BASIC REPRODUCTION NUMBER FOR THE TRANSMISSION OF *PLASMODIUM VIVAX* MALARIA

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Abstract. The possibility of relapse is introduced into a mathematical model for the transmission of *Plasmodium vivax* malaria. In the model, the human population is divided into four classes: susceptible, infected, dormant and recovered. Loss of immunity by individuals in the recovered class moves these individuals back into the susceptible class. Two equilibrium states are found, a disease-free state and an endemic state. A basic reproduction number R_0 is found. Depending on whether R_0 is less than or greater than one, the disease free state or the endemic state results. The dependence of R_0 on the rate of relapse is determined and the implication of this dependence is identified.

INTRODUCTION

Every year there are over two hundred million cases of malaria worldwide, with over one million deaths, mainly children (WHO, 1997). Malaria is caused by four species of the *Plasmodium* parasite, *P. falciparum*, *P. malariae*, *P. ovale* and *P. vivax*. Only the first three are found in substantial numbers in tropical Africa, with 80-99% of the infections due to *P. falciparum*, 1-38% to *P. malariae* and 0-11% to *P. ovale*, depending on the country. In Thailand, malaria is due to *P. falciparum*, *P. vivax* and *P. malariae*. In 1984, 70.7% of the infections were due to *P. falciparum*; 29.0% to *P. vivax* and 0.02% to *P. malariae*. (Pinichpongse, 1985). The relative distribution of the species has since changed in Thailand. Luxemberger *et al* (1996) found that 53% of the infections in one community in 1992 were due to *P. vivax*, 37% to *P. falciparum* and 10% to mixed infections. The clinical presentation in the last group suggested that co-infection by *P. vivax* reduces the severity of the *P. falciparum* infection. (Luxemberger *et al*, 1997; Maitland *et al*, 1996). It was pointed out by Luxemberger *et al* (1996), that the children in the village had experienced on average 4 times more vivax than falciparium malaria infections by the time they reached the age of four. They stated that this can not be explained entirely by relapses and went on to conjecture that the transmission rate for *P. vivax* is higher than that for *P. falciparum*. They did not attempt to quantify the statement. It is the purpose of the present paper to look at the effects of relapse on the transmission of *P. vivax*.

This is done by looking at the consequence of including a relapse phase in the mathematical model for the transmission of the *P. vivax* parasite. Mathematical modeling of malaria has a long history. In 1911, Ross developed an epidemiological model for malaria transmission. Refinement of the model was then given by MacDonald (1957) and has been discussed by Anderson and May (1991). McKenzie (2000) has recently summarized the advantages and shortcomings of modeling malaria. He states that models help us to articulate and analyze relationships among facts, to help us make decisions. Models can create the mathematical framework that could be used to guide policy formulation in the areas of public health. In the case of *P. falciparum* malaria, the policy decisions could be literally a matter of life and death. It is therefore imperative that the model used describes as closely as possible the attributes of the disease being studied.

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P. vivax infections differs from *P. falciparum* infections in that a person suffering from the latter infection will recover from the disease (if he does not die from it), while a person suffering from *P. vivax* infection will suffer relapses. Of course, the individual will eventually recover. The *P. vivax* parasites, which are introduced into the blood as sporozoites by the bite of an infected mosquito, migrate to the liver. There some will enter into the hypnozoite stage and lay dormant in the liver. Others will be transform into merozoites and invade the blood cells and produce the illness. Relapses occur when the hypnozoites transform themselves into merozoites and reinvade the blood. Only a small number of the *P. vivax* merozoites remain in the blood between the relapse episode. These relapses can occur up to five years after the initial infection. (Wernsdorfer, 1980). As is the case for *P. falciparum* malaria, immunity against further inflection by *P. vivax* in a person who has recovered from an earlier bout of the disease is short lived. To be useful, a model describing the transmission of *P. vivax* malaria must take into account all of the above features of the disease. We have not, however, included in our model the fact that during part of time the *P. vivax* parasite is in the mosquito, it is not infectious.

