EVALUATION OF ANTIMALARIAL DRUGS IN INDONESIA, 1981 - 1995

Emiliana Tjitra[*], Suriadi Gunawan[*], Ferdinand Laihad[**], Harijani Marwoto[*], Sekartuti Sulaksono[*], Sumarjati Arjoso[*], Thomas L Richie[***] dan Novianty Manurung[***]

ABSTRAK

EVALUASI OBAT ANTIMALARIA DI INDONESIA, 1981 - 1995

Telah dilakukan evaluasi obat-obat antimalaria in-vitro *dan* in-vivo *untuk menentukan pola resistensi dan memanfaatkan data ini untuk melakukan sistem pengamatan yang efektif. Semua penelitian pengobatan dan pencegahan malaria di lapangan dan rumah sakit dalam kurun waktu 1981 - 1995 ditelaah.*

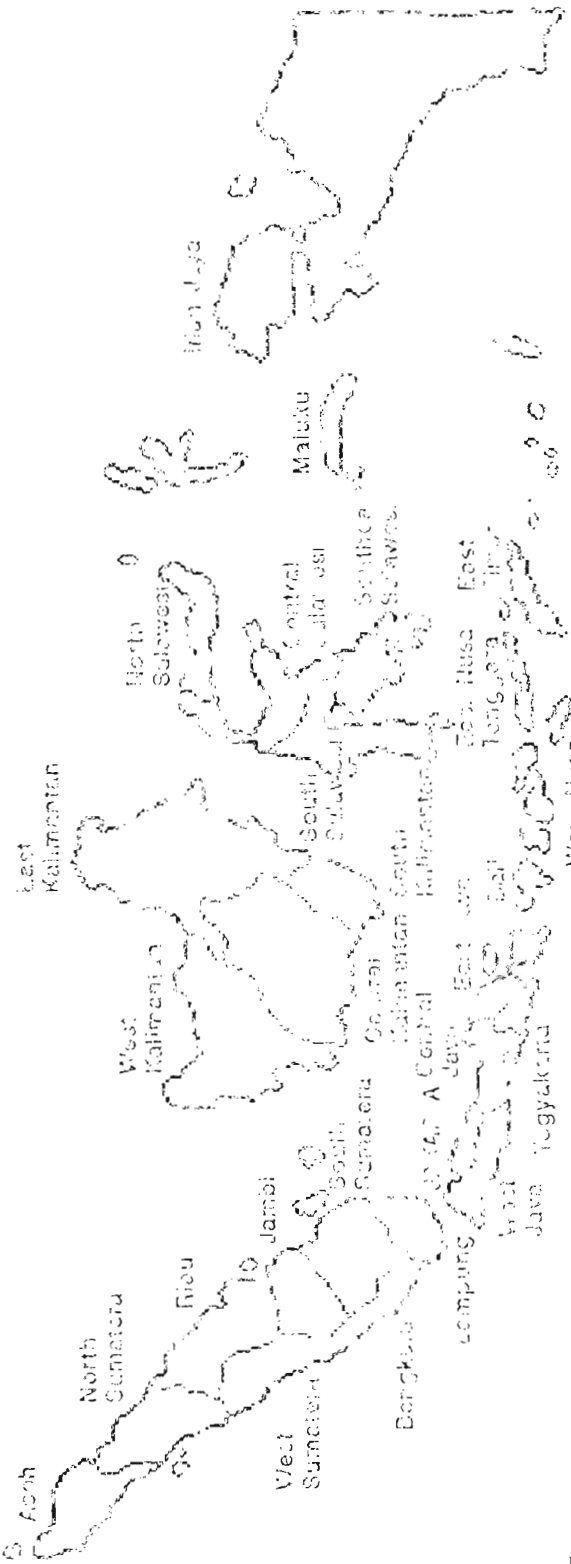
Pertama kali kasus resistensi P. falciparum *terhadap klorokuin ditemukan di Kalimantan Timur pada tahun 1973, dan telah menyebar ke seluruh (27) propinsi Indonesia dengan derajat RI - RIII. Pada saat ini, resistensi RIII telah didapatkan di 20 propinsi, sedangkan pada tahun 1981-1985 hanya di 4 propinsi. Kasus malaria vivaks resisten klorokuin dilaporkan pertama kali dari Sumatera Utara (P. Nias) pada tahun 1991, dan kemudian ditemukan di Irian Jaya (41%), Sumatera Utara (13%), Nusa Tenggara Timur (8%), Sulawesi Utara (2%) dan Jakarta (laporan kasus yang didapatkan dari transfusi darah). Malaria falsiparum yang tercatat resisten sulfadoksin-pirimetamin didapatkan di 11 propinsi dengan derajat RI - RII.* P. falciparum *resisten* in-vitro *juga didapatkan terhadap kina (6 propinsi), meflokuin (5 propinsi) dan amodiakuin (4 propinsi). Beberapa obat antimalaria baru (meflokuin, halofantrin dan derivat artemisinin) telah diteliti dan ternyata efektif untuk pengobatan malaria tanpa komplikasi. Penelitian pencegahan menunjukkan angka pencegahan untuk klorokuin 41-92%, sulfadoksin- pirimetamin 98%, primakuin 89-92%, doksisiklin 99% dan meflokuin 100 %. Efek samping obat-obat antimalaria tersebut umumnya ringan.*

Di Indonesia, penyebaran malaria falsiparum resisten klorokuin RIII dan malaria falsiparum resisten multidrug *merupakan masalah kesehatan masyarakat yang serius dan tantangan dalam pengobatan. Demikian pula kehadiran malaria vivaks resisten klorokuin menimbulkan masalah baru yang lain. Oleh sebab itu obat-obat antimalaria yang didistribusikan sebaiknya dikemas per paket untuk dosis obat pengobatan yang lengkap dengan keterangan cara minum obat yang jelas. Dengan demikian dapat dicegah pemberian dosis pengobatan yang tidak cukup dan berkembangnya resistensi obat. Selama obat antimalaria baru belum tersedia di Indonesia, perlu dilakukan penelitian perbaikan efikasi obat antimalaria yang sudah ada. Obat pencegahan alternatif yang aman dan efektif untuk anak-anak, ibu hamil dan menyusui juga perlu diteliti.*

INTRODUCTION

Indonesia is an archipelago consisting of six main islands and 13,767 smaller islands. There are 27 provinces, 241 districts and 67,033 villages with a total population of 195.3 million in 1994 (Figure 1)[1].

* National Institute of Health Research and Development, Ministry of Health, Jakarta.
** Directorate General of Communicable Disease Control & Environmental Health, Ministry of Health, Jakarta.
*** Naval Medical Research Unit No 2, Jakarta.


Aceh
North Sumatera
Riau
Jambi
West Sumatera
South Sumatera
Bengkulu
Lampung
West Kalimantan
East Kalimantan
Central Kalimantan
South Kalimantan
Java
Bali
East Nusa Tenggara
West Nusa Tenggara
North Sulawesi
Central Sulawesi
Southeast Sulawesi
South Sulawesi
Maluku
Irian Jaya

Malaria remains a major public health problem, particularly outside of Java-Bali, with province-wide *Parasite Rates* of 4.1 - 5.2% and *Slide Positivity Rates* of 29.2 - 44.3% during the period 1989 to 1993[2,3].

Since malaria vaccine is not available, management of the disease is the most important activity to control malaria. To support disease management, the Indonesian Ministry of Health has recommended rational malaria treatment policy that is based on the national malaria control programme.

Chloroquine is the standard antimalarial drug for chemoprophylaxis, clinical malaria treatment and the blood schizontocide component of radical treatment. Sulfadoxine-pyrimethamine and quinine are used as alternative antimalarial drugs for radical treatment of falciparum malaria in chloroquine resistant areas. Parenteral quinine is a life-saving antimalarial drug for severe and complicated malaria. Primaquine is a supplement to standard antimalarial drugs for radical treatment. Supportive therapy is given depending on clinical manifestations of organ dysfunction[4].

Several new antimalarial drugs, mefloquine, halofantrine and artemisinin derivatives have been studied for the treatment of falciparum malaria, vivax malaria and severe or complicated malaria, in preparation for providing alternative antimalarial drugs.

Treatment failure may be due to the increasing problem of drug resistance. Resistance to antimalarial drugs, especially chloroquine, has become a serious problem in case management throughout Indonesia. Collection of baseline data and an appropriate monitoring system for drug efficacy and resistance are required for reassessment and revision of national guidelines for malaria treatment.

All evaluations of antimalarial drugs during the period 1981 to 1995 in Indonesia are reviewed in this paper to determine the pattern of drug resistance and to create a data base for an effective monitoring system and revise treatment guidelines.

DEFINITION AND ASSESSMENT OF DRUG RESISTANCE

In malaria, drug resistance is defined as the ability of a parasite strain to survive and/or to multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within the limits of tolerance of the subjects[5]. This definition is commonly applied to the resistance of *Plasmodium falciparum* to the blood schizontocides. It has been extended to other species of malaria parasites such as *P. vivax*.

The susceptibility of *P. falciparum* to chloroquine and other antimalarial drugs was assessed by *in-vitro* and *in-vivo* sensitivity testing. Previously, the macrotest was used for *in-vitro* sensitivity testing of *P. falciparum* to chloroquine. Since 1984, the microtest has replaced the macrotest for testing chloroquine, sulfadoxine-pyrimethamine, quinine, amodiaquine and mefloquine. Interpretation was made according to the WHO guideline (Table 1)[6,7].

In most cases, field tests (28 days) were performed for *in-vivo* sensitivity testing. The resistance grading system is based on the response to normally recommended doses of chloroquine (25 mg base/kg bw in three days). This grading is also used for other blood schizontocides. The response of the parasites to blood schizontocides ranges from S to RIII (Table 2)[5].

Table 1. Concentration of several blood schizontocidal drugs indicating *in-vitro P. falciparum* resistance[6,7].

Test drug	Schizonts still grow at
Chloroquine	>= 8 pmol
Sulfadoxine/pyrimethamine	>= 1000 / 12.5 pmol
Quinine	>= 256 pmol
Amodiaquine	>= 4 pmol
Mefloquine	>= 64 pmol

Table 2. Grading of *in-vivo* resistance of asexual parasites of *P. falciparum* to blood schizontocidal drugs[5].

Response	Recommended symbol	Evidence
Sensitive	S	Clearance of asexual parasitaemia within 7 days of initiation of treatment, without subsequent recrudescence.
Resistance	RI	Clearance of asexual parasitaemia as in sensitivity, followed by recrudescence within 28 days (42 days for SP and mefloquine).
	RII	Marked reduction (75 percent or more) of asexual parasitaemia within 48 hours, but no clearance by day 7.
	RIII	No marked reduction of parasitaemia (less than 75 percent) or an increase of asexual parasitaemia in 48 hours.

