The prevalence of *Plasmodium vivax* in *Vanuatu*
Islands: Computer simulation of malaria control trails

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We have estimated the degree of transmission of *Plasmodium vivax* malaria in Vanuatu Islands, eastern Melanesia with the aid of the computer simulations, which has been carried out on the platform of a mathematical transmission model. The malaria caused by *Plasmodium vivax* has a relapse character, which arises from hypnozoites in the liver. This phenomenon makes a malaria control strategy difficult. When the mass drug administration is executed, the prevalence of *Plasmodium vivax* decreases moderately as compared with that of *Plasmodium falciparum*, and it recovers before long being affected by the relapses. The simulations suggest that one cannot attain the eradication of *Plasmodium vivax* malaria without the concentrated execution of the mass drug administration and the vector control that fairly reduces the vectorial capacity.

Key words: Plasmodium vivax, computer simulation, hypnozoite, mass drug administration, relapse

1 INTRODUCTION

Vanuatu is located in eastern Melanesia, the southern Pacific Ocean. Malaria transmission in Vanuatu, where *Plasmodium falciparum* and *Plasmodium vivax* predominate, is mesoendemic and fluctuating seasonally. In the islands of Vanuatu, *Anopheles farauti* is known as the only species of mosquito vector of malaria.

In the present paper, we have investigated the estimate of the prevalence of *Plasmodium vivax* malaria.

In this case, we should take it into consideration that a *P. vivax* parasite sometimes stays in a liver quiescently as hypnozoite and afterwards a patient relapses into the disease and develops the malaria symptom. We have adapted our malaria transmission model for *P. vivax* to the Vanuatu context, choosing the model parameters on the basis of the epidemiological data there. With regard to the transmission of *P. falciparum* in Vanuatu, we previously made estimates of various situations using our transmission model for *P. falciparum* (Ishikawa *et al.*, 1996). Our model can treat the effect of anti-malarial measures, such as the mass drug administration and the vector control project towards diminution of the vectorial capacity. In this study, we will assess the prospective prevalence of malaria through computer simulations when the mass drug administration is executed.

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2 MATERIALS AND METHODS

2.1 HYPNOZOITE

The malaria caused by *Plasmodium vivax* has a relapse character, which arises from the hypnozoites in the liver. This phenomenon makes a malaria control strategy difficult. The relapse pattern of *Plasmodium vivax* malaria was investigated by the records of patients who moved to non-endemic area for malaria and whose detailed histories were known. Sawada (1948) investigated about the imported malaria by returnees from North Korea. He estimated the relapse period as 10 months. It was also detected at the General Hospital in Sri Lanka (Fonseka and Mendis, 1987). They reported as follows: the proportion of relapses in all vivax malaria was about 18%, the relapse pattern was non symmetric and had the right heavy tail, the average period of relapses, the left standard derivation and the right one were 108, 30 and 70 days. We adopt these figures in our simulation for lack of the epidemiological data in Vanuatu.

2.2 G6PD DEFICIENCY

Primaquine is one of the most effective drug and is used for the radical treatment of *P. vivax* malaria. G6PD (glucose-6-phoshate-dehydrogenase) deficient subjects may cause hemolysis when they are dosed with primaquine. G6PD deficiency in malaria endemic region, Vanuatu, was reported in Kaneko *et al.* (1994). In a survey of about 400 male islanders in the central and southern six islands, the incidence of the deficiency was 3.7%. Especially, in the southern four islands, it was less than 1%.

2.3 PARASITE RATE

The prevalence of malaria in Vanuatu is mesoendemic. Kaneko *et al.* (1994) examined 11,590 blood samples of the islanders during 1988-91 and detected the parasite rate of *P. falciparum*, *P. vivax*, *P. malariae*. We estimated the overall parasite rate by taking an average of the field data weighted with age specified ratio of population reported in Demographic Years book published by the United Nations (1992) as follows (Ishikawa *et al.* 1996) :

P. falciparum	4.8%
P. vivax	5.2%
P. malariae	0.075%

About the climate, the months of December to April are recognized as the wet season, and the months of August to October, as the dry season. The incidence of *P. falciparum* in the wet season broke out notably more than in the dry season. On the contrary, the fluctuation of *P. vivax* malaria was mild (**Table 1**). It seems due to the relapses in the liver.

