# Transmission Model for *Plasmodium Vivax* Malaria

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*Abstract:- Plasmodium vivax* malaria differs from *P. falciparum* malaria in that a person suffering from *P. vivax* malaria can experience relapses of the disease. Between the relapses, the malaria parasite will remain dormant in the liver of the patient, leading to the patient being classified as being in the dormant class. A mathematical model for the transmission of *P. vivax* is developed in which the human population is divided into four classes, the susceptible, the infected, the dormant and the recovered. Two stable equilibrium states, a disease free state $E_0$ and an endemic state $E_1$, are found to be possible. It is found that the $E_0$ state is stable when a newly defined basic reproduction number $R_0$ is less than one. If $R_0$ is more than one then endemic state $E_1$ is stable. The conditions for the second equilibrium state $E_1$ to be a stable spiral node are established. It is found that solutions in phase space are trajectories spiraling into the endemic state. The different behavior of our numerical results are shown for the different values of parameters

*Key-Words*: Malaria transmission models, *Plasmodium Vivax* malaria, equilibrium states, local stability, basic reproduction number.

## 1   Introduction

The developmental biology [1] of the parasite Plasmodium vivax determines to a great extent the mathematical model needed to describe the transmission cycle of the human disease caused by this parasite. The sporizoites (one of the stages of the malaria parasite) are introduced into the blood stream of the human by the bite of infected mosquitoes. These then move to the liver of the human. Here some of them transform themselves into merozoites, which then invade the blood cells and cause the illness. The remaining sporizoites are transformed into hypnozoites which then lay dormant in the liver. The relapses occur when some of the hypnozoites transform themselves into schizents and then into merozoites. These new merozoites then reinvade the blood and cause the illness again. These relapses can occur up to three years after the initial infection. Only a small number of P. vivax merozoites remain in the blood between the relapse episodes. The hypnozoite stage does not occur in the three other types of malaria, Plasmodium falciparum, Plasmodium malariae and Plasmodium ovale.

The absence of the hypnozoite stage in the malaria caused by the P. falciparum parasite makes the transmission models used to describe P. falciparum malaria invalid for describing the transmission of the malaria caused the P. vivax parasite. The reasons for P. falciparum malaria to be studied more than P. vivax malaria are (1) 90% of the malaria cases in Africa is due to P. falciparum malaria, (2) most of the deaths due to malaria (2-3 million a year) occur in Africa [2] and (3) P. falciparum malaria is a life threatening disease, while P .vivax malaria is not. It was commonly assumed that information about vivax could be extrapolated from the falciparum research. This assumption was challenged at a recent conference

convened by the Multilateral Initiative on Malaria [3]. The transmission of malaria is usually described by the Ross-MacDonald (RM) model [4]. However, this model is only suitable for the transmission of the P. falciparum malaria since it does not contain a role of possible relapses of the illness. One of the present authors (IMT) has introduced a simple mathematical model [5] to describe the transmission of P. vivax malaria. In the model, we included a dormant class in which there are no merozoites in the blood, only dormant hypnozoites in the liver. A person can be reinfected when the hypnozoites are activated.

We wish to look at the model again. In the present state of concern for medical safety, there is no place for human experimentation to see what would happen if new therapies were adopted. Mathematical modeling allows one to simulate what would occur. We introduce in Section 2, the modification of the RM model which would make it applicable to the transmission of P. vivax malaria  In Section 3, we analyze our model and simulate the consequences of changing the rate of relapse and other parameters in the model. We discuss in Section 4, the implication of the insights obtained from the simulations. Part of the urgency for doing research on P. vivax malaria is due to the fact that P. vivax malaria is becoming an emerging public health problem. It is estimated that about 50% of the malaria cases outside of Africa and 10% in Africa are due to P. vivax and that the percentages are rising.