The blood concentration of chloroquine adequate for treatment has not yet been firmly established. Currently, chloroquine resistance to *P. vivax* is based on the whole blood *Minimal Effective Concentration* (MEC) of chloroquine. A viable asexual parasitaemia of *P. vivax* with

>= 100 ng/ml chloroquine plus desethyl-chloroquine in whole blood demonstrates resistance[8].

DRUG SENSITIVITY MONITORING SYSTEM

Since 1979, *in-vitro* and *in-vivo* drug sensitivity assays have been conducted in the major foci of suspected chloroquine resistance areas by the Subdirectorate of Malaria Control and by Local Health Authorities. Data obtained serve as an early warning of emerging problem of drug failure. The results of other field and clinical studies undertaken by the National Institute of Health Research and Development, by the Faculty of Medicine of the University of Indonesia and by the Naval Medical Research Unit 2 Jakarta have been very useful in supporting or clarifying preliminary reports and in early detection of treatment failures.

In recent years, studies of alternative drugs such as mefloquine, halofantrine and artemisinin derivatives have been performed. Studies on new antimalarial drugs regimens, such as chloroquine plus doxycycline, are being carried out.

EMERGENCE AND SPREADING OF DRUG RESISTANCE

The first evidence of *P. falciparum* resistant to 4-amino-quinolines was noted from Venezuela (1959) and Columbia (1960), in South America[9]. The first case reports of recurrence of *P. vivax* parasitaemia after various doses of chloroquine were reported from Papua New Guinea (1989-1992)[10-14]. It was then reported from other countries including Indonesia.

CHLOROQUINE RESISTANCE

According to the policy of the Indonesia Ministry of Health, chloroquine (4-quinoline-amino group) is used as first line treatment. The first case of chloroquine resistant *P. falciparum* infection was reported from Kutai - East Kalimantan in 1973[15]. Thereafter (1974-1979) more cases have been recorded from East Kalimantan and Irian Jaya[15-27].

During 1981 - 1995, *in-vitro* sensitivity testing of *P. falciparum* to chloroquine had been performed in 24 provinces, except in West Sumatera, South Sumatera and DI-Yogyakarta provinces (Annex 3). All of the 24 provinces had resistant cases, although resistant cases from DKI-Jakarta and Bali were imported cases. The number of samples tested per province ranged from 3 to 183 isolates in 1981-1985, 1 to 62 isolates in 1986-1990, and 1 to 159 isolates in 1991-1995. The percentage of resistant cases in 1981-1985, 1986-1990 and 1991- 1995 were 11 - 100 %, 11 - 100 %, and 23 - 100 %, respectively[16,28-42] (Table 3).

Twenty five of the 27 provinces (except Central Kalimantan and Bali) carried out *in-vivo* sensitivity testing of *P. falciparum* to chloroquine. Only West Java has not reported any resistant cases (Table 4). The numbers of patients examined per province in 1981-1985, 1986-1990 and 1991-1995 were 1 - 26 cases, 2 - 105 cases, and 1 -214 cases, respectively. Of those cases, 4 - 100 %, 10 - 100 %, and 12 - 100 % were resistance cases at level of RI - RIII. Currently, RI, RII and RIII resistance affects 19, 21 and 20 provinces compared to 8, 6 and 4 provinces in 1981-1985, and 13, 17 and 14 in 1986-1990[16,28,30,38-50] (Table 5).

Table 3. ***In-vitro P. falciparum*** **resistant to chloroquine in Indonesia, 1981 - 1995[16,28-42].**

	81 - 85	86 - 90	91 - 95
Number of provinces tested (%)*	22 (81)	13 (48)	6 (22)
Number of samples tested per province (range)	3 - 183	1 - 152	1 - 159
Number of provinces reporting resistance (%)**	22 (100)	13 (100)	5 (83)
Percentage of resistant cases (range)	11 - 100	11 - 100	23 - 100
Cumulative number of provinces reporting resistance (%)*	22 (81)	24 (89)	24 (89)

* percent by total number of provinces (27)
** percent by number of provinces tested.

Table 4. Percentage of ***P. falciparum*** **resistant to chloroquine in Indonesia, 1981 -1995[16,28,30,38-50].**

No.	Province	*In-vitro*			*In-vivo*					
		81 - 85	86 - 90	91 - 95	81 - 85		86 - 90		91 - 95	
1.	Aceh	71 (39/55)	73 (8/11)		0 (0/1)		27 (3/11)	2 RII 1 RIII	0 (0/1)	
2.	North Sumatra	69 (9/13)			11 (1/9)	1 RII	80 (4/5)	4 RII	61 (17/28)	12 RI 3 RII 2 RIII
3.	Riau	27 (4/15)	78 (14/18)	100 (1/1)	0 (0/2)		33 (3/9)	1 RII 2 RIII	75 (3/4)	2 RII 1 RIII
4.	West Sumatra						12 (1/8)	1 RI	67 (4/6)	4 RIII
5.	Bengkulu		100 (7/1)	0 (0/1)			67 (10/15)	4 RI 4 RII 2 RII	12 (4/33)	2 RI 1 RII 1 RIII
6.	Jambi		11 (1/9)				45 (9/20)	2 RI 1 RII 6 RIII		
7.	South Sumatra				100 (2/2)	2 RI	50 (2/4)	2 RII		
8.	Lampung	88 (7/8)			100 (2/2)	2 RI	65 (20/31)	2 RI 13 RII 5 RII		
9.	West Java	59 (13/22)							0 (0/1)	
10.	DKI-Jakarta	60 (6/10)	100 (1/1)		62 (13/21)	12 RI 1 RIII	100 (2/2)	2 RI		

No.	Province	*In-vitro*			*In-vivo*					
		81 - 85	86 - 90	91 - 95	81 - 85		86 - 90		91 - 95	
11.	Central Java	51 (93/183)	24 (12/50)		60 (12/20)	10 RI 2 RII	35 (37/105)	13 RI 14 RII 10 RIII	48 (13/27)	1 RI 7 RII 5 RIII
12.	D.I Yogyakarta								57 (12/21)	1 RI 5 RII 6 RIII
13.	East Java	26 (18/70)			33 (4/12)	1 RI 1 RII 2 RIII			0 (0/1)	
14.	West Kalimantan	27 (4/15)					0 (0/8)		12 (1/8)	1 RI
15.	Central Kalimantan	25 (1/4)								
16.	South Kalimantan	11 (3/27)					33 (1/3)	1 RII		
17.	East Kalimantan	67 (8/12)	66 (41/62)	61 (41/67)	67 (2/3)	1 RI 1 RII	50 (1/2)	1 RI		
18.	Bali	67 (4/6)								
19.	West Nusa Tenggara	48 (13/27)	40 (2/5)				71 (10/14)	2 RI 4 RII 4 RIII	13 (6/45)	2 RI 3 RII 1 RIII
20.	East Nusa Tenggara	73 (47/64)	50 (1/2)		24 (5/21)	5 RII	0 (0/8)		50 (27/54)	18 RI 3 RII 6 RIII
21.	East Timor	100 (9/9)	78 (118/152)		21 (4/19)	1 RI 2 RII 1 RIII	25 (17/68)	1 RI 4 RII 12 RIII	100 (1/1)	1 RI
22.	North Sulawesi	67 (6/9)	50 (6/12)	23 (9/39)	25 (1/4)	1 RIII	44 (16/36)	4 RI 7 RII 5 RIII	31 (16/52)	9 RI 5 RII 2 RIII
23.	Central Sulawesi	33 (1/3)		25 (1/4)			67 (4/6)	3 RI 1 RIII	16 (3/19)	1 RII 2 RIII
24.	South Sulawesi	35 (17/48)	100 (10/10)		4 (1/26)	1 RI	33 (18/55)	1 RI 15 RII 2 RIII	56 (10/18)	3 RI 5 RII 2 RIII
25.	South East Sulawesi	67 (2/3)					10 (1/10)	1 RIII	56 (18/32)	1 RI 14 RII 3 RIII
26.	Maluku	73 (8/11)			0 (0/2)				35 (8/23)	2 RI 6 RIII
27.	Irian Jaya	29 (2/7)	84 (27/32)	82 (130/159)			53 (51/96)	30 RI 21 RIII	71 (151/214)	67 RI 61 RII 23 RIII

Table 5. *In-vivo P. falciparum* resistant to chloroquine in Indonesia, 1981 - 1995[16,28,30,38-50].

	81 - 85	86 - 90	91 - 95
Number of provinces tested (%)*	14 (52)	21 (78)	18 (67)
Number of samples tested per province (range)	1 - 26	2 - 105	1 - 214
Number of provinces reporting resistance (%)**	11 (79)	19 (90)	16 (89)
Percentage of resistant cases (range)	4 - 100	10 - 100	12 - 100
Cumulative number of provinces reporting resistance (%)*	11 (41)	20 (74)	24 (89)
Number of provinces reporting RI resistance (%)***	8 (73)	12 (63)	12 (75)
Percentage of RI resistance cases (range)	25 - 100	6 - 100	6 - 100
Cumulative number of provinces reporting RI resistance (%)*	8 (30)	13 (48)	19 (70)
Number of provinces reporting RII resistance (%)***	6 (55)	14 (74)	13 (81)
Percentage of RII resistance cases (range)	17 - 100	11 - 100	19 - 78
Cumulative number of provinces reporting RII resistance (%)*	6 (22)	17 (63)	21 (78)
Number of provinces reporting RIII resistance (%)***	4 (36)	13 (68)	14 (87)
Percentage of RIII resistance cases (range)	8 - 100	11 - 100	6 - 100
Cumulative number of provinces reporting RIII resistance (%)*	4 (15)	14 (52)	20 (74)

* percent by total number of provinces (27)
** percent by number of provinces tested
*** percent by number of provinces reporting resistance.

Combining *in-vitro* and *in-vivo* results, the overall number of provinces reporting *P. falciparum* resistance to chloroquine was 27 provinces. In 3 provinces (West Java, Central Kalimantan and Bali) only *in-vitro* resistance was found, and another 3 provinces (West Sumatera, South Sumatera and DI-Yogyakarta) only reported *in-vivo* resistance. The other 21 provinces reported both *in-vitro* and *in-vivo* resistance. Almost all levels of resistance were present throughout Indonesia.

