continuously differentiable on the interior of Ω. The derivative of ϕ along solutions of the system of equations is

$$\phi' = \left(\frac{\beta\eta}{\eta + \lambda} - q\right)I_m + \left(\frac{bf}{f + q} - (\lambda + \gamma)\right)I_s + \left(\frac{df}{f + q} - (1 + \lambda + \theta)\right)A$$
$$+ \left(\frac{df}{f + q} - \frac{\lambda(\eta + \theta + \lambda)}{\eta + \lambda}\right)L_A - \frac{\beta\eta}{\eta + \lambda}(L_A + I_s + A)I_mI_s - \alpha\left(S_h + \frac{\lambda L_h}{\eta + \lambda}\right)$$
$$- \frac{1}{f + q}(bfI_s + df(A + L_A + hqI_m))I_sL_m - \frac{1}{f + q}(bfI_s + dfA + dfL_A + hqS_m))I_m.$$

Clearly, for $(L_A, I_s, A, L_m, I_m) = (0,0,0,0,0)$, $\phi' \leq 0$ and (L_A, I_s, A, L_m, I_m) is the largest positively invariance subset in the interior of Ω. Thus, by LaSalle's invariant principle [24], $(L_A, I_s, A, L_m, I_m) \to (0,0,0,0,0)$ as $t \to \infty$, while $(S_h, S_m) \to (1,1)$ on the boundary of Ω. Also, whenever the inequalities in equation (25) are true, we have $\phi' \leq 0$.

We now show that if the equations in (25) are true, then $R_0 < 1$. The numerator for equation (22) is

$$\beta\eta f(b(1 + \lambda + \theta) + \rho d) \Rightarrow \beta\eta(fb(1 + \lambda + \theta) + f\rho d). \quad (27)$$

Rearranging the denominator of equation (22), we have

$$(\eta+\lambda)(h+q)\{(\lambda+\gamma)(1+\lambda+\theta)(f+q)+\{\rho(1+\lambda+\theta)(f+q) +\alpha(1+\lambda+\theta)(f+q)\}\} \quad (28)$$

Comparing equations (27) and (28), we observe $\beta\eta \le (\eta+\lambda)(h+q)$ and $bf \le (\lambda+\gamma)(f+q)$. Implying $fd(1+\theta+\lambda) \le (\gamma+\lambda)(f+q)(1+\theta+\lambda)$. Since $1+\theta+\lambda > \frac{\lambda(\eta+\theta+\lambda)}{\eta+\lambda}$, it follows that $df \le \frac{(f+q)(\theta+\eta+\lambda)}{\eta+\lambda}$. Thus, the numerator of equation (22) is less than the denominator, meaning $R_0 < 1$. Implying that if conditions in equation (25) are true, then the malaria-free state is globally stable.

4. Time Scale Analysis

The asymptotic analysis on N and T_m equations depict that T_m changes on the time scale $\mathrm{O}(\varepsilon)$ while N changes on $\mathrm{O}(\varepsilon^{-2})$. Therefore, we assume that T_m/N is constant over the time scale of the model analysis. Thus, setting $\theta = 0$, the time scale analysis of our model in dimensionless form is:

$$\varepsilon^2 \frac{dS_h}{dt} = \varepsilon^4\hat{\lambda} + \varepsilon\hat{\gamma}I_S + \varepsilon^2 A - \hat{\beta}I_m S_h - \varepsilon^4\hat{\lambda}S_h + \varepsilon^4\alpha S_h I_S, \quad (29)$$

$$\varepsilon^2 \frac{dI_h}{dt} = \hat{\beta}I_m S_h - \varepsilon\hat{\eta}L_h - \varepsilon^4\hat{\lambda}L_h + \varepsilon^4\hat{\alpha}L_h I_S, \quad (30)$$

$$\varepsilon^2 \frac{dL_A}{dt} = \hat{\beta}I_m A - \varepsilon\hat{\eta}L_A - \varepsilon^4\hat{\lambda}L_A + \varepsilon^4\hat{\alpha}L_A I_S, \quad (31)$$

$$\varepsilon^2 \frac{dI_s}{dt} = \varepsilon\hat{\eta}L_h + \varepsilon\hat{\eta}L_A - (\varepsilon^4\hat{\alpha} + \varepsilon\hat{\gamma} + \hat{\rho} + \varepsilon^4\hat{\lambda})I_S + \varepsilon^4\hat{\alpha}I_S^2, \quad (32)$$

