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Very High Risk of Therapeutic Failure with Chloroquine for Uncomplicated *Plasmodium falciparum* and *P. vivax* Malaria in Indonesian Papua

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VERY HIGH RISK OF THERAPEUTIC FAILURE WITH CHLOROQUINE FOR UNCOMPLICATED *PLASMODIUM FALCIPARUM* AND *P. VIVAX* MALARIA IN INDONESIAN PAPUA

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Abstract. Chloroquine remains the first-line therapy for uncomplicated malaria in Indonesia. Among a series of trials of chloroquine for malaria on this archipelago conducted since 1990, we now report the highest risk of therapeutic failure yet observed. A clinical trial of standard chloroquine therapy for uncomplicated malaria at Arso PIR V in northeastern Indonesian Papua was conducted during 1995. We enrolled 104 non-immune subjects infected with *Plasmodium falciparum* (n = 55), *P. vivax* (n = 29), or *P. falciparum* plus *P. vivax* (n = 20) and administered supervised standard chloroquine therapy (10 + 10 + 5 mg/kg at 24-hour intervals). The 28-day cumulative incidence of therapeutic failure was 95% for *P. falciparum*, 84% for *P. vivax*, and 100% for mixed infections. Only one subject each for *P. falciparum* and *P. vivax* remained free of parasites at day 28. All recurrent parasitemias occurred with whole blood levels of chloroquine plus desethylchloroquine exceeding 100 ng/ml. These findings document almost complete failure of chloroquine against *P. falciparum* or *P. vivax* near the northeastern coast of Indonesian Papua.

INTRODUCTION

Chloroquine still constitutes first-line therapy against uncomplicated malaria caused by *Plasmodium falciparum* and *P. vivax* in many endemic areas. Combined therapeutic strategies under consideration by developing nations include chloroquine plus other standard antimalarials such as sulfadoxine/pyrimethamine.[1] Combining chloroquine with agents such as chlorpheniramine, which apparently reverse the process responsible for resistance, constitute another approach.[2] Whether used as monotherapy or in combination with other agents, chloroquine remains a mainstay for therapy of malaria in the developing world. Thus, therapeutic assessment of chloroquine constitutes a key element of strategic thinking in the development of treatment policies.[3,4]

We have conducted assessments of chloroquine for treatment of uncomplicated *P. falciparum* and *P. vivax* in northeastern Papua (formerly known as Irian Jaya), Indonesia.[5–8] Three of these reports described resistance to chloroquine in *P. vivax*. Another study[9] found relatively low risk of therapeutic failure with chloroquine therapy of *P. vivax* (22% at day 14). Subsequent studies of *P. vivax* in the same region found higher risk of therapeutic failure (31–53% at day 14).[7,8] Similar studies in the region evaluated chloroquine combined with primaquine[7] or doxycycline[10] against *P. vivax*. Risk of therapeutic failure with chloroquine for *P. falciparum* at day 14 post-therapy ranged from 57% to 84% in this region.[6,8,10]

The continued use of chloroquine for uncomplicated *P. falciparum* and *P. viv*ax malaria in Indonesian Papua points to the lack of practical therapeutic options in the setting of a frontier area of a developing nation. Indonesian authorities have not adopted policies that would permit distribution of drugs such as mefloquine, either alone or as combined therapy, largely as a consequence of prohibitive cost. Effective therapies may be purchased in bulk for as little as US $1 per adult treatment (e.g., mefloquine plus artesunate as marketed in Cambodia), but chloroquine or pyrimethamine/sulfadoxine treatments cost approximately US $0.20 (as marketed in Indonesia). Moreover, the longer and more complex dosing regimens of the new therapeutic agents carry the hidden and substantial cost of adapting the acquisition and distribution mechanism, along with educating healthcare providers and patients. In the case of Indonesia, the fourth most populous nation in the world, such commitments engage many thousands of government officers and many millions of citizens. In addition to compelling evidence of the inadequacy of current antimalarials, changes to policy and practice will require fiscal resources not currently available to the health infrastructure.

This report contributes to the case for adopting alternative therapies for uncomplicated *P. falciparum* and *P. vivax* malaria in Indonesian Papua by describing the highest risk of therapeutic failure yet documented in the region. We know of no other region in Indonesia with risk of therapeutic failure even approaching that reported here from northeastern Papua. Substantiation of this may allow singling out the region for the distribution and use of relatively expensive and effective combined therapies. Thus limiting the scale of application would substantially diminish the hidden costs of adopting new therapeutic strategies.