Table 1 The ratio of the average of the monthly malaria incidence of the wet season to that of the dry season *

year	1987	1988	1989	1990	1987-90
P. vivax	1.16	1.39	1.05	1.44	1.26
P. falciparum	1.96	1.84	1.80	1.97	1.87

* Derived from Kaneko *et al.* (1994)

2.4 MATHEMATICAL MODEL FOR *PLASMODIUM VIVAX*

To describe the transmission of *P. vivax* malaria, we have amplified a mathematical model whose fundamental structure is based on DMT-model (Dietz *et al.*, 1974). Our model can work on many situations to elucidate the diminution of the prevalence in executing chloroquine as the mass drug administration, the diminution of the parasite rate of the hypnozoite or the gametocyte in executing

primaquine, and the variety of the prevalence in carrying on the vector control measures such as the distribution of permethrin impregnated bed nets. De Zoysa *et al.* (1991) developed a model for *P. vivax* consisting 21 epidemiological classes of human population and 3 classes of vector population to investigate the immune memory for transmission blocking or enhancement using the field data in Sri Lanka. In our model, the human population is divided into 12 classes; 9 classes are defined in DMT model, z_1, z_2, z_3 are protected classes resulting from the effect of mass drug administration, z_4 is protected class resulting from the effect of the radical treatment, w represents new class of individuals having a hypnozoite (**Table 2**).

Table 2 Epidemiological classes of the human population in the model

Epidemiological class	variable
non-immune, susceptible	x_1
non-immune, incubating	x_2
immune, susceptible	x_3
immune, incubating	x_4
non-immune, infectious positive	y_1
non-immune, positive	y_2
immune, positive	y_3
non-immune, protected, noninfectious	z_1
non-immune, protected	z_2
immune, protected	z_3
protected, no hypnozoite	z_4
hypnozoite	w

The infection rate h, the recovery rate R_1 from non-immune positive stage, that R_2 from immune positive stage, the transfer rate Q from incubation stage to infection stage are defined as follows (Dietz *et al.*,

1974):

$$h(t) = g(1 - \exp(-C(t-n)y_1(t-n)))$$

$$R_i(t) = h(t)/(\exp(h(t)/r_i) - 1) \quad (i = 1,2)$$

$$Q(t) = (1 - \delta_d)^N h(t-N)$$

where g denotes the conditional probability that an infection results, r_i ($i = 1$, 2), the recovery rate for individuals from non-immune positive stage ($i = 1$), or from immune positive stage ($i = 2$), $n = 9$, the incubation period in vector, $N = 15$, the incubation period in human, $\delta_d = 1.18 \times 10^{-4}$, the death rate per person per day (The United Nations, 1992), C, the vectorial capacity. The scheme of the model is shown in **Fig. 1**. The detail of our model will be published elsewhere.
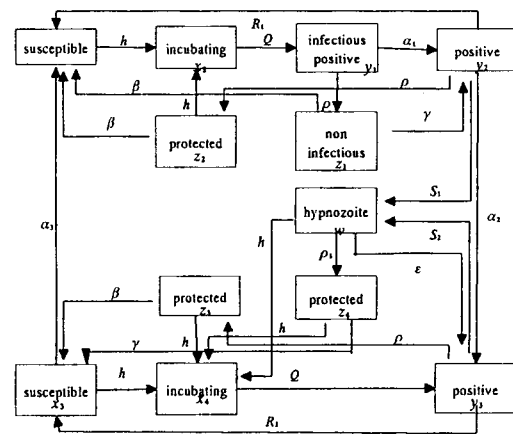
Figure 1 The scheme of the transmission model for *Plasmodium vivax* showing the transfers between the 12 epidemiological classes