MATHEMATICAL MODEL

The standard Ross-MacDonald (RM) model (Anderson and May, 1991) is best suited to describe the transmission of *P. falciparum* malaria since it does not include reinfection through relapses of the disease which is a feature of *P. vivax* malaria. In the RM model, an individual in the human population is classified as being in a noninfected state or in an infected state. It has been argued (Richard *et al*, 1993) that the human population should instead be divided into three states; noninfected, infected but without any acute clinical signs, infected with acute clinical sign, to better reflect the clinical status of the individual. In our model for the transmission of *P. vivax*, we divide the host (human) population into four

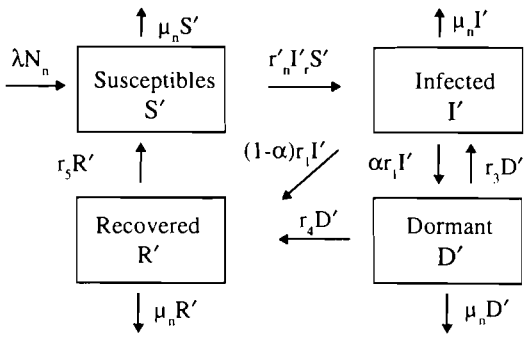

Fig 1–Flow Chart for the transmission of *Plasmodium vivax* malaria. The variables are the number of individuals in each class.

classes: susceptible (S_h'), infected (I_h'), dormant (D_h') and recovered (R_h'). Since malaria does not confer permanent immunity to further infection, we allow for the recovered class to reenter the susceptible class after a passage of time. The dormant class is introduced to place the infected individuals in whom, the hypnozoites lie dormant in the liver. We assume that an uninfected (susceptible) mosquito cannot be infected with the parasite when biting a person in this class. We also assume that a person in the dormant class cannot be reinfected by a new bite.

The flow chart of the disease is shown in Fig 1. The time rate of change of any class is equal to the number entering into the class minus the number leaving the class. In the figure, λ is the birth rate; N_h, the total human population; μ_h, the death rate; γ'_h, the rate at which the *P. vivax* parasite is transmitted from the mosquito to the human; r_1^{-1} is the mean life time for the parasite to remain infectious in the human; r_3, the rate an individual in the dormant phase suffers a relapse; r_4, the rate at which an individual in the dormant class recovers; r_5, the rate at which the recovered individual loses his immunity and α, the percentage of individuals leaving the infected class and enter into dormant class. Since *P. vivax* infection is non-lethal, the death rates will be the same for all classes of humans. For vector (mosquito) transmitted diseases, γ'_h is given by (Esteva and Vargas, 1998).

$$\gamma'_h = b \frac{\beta_h}{N_h+p} \quad (1)$$

where b is the specie-dependent biting rate of the mosquitos; p is the population of other animals that the mosquitos can feed on and β_h is the probability the parasite passed on by the mosquito will continue to thrive in the human.

The dynamic equations for the system described by the flow chart are

$$dS_h/dt = \lambda + r_5R_h - \gamma_hI_vS_h - \mu_hS_h, \quad (2a)$$
$$dI_h/dt = \gamma_hI_vS_h + r_3D_h - (\mu_h+r_1)I_h, \quad (2b)$$
$$dD_h/dt = \alpha r_1I_h - (\mu_h + r_3 + r_4)D_h, \quad (2c)$$

and

$$dR_h/dt = (1-\alpha) r_1I_h + r_4D_h - (\mu_h+ r_5) R_h \quad (2d)$$

where S_h, I_h, D_h and R_h are the normalized population densities and I_v is the density of infected mosquitos. If we only consider the incoming and outgoing components in the flow chart, we have

$$dN_h/dt = (\lambda - \mu_h) N_h \quad (3)$$

since $N_h = S_h' + I_h' + D_h' + R_h'$. If the birth rate is equal to the death rate, the total human population will be constant as can be seen from eqn. (3)

The time rates of changes of the mosquito population (susceptible (S_v') and infected (I_v') are described by the following equations:

$$dS_v'/dt = A - \gamma'_vS_v'I_h' - \mu_vS_v' \quad (4)$$

and

$$dI_v'/dt = \gamma'_vS_v'I_h - \mu_mI_m' \quad (5)$$

where γ'_v is the rate at which the mosquito becomes infected with the *P. vivax* parasites once the mosquito has bitten an infected human and is also defined by Esteva and Vargas (1998). It is assumed that the mosquitos can only be infected if they bite a human with an active infection. μ_v is the death rate for the mosquito. A is the rate at which the mosquitos are recruited into the environment. This is not equal to the mosquito's birth rate λ_v times the total number of mosquitos. As one knows, the mosquitos lay eggs which give birth to the larval stage of the mosquitos. Only a small number of the larvae will make the transition into the adult stage. This number will depend on the carrying capacity of the environment (possibly the surface area of stagnant water in which the eggs were laid). At equilibrium, the total number of mosquitos will be A/μ_v. Dividing eqns. (4) and (5) by the total number of mosquitos, we get

