Time-Scale Analysis of Malaria Dynamics in Human-Mosquito Population

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Abstract: More realistic human-mosquito population mathematical model in which reinfected asymptomatic humans are considered is presented. Six possible time-scale of events for model transition from non-endemic to endemic state are analyzed. Results show 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 of about 1-2 weeks and thus influences the mode of infection in the malaria transmission analysis.

Keywords: Malaria Transmission, Timescale Analysis, Mathematical Modeling

1. Introduction

Malaria is a vector born disease that can be transmitted to humans through infected anopheles mosquito bites. The parasite’s life cycle is well described in literatures [1, 2]. Symptoms of the disease include vague, anemia, blood stools, convulsion, myalgia, diarrhea, nausea, vomiting and others [3]. The infection can also lead to damage of human organs such as the brain, lungs, kidneys and blood vessels [3, 4]. Extensive research efforts have been focused to the study of the transmission of the malaria parasite between humans and mosquitoes and how to control the disease in the endemic regions [5-7]. Despite substantial progress, it is still a major global problem in terms of morbidity and mortality especially in the endemic regions. In 2015, the World health organization reported 214 million high risk malaria cases and over 438,000 deaths worldwide [8].

The complexity of the disease’s zoonotic nature makes it clinically impossible to understand fully the mechanism in which the disease spreads. Clinically, two methods are in use: one which reduces the risk and intensity of malaria and death and another which uses protective antimalarial immunity to reduce the number of parasites in an infected individual. In both methods, the tendency for malaria patients to become resistant to these methods makes many malaria patients temporarily asymptomatic parasite carriage [9, 10]. Although there is no standard definition for “asymptomatic” malaria infections, it is generally accepted to be malarial parasitemia of any density, in the absence of fever or other acute symptoms in individuals [7]. These infected individuals sustain malaria overtime and so are important source of malaria transmission and therefore a major obstacle to eradication programs. Ogutu et al. [11], reported in their that a large proportion of malaria infections are with microscopy-detection level as high as 39 percent on children under 10 years old in endemic regions. Based on 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.

Some recent papers have used mathematical modeling approach to provide more insight of the effects of asymptomatic parasite carriage on malaria transmission in human and mosquito populations [2, 12-15]. These models have played important roles in influencing intervention strategies for preventing and controlling the transmission of malaria. However, of these papers, only one [2] made an attempt to study the evolution of malaria based on the reproduction number ($R_0$) and a reasonable timescale to demonstrate the existence and effects of the asymptomatic group in malaria dynamics. In their paper, Annan et al. analyzed the transition model by adeddusive sufficient conditions to show that malaria free state in which asymptomatic group is present is locally and asymptotically stable if $R_0 < 1$ and unstable for $R_0 > 1$. In addition, they
2. Dimensionless Model

We adopt the dimensionless form of the model formulated in [2] as,

\[
\frac{dS_{h}}{dt} = \lambda + \gamma I_{s} + A - \beta I_{w} S_{h} \frac{T_{w}}{N} - \lambda S_{h} + \alpha S_{s} I_{s} + \theta A
\]

(1)

\[
\frac{dI_{s}}{dt} = \beta I_{w} S_{h} \frac{T_{w}}{N} - \eta L_{n} - \lambda L_{n} + \alpha L_{s} I_{s} + \theta L_{s}
\]

(2)

\[
\frac{dL_{s}}{dt} = \beta I_{w} A \frac{T_{w}}{N} - \eta L_{i} - \lambda L_{i} + \alpha L_{s} I_{s} - \theta L_{s}
\]

(3)

\[
\frac{dL_{i}}{dt} = \eta L_{i} + \eta L_{i} + \gamma + \rho + \lambda I_{s} + \alpha I_{s} + \rho L_{i} + \lambda I_{s}
\]

(4)

\[
\frac{dA}{dt} = \rho I_{s} - (1 + \beta I_{w} \frac{T_{w}}{N} + \lambda - \alpha I_{s} + \theta) A
\]

(5)

\[
\frac{dS_{n}}{dt} = q(l - S_{n}) - bI_{w} S_{n} - dA S_{n} - dL_{n} S_{w} + hI_{w} S_{w}
\]

(6)

\[
\frac{dI_{w}}{dt} = bI_{w} S_{n} + dA S_{n} + dL_{w} S_{n} - (f + g) L_{n} + hI_{w} L_{n}
\]

(7)

\[
\frac{dL_{w}}{dt} = \beta I_{w} - (h + q) I_{n} + h L_{w}
\]

(8)

With

\[
N/dt = - \alpha I_{s} N + \lambda - \mu) N,
\]

\[
dT_{w} / dt = - hI_{w} T_{n} + (q - g) T_{n},
\]

and the model’s parameter values defined in Table 1.

