CHEMOTHERAPEUTIC CONTROL TRIAL OF *PLASMODIUM FALCIPARUM* WITH A COMBINATION OF CHLOROQUINE AND PRIMAQUINE ON SELECTIVE AGE GROUP IN A COASTAL VILLAGE OF NORTH SUMATRA, INDONESIA

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Abstract: Active case detection and treatment of malaria in a selective age group of children up to the age of fifteen was carried out to control malaria in a coastal village in North Sumatra, Indonesia from September 1983 to July 1984. A combination of chloroquine for three days with primaquine for three or five days was more effective than only chloroquine for three days. The spleen rate, the parasite rate of *P. falciparum*, the parasite formula of *P. falciparum* and the parasite density index were reduced by this activity. The parasite rate and the parasite formula of *P. falciparum* did not rise up in July 1984 (12.3% and 14.3%, respectively) without any vector control activities, although the parasite rate used to rise up to 27–61% and the parasite formula of *P. falciparum* was 50–86% in July to September every year (1980–1983). Most of the patients in July 1984 were considered to be recurrent or inadequately treated cases of *P. vivax*. Furthermore the density of *P. falciparum* gametocyte in pre-school children was higher than that in school children. We should pay a special attention to pre-school children to interrupt malaria transmission aiming at the gametocyte stage. Detection of glucose-6-phosphate dehydrogenase (G6PD) deficiency was done at the same time and malaria patient with G6PD deficiency was not given primaquine.

INTRODUCTION

Malaria control programme in these days is facing to some difficulties: drug resistant *Plasmodium falciparum*, insecticide resistant anopheline mosquitoes, behavioral change of the vectors, financial problem and so on. In North Sumatra, Indonesia, there is a report of *Anopheles sundaicus*, which is a vector in a coastal village, Perupuk, having exophilic character and few indoor resting behavior (Ikemoto, 1982). The residual house spraying with DDT could not reduce the parasite rate in Perupuk village, which was explained by the exophilic character and the lack of indoor resting behavior, although *A. sundaicus* in this village was still sensitive to DDT (Karoji, 1982). As malaria control by residual house spraying for adult mosquito is not

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expected in this village, the other method for larval control, using fishes and larvicides, is now under investigation (Ikemoto *et al.*, 1986; Imai *et al.*, 1987). We plan to apply the method for the field from 1987.

Prior to introduction of the new method for mosquito control, we carried out a trial of case detection and treatment of parasite carrier with chloroquine and primaquine to cut down the transmission of malaria at the gametocyte stage. Between two species of *Plasmodium*, *P. falciparum* and *P. vivax*, we chose *P. falciparum* carrier as the main target, especially its gametocyte carrier. Furthermore we concentrated our activity on the target group of children up to the age of fifteen. For the prevalence and the density of *P. falciparum* gametocyte in young generation are reported to be higher than those in adult in a malaria endemic area (Molineaux and Gramiccia, 1980). Primaquine is effective for clearing *P. falciparum* gametocyte, however, it has a harmful effect such as haemolytic crisis on glucose-6-phosphate dehydrogenase (G6PD) deficient persons. A simple screening test for G6PD deficiency was developed (Fujii *et al.*, 1984) and 3.9% of male was detected as G6PD deficient in North Sumatra (Matsuoka *et al.*, 1986). We carried out malaria detection and G6PD test at the same time in this chemotherapeutic trial.

MATERIALS AND METHODS

Study area and epidemiological consideration

The study site was Perupuk, a village of farmers and fishermen located at 3°17' North and 99°31' East on the northeast coast of Sumatra island, Indonesia. Population size was about 6,000, composing of 13 sub-villages (Lorongs). Two coastal sub-villages (Lorong I and Lorong II) with population size of 1,240 were chosen for this study because of their high parasite rates. The parasite rate increased from June and reached a peak, which was 29.1% in August, and thereafter declined sharply to 6.5% in January (Kanbara and Panjaitan, 1983). The parasite formula of *P. falciparum* also increased in June to September and decreased after October (Matsuoka *et al.*, 1984a) (Table 1).