The first case of chloroquine resistant *P. vivax* was reported from Nias island - North Sumatera in 1991[51]. In the last five years (1991-1995), documented chloroquine resistant vivax malaria was present in 5 of 7 provinces tested. The number of patients examined per province was 1-126. The resistant cases were 41 % in Irian Jaya (Arso, Oksibil, Nabire and Timika), 13 % in North Sumatera (Nias), 8 % in East Nusa Tenggara (Sikka) and 2 % in North Sulawesi (Tomohon and Lembe). Another resistant case acquired by blood transfusion was reported from DKI- Jakarta. No resistant cases were found in Central Java and West Nusa Tenggara. Most of the resistant cases were RI resistance (Table 6, and Table 7)[48,50-4].

Table 6. Percentage of *P. vivax* resistant to chloroquine in Indonesia, 1991 -1995[48,50-4].

No.	Province	91 - 95	Study's site (year)
1.	North Sumatra	13 (3/23)	Nias (1995)
2.	DKI-Jakarta	100 (1/1)	Jakarta (transfusion vivax malaria (1993)
3.	D.I-Yogyakarta	0 (0/11)	Kokap (1994)
4.	West Nusa Tenggara	0 (0/20)	Sekotong (1995)
5.	East Nusa Tenggara	8 (2/16)	Sikka (1995)
6.	North Sulawesi	2 (1/53)	Tomohon (1993) Lembe (1995)
7.	Irian Jaya	41 (52/126)	Arso (1991, 1993) Oksibil (1994) Nabire (1995) Timika (1995)

Table 7. *In-vivo P. vivax* resistant to chloroquine in Indonesia, 1991 - 1995[48,50-4].

	91 - 95
Number of provinces tested (%)*	7 (26)
Number of samples tested per province (range)	1 - 126
Number of provinces reporting resistance (%)**	5 (71)
Percentage of resistant cases (range)	2 - 41
Cumulative number of provinces reporting resistance (%)*	5 (19)

* percent by total number of provinces (27)
** percent by number of provinces tested.

SULFADOXINE-PYRIMETHAMINE RESISTANCE

Sulfadoxine-pyrimethamine combination is recommended as a second line drug. Since 1979, *P. falciparum* resistant to this drug has been reported[25]. Thereafter, only few studies have been performed.

During 1981-1995, *in-vitro* sensitivity testing of *P. falciparum* to sufadoxine-pyrimethamine was performed in 13 provinces. Eleven provinces reported resistance: Aceh (67 %), North Sumatera (100 %), Riau (80 %), and Lampung (100 %) in 1981-1985; Central Java (22 and 71 %) in 1981-1985 and 1986-1990; East Kalimantan (85 and 100 %) in 1986-1990 and 1991-1995; East Timor (33 %) in 1986-1990; North Sulawesi (60 %) and Central Sulawesi (50 %) in 1991-1995; South Sulawesi (58 %) in 1981-1985; and Irian Jaya (81 and 82 %) in 1986-1990 and 1991-1995. The other provinces, Bengkulu and DKI-Jakarta, had not reported resistance (Annex 5). The number of samples tested per provinces in 1981-1985, 1986-1990, and 1991-1995 ranged from 2 to 38 isolates, 1 and 29 isolates, and 1 and 77 isolates, respectively. The percentage of those resistant cases were 58-100 %, 22-100 % and 50-85 %, respectively (Table 8)[16,31,34-9,41-2,45,55-6].

In-vivo sensitivity testing of *P. falciparum* to sulfadoxine-pyrimethamine was carried out in 9 provinces (Aceh, North Sumatera, Riau, Lampung, Central Java, East Timor, South Sulawesi, South-East Sulawesi and Irian Jaya) in 1981-1985. The number of patients examined per provinces was 1 - 119. Four provinces: Central Java, East Timor, South Sulawesi and Irian Jaya reported resistances of, respectively, 12 % (14/119) (RI-RII), 100 % (1/1) (RI), 2 % (1/62) (RII), and 2 % (1/41) (RII) (Table 9 and Table 10)[16,44,55,57-9].

Combining *in-vitro* and *in-vivo* results, the total number of provinces reporting *P. falciparum* resistance to sulfadoxine-pyrimethamine was 11 out of the 14 provinces where tests were performed. Seven provinces only reported resistance by *in-vitro* test and the other 4 provinces reported resistance by both *in-vitro* and *in-vivo* tests at level of RI - RII. Of the 3 provinces reporting no resistance, 2 provinces (Bengkulu and DKI-Jakarta) only conducted *in-vitro* sensitivity test and 1 province (Southeast Sulawesi) only *in-vivo* sensitivity test.

QUININE RESISTANCE

Quinine is a life-saving antimalarial for malaria treatment. Until recently, there has been no reported *in-vivo* quinine resistance by falciparum malaria. However, several isolates have shown *in-vitro* resistance.

In-vitro sensitivity testing of *P. falciparum* to quinine was performed during 1981-1985, 1986-1990 and 1991-1995 in 4, 8 and 6 provinces, with the number of isolates tested per province ranging from 1 to 17, 1 to 31, and 1 to 132 isolates. *In-vitro* resistance was reported from West Java (one case in 1981-1985), Central Java (one case in 1981-1985), East Kalimantan (3 % or 2/60 in 1991-1995), East Nusa Tenggara (one case in 1981-1985), Central Sulawesi (25 % or 1/4 in 1991-1995) and Irian Jaya (29 % or 5/17 in 1981-1985). No resistance isolates were found in Riau, Bengkulu, DKI-Jakarta, East Timor, North Sulawesi, and South Sulawesi (Table 11 and Table 12)[16,34-9,41-2,45,60-1].

Table 8. ***In-vitro P. falciparum*** **resistant to sulfadoxine pyrimethamine in Indonesia, 1981 - 1995**[16,31,34-9,41-2,45,55-6].

	81 - 85	86 - 90	91 - 95
Number of provinces tested (%)*	6 (22)	5 (19)	6 (22)
Number of samples tested per province (range)	2 - 38	1 - 29	1 - 77
Number of provinces reporting resistance (%)**	6 (100)	4 (80)	4 (67)
Percentage of resistant cases (range)	58 - 100	22 - 100	50 - 85
Cumulative number of provinces reporting resistance (%)*	6 (22)	9 (33)	11 (41)

* percent by total number of provinces (27)
** percent by number of provinces tested.

Table 9. Percentage of ***P. falciparum*** **resistant to sulfadoxine-pyrimethamine in Indonesia, 1981 - 1995**[16,44,55,57-9].

No.	Province	*In-vitro*			*In-vivo*	
		81 - 85	86 - 90	91 - 95	81 - 85	
1.	Aceh	67 (14/21)			0 (0/32)	
2.	North Sumatra	100 (2/2)			0 (0/6)	
3.	Riau	80 (12/15)		0 (0/1)	0 (0/36)	
4.	Bengkulu			0 (0/1)		
5.	Lampung	100 (3/3)		0 (0/3)		
6.	DKI - Jakarta		0 (0/1)			
7.	Central Java	71 (27/38)	22 (2/9)		12 (14/119)	3 RI 11 RII
8.	East Kalimantan		100 (29/29)	85 (45/53)		
9.	East Timor		27 (3/11)		100 (1/1)	1 RI
10.	North Sulawesi			60 (12/20)		
11.	Central Sulawesi			50 (1/2)		
12.	South Sulawesi	58 (11/19)			2 (1/62)	1 RII
13.	Southeast Sulawesi				0 (0/2)	
14.	Irian Jaya		82 (9/11)	81 (62/77)	2 (1/41)	1 RII

Tabel 10. *In-vivo P. falciparum* resistant to sulfadoxine-pyrimethamine in Indonesia, 1981 - 1995[16,44,55,57-9].

	81 - 85
Number of provinces tested (%)*	9 (33)
Number of samples tested per province (range)	1 - 119
Number of provinces reporting resistance (%)**	4 (44)
Percentage of resistant cases (range)	2 - 100
Cumulative number of provinces reporting resistance (%)*	4 (15)
Number of provinces reporting RI resistance (%)***	2 (50)
Percentage of RI resistance cases (range)	21 - 100
Cumulative number of provinces reporting RI resistance (%)*	2 (7)
Number of provinces reporting RII resistance (%)***	3 (75)
Percentage of RII resistance cases (range)	79 - 100
Cumulative number of provinces reporting RII resistance (%)*	3 (11)
Number of provinces reporting RIII resistance (%)***	0
Percentage of RIII resistance cases (range)	0
Cumulative number of provinces reporting RIII resistance (%)*	0

* percent by total number of provinces (27)
** percent by number of provinces tested
*** percent by number of provinces reporting resistance.

Of the 12 provinces tested, only 6 provinces (West Java, Central Java, East Kalimantan, East Nusa Tenggara, Central Sulawesi and Irian Jaya) presented *in-vitro P. falciparum* resistance to quinine. After 1981-1985, 3 provinces which have reported *in-vitro* resistance (West Java, Central Java and Irian Jaya) no longer reported resistance cases. In East Kalimantan where no resistance was present in 1986-1990, *in-vitro* resistance was reported in 1991-1995.

SENSITIVITY OF OTHER BLOOD SCHIZONTOCIDES

Amodiaquine resistance

Amodiaquine is a 4 amino-quinoline antimalarial drug. This drug should be at least as effective as chloroquine. In Indonesia, amodiaquine is not available and has never been used. However, several *in-vitro P. falciparum* sensitivity tests to this drug have been performed.

Table 11. Percentage of *in-vitro P. falciparum* resistant to quinine in Indonesia, 1981 - 1995[16,34-9,41-2,45,60-1].

No.	Province	81 - 85	86 - 90	91 - 95
1.	Riau		0 (0/8)	0 (0/1)
2.	Bengkulu			0 (0/1)
3.	West Java	100 (1/1)	0 (0/2)	
4.	DKI-Jakarta		0 (0/1)	
5.	Central Java	100 (1/1)	0 (0/6)	
6.	East Kalimantan		0 (0/31)	3 (2/60)
7.	East Nusa Tenggara	100 (1/1)		
8.	East Timor		0 (0/8)	
9.	North Sulawesi			0 (0/37)
10.	Central Sulawesi			25 (1/4)
11.	South Sulawesi		0 (0/6)	
12.	Irian Jaya	29 (5/17)	0 (0/10)	0 (0/132)

Table 12. *In-vitro P. falciparum* resistant to quinine in Indonesia, 1981 - 1995[16,34-9,41-2,45,60-1].

