MATHEMATICAL MODEL FOR THE INCUBATION OF THE PLASMODIUM VIVAX MALARIA

P. Pongsunpun and P. Mumtong

ABSTRACT

Malaria disease is caused by the multiplication of protozoan parasite of the genus Plasmodium. Malaria in human is due to four types; Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, and Plasmodium ovale. Most Malaria cases in Thailand are due to plasmodium falciparum and Plasmodium vivax. This disease occurs in Africa, South America, and Asia. In Thailand, Malaria is found along the border with Burma, Combodia, and Malaysia. In this study, the transmission of Plasmodium vivax malaria and the effects of incubation for Plasmodium vivax are considered by using mathematical model. The population is separated into human and mosquito populations. The application of the standard dynamical modeling method is used for analyzing the behaviors of solutions. The conditions of the parameters for the disease free and endemic states are obtained. Numerical solutions are shown to support the theoretical predictions. The results of this study point to the way for decreasing the outbreak of the disease.

Keywords: Plasmodium vivax, disease free state, disease endemic state, dynamical equation, Malaria

1. INTRODUCTION

Malaria is a major public health problem in Thailand. This disease is found along the border of Thailand. Malaria disease is caused by the multiplication of protozoa parasite of the genus Plasmodium; Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, and Plasmodium ovale. Most Malaria cases in Thailand are due to plasmodium falciparum and Plasmodium vivax [1,2]. The Anopheles mosquitoes are major vectors of Malaria. The symptoms of this disease depend on the type of infection [3]. The characteristics of the patients who is infected with Plasmodium falciparum in the first phase of the disease are fever, under the pains and aches, nausea, vomiting and abdominal pain. Some people may cough or cold in the first 4-5 days of high fever.

Symptoms of patients who is infected with Plasmodium ovale are similar to Plasmodium vivax but the symptoms are less [4]. This disease occurs in Africa, South America, and Asia [5]. In Thailand, Malaria is found along the border with Burma, Combodia, and Malaysia. The most Malaria patients are found in Songkhla, Yala, Mae Hong Son, Tak, Kanchanaburi, Prachuap Khiri Khan, Chumphon, Ranong, Chanthaburi and Narathiwat. The symptoms of Malaria patients appear after the Plasmodium incubates in the body. The period of incubation of Plasmodium depends on its type, about 10-14 days. The period of incubation for Plasmodium vivax is higher than Plasmodium falciparum. In 2001, number of patients who is infected with Malaria are 67,749 people. There are 36,044 and 31,358 cases who is infected with Plasmodium vivax and Plasmodium falciparum, respectively. The data of Malaria cases is collected from the Ministry of public Health from 1965 to 2007 [6,7,8]. Pongsunpun and Tang [10] has proposed mathematical model for the transmission of Plasmodium Vivax between human and mosquito populations. The human population is divided into four classes, susceptible, infected, dormant and recovered human populations. The vector population is divided into two classes, susceptible, infected and recovered mosquitoes. The vector population is divided into two classes, susceptible and infected mosquitoes. But they did not consider the incubation of Plasmodium. In this paper, the transmission of Malaria with the incubation of Plasmodium Vivax is studied. The formulation of model is presented in section II. The analytical and numerical results are presented in section III. Finally, the conclusion of our model is presented in section IV.

2. MATHEMATICAL MODEL

We propose a new model to study the transmission of Plasmodium Vivax. We consider the transmission of the disease between human and mosquitoes. The diagram of the Plasmodium Vivax transmission is presented in figure 1. Each population size is assumed to be constant. The human population is divided into five classes, susceptible, infected, infectious, dormant and recovered human populations. The vector population is divided into three classes, susceptible, infected and infectious mosquitoes. The dynamical equations of human and mosquito populations can be explained as follows:
The above equations are given by

\[ \frac{d}{dt}S_h = \lambda N_T + r_3 D_h + r_1 E_h + r_6 I_h + r_4 R_h \]
\[ - \left( \mu_h + \gamma_h I_v \right) S_h - \alpha r_1 I_h \] (1)

\[ \frac{d}{dt}E_h = \gamma_h I_v S_h - \left( r_1 + \rho_h + \mu_h \right) E_h \] (2)

\[ \frac{d}{dt}I_h = \rho_h E_h + r_2 D_h - \left( \mu_h + r_5 + r_6 \right) I_h \] (3)

\[ \frac{d}{dt}D_h = \alpha r_1 I_h - \left( r_2 + \mu_h + r_3 \right) D_h \] (4)

\[ \frac{d}{dt}R_h = r_5 I_h - \left( \mu_h + r_4 \right) R_h \] (5)

where \( S_h, E_h, I_h, D_h \) and \( R_h \) are the number of susceptible, infected, infectious, dormant and recovered human populations, respectively. The parameters in the above equations are given by