Table 1 Changes of the parasite rate and the parasite formula of *P. falciparum* in Perupuk village, Indonesia from 1980 to 1983

Year	Low Endemic Season				High Endemic Season			
	Month	No. of blood exam.	Parasite Rate	Parasite formula of <i>P. falciparum</i>	Month	No. of blood exam.	Parasite Rate	Parasite formula of <i>P. falciparum</i>
1980		ND*	—	—	Aug. [†]	55	29.1%	56.3%
1981	Jan. [†]	93	6.5%	16.7%	Sep. [‡]	67	26.9%	50.0%
1982	Feb. [‡]	57	10.5%	33.3%	Aug. [‡]	111	61.3%	79.4%
1983		ND*	—	—	Jul. [§]	137	40.1%	85.5%

* Malariometric survey was not carried out.

[†] Data from Kanbara and Panjaitan, 1983.

[‡] Data from Itokawa and Panjaitan, 1982.

[§] Data from Matsuoka *et al.*, 1984b.

From September 1983 to July 1984, house-to-house survey was carried out for six times and spleen and blood examination was done for four times at an elementary school in Lorong II, which was the sole elementary school in Lorong I and II. The list of families in the two Lorongs was previously prepared by the aid of the heads of each Lorong and the list of the pupils in the elementary school was obtained from the schoolmaster. Since larval control method using fishes and larvicides was studied only in laboratory level during this period, any vector control activity was not carried out.

Chloroquine resistant strain of *P. falciparum* was not found *in vivo* in North Sumatra in 1973 (Dondero *et al.*, 1974), but *in vitro*, the resistant strain had been mentioned in North Sumatra in 1983 (WHO, 1986). Residents can buy chloroquine in pharmacy or dispensary when they need for malaria. Primaquine and the other anti-malarials had, however, never been administered in Perupuk village.

House-to-house visiting

House-to-house survey was carried out every six weeks. The main target was children, especially those up to the age of seven. Its population was 310. They were examined their spleen size on the standing position. History of fever was obtained from their parents. We only examined the blood of the child who had enlarged spleen and/or a history of fever within six weeks. Drug was started to administer to parasite positive child from the next day.

Spleen and blood examination in the elementary school

All pupils attending in the elementary school in Lorong II, which had six grades and about 300 pupils whose age were seven to fourteen, were examined of their spleen and blood every three months. Spleen size was examined on the standing position and blood sample was taken by finger pricks. Two drops of blood were taken; one drop was on a slide glass to prepare a thick film for the examination of malaria parasite and another drop was on cellulose paper for G6PD test. The result was recorded individually together with their name, age, body weight, history of fever, address and their father's name. A brief talk about malaria was given to pupils and anti-malarial drug was started to administer to the pupil of parasite positive within one week after the examination.

Parasite counts

Thick film was stained with 4% Giemsa solution (pH 7.4) after being dried well. Each slide was examined more than 200 microscopic fields under oil immersion before being considered as negative. The number of parasite per 2000 white blood cells was counted and total parasite count was estimated based on an assumption that white blood cell count was 8000 cells per μl of blood. The parasite density index was calculated by the method of Bruce-Chwatt (1958).

G6PD test

When blood was taken for parasite examination, another drop of blood ($\approx 20 \mu\text{l}$) was dripped onto pre-treated cellulose paper (P81, Whatman, England), which had been saturated with 100 mM Tris-HCl buffer, pH 6.5, containing 10 mM MgCl_2 , and dried. The cellulose paper with dried blood was punched out in the size of 6 mm in diameter and G6PD test was carried out by the method as previously described (Fujii *et al.*, 1984; Matsuoka *et al.*, 1986).