MATERIALS AND METHODS

Study sites. The study was conducted during October and November 1995 in Arso PIR V, in northeastern Papua, Indonesia. This transmigration village is located within 7 km of the border with Papua New Guinea and approximately 50 km south of the Pacific Ocean coast. The residents of Arso PIR V were predominantly transmigrants from Java, consisting mostly of young families. Most residents had moved into the village by January 1995. Malaria in the region was hyperendemic to holoendemic and transmitted by mosquitoes of the *Anopheles punctulatus* group.[11] These mosquitoes feed predominantly in villages between dusk and dawn. All residents shared approximately equal risk of exposure to biting anophelines. Figure 1 shows the age-specific prevalence of malaria at enrollment. Prevalence of parasitemia among the 349 of the approximately 1,100 residents sampled was 79%, with a *P. falciparum* to *P. vivax* ratio of approximately 3:1. Prevalence across age groups was not significantly different ($P > 0.2$), and this corroborates cross-sectional studies elsewhere in the region,[12] suggesting onset of acquired immunity

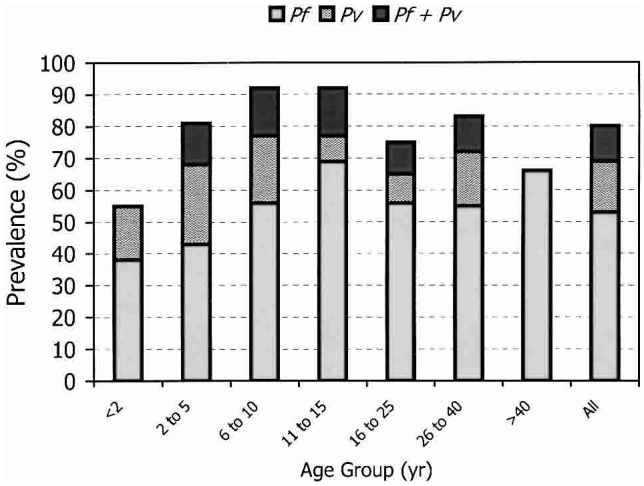

FIGURE 1. Age-specific prevalence of malaria at enrollment in the study. *Pf* = *Plasmodium falciparum*; *Pv* = *P. vivax*; yr = years.

in adults only after 12–24 months of exposure to infection. We considered these findings objective evidence of a broad lack of clinical immunity in the study population.

Study subjects. Study subjects were recruited from among those found slide-positive during the cross-sectional screening. Subjects ranged in age from 5 to 40 years (median = 24). Asexual parasitemia counts at enrollment ranged from 40 to 16,480/μL for *P. falciparum* (geometric mean = 766/μL) and 40–13,520/μL for *P. vivax* (geometric mean = 824/μL). We excluded subjects meeting the criteria of the World Health Organization for severe or complicated malaria, pregnant or lactating women, and children less than five years of age. Eligible subjects provided informed consent in accordance with U.S. Navy regulations governing the use of human subjects of medical research (SECNAVINST 3900.39B). A protocol detailing this work was reviewed and approved by American and Indonesian institutional review boards.

Therapy and follow-up. Subjects received directly observed therapy with chloroquine phosphate (uncoated scored tablets containing 150 mg base, Resochin™; P.T. Bayer Indonesia, Jakarta, Indonesia) in daily doses of 10 mg/kg on day 0 and day 1, and a 5 mg/kg dose on day 2. Subjects were observed for 30 minutes and repeated doses vomited in that time. Primaquine therapy for subjects infected by *P. vivax* was withheld until day 28 or at time of rescue therapy (oral quinine sulfate tablets; 10 mg/kg three times a day for seven days) with recurrent parasitemia. Thick and thin blood films were collected on days 0, 1, 2, 3, 4, 7, 11, 14, 18, 21, and 28, or at any time a subject complained of illness. Blood films were collected at the home or place of work/school. Subjects were queried about their recovery and well being during home visits.

Microscopy. Thick and thin blood films were stained with standard Giemsa reagents and examined under 1,000×, oil immersion light microscopy by experienced and certified research technicians. At least 200 fields were examined before a slide was considered negative. Positive blood films were recorded by the count of asexual parasites per 200 white blood cells. This value was converted to parasites per microliter of blood by assuming a white blood cell count of 8,000/μL.