	81 - 85	86 - 90	91 - 95
Number of provinces tested (%)*	4 (15)	8 (30)	6 (22)
Number of samples tested per province (range)	1 - 17	1 - 31	1 - 132
Number of provinces reporting resistance (%)**	4 (100)	0	2 (33)
Percentage of resistant cases (range)	29 - 100	-	3 - 25
Cumulative number of provinces reporting resistance (%)*	4 (15)	4 (15)	6 (22)

* percent by total number of provinces (27)
** percent by number of provinces tested.

In 1981-1985, only Irian Jaya was tested (5 samples). However in 1986-1990, 5 provinces (DKI- Jakarta, East Kalimantan, East Timor, South Sulawesi and Irian Jaya) were tested with the number of samples tested ranging from 1 - 27. Only one province (East Kalimantan) was tested (57 samples) in 1991-1996.

Of the 5 provinces tested, 4 provinces (East Kalimantan, East Timor, South Sulawesi and Irian Jaya) had resistance to amodiaquine (12 - 100 %). However, previously (1981-1985), no amodiaquine resistance was found in Irian Jaya (Table 13 and Table 14)[16,34-5,42,61].

Mefloquine resistance

Mefloquine, a synthetic 4-quinoline methanol, is a relatively new antimalarial drug. This drug has not yet been registered in Indonesia. Since 1982, several *in-vitro* and *in-vivo P. falciparum* sensitivity to this drug has been performed.

Table 13. Percentage of *in-vitro P. falciparum* resistant to amodiaquine in Indonesia, 1981 - 1995[16,34-5,42,61].

No.	Province	81 - 85	86 - 90	91 - 95
1.	DKI-Jakarta		0 (0/1)	
2.	East Kalimantan		100 (27/27)	100 (57/57)
3.	East Timor		12 (1/8)	
4.	South Sulawesi		100 (9/9)	
5.	Irian Jaya	0 (0/5)	100 (8/8)	

Table 14. *In-vitro P. falciparum* resistant to amodiaquine in Indonesia, 1981 - 1995[16,34-5,42,61].

	81 - 85	86 - 90	91 - 95
Number of provinces tested (%)*	1 (4)	5 (19)	1 (4)
Number of samples tested per province (range)	5	1 - 27	57
Number of provinces reporting resistance (%)**	0	4 (80)	1 (100)
Percentage of resistant cases (range)	-	12 - 100	100
Cumulative number of provinces reporting resistance (%)*	0	4 (15)	4 (15)

* percent by total number of provinces (27)
** percent by number of provinces tested.

In-vitro sensitivity testing of *P. falciparum* to mefloquine was run in 10, 13 and 6 provinces, with the number of samples tested ranging from 2 to 35, 1 to 60, and 1 to 145, in 1981-1985, 1986-1990 and 1991-1995. There were 2 (Central Java and Irian Jaya), 3 (East Nusa Tenggara, East Timor and Irian Jaya) and 1 (East Kalimantan) provinces with respectively 12-20%, 2-17% and 3% resistant cases in 1981-1985, 1986-1990 and 1991-1995 (Table 15 and Table 16)[16,32,34-9,42,45,57,60-2].

In-vivo sensitivity testing of *P. falciparum* to mefloquine (15 mg/kg bw, single dose) was performed in 2 (Aceh and East Kalimantan) and 1 (East Kalimantan) provinces. The numbers of patients examined were respectively 19 and 23, and 14 in 1986-1990 and 1991-1995. No resistant cases were found in these tests (Table 15 and Table 17)[32,62-3].

Combining *in-vitro* and *in-vivo* results, of the 18 provinces tested, 5 provinces (Central

Table 15. Percentage of *P. falciparum* resistant to mefloquine in Indonesia, 1981 -1995[16,32,34-9,42,45,57,60-3].

No.	Province	*In-vitro*			*In-vivo*		
		81 - 85	86 - 90	91 - 95	81 - 85	86 - 90	91 - 95
1.	Aceh	0 (0/11)	0 (0/8)			0 (0/19)	
2.	North Sumatra	0 (0/6)					
3.	Riau	0 (0/9)	0 (0/8)	0 (0/1)			
4.	Bengkulu		0 (0/7)	0 (0/1)			
5.	Jambi		0 (0/1)				
6.	West Java	0 (0/6)					
7.	DKI-Jakarta		0 (0/1)				
8.	Central Java	12 (1/8)	0 (0/28)				
9.	East Java	0 (0/6)					
10.	Central Kalimantan	0 (0/9)					
11.	East Kalimantan		0 (0/43)	3 (1/37)		0 (0/23)	0 (0/14)
12.	West Nusa Tenggara		0 (0/5)				
13.	East Nusa Tenggara	0 (0/12)	17 (1/6)				
14.	East Timor		2 (1/60)				
15.	North Sulawesi		0 (0/3)	0 (0/35)			
16.	Central Sulawesi	0 (0/2)		0 (0/4)			
17.	South Sulawesi		0 (0/10)				
18.	Irian Jaya	20 (7/35)	4 (1/28)	0 (0/145)			

Java, East Kalimantan, East Nusa Tenggara, East Timor and Irian Jaya) presented only *in-vitro P. falciparum* resistance to mefloquine (2 - 20 %). Central Java in 1981-1985 and Irian Jaya in 1981-1990 reported mefloquine resistance, but there after no resistance was detected. East Kalimantan reported mefloquine resistance in 1991-1995 and East Nusa Tenggara in 1986-1990 (Table 15).

Halofantrine resistance

Halofantrine, a phenanthrene-methanol, is a relative new antimalarial drug. This drug also has not yet been registered in Indonesia. Since 1991, several *in-vivo P. falciparum* and *P. vivax* sensitivity tests to this drug have been performed.

Table 16. *In-vitro P. falciparum* resistant to mefloquine in Indonesia, 1981 - 1995[16,32,34-9,42,45,57,60-2].

	81 - 85	86 - 90	91 - 95
Number of provinces tested (%)*	10 (37)	13 (37)	6 (22)
Number of samples tested per province (range)	2 - 35	1 - 60	1 - 145
Number of provinces reporting resistance (%)**	2 (20)	3 (23)	1 (17)
Percentage of resistant cases (range)	12 - 20	2 - 17	3
Cumulative number of provinces reporting resistance (%)*	2 (7)	4 (15)	5 (19)

* percent by total number of provinces (27)
** percent by number of provinces tested.

Table 17. *In-vivo P. falciparum* resistant to mefloquine in Indonesia, 1986 - 1995[16,62-3].

	86 - 90	91 - 95
Number of provinces tested (%)*	2 (7)	1 (4)
Number of samples tested per province (range)	19 - 23	14
Number of provinces reporting resistance (%)**	0	0
Percentage of resistant cases (range)	-	-
Cumulative number of provinces reporting resistance (%)*	0	0

* percent by total number of provinces (27)
** percent by number of provinces tested.

In-vivo sensitivity tests of *P. falciparum* to halofantrine (500 mg 6 hourly with a total dosage of 1500 mg) were performed in East Kalimantan, North Sulawesi and Irian Jaya province with numbers of patients examined 63, 59 and 36 respectively. Of the 3 provinces tested, East Kalimantan and North Sulawesi reported resistant cases of 2 % and 12 % at RI level (Table 18 and Table 19)[35-6,64].

In-vivo sensitivity test of *P. vivax* to halofantrine were performed also in North Sulawesi and Irian Jaya province with the numbers of patients examined 44 and 21. RI resistance (5 %) was found only in North Sulawesi (Table 18 and Table 19)[36,64-5].

Artemisinin derivatives recurrence

Artemisinin, a sesquiterpene-lactone-peroxide, is developed from Chinese traditional medicine. This drug and its derivatives (i.e: artesunate and artemether) possess a powerful antimalarial activity and low toxicity. No resistance to this drug has yet been demonstrated. It is not yet commercially available in Indonesia.

Table 18. Percentage of *in-vivo P. falciparum* and P. vivax resistant to halofantrine in Indonesia, 1991 -1995[35-6,64-5].

No.	Province	*P. falciparum*		*P. vivax*	
1.	East Kalimantan	2 (1/63)	Balikpapan (1991)		
2.	North Sulawesi	12 (7/59)	Tomohon (1993)	5 (2/44)	Tomohon (1993)
3.	Irian Jaya	0 (0/36)	Arso (1993)	0 (0/21)	Arso (1993)

Table 19. *In-vivo P. falciparum* and *P. vivax* resistant to halofantrine in Indonesia, 1991 - 1995[35-6,64-5].

	P. falciparum	*P. vivax*
Number of provinces tested (%)*	3 (11)	2 (7)
Number of samples tested per province (range)	36 - 63	21 - 44
Number of provinces reporting resistance (%)**	2 (67)	1 (50)
Percentage of resistant cases (range)	2 - 12	5
Cumulative number of provinces reporting resistance (%)*	2 (7)	1 (4)

* percent by total number of provinces (27)
** percent by number of provinces tested.

In-vivo sensitivity testing of *P. falciparum* (in uncomplicated falciparum malaria) to artesunate (600 mg in 5 days) was performed in East Kalimantan province. The number of patients examined was 10, with 40 % showing recurrence (late RI pattern) (Table 20 and Table 21)[66].

In-vivo sensitivity testing of *P. falciparum* (in uncomplicated *in-vitro* chloroquine resistant falciparum malaria) to artemether (480 mg in 5 days) was performed in Irian Jaya province. The number of patients examined was 31, with 10 % showing recurrence (late RI pattern)[67].

MULTIDRUG RESISTANCE

Falciparum malaria multidrug (more than one drug) resistance to chloroquine and/or sulfadoxine-pyrimethamine and /or quinine cases have been noted since 1979[26,59].

During 1991 - 1995, *in-vitro* sensitivity tests of *P. falciparum* to several antimalarial drugs (chloroquine, sulfadoxine-pyrimethamine, quinine, amodiaquine and mefloquine) were performed in 4 provinces. The number of isolates tested ranged between 20 and 80 with multidrug resistance found in 84 %, 49 %, 40 %

Table 20. Percentage of *in-vivo P. falciparum* recurrent to artemisinin derivatives in Indonesia, 1991 -1995[66].

No.	Province	Artesunate	Artemether
1.	East Kalimantan	40 (4/10), Balikpapan (1993)	
2.	Irian Jaya		10 (3/31), Tembagapura (1994)

Table 21 *In-vivo P. falciparum* recurrence to artemisinin derivatives in Indonesia, 1991 - 1995[66].