Treatment

Medication to the parasite carrier was done by the recipe as follows: on the 1st day 10 mg/kg of chloroquine and 0.25 mg/kg of primaquine, on the 2nd day the same amount as the 1st day, on the 3rd day 5 mg/kg of chloroquine and 0.25 mg/kg of primaquine. To the carrier of *P. vivax* 0.25 mg/kg of primaquine was added for more two days. We started to use primaquine after March 1984; only chloroquine was used by the three-day-schedule before February 1984. On the first treatment day all parasite carrier were given medicine by our medical staffs. After the second day the parasite carrier of under-7-year juvenile was given medicine by their parents, and pupil in the school was given medicine by the school teachers. Primaquine was not used for G6PD deficient individual, because there was a possibility of haemolytic crisis to G6PD deficient subjects. Only chloroquine was administered to them.

RESULTS

Pre-school children

The spleen rate of 0-7 years old was the highest at the first house-to-house visiting and decreased after the second visiting (Table 2). It kept at low level until the sixth visiting. The slide positivity rate ranged from 56 to 73% and did not show remarkable change throughout these activities. However, the parasite formula of *P. falciparum* decreased. Because *P. falciparum* and *P. vivax* ratio changed. The number of *P. falciparum* carrier was larger than that of *P. vivax* carrier in the first visiting. In the second and third visiting the number was same, then in the forth to sixth visiting the number of *P. vivax* carrier became higher. The species parasite density index of *P. vivax* decreased. The density of *P. falciparum* gametocyte and the number of its carrier also decreased (Figure 1).

School children

The same tendency was observed in pupils of the elementary school (Table 3). The spleen rate decreased. The parasite rate of *P. falciparum* also decreased. The parasite formula of *P.*

Table 2 Spleen and parasite examination of 0-7 years children obtained by house-to-house visiting in Lorong I and II, Perupuk village from September 1983 to May 1984

Month	No. of spleen exam.	Spleen enlarged (%)	No. of blood exam.	Plasmodium Positive				Parasite Formula of <i>P. fal.</i> (%)	Species Parasite Density Index of	
				Total (%)	<i>P. fal.</i>	<i>P. viv.</i>	mix		<i>P. fal.</i>	<i>P. viv.</i>
Sep.-Oct.	30	15 (50.0)	22	14 (63.6)	11	3	0	78.6	5.91	8.00
Nov.	101	14 (13.9)	23	16 (69.6)	8	8	0	50.0	4.88	5.78
Dec.-Jan.	128	15 (11.7)	19	13 (68.4)	6	6	1	53.8	4.14	5.43
Jan.-Feb.	124	10 (8.1)	22	16 (72.7)	1	15	0	6.3	9.00	1.96
Mar.-Apr.	141	12 (8.5)	17	12 (70.6)	4	7	1	41.7	5.40	3.00
Apr.-May	149	6 (4.0)	18	10 (55.6)	3	7	0	30.0	3.00	1.00
Total	673	72 (10.7)	121	81 (66.9)	33	46	2	43.2	5.09	3.51

Figure 1 Density of *P. falciparum* gametocyte in the case found by house-to-house visiting in Lorong I and II, Perupuk village. Fever positive (■, ●) means having a history of fever within six weeks; fever negative (□, ○) means no history of fever within six weeks.

Table 3 Spleen and parasite examination of pupils in the elementary school of Lorong II, Perupuk village from Oct. 1983 to Jul. 1984

	No. of total examination	Spleen enlarged (%)	Plasmodium Positive				Parasite Formula of <i>P. fal.</i> (%)	Species Parasite Density Index of	
			Total (%)	<i>P. fal.</i> (%)	<i>P. viv.</i> (%)	mix (%)		<i>P. fal.</i>	<i>P. viv.</i>
Oct. 1983	292	43 (14.3)	41 (14.0)	33 (11.3)	7 (2.4)	1 (0.3)	82.9	3.11	1.63
Jan. 1984	280	22 (7.9)	35 (12.5)	16 (5.7)	17 (6.1)	2 (0.7)	51.4	1.72	1.89
Apr. 1984	266	1 (0.4)	47 (17.7)	17 (6.4)	29 (10.9)	1 (0.4)	38.3	1.89	1.43
Jul. 1984	228	2 (0.9)	28 (12.3)	3 (1.3)	24 (10.6)	1 (0.4)	14.3	2.00	1.04
Total	1,066	68 (6.4)	151 (14.2)	69 (6.5)	77 (7.2)	5 (0.5)	49.0	2.43	1.44

falciparum remarkably decreased because the number of *P. falciparum* carrier decreased while the number of *P. vivax* carrier did not decrease. The parasite density index decreased. The density of *P. falciparum* gametocyte and the number of its carrier also decreased (Figure 2). The *P. falciparum* gametocyte carrier with high density had a tendency to have enlarged spleen