Whole blood chloroquine levels. Peripheral blood collected into 100-μl heparinized capillary tubes was expelled onto filter paper (No. 1; Whatman, Maidstone, United Kingdom) discs on days 0 (before therapy), 3, and 28, or the day of rescue therapy of recurrent parasitemia. These blots were air-dried for several hours and placed into individual sealable plastic envelopes. These were stored at ambient temperature and protected from exposure to light or moisture for several months prior to analysis. We extracted and measured by high-performance liquid chromatography levels of chloroquine and its primary metabolite, desethylchloroquine (DCQ), using methods detailed elsewhere.[8,13]

Classification of the therapeutic response. We considered recurrent parasitemia with *P. falciparum* during the 28-day evaluation consistent with a resistant classification, provided there was evidence of good absorption of therapy (day 3 level of chloroquine plus DCQ > 500 ng/ml). For *P. vivax*, we considered recurrent parasitemia during the 28-day evaluation resistant to chloroquine if it occurred with ≥ 100 ng/ml of chloroquine plus DCQ (the minimal effective concentration), along with evidence of good absorption of therapy (> 500 ng/ml of chloroquine plus DCQ on day 3). The rationale for *P. vivax* classification has been explained elsewhere.[14] In this non-immune population, we considered parasitemia objective evidence of risk of clinical disease, whether disease was present or not at the point of observation.

Risk of therapeutic failure. We used life tables to estimate interval-specific and cumulative incidence (risk) of therapeutic failure. Cumulative incidence (CI) was calculated as follows: $CI_x = 1 - [(1 - CI_{x-1})(1 - IR_x)]$, where IR is the interval risk, X is the interval, and X - 1 is the prior interval. Recurrences consistent with a resistance classification were considered incident cases in the life table calculation.

Interpretation of the life table estimates of risk was according to species and interval of risk. For both *P. falciparum* and *P. vivax*, the 14-day cumulative risk of therapeutic failure was viewed as a conservative estimate of the prevalence of resistance to chloroquine in the community. These relatively early recurrences were considered more likely to be recrudescence than those appearing relatively late (days 15–28) when reinfection or relapse was more likely to confound the estimate of risk. The 28-day cumulative risk of recurrence was viewed as an estimate of therapeutic failure due to resistance, reinfection, or relapse.

RESULTS

Chloroquine plus DCQ blood levels. Table 1 lists the chloroquine plus DCQ whole blood levels prior to therapy on day 0, on day 3, or the day of recurrent parasitemia for *P. falciparum* or *P. vivax*. The mean level of chloroquine plus DCQ prior to administration of supervised therapy was 198, 200, and 234 ng/ml for *P. falciparum*, *P. vivax*, and mixed infections, respectively. The proportion of subjects with evidence of chloroquine on day 0 was 92% for *P. falciparum*, 83% for *P. vivax*, and 90% for mixed infections. The chloroquine plus DCQ levels at day 3 confirmed uniformly good absorption, with all subjects having > 500 ng/ml. The chloroquine plus DCQ levels on the day of persistent or recurrent parasitemia prompting alternative therapy were at least 142 ng/ml and as high as 4,423 ng/ml. The proportion of subjects with persistent or recurrent parasitemia with chloroquine plus DCQ levels

TABLE 1
Mean (range) whole blood levels of chloroquine plus desethylchloroquine during evaluation

Infection	Day 0		Day 3		Day of recurrence		
	n	ng/ml (range)	n	ng/ml (range)	n	ng/ml (range)	% > MEC*
P. falciparum	51	198 (0–922)	51	2,069 (866–8,870)	49	714 (142–3,583)	98
P. vivax	29	200 (0–843)	29	1,704 (914–3,489)	25	889 (180–2,754)	100
P. falciparum plus *P. vivax*	20	234 (0–795)	20	1,588 (997–2,368)	18	953 (238–4,423)	100

* MEC = minimal effective concentration: 200 ng/ml for *Plasmodium falciparum* and 100 ng/ml for *P. vivax.*

exceeding the minimal effective concentration (200 ng/ml for *P. falciparum* and 100 ng/ml for *P. vivax*) was 98% for *P. falciparum*, 100% for *P. vivax*, and 100% for mixed infections.