$$\varepsilon^2 \frac{dA}{dt} = \hat{\rho}I_S - (\varepsilon^2 + \hat{\beta}I_m + \varepsilon^4\hat{\lambda} - \varepsilon^4\hat{\alpha}I_S)A, \quad (33)$$

$$\varepsilon \frac{dS_m}{dt} = \hat{q}(1-S_m) - \hat{b}I_S S_m - \hat{d}AS_m - \hat{d}L_A S_m + \varepsilon\hat{h}I_m S_m, \quad (34)$$

$$\varepsilon \frac{dL_m}{dt} = \hat{b}I_S S_m + \hat{d}AS_m + \hat{d}L_A S_m - (\hat{f}+\hat{g})L_m + \varepsilon\hat{h}I_m L_m, \quad (35)$$

$$\varepsilon \frac{dI_m}{dt} = \hat{f}L_m - (\varepsilon\hat{h} + \hat{q})I_m + \varepsilon\hat{h}I_m^2, \quad (36)$$

with initial conditions

$$S_h(0)=1,\quad L_h(0)=0,\quad L_A(0)=0,\quad I_s(0)=0,\quad \mathrm{A}(0)=0,$$
$$L_m(0)=l_0,\quad S_m(0)=1-l_0,\quad I_m(0)=0,\quad \varepsilon \ll 1,\quad l_0 \ll \varepsilon,$$

and the parameters expressed in terms of their size as powers of ε as follows,

$$\beta=\frac{\hat{\beta}}{\varepsilon^2},\quad b=\frac{\hat{b}}{\varepsilon},\quad d=\frac{\hat{d}}{\varepsilon},\quad \eta=\frac{\hat{\eta}}{\varepsilon},\quad \mu=\varepsilon^2\hat{\mu},\quad \lambda=\varepsilon^2\hat{\lambda},$$
$$\alpha=\varepsilon^2\hat{\alpha},\quad \gamma=\frac{\hat{\gamma}}{\varepsilon},\quad \rho=\frac{\hat{\rho}}{\varepsilon^2},\quad f=\frac{\hat{f}}{\varepsilon},\quad q=\frac{\hat{q}}{\varepsilon},\quad g=\frac{\hat{g}}{\varepsilon},\quad h=\hat{h}.$$

The left hand side of equations (29)-(36) suggest an initial guess of two time scales: $\mathrm{O}(\varepsilon^2)$ and $\mathrm{O}(\varepsilon)$. Using singular perturbation method and setting the time scale $t=\varepsilon^2\hat{t}$, we assume that for a small amount l_0 of infected mosquitoes introduced into the population, only a smaller proportion εl_0 becomes infectious. Thus, the leading order solutions will be

$$S_h \sim 1+\varepsilon l_0\hat{S}_{h_1},\quad L_h \sim \varepsilon l_0\hat{L}_0,\qquad L_A \sim \varepsilon^3 l_0^2\hat{L}_{A_0},\quad I_s \sim \varepsilon^2 l_0\hat{I}_{s_0}, \quad (37)$$
$$\mathrm{A} \sim \varepsilon^2 l_0\hat{A}_0,\quad S_m \sim 1-l_0+\varepsilon l_0\hat{S}_{m_1},\quad L_m \sim l_0+\varepsilon l_0\hat{L}_{m_1},\quad I_m \sim \varepsilon l_0\hat{I}_{m_0}.$$

Substitute (37) into equations (29)-(36), yields the following leading order system

$$\frac{d\hat{S}_{h_1}}{d\hat{t}} = -\hat{\beta}\hat{I}_{m_0},\quad \frac{d\hat{L}_{h_0}}{d\hat{t}} = \hat{\beta}\hat{I}_{m_0},\quad \frac{d\hat{L}_{A_0}}{d\hat{t}} = \hat{\beta}\hat{A}_0\hat{I}_{m_0},\quad \frac{d\hat{I}_{s_0}}{d\hat{t}} = \hat{\eta}\hat{L}_{h_0} - \hat{\rho}\hat{I}_{s_0}, \quad (38)$$
$$\frac{d\hat{A}_0}{d\hat{t}} = \hat{\rho}\hat{I}_{s_0},\quad \frac{d\hat{S}_{m_1}}{d\hat{t}} = \hat{q},\qquad \frac{d\hat{L}_{m_1}}{d\hat{t}} = -(\hat{f}+\hat{q}),\quad \frac{d\hat{I}_{m_0}}{d\hat{t}} = \hat{f}.$$