Figure 2 Density of *P. falciparum* gametocyte in the pupil found by blood examination in the elementary school of Lorong II, Perupuk village. Fever positive (■, ●) means having a history of fever within six weeks; fever negative (□, ○) means no history of fever within six weeks.

Figure 3 Distribution of *P. falciparum* gametocyte density by age in all cases obtained through the activities from September 1983 to July 1984.

and/or history of fever.

The younger the age, the higher was the gametocyte density of *P. falciparum* (Figure 3). Over 7 years old there was no case having *P. falciparum* gametocyte beyond 200/ μ l.

Treatment

The effect of therapy to parasite carrier is showed in Table 4. The rate of the cases from positive to positive in Term III (8.8%) was statistically lower than the average conversion rate of the cases from positive to positive in Term I and Term II (29.0%) ($\chi^2=4.13$; $p<0.05$). On the other hand, the rates of the cases from negative to positive in each Term were not different (9.3%, 14.4% and 13.5%, respectively). The majority of the positive cases in each Term were occurred in the negative group at three months before.

Table 4 Tri-monthly follow-up of malaria positive and negative case in school children

Period	Result of Initial Blood Examination		Treatment	Result of re-examination of blood after three months					Not examined
				Positive (%)	<i>P. fal.</i>	<i>P. viv.</i>	mix	Negative (%)	
Term I									
	Negative case	251		20 (9.3)	12	8	0	195 (90.7)	36
Oct. 1983	Positive case	41	Chloroquine	7 (21.2)	4	2	1	26 (78.8)	8
to	<i>P. falciparum</i>	33		6 (21.4)	3	2	1	22 (78.4)	5
Jan. 1984	<i>P. vivax</i>	7		1 (20.0)	1	0	0	4 (80.0)	2
	mix	1		0	0	0	0	0	1
Term II									
	Negative case	245		29 (14.4)	9	19	1	173 (85.6)	43
Jan. 1984	Positive case	35	Chloroquine	11 (37.9)	6	5	0	18 (62.1)	6
to	<i>P. falciparum</i>	16		5 (41.7)	3	2	0	7 (58.3)	4
Apr. 1984	<i>P. vivax</i>	17		4 (26.7)	3	1	0	11 (73.3)	2
	mix	2		2 (100)	0	2	0	0	0
Term III									
	Negative case	219		18 (13.5)	2	16	0	115 (86.5)	86
Apr. 1984	Positive case	47	Chloroquine and	3 (8.8)	1	1	1	31 (91.2)	13
to	<i>P. falciparum</i>	17		2 (18.2)	1	0	1	9 (81.8)	6
Jul. 1984	<i>P. vivax</i>	29	Primaquine	1 (4.5)	0	1	0	21 (95.5)	7
	mix	1		0	0	0	0	1 (100)	0

P. falciparum gametocyte carriers in the school were followed up of the blood after being given chloroquine and primaquine by the regimen and schedule as described above. No gametocyte was found in the blood on the day 7, 28 and 90 after the treatment (Table 5).

G6PD test

The result of G6PD test was showed in Table 6. Twelve cases were detected to be G6PD deficient in 286 males (4.0%). There was no G6PD deficient in female. One of the twelve cases was *P. vivax* positive. He was treated with only chloroquine for 3 days.