Risk of therapeutic failure. Table 2A lists the life table calculation for estimating risk of therapeutic failure of chloroquine against *P. falciparum*. The evaluation began on day 0 with 55 subjects at risk. Almost half the subjects failed to clear parasitemia by day 4 and thus prompted rescue therapy with quinine. By day 14 of the evaluation, only 14 subjects remained at risk, and by day 28, only one subject remained free of parasitemia. One subject was lost to follow-up and three others required alternative therapy as a consequence of intercurrent parasitemia by *P. vivax*. The 14-day risk of therapeutic failure was 84%. At day 28, the risk was 95%.

Table 2B lists the life table calculation for estimating risk of therapeutic failure of chloroquine against *P. vivax*. The evaluation began on day 0 with 29 subjects at risk. Seven subjects failed to clear parasitemia by day 4 and thus prompted rescue therapy with quinine. Three subjects had intercurrent *P. falciparum* parasitemia and received rescue therapy with quinine by day 4. By day 14, only nine subjects remained at risk, and by day 28, only one subject remained free of parasitemia. All losses to follow-up listed in the withdrawals column were due to intercurrent *P. falciparum* prompting rescue therapy. Evaluation of therapeutic failure for *P. falciparum* and *P. vivax* mixed infections began on day 0 with 20 subjects at risk. Thirteen of these failed to clear parasitemia by day 4 (10 *P. falciparum* and 3 *P. vivax*). By day 14, all of the remaining seven subjects had recurrent parasitemia (6 *P. falciparum* and 1 *P. vivax*).

Table 3 lists the proportion of infections in this study population having parasitologic evidence and chloroquine plus DCQ levels supporting the diagnosis of resistance to chloroquine. The total number of infections by *P. falciparum* or *P. vivax* (placing the mixed infections in both columns) was 75 and 49. All withdrawals except one were due to the administration of alternative therapy for parasitemia by the other species: 7 for *P. falciparum* and 25 for *P. vivax*. *Plasmodium falciparum* interfered with the *P. vivax* evaluation in approximately half of the infections. Among the 67 *P. falciparum* infections (all had adequate absorption), all but one required alternative therapy, and all but another one occurred with chloroquine plus DCQ levels above the minimal effective concentration. Therefore, 99% of the *P. falciparum* infections successfully evaluated ended with therapeutic failure. Among the 24 infections by *P. vivax* that were evaluated (all had adequate absorption), 23 ended with a requirement for alternative therapy. Therefore, 96% of infections by *P. vivax* fully evaluated ended with a requirement for alternative therapy.

In almost all instances of early therapeutic failure, the subjects had substantially lower parasite counts and had recovered clinically. Later recurrences also had substantially lower parasite counts relative to enrollment and most remained asymptomatic. No enrolled subject progressed to severe or complicated disease, and none required hospitalization during the evaluation.

TABLE 2
Life table estimates of risk of therapeutic failure of chloroquine

A *Plasmodium falciparum*

Interval (day)	Sample at risk	Incident cases	Withdrawals	Interval risk	Cumulative risk
0	55	0	0	0	0
4	54	25	0	0.4630	0.4630
7	29	5	0	0.1724	0.5556
11	24	10	0	0.4167	0.7408
14	14	5	1	0.3707	0.8368
18	8	5	1	0.6667	0.9456
21	2	0	1	0	0.9456
28	1	0	1	0	0.9456

B *Plasmodium vivax*

Interval (day)	Sample at risk	Incident cases	Withdrawals	Interval risk	Cumulative risk
0	29	0	0	0	0
4	29	7	0	0.2545	0.2545
7	29	5	3	0.1714	0.3827
11	19	3	3	0.2400	0.5309
14	9	1	0	0.1111	0.5830
18	8	4	3	0.6154	0.8396
21	1	0	0	0	0.8396
28	1	0	0	0	0.8396

DISCUSSION

These findings demonstrate very high risk of therapeutic failure with standard chloroquine therapy for uncomplicated *P. falciparum* and *P. vivax* malaria in northeastern Indonesian Papua. The proportion of subjects successfully completing the *in vivo* test and presenting evidence of resistance was 99% and 96% for *P. falciparum* and *P. vivax*, respectively (Table

TABLE 3
Confirmed resistance to chloroquine at Arso PIR V, Papua

	Plasmodium falciparum	*Plasmodium vivax*
Sample at risk	75	49
Withdrawals	8	25
Adequate absorption*	67	24
Recurrence with >MEC†	66	23
Resistant to chloroquine	66	23
% resistant to chloroquine	99	96