$$dS_v/dt = \mu_v - \gamma_vI_hS_v - \mu_vS_v, \quad (6a)$$

and

$$dI_v/dt = \gamma_v(1 - I_v) I_h - \mu_vI_v. \quad (6b)$$

The new transmission rates are $\gamma_h = \gamma'_h(A/\mu_v)$ and $\gamma_v = \gamma'_{mv}N_h$. Only four of the six equations ((2a)-(2d) and (6a)-(6b)) are needed since $dR_h/dt = - (dS_h/dt + dI_h/dt + dD_h/dt)$ and $dS_v/dt = - dI_v/dt$. The equilibrium (or steady) states are the set of values of S_h, I_h, D_h and I_v for which the RHS of eqns. (2a), (2b), (2c) and (6b) are equal to zero. To be of biological interests, the values should be in the domain $\Omega = \{(S_h, I_h, D_h, I_v), 0 \le S_h \le 1, 0 \le I_h \le 1, 0 \le D_h \le 1, 0 \le I_v \le 1\}$. This domain is positively invariant under the flow induced by the four equations as the vector field on the boundary does not point to the exterior.

EQUILIBRIUM STATES

Setting the RHS of the four equations to zero and solving for the four variables (noting that $R_h = 1 - S_h - I_h - D_h$), we obtain two equilibrium states; a disease free state E_0

$$E_0 = (1,0,0,0) \quad (7)$$

and the endemic state E_1

$$E_1 = (S^*, I^*, D^*, I^*_v) \quad (8)$$

where

$$S^* = \frac{\beta + M}{\beta + R_0M},$$

$$I^* = \frac{R_0 - 1}{\beta + R_0M} \quad \text{and}$$

$$D^* = \frac{\alpha r_1}{\mu_h + r_3 + r_4} I^* \quad (9)$$

with

$$\beta = \gamma_v/\mu_v,$$

$$M = 1 + \frac{r_1}{\mu_h + r_5} - \frac{\alpha r_1 (r_3 - r_5)}{(\mu_h + r_5)(\mu_h + r_3 + r_4)}$$

and

$$R_0 = \frac{b^2 \beta_v \beta_h (A/\mu_v) N_h}{\mu_v (N_h + p)^2 \left(\mu_h + r_1 - \frac{\alpha r_1 r_3}{(\mu_h + r_3 + r_4)}\right)} \qquad (10)$$

We have not written down the form of I^*_v since it is not needed in further discussions. S^* and I^* have the same form as the expressions for the susceptible and infected populations obtained by Esteva and Vargas in their model for the transmission of dengue hemorrhagic fever except for the definitions of M and R_0. The local stability of the equilibrium state is determined by the gradient (Jacobian) matrix evaluated at the equilibrium states, finding its eigenvalues (by solving the determinant equations $\det|J - \lambda I| = 0$) and then checking to see if the real parts of each eigenvalues are negative (Marsden and McCracken (1976). Doing this, we find that the disease-free state is locally asymptotically stable when $R_0 < 1$ and that the endemic state E_1 is locally asymptotically stable when $R_0 > 1$. Following the steps taken by Esteva and Vargas, it can be shown that the two states are also globally stable.

The square root of R_0 is often called the basic reproduction number. (Diekmann *et al,* 1990). It is the number of secondary infections resulting from a primary infectious bite. The expression for R_0 is different from that given by MacDonald (1957) for falciparum infection;

$$\frac{m a^2 b_1 b_2 \, e^{-\mu T}}{\mu r} \qquad (11)$$

In MacDonald's expression, m is the ratio of mosquito to human density; $b_1(b_2)$, the transfer of the infectiousness from an infected human (mosquito) to a mosquito (human); μ, the daily mortality of the mosquito; T, the parasite's developmental period in the mosquito and r is the recovery rate of a human. 1/r is the typical