## 2    Transmission model

The mathematical modeling of the epidemiology of malaria (*P. falciparum*) was started by Ross [6] in 1911and improved on by MacDonald [7]. In the Ross model, an individual in the human population is classified as being in a non-infected or infected state. This gives rise to what is known as a SIS (susceptible-infected-susceptible) model. It has been suggested [7] that the human population should instead be divided into three states; non-infected, infected but without any acute clinical signs, infected with acute

clinical sign, to better reflect the clinical status of the individual. Others believe that the population should be divided into susceptible, infected but not infectious and infected and infectious. In our model for the trans-mission of *P. vivax*, we divide the host (human) population into susceptible $(\bar{S}_h)$, infected $(\bar{I}_h)$, dormant $(\bar{D}_h)$ and recovered $(\bar{R}_h)$ classes. The last category, the recovered are susceptible to further infections and so they reenter into the $\bar{S}_h$ class. In Figure 1, we show the flow chart describing what is occurring in the human population. As we see, $\lambda N_T$ humans are entering into the susceptible class through birth and $(1-\alpha)r_1\bar{I}_h$ , $r_3\bar{D}_h$ and $r_6\bar{R}_h(t)$ through the recovery of members of the infected and dormant categories (with $\lambda$ being the birth rate; $N_T$, the total human population; $r_1$, the recovery rate of a person in the infected category; $r_3$, the recovery rate of a member of the dormant population and $\alpha$ being the percentage of infected people in whom some hypnozoites remain dormant in the liver). $(1-\alpha)$ is the percentage of infected humans who recover and become susceptible again. The time rate of change of the number of susceptible members is equal to the number entering minus the number leaving. This gives us the following differential equation for the time rate of change of the susceptible population;

$$\frac{d}{dt}\bar{S}_h(t)=\lambda N_T+r_3\bar{D}_h(t)+(1-\alpha)r_1\bar{I}_h(t)$$

$$-\gamma'_h\bar{I}_v(t)\bar{S}_h(t)-\mu_h\bar{S}_h(t)+r_4\bar{R}_h(t)$$

(1a)

Applying similar considerations to the other population classes, we obtain

$$\frac{d}{dt}\bar{I}_h(t)=\gamma'_h\bar{I}_v(t)\bar{S}_h(t)-(r_1+\mu_h)\bar{I}_h(t)$$

$$+r_2\bar{D}_h(t)-r_5\bar{I}_h(t),$$

(1b)

$$\frac{d}{dt}\bar{D}_h(t)=\alpha r_1\bar{I}_h(t)-(r_2+r_3+\mu_h)\bar{D}_h(t)$$

(1c)

and

$$\frac{d}{dt}\overline{R}_h(t) = r_5\overline{I}_h(t) - (r_4 + \mu_h)\overline{R}_h(t) \quad (1d)$$

where the parameters in the above equations are defined as

$\lambda$ is the birth rate of human population,

$\mu_h$ is the death rate of human population,

$N_T$ is the total number of human population,

$\alpha$ is the percentage of infected human in whom some hypnozoites remain dormant in the liver,

$r_1$ is the rate at which a person leaves the infected class by recovering or by entering into the dormant class,

$r_2$ is the rate at which the dormant human relapses back to the infected human,

$r_3$ is the recovery rate of the dormant human,

$r_4$ is the rate at which the recovered human relapses back to the susceptible human,
and

$r_5$ is the rate at which the infected human recovers, since *P. vivax* infection is non lethal, the death rates will be the same for all human classes and we will have $N_T = \overline{S}_h + \overline{I}_h + \overline{D}_h + \overline{R}_h$

Eqn. (1a) also contains the term $\gamma'_h\overline{I}_v(t)\overline{S}_h(t)$. This term represents the lost of the susceptible person due to a bite of a infected mosquitoes. $\gamma'_h$ is the rate at which the *P. vivax* parasite is transmitted from the mosquito to the human and is given by [8]

$$\gamma'_h = b\frac{\beta_h}{N_T + m} \quad (2)$$

where b is the specie-dependent biting rate of the mosquitoes; m is the population of other animals that the mosquitoes can feed on and $\beta_h$ is the probability the parasite passed on by the mosquito will continue to thrive in the human. $\beta_h$ depends partly on the immune response of the host to the infection. $\overline{I}_v$ is the number of infected mosquitoes. The dynamics of the mosquitoes populations are given by

$$\frac{d\overline{S}_v}{dt} = A - \gamma'_v\overline{S}_v(t)\overline{I}_h(t) - \mu_v\overline{S}_v(t) \quad (3a)$$

and

$$\frac{d\overline{I}_v}{dt} = \gamma'_v\overline{S}_v(t)\overline{I}_h(t) - \mu_v\overline{I}_v(t). \quad (3b)$$