Table 5 Follow-up of *P. falciparum* gametocyte carriers treated with chloroquine and primaquine* in the school of Lorong II, Perupuk village from April to July 1984

Age	Sex	Number of <i>P. falciparum</i> gametocyte per μ l of blood			
		Day 0	Day 7	Day 28	Day 90
7	F	8	ND**	0	ND**
8	M	4	0	0	0
10	F	4	0	0	0
10	M	80	0	0	0
10	F	8	0	0	0
14	M	8	0	ND**	ND**
14	M	4	0	0	ND**

* All patients were G6PD normal and started to take chloroquine and primaquine from Day 1 by the principle described in Materials and Methods.

** Blood examination was not done.

Table 6 Prevalence of G6PD deficiency in Perupuk village, North Sumatra

Blood Obtained at	Male No. (%)		Female No.	
	G6PD deficient	G6PD normal	G6PD deficient	G6PD normal
House-to-house visits Feb.-May 1984	1 (2.0)	48 (98.0)	0	36
Blood exam. in the school of Lorong II, Apr. 1984	6 (4.2)	137 (95.8)	0	123
Blood exam. in the school of Lorong II, Jul. 1984	5 (4.7)	101 (95.3)	0	121
Total	12 (4.0)	286 (96.0)	0	280

DISCUSSION

Several kinds of approach such as vector control, vaccination, case control and others are considered to control malaria by cutting off the life cycle of the parasite. In case control there is a possibility to administer gametocytocidal drug to gametocyte carrier in order to intercept malaria transmission to mosquito. First of all we found that the carrier of *P. falciparum* gametocyte with high density had a tendency to have enlarged spleen and/or a history of fever prior to several weeks (Figures 1, 2). The density of *P. falciparum* gametocyte in pre-school children was higher than that in elementary school children in this village (Figure 3). Rieckmann *et al.* (1968, 1969) observed sporozoite in salivary gland of *A. stephensi* using human volunteer with *P. falciparum* gametocyte to study the effect of primaquine. After biting blood with *P. falciparum* gametocyte at the density of roughly over 100 per μ l of blood, sporozoites were appeared in salivary gland of the mosquitoes. However, under 100 per μ l of blood, no sporozoite was observed. According to their records, it is important for cutting the life cycle of *P. falciparum* at the gametocyte stage to give medicine to the carriers having gametocyte over 100 per μ l in the blood. Thus a special attention should be paid to pre-school children who have a tendency of high gametocyte density to interrupt malaria transmission aiming at the gametocyte stage.

We used primaquine to the carrier of *P. falciparum* gametocyte for three days, and demonstrated the effectiveness of primaquine to clear gametocyte in the blood (Table 5). Since we had few cases with the gametocyte density over 100 per μ l after we started administering primaquine, we did not follow up those cases. Further study is needed.

We compared the effect of treatment with chloroquine only and with chloroquine and primaquine (Table 4). The rates of the cases from negative to positive were not different in each Term but the rate of the cases from positive to positive in Term III was lower than that in Term I and II. This fact indicates that the condition of new infection and relapse was same in each Term and the effect of the treatment in Term III was better than that in Term I and II. We consider two reasons for this. The first is the effect of primaquine to exoerythrocytic form of *P. vivax*. The administration of primaquine for five days protected relapse of *P. vivax* in some degree. The second reason is the effect of drug combination with chloroquine and primaquine to asexual form of *P. falciparum*. In Perupuk village, chloroquine resistant strain of *P. falciparum* was found *in vitro* in 1983 (WHO, 1986). Drug combination was recommended in treatment of *P. falciparum* cases in the area where chloroquine resistant strain *in vitro* was reported (Onori *et al.*, 1985). Since the resistance to chloroquine *in vivo* was not so severe according to the result in Term I and II, the medication of the combination with chloroquine and primaquine was carried out.

