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MAJOR ARTICLE

Randomized, Parallel Placebo-Controlled Trial of Primaquine for Malaria Prophylaxis in Papua, Indonesia

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Malaria causes illness or death in unprotected travelers. Primaquine prevents malaria by attacking liver-stage parasites, a property distinguishing it from most chemoprophylactics and obviating 4-week postexposure dosing. A daily adult regimen of 30 mg primaquine prevented malaria caused by *Plasmodium falciparum* and *P. vivax* for 20 weeks in 95 of 97 glucose-6-phosphate dehydrogenase (G6PD)–normal Javanese transmigrants in Papua, Indonesia. In comparison, 37 of 149 subjects taking placebo in a parallel trial became parasitemic. The protective efficacy of primaquine against malaria was 93% (95% confidence interval [CI] 71%–98%); against *P. falciparum* it was 88% (95% CI 48%–97%), and >92% for *P. vivax* (95% CI >37%–99%). Primaquine was as well tolerated as placebo. Mild methemoglobinemia (mean of 3.4%) returned to normal within 2 weeks. Blood chemistry and hematological parameters revealed no evidence of toxicity. Good safety, tolerance, and efficacy, along with key advantages in dosing requirements, make primaquine an excellent drug for preventing malaria in nonpregnant, G6PD-normal travelers.

A global resurgence in the incidence and range of malaria, together with deteriorating susceptibility to drugs, substantially increases risk to travelers [1]. Available drugs for preventing malaria include chloroquine, chloroquine or atovaquone plus proguanil, mefloquine, and doxycycline [2]. The efficacy of chloroquine or chloroquine plus proguanil is rarely >75%. Resistance to mefloquine occurs in parts of Southeast Asia, and some travelers tolerate it poorly [3, 4]. Pregnant women or young children cannot use doxycycline, and it may be poorly tolerated [5]. Atovaquone plus proguanil has only recently been licensed for prophylaxis, and there is limited experience with it. Resistance, contraindications, or poor tolerance limits choices for health care providers assisting travelers at risk. Poor compliance to postexposure suppressive prophylaxis accounts for many cases of malaria among travelers [6, 7]. Travelers with brief exposure, a week or less, may be especially unlikely to comply.

Malarone prevents *Plasmodium falciparum* with only 7 days postexposure dosing [8] by killing liver stage parasites (i.e., by causal prophylaxis). Early clinical trials of primaquine [9, 10], since 1950 the only drug recommended for therapy against relapses of malaria,

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This study was reviewed and approved by American and Indonesian committees for the ethical treatment of human subjects of medical research, and informed consent was obtained in accordance with US Navy regulations covering human subjects of medical research (SECNAVINST 3900.39B).

The views and opinions of the authors expressed herein are their own and do not purport to reflect those of the US Navy, the US Department of Defense, or the Indonesian Ministry of Health and Social Welfare.

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demonstrated causal prophylactic activity against *P. falciparum* and *P. vivax*. Primaquine was not then developed as a chemoprophylactic. Almost universal susceptibility of plasmodia to weekly chloroquine during the 1960s, and perceived poor tolerance and toxicity of primaquine [11], overshadowed the appealing advantages of primaquine for prophylaxis. In 1991, Hoffman [12] proposed primaquine for prophylaxis, and in 1995 we reported the results of 4 clinical trials in people exposed to infection in Indonesia and Kenya [13–15]. These trials showed good tolerance, safety, and efficacy of a 30-mg daily adult regimen (or 15 mg daily for children). Soto et al. [16] corroborated those findings in Colombian soldiers. A study of Israeli travelers by Schwartz and Regev-Yochay [17] affirmed good effectiveness of the regimen compared to mefloquine or doxycycline. The present report describes a trial of primaquine for the prevention of malaria in people lacking clinical immunity who are living in Papua.

SUBJECTS AND METHODS

Study sites. The transmigration villages SP4, SP5, and SP6, located in the Bonggo district of northeastern Papua (formerly Irian Jaya), served as study sites. Each village was within 2 km of the Pacific Ocean and surrounded by dense rain forest. Homes within the village were of uniform wood plank and tin roof construction. The total populations of the villages were ~980, 1410, and 1510 persons, respectively. The residents were predominantly Javanese (65%) but included people from other major islands of Indonesia (20%) and people indigenous to the region (15%). Perennial transmission of *P. falciparum, P. vivax, P. malariae,* and *P. ovale* occurs in the region [18, 19]. The vectors of malaria, members of the *Anopheles punctulatus* group, feed within villages from dusk to dawn and efficiently transmit malaria [20].