At equilibrium, the total number of female mosquitoes will be $A/\mu_v$. A is the rate at which the mosquitoes are recruited and $\mu_v$ is the death rate for the mosquitoes. It should be noted that a mosquito can not be infected through a bite of a human belonging to the dormant class. $\gamma'_v$ is the rate at which the mosquitoes become infected with the Plasmodium Vivax parasite once the mosquito has bitten an infected human. We also assume $N_V = \overline{S}_v + \overline{I}_v$. The working equations of the model are obtained by dividing Eqns. (1a), (1b), (1c) and (1d) by $N_T$ and Eqns. (3a) and (3b) by $A/\mu_v$. This would give us six equations expressed in terms of the renormalized variables; $S_h = \overline{S}_h/N_T, I_h = \overline{I}_h/N_T, R_h = \overline{R}_h/N_T,$ $S_v = \overline{S}_v/(A/\mu_v)$ and $I_v = \overline{I}_v/(A/\mu_v)$. The conditions $S_h + I_h + D_h + R_h = 1$ and $S_v + I_v = 1$, leads to only four of these equations being needed. We pick the four equations to be

$$\frac{d}{dt}S_h(t) = \mu_h + r_3D_h(t) + (1-\alpha)r_1I_h(t)$$
$$- \gamma_hI_vS_h(t) - \mu_hS_h(t)$$
$$+ r_4(1 - S_h(t) - I_h(t) - D_h(t))$$
$$(4a)$$

$$\frac{d}{dt}I_h(t) = \gamma_hI_vS_h(t) - (r_1 + \mu_h)I_h(t) + r_2D_h(t)$$
$$- r_5I_h(t) + r_5(1 - S_h(t) - I_h(t) - D_h(t))$$
$$(4b)$$

$$\frac{d}{dt}D_h(t) = \alpha r_1I_h(t) - (r_2 + r_3 + \mu_h)D_h(t)$$
$$(4c)$$

and

$$\frac{d}{dt}I_v(t) = \gamma_v(1 - I_v(t))I_h(t) - \mu_vI_v(t)$$
$$(4d)$$

where the new transmission rates are $\gamma_h = \gamma'_h(A/\mu_v)$ and $\gamma_v = \gamma'_v N_T$. The domain of solutions is

$$\Omega = \{(S_h, I_h, D_h, S_v, I_v)|$$
$$0 \le S_h + I_h + D_h \le 1, 0 \le S_v + I_v \le 1\}.$$

# 3    Analysis of the Mathematical Model

## 3.1    Analytical results.

To find the equilibrium points, we set the RHX's of Eqns. (4a) to (4d) to zero. Doing this, we get

i)   the disease free equilibrium state
     $E_O = (1, 0, 0, 0)$
ii)  the endemic equilibrium state
     $E_1 = (S_h^*, I_h^*, D_h^*, I_v^*)$

where

$$S_h^* = \frac{BN}{\gamma_v \mu_{h_{23}} \mu_{h_{46}} P},$$

$$I_h^* = \frac{X_0 - R}{\gamma_v P},$$

$$D_h^* = \frac{(\alpha \mu_{h_{46}} r_1)(X_0 - R)}{\gamma_v \mu_{h_{23}} \mu_{h_{46}} P},$$

$$I_v^* = \frac{X_0 - R}{B\gamma_h} \tag{5}$$

with

$$N = \mu_{h_{46}}(\mu_h(\mu_h + r_{13}) + r_1(r_2(1-\alpha) + r_3))$$
$$+ (\mu_h(\mu_h + r_{26}) + r_2 r_4 + r_3 r_6)r_5,$$

$$B = \mu_{h_{46}}(\mu_h(\mu_v + \gamma_v) + \alpha \mu_v r_1$$
$$+ (\mu_v + r_v)(r_2 + r_3)) + \mu_v(\mu_{h_{23}} + r_4)r_5,$$