	Artesunate	Artemether
Number of provinces tested (%)*	1 (4)	1 (4)
Number of samples tested per province (range)	10	31
Number of provinces reporting resistance (%)**	1 (100)	1 (100)
Percentage of resistant cases (range)	40 (RI)	10 (RI)
Cumulative number of provinces reporting resistance (%)*	1 (4)	1 (4)

* percent by total number of provinces (27)
** percent by number of provinces tested.

and 11 % in East Kalimantan, Irian Jaya, North Sulawesi and East Timor, respectively. Combined resistance to chloroquine and sulfadoxine-pyrimethamine were found in all the 4 provinces. Combined resistance to chloroquine and amodiaquine, and to chloroquine, sufadoxine-pyrimethamine and amodiaquine were found in East Kalimantan and East Timor. Combined resistance to chloroquine and quinine, and to sulfadoxine-pyrimethamine and amodiaquine, and to chloroquine and sulfadoxine-pyrimethamine and quinine and amodiaquine and mefloquine were only found in East Kalimantan. Combined resistance to chloroquine and mefloquine was found only in East Timor[35-7,61] (Table 22 and Table 23).

In 1993, vivax malaria resistance to chloroquine and quinine was reported from a patient who acquired malaria from a blood transfusion in DKI-Jakarta (Table 22)[54].

EFFICACY OF SEVERAL NEW ANTIMALARIAL DRUGS FOR TREATMENT

Several clinical trials of new antimalarial drugs (mefloquine, halofantrine and artemisinin derivatives) have been performed for the treatment of falciparum malaria patients and vivax malaria patients in order to prepare alternative antimalarial drugs for possible future use.

Table 22. Percentage of *in-vitro P. falciparum and in-vivo P. vivax* resistant to several (>1) antimalarial drugs in Indonesia, 1991 -1995[35-7,61].

No.	Province	*P. falciparum*		*P. vivax*
1.	East Kalimantan	84 (59/70)	CQ+SP, CQ+Q, CQ+AQ, AQ+SP, CQ+SP+AQ, CQ+SP+Q+AQ+MQ	
2.	East Timor	11 (9/80)	CQ+SP, CQ+AQ, CQ+MQ, CQ+SP+AQ	
3.	North Sulawesi	40 (8/20)	CQ+SP	
4.	Irian Jaya	49 (25/51)	CQ+SP	
5.	DKI-Jakarta			100 (1/1) CQ+QN

CQ = Chloroquine
SP = Sulfadoxine-Pyrimethamine
Q = Quinine
AQ = Amodiaquine
MQ = Mefloquine.

Table 23. *In-vitro P. falciparum* resistant to several (>1) antimalarial drugs in Indonesia, 1991 - 1995[35-7,61].

	P. falciparum
Number of provinces tested (%)*	4 (15)
Number of samples tested per province (range)	20 - 80
Number of provinces reporting resistance (%)**	4 (100)
Percentage of resistant cases (range)	11 - 84
Cumulative number of provinces reporting resistance (%)*	4 (15)

* percent by total number of provinces (27)
** percent by number of provinces tested.

Mefloquine

At a single oral dose of 750 mg (15 mg base/kg bw) mefloquine with or without sulfadoxine-pyrimethamine was shown to be effective and safe for the treatment of uncomplicated falciparum malaria resistant chloroquine as well as multidrug resistant cases.

In studies conducted in the border areas of East Kalimantan and Irian Jaya, the parasite clearance rates were 94 - 100 %. Resistance at the level of RII and RIII was found only in Irian Jaya. Fever and parasite clearance times were 9 - 25 hours and 47 - 59 hours, respectively (Table 24)[32,57,62-3].

Halofantrine

Halofantrine at 500 mg (salt) 6 hourly for 3 doses was shown to be effective and safe for the treatment of uncomplicated falciparum malaria resistant to chloroquine as well as for the treatment of vivax malaria cases.

Studies in East Kalimantan, North Sulawesi and Irian Jaya in patients with uncomplicated falciparum malaria had parasite clearance rates of 88 - 100 %. Resistance at level of late RI was found in East Kalimantan and North Sulawesi. Fever and parasite clearance times were 17 - 30 hours and 52 - 61 hours respectively. In vivax malaria, parasite clearance rates were 95 - 100 %, the fever and parasite clearance times were 22 and 61 hours, respectively (Table 24)[35-6,64-5,68-9].

Artesunate

A total dose of 600 mg of artesunate given as 200 mg loading dose followed by 100 mg daily for 4 days was shown to be safe and effective for the treatment of uncomplicated falciparum malaria in a multidrug resistance area using a 14 day evaluation.

This artesunate trial was performed in East Kalimantan. The parasite clearance rate dropped to 60 % because of recrudescence after 14 days following 100 % clearance at 14 days (late RI pattern) (days 21-28). The fever and parasite clearance times were 14 and 32 hours, respectively (Table 24)[66].

Table 24. Efficacy of several new antimalarial drugs for uncomplicated malaria in Indonesia, 1991 - 1995[32,35-6,57,62-9].

Antimalarial drug	Parasite Clearance Rate (%)	Fever Clearance Time (hours)	Parasite Clearance Time (hours)
Falciparum malaria			
Mefloquine	94 - 100	9 - 25	47 - 59
Halofantrine	88 - 100	17 - 30	52 - 61
Artesunate	60	14	32
Artemether	90	8	29
Vivax malaria			
Halofantrine	95 - 100	22 ± 25	61 ± 22

Artemether

Oral artemether at the total dose of 480 mg given as 160 mg loading dose followed by 80 mg daily for 4 days was shown to be effective and safe for the treatment of uncomplicated *in-vitro* chloroquine resistance falciparum malaria.

A study in Irian Jaya had a parasite clearance rate of 90 % with recrudescence (late RI pattern) (days 21-28). The fever and parasite clearance times were very fast, 8 and 29 hours, respectively (Table 24)[67].

EFFICACY OF SEVERAL ANTIMALARIAL DRUGS FOR PROPHYLAXIS

Several antimalarial drugs such as chloroquine, sulfadoxine-pyrimethamine, primaquine, mefloquine and doxycycline were studied as prophylactic agents against malaria in 38 - 200 nonimmune transmigrants and soldiers in the hyperendemic areas of eastern Indonesia.

Chloroquine

Chloroquine is still used for malaria chemoprophylaxis in Indonesia. In East Timor and Irian Jaya, chloroquine 5 mg base/kg bw weekly for 6 and 4 months, had protective efficacy of 93 % and 44 % respectively (Table 25)[70-1].

Sulfadoxine-pyrimethamine

Sulfadoxine-pyrimethamine is not used for malaria chemoprophylaxis by the malaria control programme in Indonesia. In East Timor, sulfadoxine-pyrimethamine 1 tablet weekly for 6 months had a protective efficacy of 98 % (Table 25)[70].

Table 25. Protective rates of several antimalarial drugs as chemoprophylaxis in Indonesia, 1981 - 1995[70-3].

Antimalarial drug	Dosage	Protective rate (%)	Study's site (year)
Chloroquine	5 mg/kg bw/ week	44 - 93 (24/54 - 180/194)	East Timor (83), Irian Jaya (92, 94)
Sulfadoxine-pyrimethamine	1 tablet/week	98 (196/200)	East Timor (83)
Primaquine	0.5 mg/kg bw/2d or daily	89 - 92 (40/45 - 35/38)	Irian Jaya (92, 94)
Doxycycline	100 mg/day	99 (66/67)	Irian Jaya (94)
Mefloquine	250 mg/d-3d than 250 mg / week	100 (68/68)	Irian Jaya (94)

Primaquine

Primaquine could be used as a causal malaria prophylactic. However this drug is still not used for malaria chemoprophylaxis in Indonesia. In Irian Jaya, primaquine 0.5 mg base/kg bw every other day or 0.5 mg base/kg bw daily for 16 - 52 weeks had a protective efficacy of 89 % and 92 % respectively (Table 25)[71-2].

Mefloquine

Mefloquine is a relatively new antimalarial drug and is not available in Indonesia. In Irian Jaya, mefloquine 250 mg base weekly following a loading dose of 250 mg base daily for 3 days, given for 13 weeks had a protective efficacy of 100 % (Table 25)[73].

Doxycycline

In Indonesia, doxycycline is registered as an antibiotic. This drug is not used as an antimalarial drug by the malaria control programme. In Irian Jaya, doxycycline 100 mg daily for 13 weeeks had a protective efficacy of 99 % (Table 25)[73].

SIDE-EFFECTS OF ANTIMALARIAL DRUGS

In the many antimalarial drug trials, the medications have usually been well tolerated at the dose given.

Serious side-effects of chloroquine have never been reported. Headache, dizziness, palpitation, itching, epigastric pain, abdominal pain, nausea, vomiting, and diarrhoea had been noted (Table 26)[36-7,65,70].

The most important side-effect of sulfadoxine-pyrimethamine is skin reaction (Steven Johnson syndrome). It had been reported from Irian Jaya. Itching, epigastric pain and rash were noted in East Timor (Table 26)[70].

Table 26. Reported side-effects of several antimalarial drugs in Indonesia, 1991 - 1995[35-7,63,65-9,70-4].

Side-effects	Chloroquine	Sulfadoxine-pyrimethamine	Quinine	Primaquine	Mefloquine	Halofantrine	Artesunate	Artemether
Headache	V			V	V			
Dizziness	V		V		V	V		
Tinitus			V					
Epistaxis						V		
Rash		V						
Itching	V	V						
Palpitation	V					V		
Epigastric pain	V	V		V				
Nausea	V		V		V	V		
Vomiting	V			V		V		
Diarrhoea	V			V	V	V		
Abdominal pain	V				V	V		V
Insomnia					V			V

Usually quinine is given as a life-saving drug in severe malaria patients. Only dizziness, tinitus and nausea have been reported (Table 26)[74].

The side-effects of primaquine when given alone as a chemoprophylactic were headache, epigastric pain, vomiting and diarrhoea (Table 26)[71-2].

The common side-effects of mefloquine reported were headache, dizziness, abdominal pain, nausea, diarrhoea and insomnia (Table 26)[63,73].

Abdominal pain, nausea, vomiting and diarrhoea were common side-effects of halofantrine. Also reported were dizziness, epistaxis and palpitation (Table 26)[35-6,65,68-9].

The side-effects of oral and parentral artemether were abdominal pain and diarrhoea, while no side-effects were noted in oral artesunate (Table 26)[37,66-7,74].

DISCUSSION

All the drug sensitivity tests were performed to confirm the *P. falciparum* and *P. vivax* resistant to chloroquine and/or other antimalarial drugs presence in Indonesia. These tests were mainly conducted in major foci of suspected chloroquine resistance. No follow up or continuing studies have been carried out.