Study subjects. Residents of the study villages between the ages of 12 and 65 years living in Papua for >3 and <26 months were eligible for enrollment. Eligible subjects came from Jaya or other nonendemic areas and had lived in areas free of malaria for ⩾2 years prior to relocation. Eligible subjects weighed ⩾40 kg. We excluded pregnant or lactating women and those expressing plans to become pregnant. Seven volunteers (0.8%) who tested positive for glucose-6-phosphate dehydrogenase (G6PD) deficiency (NADP+ spot test, Sigma Chemical) among the 837 screened were excluded. Volunteers referred to hospital for treatment of acute or chronic diseases were excluded.

Enrollment. From April through December 1999, we screened volunteers for enrollment. Eligible volunteers submitted to a physical examination including measuring vital signs, palpation of the spleen, and examination by a physician. Blood cell counts were analyzed (Becton Dickinson QBCII Plus Analyzer system and reagents), as were blood chemistries (Kodak VITROS DTII). Women of childbearing age were asked to contribute a urine specimen for pregnancy testing by analysis for human chorionic gonadotropin (HCG; Abbott Laboratories). A total of 837 volunteers were screened, and 421 were enrolled for treatment against both the blood and liver stages of the parasite (hereafter referred to as "radical cure"). Plans to leave the study area, history of recent residence in an endemic area, or unwillingness to provide consent to participate constituted the 3 most common reasons for exclusion (29%, 24%, and 11% of exclusions, respectively).

Radical cure. The subjects received directly observed, signature-affirmed radical curative therapy with atovaquone-proguanil (tablets combining 250 mg atovaquone + 100 mg proguanil hydrochloride; Malarone; GlaxoSmithKline) and primaquine phosphate (Sanofi-Winthrop). The cure consisted of single daily doses of 4 tablets of atovaquone-proguanil on days 0, 1, and 2, followed by single daily doses of 30 mg primaquine base (2 tablets) on days 3–16.

Randomization. A total of 394 subjects completed radical cure with adequate compliance: 385 missed no dose; 6 missed a single dose of primaquine; 2 missed 2 doses of primaquine; and 1 missed 3 doses of primaquine. Randomization of subjects occurred on the last day of radical cure. The clinical statistics department at Glaxo Wellcome (USA) generated a randomization code assigning sequential numbers to either inclusion in a parallel double-blind, placebo-controlled trial of atovaquone-proguanil for prophylaxis or exclusion from that trial in a 3:1 ratio. The 97 subjects randomized to exclusion were offered the opportunity to enter the open label trial of primaquine prophylaxis and all accepted. These subjects again provided informed consent specific to that study and began prophylaxis the following day.

Prophylaxis. The study drug was 15 mg of primaquine base as phosphate salt in a coated, unscored tablet (Sanofi-Winthrop). The drug was dispensed to health workers on a daily basis. Each health worker was assigned 8–12 subjects and tasked with visiting their homes each morning to administer the drug with morning meal. A packet of 3 cookies was provided with each dose (30 mg primaquine base as a single daily dose). The health worker and subject verified compliance by signatures on a dosing card. At the end of each day, supervisors crosschecked the signatures of dosing cards and affirmed agreement by signing a record sheet.

Any complaint consistent with onset of malaria (i.e., headache, fever, chills, nausea, vomiting, or malaise) prompted an immediate blood film examination. Routine blood films were collected once a week, regardless of symptoms. Female subjects of childbearing age donated a urine sample for monthly HCG testing, or any time pregnancy was suspected. We evaluated a sample of venous blood for hematological and blood chemistry parameters at weeks 4 and 20 of prophylaxis.

Table 1. Demographic characteristics of patients in study groups.

Variable	Primaquine (n = 97)	Placebo (n = 149)	P
Mean age in years (range)	33.3 (14–60)	33.6 (12–60)	.808
Mean weight in kg (range)	51.4 (40–73)	51.2 (40–71)	.814
Male:female	61:36	101:48	.43
Mean exposure, months[a]	20.8	20.5	.26
Dropout rate[b]	15 (0.155)	27 (0.181)	.59

[a] Time resident in Papua prior to enrollment.
[b] Subjects lost to follow-up for reasons other than study end points during prophylaxis.