$$P = \mu_{h_{46}}(\gamma_h(\mu_{h_{23}} + \alpha r_1) + \mu_h(\mu_h + r_{13})$$
$$+ r_1(r_2(1-\alpha) + r_3)) + (\mu_h(\mu_h + r_{26})$$
$$+ \gamma_h \mu_{h23} + r_2 r_4 + r_3 r_4)r_5,$$

$$X_0 = \mu_{h_{46}}(\gamma_h \gamma_v \mu_{h_{23}} + \alpha \mu_v r_1 r_2),$$

$$R = \mu_v(\mu_{h_{46}}(\mu_h(\mu_h + r_{13}) + r_1(r_2 + r_3))$$
$$+ (\mu_h(\mu_h + r_{26}) + r_2 r_4 + r_3 r_4)r_5),$$

where

$$\mu_{h23} = \mu_h + r_2 + r_3, \quad \mu_{h46} = \mu_h + r_4,$$

$$r_{13} = r_1 + r_2 + r_3$$

$$r_{26} = r_2 + r_3 + r_4. \tag{6}$$

We observe that endemic equilibrium point exists when $X_0 > R$ or $\frac{X_0}{R} > 1$.

The local stability of each equilibrium point is determined by the sign of all eigenvalues. If all eigenvalues have negative real parts, then that equilibrium point is locally stable. Eigenvalues for each equilibrium point are obtained by setting

$$\det(J - \lambda I) = 0 \tag{7}$$

Where J is the gradient matrix evaluated at the equilibrium point.

The correspondent eigenvalues for each equilibrium point are found by solving the characteristic equation; which is in the form

$$\lambda^4 + s_3 \lambda^3 + s_2 \lambda^2 + s_1 \lambda + s_0 = 0 \tag{8}$$

By using Routh-Hurwitz criteria [9], each equilibrium point is locally stable if the following conditions are satisfied;

i) $s_3 > 0$, $\qquad\qquad$ (9)

ii) $s_1 > 0$, $\qquad\qquad$ (10)

iii) $s_0 > 0$, $\qquad\qquad$ (11)

iv) $s_3 s_2 s_1 > s_1^2 + s_3^2 s_0$ $\qquad$ (12)

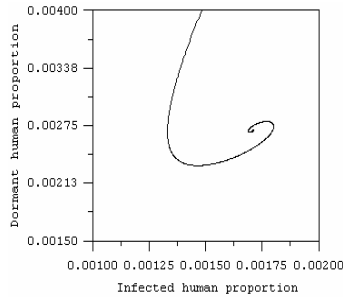We check the above conditions by using MATHEMATICA (Wolfram Research, Champaign, IL), then we found that $E_0$ is locally stable for $R_0 < 1$ and $E_1$ is locally stable for $R_0 > 1$; where
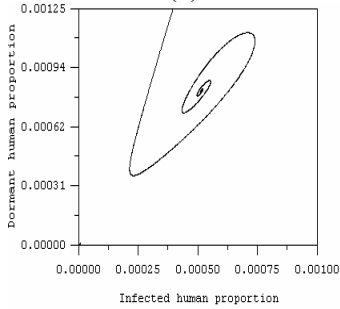
$$R_0 = \frac{X_0}{R}.$$

## 3.2    Numerical Results

In this section, we compare the susceptible of our model for the different parameters.

**Case I**, $r_4$ is changed and the other parameters are fixed.
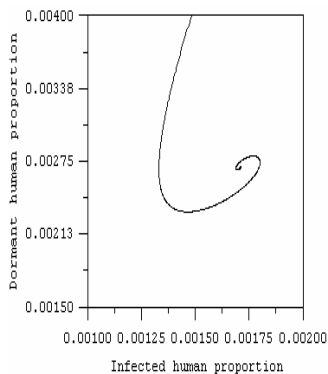
1(a)



1(b)



2(b)