Therefore findings are limited to these reported cases. However, this evaluation has confirmed resistance to chloroquine, sulfadoxine-pyrimethamine, quinine, amodiaquine and to several new antimalarial drugs (mefloquine and halofantrine) by *P. falciparum* (Table 27) and to chloroquine by *P. vivax*.

Many mechanisms theoretically might induce changes in drug sensitivity of *Plasmodium* species, such as : physiological adaptation, selection among mixed sensitive and resistant parasite populations already present, spontaneous mutation and subsequent selection of resistance strains, and introduction of resistance transfer factors or plasmids[75].

Subtherapeutic dosage is observed to be the most likely cause of increasingly resistant *Plasmodium* species in Indonesia. Subcurative blood levels of drug encourage the survival of tolerant strains of parasites. Evolution toward drug resistance may thereby be facilitated.

This drug pressure has probably contributed heavily to the development of resistance in Indonesia. The first line and the most commonly available antimalarial drug in Indonesia is chloroquine. Chloroquine is retained in mosquito tissues after a blood meal is taken from a chloroquine-treated person. This exerts drug pressure on the sporogonic phase.

Table 27. Cumulative number of province reporting *in-vitro* and *in-vivo* resistant or recurrent to antimalarial drugs in Indonesia, 1981 - 1995.

Antimalarial drug	Cumulative number of provinces tested			Cumulative number of provinces reporting resistance/recurrence			%*	%**
	in-vitro	*in-vivo*	total	*in-vitro*	*in-vivo*	total		
Chloroquine	24	25	27	24	24	27	100	100
Sulfadoxine-pyrimethamine (SP)	13	9	14	11	4	11	79	41
Quinine (QN)	12		12	6		6	50	22
Mefloquine (MQ)	18	2	18	5		5	28	19
Amodiaquine (AQ)	5		5	4		4	80	15
CQ+SP, CQ+Q, CQ+AQ, CQ+MQ, SP+AQ, CQ+SP+AQ, CQ+SP+Q+AQ+MQ	4		4	4		4	100	15
Halofantrine		3	3		2	2	67	7
Artesunate		1	1		1	1	100	4
Artemether		1	1		1	1	100	4

* percent by total number of provinces (27)
** percent by number of provinces tested.

Mutation may be one-step or multi-step, where total sensitivity is replaced by RIII resistant in one step or a series of mutations level to successively higher drug resistance levels.

Antimalarial drugs should be distributed properly with one course of treatment per package and with clear information on drug administration to prevent inadequate treatment and to combat drug resistance.

The emergence of chloroquine resistance, the unrelenting spread of RIII resistance and the presence of multidrug resistant falciparum malaria are important reasons to study the efficacy of several new antimalarial drugs. Mefloquine, halofantrine and artemisinin derivatives showed effectiveness and safety for treatment of uncomplicated falciparum malaria in chloroquine or multidrug resistant areas[35-6,57,62-9]. However, these drugs are expensive and still not available in Indonesia. This poses a continuing therapeutic challenge to improve the efficacy of drugs currently available by combination of several antimalaria drugs or other drugs such as antibiotics or adjustment of dosages. Additional studies are needed.

Resistance of *P.vivax* to chloroquine is an emerging problem. Even though halofantrine was very effective in treating vivax malaria in *P. vivax* resistant areas[64-5], no obvious replacement for chloroquine is presently available in Indonesia. Sulfadoxine-pyrimethamine is not as effective as chloroquine in treating vivax malaria[76]. Quinine suffers from poor compliance and higher doses may be needed to cure the Chesson strain of *P. vivax*[77]. The current time, retreatment of chloroquine resistant *P. vivax* with standard regimen of chloroquine 25 mg base/kg bw for 3 days combined with primaquine 15 mg base daily for 14 days, may be effective. If resistance remains, repeated treatment with chloroquine 10 mg base/kg bw and primaquine 45 mg base, single dose, weekly for 12 weeks should be applied[78].

Chloroquine is no longer the drug of choice for both *P. falciparum* and *P. vivax* prophylaxis in Irian Jaya due to increasing levels of resistance in that area[71]. Occurence of rare cases of Stevens-Johnson syndrome has limited the usefulness of sulfadoxine-pyrimethamine in prophylaxis[70]. However, although primaquine was shown very effective and safe as a causal prophylactic[71-2], it is still not recommended because it has not been studied in large numbers of patients. Mefloquine was also shown to be very effective and safe[73] but it is expensive and still not available in Indonesia. Doxycycline performs well as a prophylaxis, but there are contraindications for children and pregnant women[73]. An alternative prophylactic drug which is safe and effective for children, pregnant and lactating women should also be studied, e.g. azithromycin.

SUMMARY AND CONCLUCIONS

Resistance to antimalarial drugs, especially chloroquine, has become a serious problem in case management throughout Indonesia. Appropriate baseline data and monitoring system for drug efficacy and resistance are required for reassessment and revision of national guidelines for malaria treatment.

All studies of resistance of antimalarial drugs using *in-vitro* and *in-vivo* methods in Indonesia, were reviewed to determine the pattern of drug resistant malaria and to use this data to establish an effective monitoring system. Malaria treatment and prophylaxis, field and hospital based studies during the period 1981 to 1995 were included.

Resistance of *P. falciparum* to chloroquine was detected for the first time in East Kalimantan in 1973, and has spread to all (27) provinces at level of RI - RIII. Three provinces (West Java, Central Kalimantan and Bali) reported only *in-vitro* resistance, and 3 other provinces (West Sumatera, South Sumatera and DI-Yogyakarta) reported only *in-vivo* resistance, while in the other 21 provinces *in-vitro* and *in-vivo* resistance were detected. Currently, RIII resistance affects 20 provinces compared to 4 provinces in 1981 - 1985. Chloroquine resistant vivax malaria has been detected since 1991 in Irian Jaya (41%), North Sumatera (13%), East Nusa Tenggara (8%), North Sulawesi (2%) and Jakarta (one case acquired by blood transfusion).

The total number of provinces reporting *P. falciparum* resistance to sulfadoxine-pyrimethamine is 11 out of the 14 provinces undertaking testing. Seven provinces have only reported resistance by *in-vitro* test and the other 4 provinces reported resistance by both *in-vitro* and *in-vivo* test at level of RI - RII. Of the 3 provinces reporting no resistance, 2 provinces (Bengkulu and DKI-Jakarta) only conducted the *in-vitro* sensitivity test and 1 province (Southeast Sulawesi) only the *in-vivo* sensitivity test.

Of the 12 provinces tested, only 6 provinces (West Java, Central Java, East Kalimantan, East Nusa Tenggara, Central Sulawesi and Irian Jaya) show *in-vitro P. falciparum* resistance to quinine with resistant cases ranging from 3 to 100 %. After 1981-1985, 3 provinces that had reported resistance (West Java, Central Java and Irian Jaya) did not report any for the resistant cases. In East Kalimantan where no resistance was present in 1986-1990, *in-vitro* resistance was reported in 1991-1995.

Of the 5 provinces tested, 4 provinces (East Kalimantan, East Timor, South Sulawesi and Irian Jaya) had resistance to amodiaquine (12 - 100 %). Previously (1981-1985), no amodiaquine resistance was found in Irian Jaya.

Of the 18 provinces tested, 5 provinces (Central Java, East Kalimantan, East Nusa Tenggara, East Timor and Irian Jaya) presented only *in-vitro P. falciparum* resistance to mefloquine (2 - 20 %). Central Java in 1981-1985 and Irian Jaya in 1981-1990 reported mefloquine resistance, but thereafter no resistance was detected, while East Nusa Tenggara reported mefloquine resistance in 1986-1990 and East Kalimantan in 1991-1995.

In-vitro P. falciparum multidrug resistance was found respectively in 84 %, 49 %, 40 % and 11 % of cases in East Kalimantan, Irian Jaya, North Sulawesi and East Timor. Resistance to chloroquine and sulfadoxine-pyrimethamine was found in all 4 provinces. Resistance to chloroquine and amodiaquine, and to chloroquine and sufadoxine-pyrimethamine and amodiaquine were found in East Kalimantan and East Timor. Resistance to chloroquine and quinine, to sulfadoxine-pyrimethamine and amodiaquine, to chloroquine and sulfadoxine-pyrimethamine and quinine and amodiaquine and mefloquine were only found in East Kalimantan. Resistance to chloroquine and mefloquine was found only in East Timor

At a single oral dose of 750 mg (15 mg base/kg bw) mefloquine with or without sulfadoxine-pyrimethamine for the treatment of uncomplicated falciparum malaria resulted in parasite clearance rates of 94 - 100 % in several studies in border areas of East Kalimantan and Irian Jaya. Resistance at level of RII and RIII were found in Irian Jaya. Fever and parasite clearance times were 9 - 25 hours and 47 - 59 hours, respectively.

Halofantrine at 500 mg (salt) 6 hourly for 3 doses for the treament of uncomplicated falciparum malaria in East Kalimantan, North Sulawesi and Irian Jaya had parasite clearance rates of 88 - 100 %. Resistances at level of late RI were found in East Kalimantan and North Sulawesi. Fever and parasite clearance times were 17 - 30 hours and 52 - 61 hours, respectively. In vivax malaria, parasite clearance rates were 95 - 100 %, the fever and parasite clearance times were 22 and 61 hours, respectively.

A total dose of 600 mg of artesunate given as 200 mg loading dose followed by 100 mg daily for 4 days for the treatment of uncomplicated falciparum malaria in East Kalimantan, had parasite clearance rate 60 % with recrudescence (late RI pattern) on day 21-28. The fever and parasite clearance times were 14 and 32 hours, respectively.

Oral artemether at the total dose of 480 mg given as 160 mg loading dose with subsequent 80 mg daily for 4 days for the treatment of uncomplicated falciparum malaria in Irian Jaya, had parasite clearance rate of 90 % with recrudescence (late RI pattern) on day 21-28. The fever and parasite clearance times were very fast, 8 and 29 hours, respectively.

Studies on prophylaxis showed protection rates of respectively 41 % and 93 % to chloroquine in Irian Jaya and East Timor, sulfadoxine-pyrimethamine 98% in East Timor, primaquine 89-92% and doxycycline 99% and mefloquine 100% in Irian Jaya.

The side-effects of those antimalarial drugs were mostly mild.

This evaluation confirms the existence of drug resistant *P. falciparum* and *P. vivax* in Indonesia. The unrelenting spread of RIII level resistance to chloroquine of falciparum malaria and the presence of multidrug resistant falciparum malaria are serious public health problems and pose a continuing therapeutic challenge. Chloroquine resistant vivax malaria is a newly emerging problem. The antimalarial drugs should be distributed properly for one course of treatment per package with clear information on drug administration to prevent inadequate treatment and combat drug resistance. Since new antimalarials are not available yet in Indonesia, the efficacy of drugs currently available (chloroquine, sulfadoxine-pyrimethamine, quinine and primaquine) should be studied, for example, in combination. Alternative prophylactic drugs (e.g azithromycin) which are safe and effective for children, pregnant and lactating women should also be considered.