- \( \mu_h \) is the death rate of human population,
- \( \gamma_h \) is the transmission rate of Plasmodium vivax from the mosquito to the human,
- \( \gamma_h \) is the transmission rate of Plasmodium vivax from the mosquito to the mosquito,
- \( \lambda N_T \) is the birth rate of human population,
- \( N_T \alpha \) is the total number of human population,
- \( \alpha r_1 \) is the percentage of infected human in whom some hypnozoites remain dormant in the liver,
- \( r_1 \) is the rate at which a person who infected with Plasmodium vivax leaves the infected class,
- \( r_2 \) is the rate at which the dormant human relapses back to the infectious human due to Plasmodium vivax,
- \( r_3 \) is the recovery rate of the dormant human due to Plasmodium vivax,
- \( r_4 \) is the rate at which the recovered human due to Plasmodium vivax relapses back to the susceptible human,
- \( r_5 \) is the rate at which the infectious human due to Plasmodium vivax recovers,
- \( r_6 \) is the rate at which a person who be infected with Plasmodium vivax leaves the infectious class,
- \( \rho_h \) is the rate at which the infected human becomes to be infectious human,
- \( \rho_v \) is the rate at which the infected vector becomes to be infectious vector,
- \( \mu_v \) is the death rate of the vector,
- \( A \) is the constant recruitment rate of the vector population.

The dynamical equations of the vector population are described by

\[ \frac{d}{dt}S_v = A - \left( \mu_v + r_v I_h \right) S_v \] (6)

\[ \frac{d}{dt}E_v = r_v I_h S_v - \left( \mu_v + \rho_v \right) E_v \] (7)

\[ \frac{d}{dt}I_v = \rho_v E_v - \mu_v I_v \] (8)

where \( S_v, E_v \) and \( I_v \) are the number of susceptible, infected and infectious vector, respectively. \( N_T = S_h + E_h + I_h + D_h + R_h \) is the total number of human population, \( N_v = S_v + E_v + I_v \) is the total number of the vector population. We assume that the total populations of human and vector are constant. Therefore \( \frac{dN_T}{dt} = 0 \) and \( \frac{dN_v}{dt} = 0 \). Since \( N_T = S_h + E_h + I_h + D_h + R_h \), therefore the new equation becomes:

\[ \frac{d}{dt}N_T = \frac{d}{dt}S_h + \frac{d}{dt}E_h + \frac{d}{dt}I_h + \frac{d}{dt}D_h + \frac{d}{dt}R_h \] (9)

The rate of change in each class is equal to zero. Setting the right hand side of (9) to zero, we obtain \( \lambda = \mu_h \) (birth rate equals to the death rate). From \( N_v = S_v + E_v + I_v \), the new equation is as follows.

\[ \frac{d}{dt}N_v = \frac{d}{dt}S_v + \frac{d}{dt}E_v + \frac{d}{dt}I_v \] (10)

The rate of change in each class is equal to zero. Setting the right hand side of (2) to zero, we obtain \( \mu_v = A/N_v \) (Mortality rate equal to the ratio between the constant recruitment rate and the total number of vector). This gives \( N_v = A/\mu_v \). We introduce the normalized populations \( S_h' = S_h/N_T, I_h' = I_h/N_T, E_h' = E_h/N_T, R_h' = R_h/N_T, D_h' = D_h/N_T, S_v' = S_v/N_v, I_v' = I_v/N_v \) and \( E_v' = E_v/N_v \). Then (1)-(8) can be rewritten as
We get two equilibrium points, the disease free state needed, are obtained by setting the characteristic equation for the disease free state is given by. The solutions of (23) are given by

\[ I^*_h = \frac{\gamma^*_h N_I \rho v}{(\mu_v + \gamma^*_h N_T I^*_h) (\mu_v + \rho_v)} \]  \hspace{1cm} (21)

\[ E^*_v = \left[ \frac{\gamma^*_v N_T I^*_h \mu_v}{(\mu_v + \mu_v + \rho_v + \rho_v) I^*_h} \right] \]  \hspace{1cm} (22)

where \( \mu_0 = r_1 + \mu_h + \mu_h, \mu_0 = r_2 + \mu_h + r_3, \mu_0 = \mu_v + \rho_v, \alpha_1 = r_0 - r_4 - \alpha r_1, r_3 = r_3 - r_4 \) and \( I^*_h \) are the solution of

\[ A_1 (I^*_h)^2 + A_2 I^*_h = 0 \]  \hspace{1cm} (23)