2.5 MASS DRUG ADMINISTRATION

According to the malaria control project, the mass drug administration is attempted. For the radical cure of *P. vivax*, a patient is dosed with primaquine (15mg) during 14 days. We assume that a single dose of primaquine (15mg) kills hypnozoites in the liver at a proportion ρ_{h15}, namely $\rho_{h15} = 0.49$, satisfying the prescription of the radical treatment kills them more

than 99.99% and also assume that on primaquine ($45mg$) being administered to a patient, a proportion killing hypnozoites is $p_{h45} = 1 - (1 - p_{h15})^2 = 0.74$. The parameter d_{G6} denotes a rate of G6PD deficiency in the population. When primaquine ($45mg$) is administered to the population, we provide a proportion ρ of intake to ward off hemolysis as $\rho = 1 - d_{G6}$. The number of days d_1, d_2 of protection by chloroquine, primaquine are estimated as (Collett and Lye, 1987) :

$$d_1 = 10, d_2 = 15$$

Then the transfer rate β from z_1, z_2, z_3-class to x_1, x_3-class, γ from z_1, z_4-class to y_2, x_3-class are given by

$$\beta = 1 - \exp(-1/d_1) = 0.09516$$
$$\gamma = 1 - \exp(-1/d_2) = 0.06499$$

3 RESULTS AND DISCUSSIONS

3.1 EPIDEMIOLOGICAL PARAMETERS

The model involves 6 epidemiological parameters: the rate α_1 of loss of infectiousness per day, the rate α_2 of acquisition of immunity per day, the rate α_3 of loss of immunity per day, the recovery rate r_1, r_2, the susceptibility g. To fit the model for the field data of Vanuatu, we have determined the above parameters. Using the comparison between the observational age prevalence rate of $P.$ $vivax$ and the age prevalence curve described by the model, the parameters have been chosen as follows:

$$\alpha_1 = 0.0064, \alpha_2 = 0.0020, \alpha_3 = 0.000035$$
$$r_1 = 0.00055, r_2 = 0.021, g = 0.017$$

The value of χ^2 goodness-of-fit is estimated at 0.12 on 10 data points (Fig. 2). The probability p_h that a parasite stands still in the liver has been decided so as to realize the settled proportion of relapses in all vivax malaria in subsection 2.1:

$$p_h = 0.0026$$

Vectorial capacity has been established at C $=2.5$, so that the equilibrium of the overall parasite rate in the model coincides with the observational overall parasite rate.
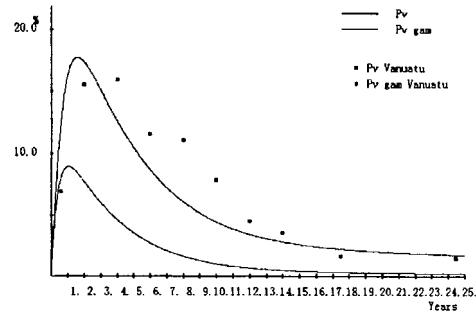

Figure 2 The comparison between the observational age prevalence rate of $P.$ $vivax$ and the age prevalence curve described by the model

3.2 SIMULATIONS

The transmission model for $P.$ $vivax$ which is constructed by the system of difference equations has been programed by FORTRAN 90 TM., which works on the Microsoft Windows TM. platform. From now on, we discuss about the results of various simulations.

1.   We investigate the transition of the prevalence for $P.$ $vivax$ malaria when the mass drug administration, say MDA, is put into practice. In the case that MDA is executed once or twice at an interval one week, both the overall parasite rate and the parasite rate of gametocyte return to the half level one year after the execution of MDA, and rebound beyond the initial level after two years, on the other hand, the rate of hypnozoite-carriers in the population still remains at 3% after MDA and leniently recovers at the equilibrium level after 4 or 5 years (Fig. 3). If the vectorial capacity reduces in the proportion of 10% simultaneously with MDA, the overall parasite rate, the rate of gametocyte and the rate of hypnozoite-carriers still increase towards the initial level, though

the recovery of the prevalence is slower than the case of the unchanged vectorial capacity. It seems that the execution of once or twice MDA has little effect on the control for *P. vivax* malaria.
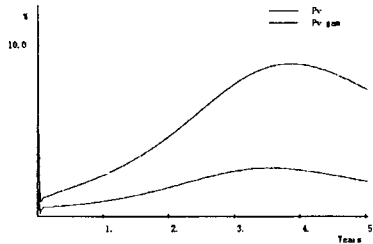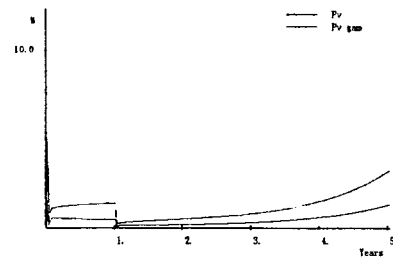