ACKNOWLEDGEMENTS

The authors would like to thank the following for their invaluable assistance:

1. The staff of Subdirectorate of Malaria, Directorate of Vector Borne Diseases, Directorate General Communicable Diseases Control and Environmental Health, Ministry of Health, Jakarta, Indonesia.

2. United States Naval Medical Research Unit - 2, Jakarta, Indonesia.

3. Professor Karl Rieckmann, Director Army Malaria Research Unit, Liverpool Military Area, NSW, Australia.

4. Akira Kaneko, MD, DTM&H, PhD, WHO Vanuatu.

5. Rhone Poulenc Rorer Doma, Jakarta, Indonesia.

REFERENCES

1. Biro Pusat Statistik. Statistik Indonesia. Statistical Pocketbook of Indonesia 1994. BPS Jakarta,Indonesia.

2. Sub-directorate of Malaria. Rekapitulasi survei malaria di luar Jawa-Bali dari tahun 1989 - 1993 (Recapitulation of malariometric survey during 1989 to 1993 in Outer Java-Bali). Directorate General of Communicable Disease Control and Environmental Health, Ministry of Health, Jakarta, Indonesia, 1994.

3. Sub-directorate of malaria. *Passive Case Detection* (PCD) di luar Jawa-Bali dari tahun 1989-1993 (Passive case Detection during 1989 to 1993 in Outer Java-Bali. Directorate General of Communicable Disease Control and Environmental Health, Ministry of Health, Jakarta, Indonesia, 1994.

4. Sub-directorate of Malaria. Pengobatan. Malaria no 6 (Treatment. In Malaria Series no 6). Directorate General Communicable Disease Control and Environmental Health. Ministry of Health, Jakarta, Indonesia, 1995.

5. WHO Tech Rep Ser 1967; 375: 42.

6. WHO. *In-vitro* microtest (Mark II) for the assessment of the response of *Plasmodium falciparum* to chloroquine, mefloquine, quinine, suffadoxine/pyrimethamine and amodiaquine, 1987; MAP/87.2.

7. WHO. Drug resistant malaria report of an Intercountry Meeting, New Delhi, 29 September - 3 October 1988. SEA/Mal/165.

8. Rombo L, Bjoerkman A, Sego E and Ericsson O. Whole blood concentrations of chloroquine and desethylchloroquine during and after treatment of adult patients infected with *Plasmodium vivax, Plasmodium ovale* or *Plasmodium malariae*. Trans R Soc Trop Med Hyg 1986; 80: 763-6.

9. Young MD and Moore DV. Chloroquine resistance in *Plasmodium falciparum*. Am J Trop Med Hyg 1961; 10: 5-9.

10. Schuurkamp GJ, Spicer PE, Kereu RK and Bulungol PK. A mixed infection of vivax and falciparum malaria apparently resistant to 4-aminoquinoline: a case report. Trans Roy Soc Trop Med Hyg 1989; 83: 607-8.

11. Rieckmann KH, Davis DR and Hutton DC. *Plasmodium vivax* resistance to chloroquine? Lancet 1989; ii: 1183-4.

12. Whitby M, Wood G, Veenendaal JR and Rieckmann K. Chloroquine resistant *Plasmodium vivax*. Lancet 1989; ii: 1395.

13. Collignon P Chloroquine resistance in *Plasmodium vivax*. I Infect Dis 1991; 164: 222-3.

14. Schuurkamp GJ, Spicer PE, Kereu RK et al. Chloroquine resistant *Plasmodium vivax* in Papua New Guinea. Trans Roy Soc Trop Med Hyg 1992; 86: 121-22.

15. Subdirectorate Malaria Control. Tes resistensi untuk *P. falciparum*. Malaria no 9 (Resistancy test of *P. falciparum*. In Malaria Series no 9). Directorate General of Communicable Disease Control and Environmental Health, Ministry of Health, Jakarta, Indonesia, 1995.

16. Subdirectorate Malaria Control. Kumpulan data-data *P. falciparum* resisten terhadap obat antimalaria (Compiling data of *P. falciparum* resistant to antimalarial drugs). Directorate General of Communicable Disease Control and Environmental Health, Ministry of Health, Jakarta, Indonesia, 1996.

17. Verdrager J and Arwati. Resistant *Plasmodium falciparum* infection from Samarinda, Kalimantan. Bull Hlth Studies Indon 1974; 2: 43-50.

18. Verdrager J and Arwati. Effect of a single dose of minocycline on a chloroquine resistant falciparum infection from Balikpapan, Kalimantan. Bull Hlth Studies Indon 1975; 2: 41-6.

19. Ebisawa I and Fukuyama T. Chloroquine resistant falciparum malaria from West Irian and East Kalimantan. Ann Trop Med Parasit 1975; 69 (1): 131-2.

20. Ebisawa I and Fukuyuma T. Chloroquine resistance of *Plasmodium falciparum* in West Irian and East Kalimantan. Ann Trop Med Parasit 1975; 69 (1): 276- 82.

21. Ebisawa I, Fukuyuma T and Kawamura Y. Additional foci of chloroquine resistant falciparum malaria in East Kalimantan and West Irian, Indonesia. Trop Geogr Med 1976; 28: 349-54.

22. Verdrager J, Arwati, Simandjuntak CH and Saroso S. Chloroquine resistant falciparum malaria in East Kalimantan, Indonesia. Am J Trop Med Hyg 1976; 79 (3): 58-66.

23. Verdrager J, Saroso SJ, Arwati and Simandjuntak CH. Response of falciparum malaria to a standard regimen of chloroquine in Jayapura, Irian Jaya (Indonesia). Bull Hlth Studies Indon 1976; 4: 19.

24. Dakung LS, Pribadi W and Ismid IS. *Plasmodium falciparum* yang tersangka resisten terhadap klorokuin di Jakarta (Suspected chloroquine resistant *Plasmodium falciparum* in Jakarta). Maj Kedokt Indon 1978; 28 (10, 11, 12): 114-7.

25. Hutapea AM. Treatment of malaria falciparum with combined sulfadoxine and pyrimethamine in Jayapura, Indonesia. Indon Med J 1979; 29: 47-8.

26. Rumans LW, Dennis DT and Atmosoedjono S. Fansidar^{R} resistant falciparum malaria in Indonesia. Lancet 1979; 2: 581.

27. Pribadi W. Resistensi *Plasmodium falciparum* terhadap klorokuin di Indonesia (Chloroquine resistant *Plasmodium falciparum* in Indonesia). Cermin Dunia Kedokteran 1980; special edition.

28. Simanjuntak C, Arbani PR and Kumara Rai N. *P. falciparum* resisten terhadap klorokuin di Kabupaten Jepara, Jawa Tengah (*P. falciparum* resistant to chloroquine in Jepara district, Central Java). Bull Hlth Studies 1981; IX (2): 1-8.

29. Smrkovski LL, Hoffman SL, Purnomo et al. Chloroquine resistant *Plasmodium falciparum* on the islands of Flores, Indonesia. Trans Roy Soc Trop Med Hyg 1983; 77 (4): 459-62.

30. Hoffman SL, Masbar S, Hussein PR et al. Absence of malaria mortality in villagers with chloroquine. Trans Roy Soc Trop Med Hyg 1984; 78: 175-8.

31. Ompusunggu S, Arbani PR, Marwoto HA et al. Hubungan sensitivitas *Plasmodium falciparum* terhadap kombinasi pirimetamin/sulfadoksin dan klorokuin secara *in vitro* (The relationship *In-vitro P. falciparum* sensitivity with combination of pyrimethamine/sulfadoxine and chloroquine). Bull Hlth Studies 1987; 15 (2): 19-23.

32. Ompusunggu S, Arbani PR, Marwoto HA et al. Sensitivitas *Plasmodium falciparum* secara *in vitro* terhadap beberapa macam obat di Sabang, Aceh (*In-vitro P. falciparum* sensitivity against several antimalarial drugs in Sabang, Aceh). Cermin Dunia Kedokteran 1989; 54: 19-21

33. Ompusunggu S, Sulaksono S, Marwoto HA and Dewi RM. Situasi kepekaan *Plasmodium falciparum* terhadap obat dan mobilitas penduduk di Nunukan, Kalimantan Timur (*Plasmodium falciparum* sensitivity situation against antimalarial drugs and mobility of the community in Nunukan, East Kalimantan). Cermin Dunia Kedokteran 1989; 55: 8-11

34. Tjitra E, Suwarni, Harun S et al. Malaria di Kepulauan Seribu (Malaria in Seribu islands). Cermin Dunia Kedokteran 1991; 70: 31-4.

35. Tjitra E. Laporan uji coba penggunaan halofantrin pada penderita malaria falsiparum di daerah resisten klorokuin (Report of A clinical trial of halofantrine in falciparum malaria patients in a chloroquine resistant area). Communicable Disease Research Center, National Institute of Health Research and Development, Ministry of Health, Jakarta, 1991.

36. Tjitra E. Report of A clinical trial of halofantrine treatment of falciparum and vivax malaria patients in Manado, North Sulawesi, Indonesia. Communicable Disease Research Center, National Institute of Health Research and Development, Ministry of Health, Jakarta, 1994.

37. Tjitra E. Report of A clinical trial of artemether in malaria patients in Timika. Communicable Disease Research Center, National Institute of Health Research and Development, Ministry of Health, Jakarta, 1995.

38. Tjitra E. Laporan diagnosis dini dan pengobatan cepat malaria melalui peran serta masyarakat di daerah transmigrasi Indonesia Bagian Barat (Report of Early diagnosis and prompt treatment of malaria through community participation in transmigration areas of western part of Indonesia). Communicable Disease Research Center, National Institute of Health Research and Development, Ministry of Health, Jakarta, 1995.

39. Marwoto HA, Sulaksono S, Tjitra E et al. Laporan sensitivitas obat antimalaria di kecamatan Sindue (Report of malaria drug sensitivity in Sindue subdistrict). Communicable Disease Research Center, National Institute of Health Research and Development, Ministry of Health, Jakarta, Indonesia, 1995.

40. Pribadi W, Sutanto I, Rasidi I et al. Malaria di Timika (Malaria in Timika). Irian Jaya. 8th Indonesia Parasitology Seminar and 6th National Congress of Association of Parasitic Diseases Control, 23-25 Agustus 1993, Denpasar, Bali.