The solutions of (23) are given by

\[ I^*_h = 0 \]  \hspace{1cm} (24)

\[ I^*_h = A_2 / A_1 \]  \hspace{1cm} (25)

The local stability of an equilibrium point is determined from the signs of eigenvalues of the Jacobian matrix of the right hand side of the above set of differential equations [9].

2.1 Local Asymptotical Stability

The local stability of an equilibrium point is determined from the signs of eigenvalues of the Jacobian matrix of the right hand side of the above set of differential equations [9].

2.2 Equilibrium Points

The equilibrium points are obtained by setting the right hand side of (11)-(16) equal to zero. We get two equilibrium points, the disease free state \( E_1 (0, 1, 0, 0, 0, 0) \) and the endemic disease state \( E_2 (I^*_h, S^*_h, E^*_h, D^*_h, I^*_v, E^*_v) \) where

\[ \frac{d}{dt} S^*_h = \mu_h + r_3 D^*_h + r_1 E^*_h + r_6 I^*_h + \frac{r}{\alpha_1} I^*_h - \left( \mu_h + \gamma^*_h N_T I^*_h \right) S^*_h \]  \hspace{1cm} (11)

\[ \frac{d}{dt} I^*_h = \mu_h E^*_h + r_2 D^*_h - \left( \mu_h + r_5 + r_6 \right) I^*_h \]  \hspace{1cm} (12)

\[ \frac{d}{dt} D^*_h = \alpha_1 I^*_h - \left( \alpha_2 + \mu_3 + \alpha_3 \right) D^*_h \]  \hspace{1cm} (13)

\[ \frac{d}{dt} I^*_v = \rho_v E^*_v - \frac{\rho_v}{\alpha} I^*_v \]  \hspace{1cm} (14)

\[ \frac{d}{dt} E^*_v = \gamma^*_v N_T S^*_h - \left( \mu_v + \rho_v \right) E^*_v \]  \hspace{1cm} (15)

\[ \frac{d}{dt} I^*_h = \rho_h E^*_h + r_2 D^*_h - \left( \mu_h + r_5 + r_6 \right) I^*_h \]  \hspace{1cm} (16)

The dynamic equations for \( R^*_h \) and \( S^*_h \) are not needed, \( S^*_h + I^*_h + R^*_h + E^*_h + D^*_h = 1 \) since and \( S^*_h + I^*_h + E^*_h = 1 \).

2.3 Disease Free State

For the equations (11)-(16), the Jacobian matrix evaluated at \( E_1 \) is given by

\[ \begin{pmatrix}
\frac{\partial}{\partial S^*_h} \\
\frac{\partial}{\partial I^*_h} \\
\frac{\partial}{\partial D^*_h} \\
\frac{\partial}{\partial I^*_v} \\
\frac{\partial}{\partial E^*_v} \\
\frac{\partial}{\partial I^*_h}
\end{pmatrix}
\]

\[ \begin{pmatrix}
\frac{\partial}{\partial S^*_h} \\
\frac{\partial}{\partial I^*_h} \\
\frac{\partial}{\partial D^*_h} \\
\frac{\partial}{\partial I^*_v} \\
\frac{\partial}{\partial E^*_v} \\
\frac{\partial}{\partial I^*_h}
\end{pmatrix}
\]

\[ D^*_h = \frac{\alpha_1 I^*_h}{\mu_3 a_3} \]  \hspace{1cm} (20)

The eigenvalues are obtained by solving the characteristic equation; det \( (J - \lambda I_6) = 0 \) where \( I_6 \) is the identity matrix dimension 6 \( \times \) 6. If all eigenvalues for each equilibrium state have negative real parts, then that equilibrium state is locally stable. The characteristic equation for the disease free state is given by

\[ \left( \frac{\mu + \gamma^*_h N_T I^*_h}{\mu_v + \gamma^*_h N_T I^*_h} \right) = 0 \]  \hspace{1cm} (26)
From the characteristic equation (26), eigenvalues are given by \( \lambda_1 = -\mu_h - r_5 - r_6 \), \( \lambda_2 = -\mu_h - r_4 \), \( \lambda_3 = -r_1 - \mu_h - \mu_h \), \( \lambda_4 = -r_2 - \mu_h - r_3 \), \( \lambda_5 = -\mu_e \) and \( \lambda_6 = -\mu_e - \mu_e \).