**Table 1. Dimensionless parameters and their values.**

| Dimensional | Dimensionless | Value | Value in \( \mathcal{E} \) |
|-------------|---------------|-------|---------------------------|
| \( \beta I_{w} T_{w} / (h, N) \) | \( \beta \) | 62.43 | \( O(\mathcal{E}^{-1}) \) |
| \( \eta / I_{s} \) | \( \eta \) | 11.1 | \( \epsilon \) |
individual in the $I_s$ group die at rate $\alpha_s I_s$ from the 
infection. Those who survive receive treatment and are 
recovered with complete clearance to join the susceptible 
without clearance to join the $A$ class at a rate $r_A I_s$. The post 
symptomatic class $A$ still carry merozoites and produce 
gametocytes. So, they can infect biting mosquitoes. Since 
patients can be hospitalized for several weeks or months they 
can play an important role in sustaining an epidemic. Thus, 
consider a putative treatment which removes individuals from 
$A$ and $L_s$ classes down to $S_h$ and $L_s$ respectively, with 
the effect of the treatment parameter being $\psi t_A$, where $\psi$ 
are those being treated. Similarly, mosquitoes in the 
incubating class die naturally at a rate $\mu_m I_m$ and the rest get 
infected at a rate $\eta_m I_m$ to join the infectious class which 
remain until their death either naturally or are killed by the 
parasite at rate $\alpha_m I_m$.

3. The Basic Reproduction Number

Since there are no trivial equilibrium points as long as 
$S_h$ and $S_m$ are not zero. The implication is that 
$(S_h, I_h, I_s, A, T_m, S_m, L_s, I_m) \neq (0, 0, 0, 0, 0, 0, 0, 0)$ and 
the population is not extinct. Therefore, we define a domain 
of biological interest for the model in the form

$$\Omega = \{(S_h, I_h, I_s, A, T_m, S_m, L_s, I_m, N) \in \mathbb{R}^n \mid \text{they are } \geq 0 \text{ for all } t > 0\},$$

such that the basic reproduction number, $R_0$, is determined by 
the Next Generation Matrix (NGM) method by [2] as

$$R_0 = \frac{\beta \eta I_h}{\mu_m I_m} \frac{f(q)(h+q)(\eta + \lambda)(1 + \lambda + \theta)(\alpha + \gamma + \rho + \lambda)}{(f + q)(h+q)(\eta + \lambda)(1 + \lambda + \theta)(\alpha + \gamma + \rho + \lambda)}. \quad (9)$$

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. When 
$R_0 < 1$, each infected individual produces on average less 
than one new infected individual so we would expect the 
disease to die out. On the other hand if $R_0 > 1$, each 
individual produces more than one new infected individual so 
we would expect the disease to spread in the population. This 
implies that the threshold quantity for eradicating the disease 
is to reduce $R_0$ to less than one.

Using equation (9), the stability analysis of the 
equilibrium in the domain $\Omega$ is attained from the 
eigenvalues of the Jacobian matrix evaluated at equilibrium 
point detailed in [2]. The analysis revealed that the 
disease-free equilibrium is locally and globally 
stable if $R_0 < 1$ and an endemic equilibrium is not feasible.

However, since normally $R_0 \gg 1$ and the asymptomatic 
infectious humans to mosquitoes is significantly large, a 
possible treatment is to reduce the infectivity of the 
asymptomatic humans, $d$, and the symptomatic humans, $b$
by increasing the parameters $\theta$ and $\lambda$.

4. Time Scale Analysis

The asymptotic analysis on $N$ and $T_m$ equations depict 
that $T_m$ changes on the time scale $O(\varepsilon)$ while $N$ changes 
on $O(\varepsilon^{-2})$. Therefore, an assumption that $T_m/N$ is constant 
over the time scale of the model by setting $\theta = 0$ gives,

$$\varepsilon^3 \frac{dS_h}{dt} = \varepsilon^4 \lambda I_s + \varepsilon^3 A - \beta I_h S_h - \varepsilon^4 \lambda S_h + \varepsilon^4 \alpha S_h I_s, \quad (10)$$

$$\varepsilon^3 \frac{dI_h}{dt} = \varepsilon^4 \Lambda I_s - \eta \varepsilon I_s - \varepsilon^4 \Lambda I_s + \varepsilon^4 \alpha I_s I_s, \quad (11)$$

$$\varepsilon^3 \frac{dL_s}{dt} = \beta I_s S_h - \varepsilon^3 \Lambda I_s + \varepsilon^4 \Lambda I_s + \varepsilon^4 \alpha I_s I_s, \quad (12)$$

$$\varepsilon^3 \frac{dI_m}{dt} = \varepsilon^4 \Lambda I_s - \varepsilon^4 \Lambda I_s - \varepsilon^3 \Lambda I_s + \varepsilon^4 \alpha I_s I_s, \quad (13)$$