41. Sisirawaty, Pribadi W, Oemijati S and Arbani PR. Pemeriksaan sensitivitas *P. falciparum in vivo* dan *in vitro* terhadap klorokuin pada penderita malaria falsiparum di Timor Timur (*In-vivo* and *in-vitro* sensitivity test to chloroquine in falciparum malaria patients in East Timor). 7th National Parasitology Seminar, Bali, 23-25 August, 1993.

42. Baird JK, Basri H, Jones TR et al. Resistance to antimalarials by *Plasmodium falciparum* in Arso PIR, Irian Jaya, Indonesia. Am J Trop Med Hyg 1991; 44 (6): 640-4.

43. Pribadi W, Dakung LS, Gandahusada S and Daldyono. Chloroquine resistant *Plasmodium falciparum* from Lampung and South Sumatera, Indonesia. Southeast Asian J Trop Med Pub Hlth 1981; 12 (1): 69-73.

44. Pribadi W, Dakung LS and Adjung SA. Infeksi *P. falciparum* resisten terhadap klorokuin dari beberapa daerah di Indonesia (*P. falciparum* infection resistant to chloroquine from several areas of Indonesia). Medika 1983; 8: 689-93.

45. Tjitra E, Sulaksono S, Renny M et al. Sensitivitas *P. falciparu* terhadap beberapa obat antimalaria di desa Pekandangan, Jawa Tengah (Sensitivity of *P. falciparum* to several antimalarial drugs in Pekandangan, Central Java. Cermin Dunia Kedokteran 1993; 82: 53-6.

46. Tjitra E, Dewi RM, Marwoto et al. *P. falciparum* resisten klorokuin dari Mamuju, Sulawesi Selatan (*Plasmodium falciparum* resistant to chloroquine from Mamuju, South Sulawesi). Unpublished report. Communicable Disease Research Center, National Institute of Health Research and Development, Ministry of Health, Jakarta, Indonesia, 1996.

47. Baird JK, Purnomo, Fryauff DJ et al. In-vivo survey of resistance chloroquine by *Plasmodium falciparum* at Oksibil, Irian Jaya. Bull Hlth Studies Indon 1995; 23 (2): 49-55.

48. Baird JK, Nalim S, Basri H et al. Survey revealing resistance to chloroquine by *Plasmodium vivax* at Nias, North Sumatra,

Indonesia. Trans Roy Soc Trop Med Hyg (inpress).

49. Fryauff DJ, Baird JK, Chandradikusuma D et al. Survey of in-vivo sensitivity to chloroquine by *Plasmodium falciparum* and *P. vivax* at Lombok, Indonesia. Am J Trop Med Hyg (inpress).

50. Fryauff DJ, Baird JK, Leksana B et al. Survey of chloroquine resistant falciparum and vivax malaria in Indonesia and the development of a new treatment strategy for chloroquine resistant *Plasmodium vivax*. Unpublished 1996, Naval Medical Research Unit 2, Jakarta, Indonesia.

51. Schwartz IK, Lackritz EM, Patchen IC. Chloroquine resistant *Plasmodium vivax* from Indonesia. N Engl J Med 1991; 324: 927.

52. Baird JK, Basri H, Purnomo et al. Resistance to chloroquine by *Plasmodium vivax* in Irian Jaya, Indonesia. Am J Trop Med Hyg 1991; 44 (5): 547-52.

53. Murphy GS, Basri H, Purnomo et al. Vivax malaria resistant to treatment and prophylaxis with chloroquine. Lancet 1993; 341: 96-100.

54. Tjitra E, Lukito B and Gunawan S. Multidrug resistant transfusion vivax malaria. Paediatrica Indonesiana 1994; 34 (5-6): 175-8.

55. Marwoto HA, Simandjuntak CH, Sulaksono S et al. Penelitian resistensi *Plasmodium falciparum* terhadap pirimetamin dan Fansidar di Indonesia (Resistance study of *Plasmodium falciparum* to pyrimethamine and Fansidar in Indonesia). Prociding of National Seminar of the University Study Results 1985: 21-31.

56. Marwoto HA, Sulaksono S, Arbani PR and Ompusunggu S. Tes resistensi secara *in vitro Plasmodium falciparum* terhadap obat yang mengandung sulfadoksin (*In-vitro* resistance test of *Plasmodium falciparum* to sulfadoxine). Cermin Dunia Kedokteran 1987; 45: 60-3.

57. Hoffman SL, Dimpudus AJ, Rustama D et al. RII and RIII type resistance of *Plasmodium falciparum* to combination of mefloquine and sulfadoxine/pyrimethamine in Indonesia. Lancet 1985 : 1039-40.

58. Marwoto HA, Arbani PR, Sulaksono S et al. Laporan akhir Penelitian Resistensi *Plasmodium falciparum* terhadap Fansidar di Indonesia (Report of Resistancy test of *Plasmodium falciparum* to Fansidar in Indonesia). Communicable Disease Research Center, National Institute of Health Research and Development, Ministry of Health, Jakarta, Indonesia, 1985.

59. Adjung SA, Dakung LS and Pribadi W. *Plasmodium falciparum* dari Timor Timur yang *in vivo* resisten terhadap klorokuin dan Fansidar (*Plasmodium falciparum* from East Timor *in vivo* resistant to chloroquine and Fansidar^{R}). Malaria Technical Meeting, Jakarta, May 1982.

60. Hoffman SL. *In-vitro* studies of the sensitivity of *Plasmodium falciparum* to mefloquine in Indonesia. Panel Discussion at National Parasitology Seminar, Bandung, August 1983.

61. Pribadi W. *In vitro* sensitivity of *Plasmodium falciparum* to chloroquine and other antimalarials in East Timor and East Kalimantan, Indonesia. In : Advanced knowledge on malaria in Southeast Asia. The Southeast Asian J Trop Med and Publ Hlth 1992; 23 (suppl 4): 143- 151.

62. Sulaksono S, Marwoto HA, Arbani PR et al. Sensitivitas *P. falciparum* terhadap meflokuin di beberapa daerah perbatasan (Sensitivity of *Plasmodium falciparum* to mefloquine in several border areas). National Parasitology Seminar, Surabaya, 23-25 June 1990.

63. Tjitra E, Oemijati S, Pribadi W et al. Pengobatan malaria falsiparum tanpa komplikasi dengan meflokuin di daerah resisten klorokuin (Treatment of uncomplicated falciparum malaria with mefloquine in a chloroquine resistant area). Bull Hlth Studies 1992; 20(3): 25-33.

64. Fryauff DJ, Baird JK, Basri H et al. Primaquine adjunct to 28 day evaluation of halofantrine vs chloroquine for therapy of malaria people remaining exposed to infection. Annual Meeting of the American Society of Tropical Medicine and Hygiene, Atlanta, Georgia, 30 October - 4 November 1993.

65. Tjitra E, Oemijati S, Pribadi W et al. Randomized comparative study of chloroquine and halofantrine in vivax malaria patients. Med J Indon 1995, 4 (1): 30-6.

66. Tjitra E, Oemijati S, Arbani PR and Pribadi W. Clinical trials of artesunate and artemether on falciparum malaria in chloroquine resistant area (A preliminary report). J Indon Med Assoc 1995; 45(4): 273-30.

67. Tjitra E, Pribadi W, Rahardjo K et al. Treatment of uncomplicated *in-vitro* chloroquine resistant falciparum malaria with artemether in Irian Jaya. Med J Indon 1996, 5(1): 33-41.

68. Tjitra E, Oemijati S, Pribadi W et al. Pengobatan malaria falsiparum tanpa komplikasi dengan halofantrin di daerah resisten klorokuin (Treatment of uncomplicated falciparum malaria with halofantrine in a chloroquine resistant area). Bull Hlth Studies 1992; 20 (1): 1-8.

69. Tjitra E, Oemijati S, Pribadi W et al. Studi perbandingan pengobatan halofantrin pada penderita malaria falsiparum tanpa komplikasi yang *in vitro* sensitif dengan yang resisten klorokuin (Comparative study of halofantrine treatment on uncomplicated *in-vitro* chloroquine sensitive falciparum malaria and uncomplicated *in-vitro* chloroquine resistant falciparum malaria). Bull Hlth Studies 1993; 21 (1): 22-31.

70. Lestiadi J, Purnomo, Soemedhi et al. Perbandingan efektivitas antara chloroquine dan Fansidar terhadap malaria di daerah Timor Timur (Comparative efficacy of chloroquine and Fansidar on malaria in East Timor). Medika 1983; 11 : 927-32.

71. Baird JK, Fryauff DJ, Basri H et al. Primaquine for prophylaxis against malaria among nonimmune transmigrants in Irian Jaya, Indonesia. Am J Trop Med Hyg 1995; 52 (6): 479-84.

72. Fryauff DJ, Baird JK, Basri H et al. Randomized placebo-controlled trial of primaquine for prophylaxis of falciparum and vivax malaria. Lancet 1995; 346 (8984): 1190-3.

73. Ohrt C, Richie TL, Widjaja H et al. Mefloquine compared with doxycycline for the prophylaxis of malaria in Indonesian soldiers. Annals of Internal Medicine 1997; 126 (12): 963-72.

74. Tjitra E, Oemijati S, Oey TS, Pribadi W, Tjiptaningsih B, Leman Y dkk. Comparative Study of Artemether and Quinine Treatment in Severe and Complicated Falciparum Malaria Patients at Balikpapan General Hospital. Med J Indones 1996; 5(4): 218-27.

75. Looareesuwan S, Harinasuta T and Chongsuphajaisiddhi T. Drug resistant malaria, with special reference to Thailand. Special report. Southeast Asean J Trop Med Publ Hlth 1992; 23 (4): 621-34.

76. Doberstyn EB, Teerakiartkamjorn C, Andre RG et al. Treatment of vivax malaria with sulfadoxine-pyrimethamine and with pyrimethamine alone. Trans R Soc Trop med Hyg 1979; 73:15-7.

77. Schmidt LH. *Plasmodium falciparum* and *Plasmodium vivax* infection in the owl monkey (*Dotus trivirgatus*) II. Response to chloroquine, quinine and pyrimethamine. Am J Trop Med Hyg 1978; 27: 703-17.

78. Sub-directorate of Malaria. Pedoman Pelita VI. Malaria no 15 (The Manual of the 6th Five Years Development Plan. In Malaria Series no 15). Directorate General Communicable Disease Control and Environmental Health. Ministry of Health, Jakarta, Indonesia, 1995.