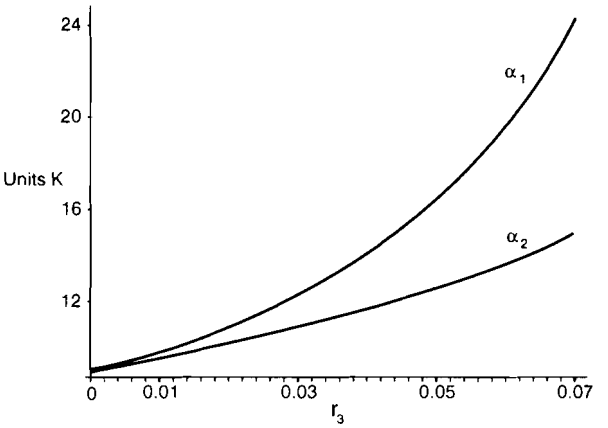

Fig 2–Dependence of the basic reproduction number on relapse rates. Two values of α, the% of primary infected individuals who suffer relapses, are used. α_1 (63%) is the value for untreated patients (Bruce-Chwatt, 1980) and α_2 (40%) is the value for chloroquine treated patients (Looareesuwan *et al,* 1999). r_1 is taken to be 1/9 days while $r_3 + r_4$ is set to 0.07 and kept constant as r_3 is varied. The values of all the other parameters are chosen so that in the absence of relapse, R_0 would be equal to a constant (K) greater then one.

duration of infectiousness in the human host; $1/\mu$, period of infectiousness of the mosquito and $e^{-\mu T}$ is the probability that the mosquito survives the developmental period of the parasite from the initial infection to become infectious. From the sensitivity of the basic reproduction number to changes in the various parameters, MacDonald concluded that changes in the mosquito's mortality would have the largest impact on the parasite's overall chances of success and so he suggested that this parameter should be the target of any public health initiative.

We are interested here in seeing the effects of the relapse on the transmission of *P. vivax* malaria. In Fig 2, we have plotted the changes in the R_0 (given by eqn (10)) as r_3 is varied for two values of α. The values of the other parameters are typical of those seen in Thailand (the values are given in the figure caption). As we see, R_0 increases as the relapse rates increase. R_0 does not depend on r_5, the rate at which the recovered patient loses immunity. This does not mean that the inci-

dence rate is not affected by the loss of immunity. We note that the constant M depends on both r_3 and r_5 and can increase or decrease depending on the relative magnitudes of these two rate constants. The increase in R_0 as the rate of relapse increases would lead to an increase in the incidence rate (see eqn 9). This dependence of the incidence rates of *P. vivax* malaria on the relapse rate is especially significant in light of a study by Looareesuwan *et al* (1987), who found that the rate of relapse of *P. vivax* malaria increased after treatment for *P. falciparum* malaria. This touches on the largely unstudied question of how public health treatment of one disease impacts on the progression of another disease, which must be deterrmined when formulating public health policies.

Concerning the conjecture about the higher transmission rate of *P.* vivax compared to that of *P. falciparum*, we note the following: In the absence of another animal for the mosquitos to fed on, *ie*, p = 0, the factor $(A/\mu_v)N_h/(N_h+p)^2$ appearing in the expression for R_0 (eqn 10) becomes m. MacDonald's expression (eqn 11) for the *falciparum* basic reproduction number (ignoring the exponential factor) differs from the R_0 for *vivax* by the replacement of recovery rate by the factor $[\mu_h + r_1 - \alpha r_1 r_3/(\mu_h + r_3 + r_4)]$ which in the absence of any relapse becomes $(\mu_h + r_1) \rightarrow r$. If the transmission rate for the two *Plasmodium* strains are nearly the same, then the ratio $R_0(vivax)/R_0(falciparum)$ would be equal to the ratio between $(\mu_h + r_1)$ and $[\mu_h + r_1 - \alpha r_1 r_3/(\mu_h + r_3 + r_4)]$. Since the second term is smaller than the first, it would be possible for $R_0(vivax) > R_0(falciparum)$ without having to invoke the conjecture that the transmission rate for *P. vivax* is higher than that for *P. falciparum*. The conjecture might not be supported by the direct data. Maitland *et al* (1996) state, "At present it is not possible to determine from entomological data whether there were differences in the rate of transimission of *P. vivax* and *P. falciparum* by *An. farauti*".

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