Fig.2(a)Behavior of our model for

$$r_2 = 1/(365*5)^{-1} \text{day},$$
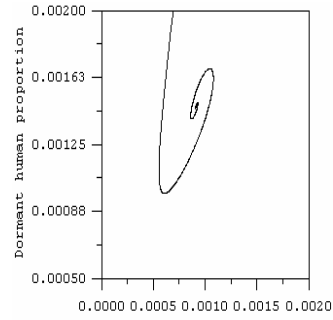
$$r_4 = 1/(365*5)^{-1} \text{day and R}_0 = 38.6.$$
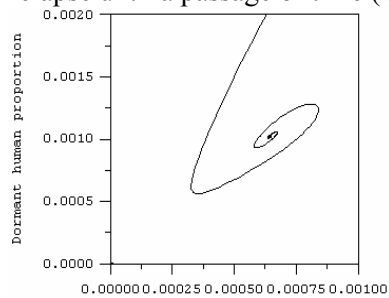
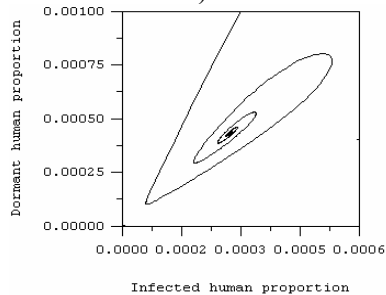   (b)Behavior of our model for

$$r_2 = 1/(365*20)^{-1} \text{day},$$

$$r_4 = 1/(365*10)^{-1} \text{day and R}_0 = 38.5.$$

   The other similar parameters for fig.2(a) and fig.2(b) are $r_1 = 1/14^{-1}$ day, $\mu_h = 1/(365*70)^{-1}$day, $r_3 = 1/30^{-1}$day, $\alpha = 0.75$, $\mu_v = 0.04$ $\gamma_h = 2.5$, $\gamma_v = 0.25$, $r_5 = 1/3^{-1}$day.

Fig.1(a). Behavior of our model for

$$r_4 = 1/(365*5)^{-1} \text{day, R}_0 = 38.6.$$

   (b). Behavior of our model for

$$r_4 = 1/(365*20)^{-1} \text{day, R}_0 = 38.7.$$

   The other similar parameters for fig.1(a) and fig.1(b) are $r_1 = 1/14^{-1}$ day, $r_2 = 1/(365*5)^{-1}$ day, $\mu_h = 1/(365*70)^{-1}$ day, $r_3 = 1/30^{-1}$ day, $\alpha = 0.75$, $\mu_v = 0.04$ $\gamma_h = 2.5$, $\gamma_v = 0.25$, $r_5 = 1/3^{-1}$ day, $\mu_h = 1/(365*70)$.

**Case II**, $r_2$ and $r_4$ are changed and the other parameters are fixed.

**Case III,** When we input the effect of time delay into our model. In this case, the members of the dormant class do not relapse until a passage of time ($\tau$).



2(a)



3a)



3b)

Fig.3(a)Behavior of our model for

$r_4 = 1/(365*15)^{-1}$ day and

$\tau = 365*30$ day.

(b)Behavior of our model for

$r_4 = 1/(365*50)^{-1}$ day and

$\tau = 365*50$ day.

The other similar parameters for fig.3(a) and fig.3(b) are $r_1 = 1/14^{-1}$ day,

$\mu_h = 1/(365*70)^{-1}$day,

$r_2 = 1/(365*5)^{-1}$day, $r_3 = 1/30^{-1}$day,

$\alpha = 0.75$, $\mu_v = 0.04$  $\gamma_h = 2.5$,

$\gamma_v = 0.25$, $r_5 = 1/3^{-1}$day.

## 4    Conclusion

In this study, we have compared the results of the simulation when different values of several parameters are used. Figures 1 to 3 show the trajectories of the behaviors in (human) infected-dormant vector space.  They all indicate a spiraling of the trajectories into the endemic state. Each pair of figures 1a) & 1b), 2a) & 2b) and 3a) & 3b) shows the behavior when the parameter is changed.  When the time at which the recovered human relapses back to the susceptible human is longer, the spiraling in is more severe as shown in figure 1. When the time at which the dormant human relapses back to the infected human is longer than the time at which the recovered human relapses back to the susceptible human, the spiral pattern is more severe.

We have also looked at the effects of there being a time delay before a person in the dormant class relapses into the infected class, i.e., the symptoms returns.  We have simulated the course of the disease (malaria) delay time is changed.  In Figure 3, we show the results of our numerical simulation.  As we see, when the time delay is longer, the spiral pattern is more severe.

## 5 Acknowledgements

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