For $l_0 \ll \varepsilon \ll 1$, and with initial conditions $\hat{S}_{h_1}(0)=0,\ \hat{L}_{h_0}(0)=0,\ \hat{L}_{A_0}(0)=0,\qquad \hat{I}_{s_0}(0)=0,$ $\hat{\mathrm{A}}_0(0)=0, \hat{L}_{m_1}(0)=0,\ \hat{S}_{m_1}(0)=0,\ \hat{I}_{m_0}(0)=0,$ the following leading order solutions are obtained

$$\hat{S}_{h_1} \sim -\frac{1}{2}\hat{\beta}\hat{f}\hat{t}^2,\quad \hat{L}_{h_0} \sim \frac{1}{2}\hat{\beta}\hat{f}\hat{t}^2,\quad \hat{L}_{A_0} \sim \frac{1}{30}\hat{\beta}^2\hat{\eta}\hat{f}^2\hat{t}^5,\quad \hat{I}_{s_0} \sim \frac{1}{2\hat{\rho}}\hat{\beta}\hat{\eta}\hat{f}\hat{t}^2,$$
$$\hat{A}_0 \sim \frac{1}{6}\hat{\beta}\hat{\eta}\hat{f}\hat{t}^3,\quad S_{m_1} \sim \hat{q}\hat{t},\qquad L_{m_1} \sim -(\hat{f}+\hat{q})\hat{t},\qquad I_{m_0} \sim \hat{f}\hat{t}.$$

We note that susceptible humans (S_h) and latent mosquitoes (L_m) are decaying linearly in time from their initial values due to i) the latent mosquitoes converting to the infectious class and ii) the susceptible becoming infected as a result of infectious contact with mosquitoes in the L_m class.

Setting $t=\varepsilon^{4/3}\hat{t}$ and substituting into (29)-(36), we observe that all the leading order solutions are the same as equation (38) except that S_m and L_m have an additional term, $\hat{d}\hat{A}_0$. This introduces a reaction of infection from asymptomatic class in the susceptible mosquitoes into the susceptible human population. Thus, creating a stability between the amount of mosquitoes converting to the infectious class and the amount becoming infected by biting humans in the asymptomatic infectious class.

By setting the initial conditions $\hat{S}_{h_1}(0)=0,\ \hat{L}_{h_0}(0)=0,\ \hat{L}_{A_0}(0)=0,\ \hat{I}_{s_0}(0)=0,\qquad \hat{\mathrm{A}}_0(0)=0, \hat{L}_{m_1}(0)=0,$ $\hat{S}_{m_1}(0)=0,\ \hat{I}_{m_0}(0)=0,$ we observe a notable difference in the S_m and L_m with an accelerated rate of mosquitoes infection from asymptomatic infectious humans as follows $S_{m_1} \sim -\frac{1}{24}\hat{\beta}\hat{\eta}\hat{f}\hat{d}\hat{t}^4\hat{q}\hat{t}$ and $L_{m_1} \sim \frac{1}{24}\hat{\beta}\hat{\eta}\hat{f}\hat{d}\hat{t}^4\hat{q}\hat{t}$. The inference is that the flow of the solution may change direction especially when the amount of mosquitoes being infected becomes

greater than the inflow of new born mosquitoes. This may happen at the point of where L_{m_1} becomes $O(l_0)$.

5. Conclusions

In order to use our model to provide more insight and effective control of malaria, we setup and analyzed the transition model by presenting sufficient conditions to show that malaria free state is locally and globally asymptotically stable if $R_0 < 1$ and unstable for $R_0 > 1$. Timescale analysis is conducted to study the scenario in which $R_0 > 1$ to demonstrate the existence of an endemic state. We notice that the buildup of the latent asymptomatic humans at steady state is the main dynamics of malaria in the endemic region. This become evident in the time scale $t = \varepsilon^{4/3}\hat{t}$ and influences the mode of infection in our analysis.

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