We found that the disease free state is locally stable when \( R_0 < 1 \).

### 2.4 Endemic Disease State

The local stability of the endemic state, \( E_2 \), is determined by looking at the signs of the eigenvalues of the Jacobian evaluated at \( E_2 \). The Jacobian matrix for this state is

\[
\begin{bmatrix}
\lambda & \alpha & \gamma & \beta & \delta & \epsilon \\
\alpha & \lambda & \rho & \sigma & \tau & \upsilon \\
\gamma & \rho & \lambda & \mu & \nu & \xi \\
\beta & \sigma & \mu & \lambda & \nu & \eta \\
\delta & \tau & \nu & \alpha & \lambda & \zeta \\
\epsilon & \upsilon & \xi & \eta & \zeta & \theta
\end{bmatrix}
\]

where \( \lambda_6 \) is defined in and \( I_{h}^*, S_{h}^*, E_{h}^*, D_{h}^*, T_{h}^* \) and \( E_{e}^* \) are defined in (17)-(22) and \( R_0 > 1 \). The characteristic equation for the endemic state is given by

\[
\lambda^6 + T_5 \lambda^5 + T_4 \lambda^4 + T_3 \lambda^3 + T_2 \lambda^2 + T_1 \lambda + 1 = 0 \tag{27}
\]

where

\[
T_1 = \mu_h \rho I_h^* N_e + \rho \nu \left( r_1 - r_4 \right)
\]

\[
T_2 = \mu_h \rho I_h^* N_e + \mu_h \rho \left( r_1 - r_4 \right)
\]

\[
T_3 = \mu_h \rho I_h^* N_e + \mu_h \rho \left( r_1 - r_4 \right)
\]

\[
T_4 = \mu_h \rho I_h^* N_e + \mu_h \rho \left( r_1 - r_4 \right)
\]

\[
T_5 = \mu_h \rho I_h^* N_e + \mu_h \rho \left( r_1 - r_4 \right)
\]

\[
T_6 = \mu_h \rho I_h^* N_e + \mu_h \rho \left( r_1 - r_4 \right)
\]

with \( \mu_h = \left( \mu_h + r_5 + r_6 \right) \left( \mu_h + \gamma \beta I_h^* N_e + r_4 \right) \), \( \mu_h \rho = \mu_h \rho + \mu_h \rho \), \( \mu_h \rho = \mu_h \rho + \mu_h \rho \), \( \mu_h \rho = \mu_h \rho + \mu_h \rho \), \( \mu_h \rho = \mu_h \rho + \mu_h \rho \). The eigenvalues are found by solving \( \lambda^6 + T_5 \lambda^5 + T_4 \lambda^4 + T_3 \lambda^3 + T_2 \lambda^2 + T_1 \lambda + 1 = 0 \). The signs of these eigenvalues are negatives when they satisfy the Routh-Hurwitz criteria[10]:

\[
T_6 > 0 \tag{28}
\]

\[
T_6 T_5 - T_4 > 0 \tag{29}
\]

\[
T_6 T_5 T_4 + T_6 T_2 - T_3 T_6^2 - T_4^2 > 0 \tag{30}
\]

\[
T_6 (T_6 T_5 T_4 - T_4^2 - T_6^2 T_3) + T_4 T_7 (T_6 T_5 - T_4) - T_2 (T_6 T_5^2 - T_5 T_4 - 2 T_6 T_4 + T_2) > 0 \tag{31}
\]

\[
T_2 (T_3 (T_6 T_5 T_4 - T_4^2 - T_6^2 T_3) - T_2 (T_6 T_5^2 - T_5 T_4 - 2 T_6 T_4 + T_2) + T_1 (T_6 T_4 (T_4 T_3 - 3 T_2) + T_4^2) \tag{32}
\]

\[
T_4 (T_6 T_5 T_2 - T_5 T_4^2 - T_6^2 T_3)) > 0 \tag{33}
\]

The inequalities (29)-(33) are shown in the following figures.

\[
\begin{align*}
T_6 (T_6 T_5 T_4 - T_4^2 - T_6^2 T_3) + T_4 T_7 (T_6 T_5 - T_4) - T_2 (T_6 T_5^2 - T_5 T_4 - 2 T_6 T_4 + T_2) > 0 \tag{31}
\end{align*}
\]

The inequality (28) satisfy Routh-Hurwitz criteria because all terms in \( T_6 \) have positive value. From the
above figures; Routh-Hurwitz criteria (29) to (33) are satisfied for $R_0 > 1$. Thus, the endemic equilibrium state is locally stable for $R_0 > 1$.