After the case detection and treatment from October 1983 to July 1984 in Perupuk village, the spleen rate, the parasite rate of *P. falciparum*, the parasite formula of *P. falciparum* and the parasite density index were decreased (Tables 2, 3). In July 1984 the parasite rate did not rise up and remained 12.3% with the parasite formula of *P. falciparum* 14.3%. These rates in this season were statistically lower than those of former years ($p < 0.005$; $p < 0.025$). The majority of the positive cases of *P. vivax* in January, April and July 1984 were occurred in the negative group at three months before (Table 4). During three months, recurrence and new infection occurred in the negative group. Since the parasite density index of *P. vivax* was low (Table 2, 3), new infection cases might be few, based on the idea that new infection generally showed higher parasitemia than old one (Kanbara and Panjaitan, 1983). Primaquine or the other medicines for exoerythrocytic form of *P. vivax* had not been administered in Perupuk village, most of children had a possibility of recurrence of *P. vivax*. Therefore the parasite rate of *P. vivax* did not decrease within one year. If primaquine is applied routinely, the parasite rate of *P. vivax* will also decrease.

In administering primaquine, we should be careful of haemolysis in G6PD deficient persons. Primaquine is known of this problem, therefore, it is difficult to use primaquine in the field where malaria is endemic with a possibility of high occurrence of G6PD deficiency. According to Clyde (1981), in the treatment of malaria of G6PD deficient individuals, primaquine should not be given or it should be administered under supervision with close attention to the dosage and duration of treatment. In the present trial, we established a system of detecting both G6PD deficiency and malaria at the same time in order not to use primaquine for the malaria patients with G6PD deficiency. The G6PD screening method we employed this time needs no special equipment. The procedure is so simple and reading is so easy that hundreds of sample can be tested in one day. If the budget allows, malaria patient had better be examined for G6PD test before taking primaquine. It costs \$0.04 for test of one sample.

Case detection and treatment is one of the malaria control method in the area where malaria endemism is well confined. Perupuk village was composed of 13 sub-villages but the high

parasite rate was limited to two or three sub-villages near coast. The vector of *Anopheles sundaicus* was restricted to coastal area and showed patchy distribution along the coastal zone (Kanbara and Panjaitan, 1983). Therefore there is a possibility to control malaria by the case detection and treatment in this village. However these activities must be done periodically because the vector mosquitoes still remained. In Nicaragua, mass drug administration of both chloroquine and primaquine was carried out in the whole country. The incidence rates of *P. vivax* and *P. falciparum* infection were both reduced but the effects were limited. That is, the impact of the treatment on *P. vivax* cases lasted for four months and on *P. falciparum* for seven months (Garfield and Vermund, 1983). To keep the parasite rate at a low level, the activity of the case detection and treatment might be carried out at least two or three times in one year. In this trial, selective age group treatment resulted in a reduction of malaria indices without any vector control activities. Since larval control method using fishes and larvicides is investigated in Perupuk village, the new vector control method and the case detection and treatment will be combined in near future. It will be more effective for control malaria in this village.

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インドネシア国北スマトラ州の1村落における小児を
対象としたクロロキンとプリマキンによる
熱帯熱マラリアのコントロールの試み

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インドネシア国北スマトラ州の海岸に面した1村落で、15歳以下のマラリア患者を集中的に診断・治療することでマラリアのコントロールを試みた。この村には熱帯熱と三日熱マラリアが流行しており、例年7-9月には原虫陽性率は27~61%に上昇し、うち熱帯熱マラリア原虫が50~86%を占める(1980-83)。1983年9月から1984年7月まで、active case detectionを6回、学童の集団採血を4回行い、原虫陽性者にクロロキン3日間、プリマキン3日間(熱帯熱)または5日間(三日熱)を投与した。プリマキンの使用にあたってはG6PDのスクリーニングを同時に行い、欠損者には投与しなかった。

11カ月にわたる活動の間に、学童における脾腫率は14.3%から0.9%に、熱帯熱マラリア原虫陽性率は11.6%から1.7%に低下した($p<0.001$)。最終的に1984年7月の原虫陽性率は12.3%にとどまり、熱帯熱マラリア原虫はそのうち14.3%であった。この時の原虫陽性者の多くは低い原虫濃度の三日熱マラリアで、再発例または治療不十分例と考えられた。この村では熱帯熱マラリアの生殖母体保有者は低年齢層に多く、その血中濃度も高い傾向であった。小児を対象とした診断・治療活動により生殖母体保有者が効率よく治療され、蚊による伝播も低下したものと考察した。

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