Figure 3 Variation of the overall parasite rate (%) of *P. vivax* and the parasite rate of *P. vivax* gametocyte under the rate 80% of intake compliance, when two times MDA is executed at an interval of one week

2.   We simulate the case of reiteration of MDA each year. In the case that two times MDA is repeated twice at an interval one year with the vectorial capacity diminishing in the proportion of 10%, both the overall parasite rate and the parasite rate of gametocyte still come back within 3 or 4 years, though these rates fairly reduce once after the last execution of MDA. (**Fig. 4**). The reiteration of MDA each year at an interval one year holds the prevalence low level, but once MDA is interrupted, the prevalence resurges. This method may not attain the eradication of *P. vivax* malaria.
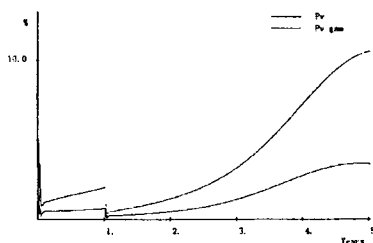
Figure 4 Variation of the overall parasite rate of *P. vivax* and the parasite rate of *P. vivax* gametocyte under the rate 80% of intake compliance, when two times MDA is executed at an interval of one week, the vectorial capacity diminishing in the proportion of 10%

3.   We simulate the strategy that the vectorial capacity is made lower, such as the distribution of bed nets. We assume that the vectorial capacity is decreasing gradually in the proportion of 30% after one month and two times MDA is executed twice at an interval of one year. In this case, the prevalence appears scarcely and remains this state for a few years. Then it is rising a little (**Fig. 5**). On the other hand, in the same situation as above, the prevalence of *P. falciparum* still keeps low level for a long time (Ishikawa et al., 1996). As the result, in an endemic region of both *P. falciparum* and *P. vivax*, only the resurgence of *P. vivax* comes in sight.

Figure 5 Variation of the overall parasite rate of *P. vivax* and the parasite rate of *P. vivax* gametocyte under the rate 80% of intake compliance, when two times MDA is executed at an interval of one week, the vectorial capacity diminishing in the proportion of 30%

4.   We treat the case of a full execution of MDA with the sufficient diminution of vectorial capacity to extinguish hypnozoite carriers and to eradicate *P. vivax* malaria. Kaneko et al. (1994) carried out nine times MDA of chloroquine 600 *mg*, primaquine 45mg and also distributed permethrin impregnated bed nets for all islanders in Aneityum Island of Vanuatu. We carry out the simulation in such a case. Here, we assume the vectorial capacity diminishes in the proportion of 30% by the distribution of bed nets. It shows that the prevalence disappears for several years and resurges a little after 4 years (**Fig. 6**). It seems that the resurgence shown in the figure is attributed to the model structure

which involves a factor of the loss of immunity for gametocyte. Unless the eradication is achieved, it would occur the resurgence. It is efficient to decrease of the vectorial capacity from a point of view to prevent the resurgence.
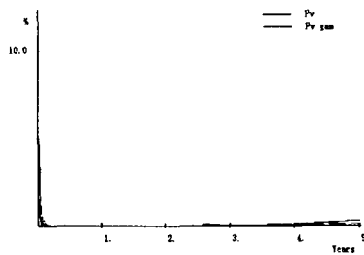
Figure 6 The simulation of the Aneityum context (Kaneko *et al.* 1994). Variation of the overall prevalence rate of *P. vivax* and the parasite rate of *P. vivax* gametocyte under the rate 88% of intake compliance, when nine times MDA is executed at an interval of one week, the vectorial capacity diminishing in the proportion of 30%

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