2.5 Numerical Results

In this section, we analyze the model given by equation (11)-(16). The trajectories of the solutions when the parameter values will lead to a disease free equilibrium state and when they will lead to the endemic equilibrium state are shown in the following figures.

![Fig.3: Numerical solutions demonstrate the solution trajectories, projected into the 3D-space $(S_h, I_h, D_h), (S_h, I_h, E_h), (S_h, D_h, E_h)$, respectively. The value of parameters are $\mu_h = 0.0000391 \text{day}^{-1}, r_1 = 0.0714285 \text{day}^{-1}, r_2 = 0.0005479 \text{day}^{-1}, r_3 = 0.0333333 \text{day}^{-1}, r_4 = 0.0001826 \text{day}^{-1}, r_5 = 0.0333333 \text{day}^{-1}, r_6 = 0.1 \text{day}^{-1}, \alpha = 0.75, \gamma_h = 0.22, \gamma_v = 0.0016$. (a) $R_0 < 1, R_0 = 0.342116$. The fractions of populations $I^*_h, S^*_h, E^*_h, D^*_h, I^*_v, E^*_v$ approach to the disease free state $(0, 1, 0, 0, 0, 0)$. (b) $R_0 < 1, R_0 = 37.6073$. The trajectory of the six state variable solution $(I^*_h, S^*_h, E^*_h, D^*_h, I^*_v, E^*_v)$ spirals into the endemic disease equilibrium state $(0.00064586, 0.0266009, 0.000872935, 0.00102003, 0.0000583927, 0.0003238973)$.](image1)

We compare the behavior of our solutions for the different basic reproductive numbers. The results are shown in figure 4.

![Fig.4: (a) Behavior of our model for $R_0 = 997.326, N_v = 1,400$. (b) Behavior of our model for $R_0 = 97.326, N_v = 700$. The other similar parameters for fig 4(a) and 4b) are $\mu_h = 0.0000391, \mu_v = 0.35, r_1 = 0.0714285, r_2 = 0.0005479, r_3 = 0.0333333, r_4 = 0.0001826, r_5 = 0.3333333, r_6 = 0.1, \alpha = 0.75, \gamma_h = 0.22, \gamma_v = 0.0016$.](image2)
3. DISCUSSION AND CONCLUSION

In this study, we analyzed the model of Malaria with the incubation of the Plasmodium Vivax. The basic reproduction number is defined by $R_0$ where

$$R_0 = \frac{\mu h \gamma_1 \gamma' \eta (N_v - \mu \eta)}{\mu (\mu h + r_5 \mu h + r_6 \mu h - r_2 \alpha_1) \mu h \eta \kappa}$$  \hspace{1cm} (34)

Fig. 3 shows the solution move towards its equilibrium state. We can see that the trajectory approaches to the disease free equilibrium state (0,1,0,0,0,0) for $R_0 > 1$. When $R_0 > 1$, we can see that the trajectory is spiraling into the endemic equilibrium state (0.00064586, 0.0266009, 0.000872935, 0.000102003, 0.000583927, 0.000328973). Fig. 4 shows the solution for $R_0 = 97.329$ moving towards its equilibrium state faster than $R_0 = 13.5103$.

Fig. 5: Bifurcation diagrams of the solutions of equations (11)-(16) for the different values of $R_0$. —- denote the stable solutions while — denote the unstable solutions.

The bifurcation diagrams of (11)-(16) are shown in Fig. 5. We can see that, when $R_0 < 1$, $E_1$ will be stable and for $R_0 > 1$, $E_2$ will be stable. If the basic reproductive number is greater than one, the susceptible population decreases. The normalized infected, infectious, dormant human populations infected and infectious vector population increase. These subsequent behaviors occur because there is enough susceptible population to be infected from infectious vector. The ultimate goal of any control effort would be the reduction of $R_0$ to a value below one. If we can reduce the threshold number as defined in (34), then the number of infected human population will be decreased. This will reduce the outbreaks of Plasmodium Vivax Malaria [11,12,13,14,15, 16,17].

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