$$\varepsilon^3 \frac{dA}{dt} = \varepsilon^4 \Lambda I_s - \varepsilon^4 \Lambda I_s - \varepsilon^4 \Lambda I_s + \varepsilon^4 \alpha I_s I_s, \quad (14)$$

$$\varepsilon^3 \frac{dS_m}{dt} = \varepsilon^3 \Lambda I_s - \varepsilon^4 \Lambda I_s - \varepsilon^3 \Lambda I_s + \varepsilon^4 \alpha I_s I_s, \quad (15)$$

$$\varepsilon^3 \frac{dL_m}{dt} = \varepsilon^4 \Lambda I_s - \varepsilon^4 \Lambda I_s - \varepsilon^3 \Lambda I_s + \varepsilon^4 \alpha I_s I_s, \quad (16)$$

$$\varepsilon^3 \frac{dI_m}{dt} = \varepsilon^4 \Lambda I_s - \varepsilon^4 \Lambda I_s - \varepsilon^3 \Lambda I_s + \varepsilon^4 \alpha I_s I_s, \quad (17)$$

with initial conditions

$$S_h(0) = 1, \quad L_h(0) = 0, \quad L_s(0) = 0, \quad I_s(0) = 0, \quad A(0) = 0, \quad L_m(0) = l_h, \quad S_m(0) = 1 - l_h, \quad I_m(0) = 0, \quad \varepsilon \ll 1, \quad l_h \ll \varepsilon,$$

and the parameters expressed in terms of their size as powers of $\varepsilon$ as follows,

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

Using singular perturbation method and setting the time 
scale $t = \varepsilon^{\sigma} \tau$, we notice that susceptible humans ($S_h$) 
and latent mosquitoes ($L_m$) are decaying linearly in time from 
their initial values due to the i) latent humans converting to 
the infectious class and ii) susceptible becoming infected as a 
result of infectious contact with mosquitoes in the $L_m$ class.

Similarly, by setting $t = \varepsilon^{\sigma} \tau$, we observe that all the leading 
order solutions are the same except that variables $S_m$ and $L_m$
have an additional term, $\tilde{d}_h$. 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. However, there is a notable difference between $S_m$ and $L_m$ with an accelerated rate of mosquito infection from asymptomatic infectious humans when the initial conditions $S_{h_0}(0) = 0$, $L_{h_0}(0) = 0$, $L_h(0) = 0$, $\tilde{I}_h(0) = 0$, $\tilde{A}_h(0) = 0$, $\tilde{S}_h(0) = 0$, $\tilde{I}_m(0) = 0$, are used.

Thus, 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.

By setting $t = \varepsilon^{3/2} \tilde{t}$, we observe that equations (10)-(17) are unchanged. However, due to the dominant contribution of the asymptomatic infectious humans on the infection of mosquitoes, the rate of change of $L_m$ and $S_m$ are proportional to the amount of asymptomatic humans. In addition, $I_{m_0}$ is proportional to $L_m$. So, with the following initial conditions

$$S_{h_0}(0) = 0, \quad L_{h_0}(0) = 0, \quad L_h(0) = 0, \quad I_{h_0}(0) = 0, \quad A_{h_0}(0) = 0, \quad L_{m_0}(0) = 1, \quad S_{m_0}(0) = -1, \quad I_{m_0}(0) = I_{m_0}(0) = I_{m_0}(0) = 0, \quad$$

The time solution for our system equations grow exponentially as follows

$$\dot{S}_h = - \beta \frac{A_h}{4 \delta} e^{\nu_h}, \quad \dot{I}_h = - \beta \frac{A_h}{4 \delta} e^{\nu_h}, \quad \dot{L}_h = - \beta \frac{A_h}{4 \delta} e^{\nu_h}, \quad \dot{I}_m = - \beta \frac{A_h}{4 \delta} e^{\nu_h}, \quad \dot{L}_m = - \beta \frac{A_h}{4 \delta} e^{\nu_h},$$

where we have set $\delta = \beta \frac{A}{4 \delta}$. If we allow $\delta_h = \delta^{1/6}$, the approximations for this time-scale is not a good one because $S_h = O(e^{\delta \hat{t}})$ is $O(e^{1/6} \hat{t})$. In other words, when $\hat{t} = \ln(e^{1/6} \hat{t}) \frac{\delta_h}{\delta_h}$, the asymptomatic human becomes infected with new asexual parasites due to contact with infectious mosquitoes.