* Adequate absorption was >500 ng/ml of chloroquine plus desethylchloroquine on day 3.
† MEC = minimal effective concentration: 200 ng/ml for *P. falciparum* and 100 ng/ml for *P. vivax.*

3). The estimates of 28-day cumulative incidence of therapeutic failure (Table 2) for these species were lower (95% and 84%) due to withdrawals caused by intercurrent parasitemia by the other species, prompting therapy. By either method of estimating risk for both species, chloroquine therapy routinely failed within 28 days. Comparing these estimates of risk with earlier studies in the same region,[5–9] suggests an apparently rapid deterioration of therapeutic efficacy for *P. vivax*.

An attractive option for bringing combined therapies to bear on the problem of drug-resistant malaria is chloroquine plus pyrimethamine/sulfadoxine. The interest in this regimen, with good efficacy demonstrated in a few studies and interventions,[15,16] stems largely from the relative ease with which it could be adopted. Both drugs are already stocked by government-operated clinics across Indonesia. Health care providers need only change how they administer the drugs, thereby substantially saving on administrative/education costs compared with introducing new therapies. A critical question for this strategy is efficacy against a backdrop of resistance to chloroquine and pyrimethamine/sulfadoxine as monotherapies. When is it too late to apply the combined therapy with a reasonable expectation of good efficacy? Finding that threshold becomes a vital public health issue where deployment of combined chloroquine and sulfadoxine/pyrimethamine may be considered. Areas having risk of therapeutic failure exceeding that threshold may be targeted for more effective (and expensive) therapies. Reliable estimates of resistance to chloroquine and sulfadoxine/pyrimethamine should guide information-based decisions on adopting either a new first line combined therapy, or deploying relatively expensive alternatives. In the specific case of northeastern Papua, the available data[6,8,10] support abandoning chloroquine therapy either as monotherapy or combined with another agent. This heavily malarious region seems a good candidate for targeted distribution of artemisinin derivatives combined with mefloquine or another agent that has not yet lost clinical efficacy.

Standard protocols for therapeutic assessments of drugs for the treatment of uncomplicated malaria strive to accomplish uniformity across laboratories and investigators representing a wide range of capabilities. The tests present realistic goals with respect to obtaining useful information in the setting of a rural health clinic in the tropics. A national program successfully developing such a surveillance network will possess a powerful tool for information-based decisions on malaria therapy policies and practice. Indonesia has not yet developed such a network. The relatively few studies of the therapeutic response to standard antimalarials come from research laboratories. Research laboratories may have compelling reasons to not follow standardized protocols for surveillance of resistance. These facilities typically send a team of specialists to a remote area with the intent of obtaining as much useful information as possible within a practical time. For example, teams of specialists living in Jakarta cannot remain indefinitely at a remote health clinic in far off Papua. Personal and economic priorities necessarily minimize time spent in the field. Therefore, it is not often possible to follow standardized protocols designed and intended for rural health clinic staff resident at the site. The passive collection of study subjects is not practical for the visiting research team. Instead, research teams actively seek out study subjects by mass slide screening, essentially as described in this study. Also, we have found it impractical to exclude patients with parasitemias less than 1,000/μL for *P. falciparum* or less than 300/μL for *P. vivax*. In the areas we work, 85% of otherwise eligible subjects fall below these levels. Strict adherence to this criterion would result in a diminishingly small sample size within the time constraints imposed by a visiting research team. Moreover, systematic exclusion of relatively low-grade parasitemia, often representing the majority of patients presenting for treatment, could create a deeply biased sample with respect to estimating risk of therapeutic failure in a community. We also include patients with mixed infections of *P. falciparum* and *P. vivax*. Our microscopists consistently and reliably detect mixed infections and are not confused by the species identity of the recurrence. The intent of broader inclusion criteria is maximizing the collection of useful information obtained from the remote post with a fixed and relatively brief period, while also minimizing risk of sample bias in the estimate of risk.

In summary, we documented nearly complete resistance to chloroquine by *P. falciparum* and *P. vivax* in non-immune Javanese migrants taking residence in hyperendemic to holoendemic northeastern Papua, Indonesia. We know of no other area of Indonesia with such high risk of therapeutic failure with chloroquine. These findings support adopting a therapeutic strategy tailored to this region, and provide a backdrop of risk of therapeutic failure for evaluations of combined therapies that include chloroquine as treatment options.

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