Now, we set $t = \varepsilon^{3/2} \ln(e^{1/6} \hat{t}) \frac{\delta_h}{\delta_h} + \varepsilon^{5/4} \hat{t}$, we are saying that the initial small amount of infection has developed into a full blown epidemic with $S_h$ and $L_h$ becoming $O(1)$ and not depending on $L_h$. After rescaling our model equations reduces to

$$\begin{align*}
\frac{dS_h}{dt} & = - \beta S_h I_h, \\
\frac{dI_h}{dt} & = \beta S_h I_h - \beta A_h I_h, \\
\frac{dL_h}{dt} & = \beta A_h I_h, \\
\frac{d\tilde{S}_h}{dt} & = - \beta \tilde{S}_h I_h, \\
\frac{d\tilde{I}_h}{dt} & = - \beta \tilde{S}_h I_h, \\
\frac{dL_m}{dt} & = \beta I_h + \beta \tilde{I}_h, \\
\frac{d\tilde{S}_m}{dt} & = - \beta \tilde{S}_h I_h, \\
\frac{d\tilde{I}_m}{dt} & = - \beta \tilde{S}_h I_h, \\
\frac{d\tilde{L}_m}{dt} & = - \beta \tilde{S}_h I_h, \\
\frac{dI_m}{dt} & = - \beta \tilde{S}_h I_h.
\end{align*}$$

Here, the asymptomatic humans become infected with new asexual parasites after contact with infectious mosquitoes and eventually reduce the number of the asymptomatic class ($A$) to the latent asymptomatic class, ($L_{h_0}$). Further examination shows that

$$\frac{d\tilde{S}_h}{dt} + \frac{d\tilde{I}_h}{dt} = 0, \quad \frac{dL_h + \tilde{A}_h}{dt} = \eta \tilde{I}_m, \quad \frac{d\tilde{I}_m}{dt} = \eta \tilde{d} L_m.$$
steady states remain unchanged except $L_a \sim 1$. Furthermore, the fraction of latent humans, $L_a$ increases as $S_a$ decreases. We also observed that $L_a$ is no longer $O(1)$ as $L_a$ grows to overtake $L_a$.

5. Discussions

We have analyzed six main time scales with appropriate rescaling to elucidate the dynamics of malaria disease as they evolve from small infection to endemic state. At $t = O(e^\tau) = 1-3$ days, introducing a small amount of infected mosquitoes into the system and biting susceptible humans causes human to get infected. The early infection indices itself into the population and grows linearly but their effect remains unnoticeable in the latent asymptomatic group.

When $t = O(e^{9/3}) = 7-8$ days, the susceptible mosquitoes get infected by biting asymptomatic infectious humans. We noticed that the amount of mosquitoes converting to the infectious group is balanced by the amount of mosquitoes being infected by biting humans in the asymptomatic infectious group. This observation is expected because individuals with clinical malaria have low level of gametocytes. Thus, the early infection of susceptible mosquitoes is likely to come from contact with asymptomatic infectious humans since they have high gametocyte density. The contribution of asymptomatic infectious humans has a significant effect on the dynamics of the disease. Now, as more mosquitoes get infected through contact with asymptomatic infectious population, (i.e. when $t = O(e^{9/3}) = 9-10$ days ), the amount of susceptible mosquitoes become optimized and starts to decline. However the feedback from infectious humans offsets the linear growth of the initial amount of infected mosquitoes introduced. Thus, causing the amount of latent mosquitoes to grow exponentially.

For $t = e^{5 \ln (e^{15/2}/L_a)/\delta_5 + e^{2/3}t}$ where $\delta_5 = (\beta h \delta y)^{1/4} = 2$ weeks, the asymptomatic humans become infected with new asexual parasite as a result of contact with infectious mosquitoes. The amount of infected humans to the asymptomatic status is being balanced by the amount of asymptomatic human to the latent asymptomatic group due to a boost in their partial immunity level. Thus, more mosquitoes become infected and the overall distribution of infection results in a fast shift of susceptible humans into the latent group. After this time the disease is now visible with infected humans equal to $O(1)$. Also, the latent asymptomatic humans may still be infectious to the mosquitoes as $S_a, I_a$, and $A$ adjust to their equilibrium values and $L_a$ decaying exponentially. At approximately two months after the initial introduction of infected mosquitoes, all human classes equilibrate and latent individuals become symptomatic. The mosquito classes also adjust to assume their equilibrium state.

6. Conclusions

We completed a detailed six main timescale analysis on the model adapted from [2] with appropriate rescaling to elucidate the dynamics of malaria from small infection to endemic state. In our analysis, $S_a$ remain proportional to $L_a$, thus showing that the level of the disease depends on the non-immune humans becoming infected. Thus, the buildup of the latent asymptomatic humans at steady state is the main dynamics of malaria in the endemic region. Also, we find that intervention programs may yield better result if implemented before the fourth timescale. During that time, the feedback from infection humans offsets the linear growth effect of the initial amount of infected mosquitoes and this equates to about 2-3 weeks from the initial infection. We also 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 of about 1-2 weeks and thus influences the mode of infection in our analysis.

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