End points. Prophylaxis continued for 20 weeks or until a subject had a blood film positive for plasmodia. Study microscopists were examined and certified to be >95% sensitive and 100% specific in diagnosis of a set of 25 slides containing confirmed negative or positive blood films ascertained by 3 expert microscopists, each with >20 years of experience. Study microscopists read 200 ocular fields of Giemsa-stained thick films magnified to 1000× by standard oil immersion light microscopy. A second microscopist affirmed positive blood films. A third expert microscopist adjudicated discordant readings. Parasitemia density was calculated as parasites per 200 WBCs in the thick film × 8000 WBCs/μL whole blood. Subjects positive for plasmodia received atovaquone-proguanil (as per radical cure) and were dropped from the study after successful therapy was affirmed with 28 days follow-up. Subjects missing >2 doses primaquine in any 7-day period were considered noncompliant and dropped from the study. Subjects leaving the study site for ≤7 days took along a travel pack containing daily primaquine and a signature card. Travel for >7 days prompted withdrawal from the study.

Postprophylaxis follow-up. Subjects completing 20 weeks of prophylaxis were followed for 4 weeks. Blood film samples were examined at 2 and 4 weeks. A 100-μL sample of peripheral blood was taken by finger stick from subjects on the last day of primaquine or placebo prophylaxis and then daily for 18 days. We measured levels of total hemoglobin, oxyhemoglobin, and methemoglobin from these samples, using a co-oximeter (OSM3, Radiometer Copenhagen) within 30 min of collection.

Statistical analyses. The primary end point of the study was parasitemia. Protective efficacy was defined as $(1 - \text{incidence density}_{drug}/\text{incidence density}_{placebo}) \times 100$. Adverse events were reported as incidence density, or the number of events per person-time of follow-up. Differences in means were assessed using the paired or unpaired Student's t test, or Mantel Haenszel test. P values ≤.05 were considered significant. Anal-

Table 2. Adverse events during 20 weeks of daily primaquine prophylaxis.

	Primaquine		Placebo				
Adverse event	No. of events	Incidence density	No. of events	Incidence density	RR	95% CI	P
Headache	34	1.01	74	1.63	0.62	0.41–0.93	.02
Abdominal pain	34	1.01	33	0.73	1.39	0.86–2.23	.18
Cough	31	0.92	84	1.85	0.50	0.33–0.74	<.001
Nausea	20	0.59	34	0.75	0.79	0.46–1.38	.41
Dizziness	19	0.56	19	0.42	1.35	0.72–2.53	.36
Neck/back pain	18	0.53	19	0.42	1.28	0.67–2.42	.46
Cold/flu	18	0.53	30	0.66	0.81	0.45–1.45	.47
Pruritis	15	0.45	30	0.66	0.67	0.36–1.25	.21
Myalgia	15	0.45	22	0.49	0.92	0.47–1.78	.80
Fever	14	0.42	29	0.64	0.65	0.35–1.23	.18
Malaise	12	0.33	14	0.31	1.15	0.54–2.48	.72
Arthralgia	12	0.36	21	0.46	0.77	0.38–1.56	.47
Diarrhea	9	0.27	13	0.29	0.93	0.39–2.20	.87
Vomiting	9	0.27	8	0.18	1.51	0.59–3.89	.39
Chills	7	0.21	5	0.11	1.88	0.61–5.82	.27
Chest pain	6	0.18	6	0.13	1.35	0.44–4.14	.61
Sore throat	6	0.18	24	0.53	0.34	0.14–0.79	.01
Respiratory difficulty	5	0.15	15	0.33	0.45	0.17–1.20	.11
Anorexia	4	0.12	2	0.04	2.69	0.53–13.7	.23
Insomnia	5	0.15	3	0.07	2.24	0.56–9.0	.26

Table 3. Findings of hematological assays (mean ± SD) among subjects taking primaquine or a parallel placebo.

Parameter	Enrollment		Week 4		Week 20	
	Placebo (n = 149)	Primaquine (n = 97)	Placebo (n = 137)	Primaquine (n = 92)	Placebo (n = 116)	Primaquine (n = 82)
Total lymphocytes + monocytes × 10^9 cells/L	3.68 ± 1.3	3.63 ±1.3	3.38 ± 1.1	3.09 ± 0.96	3.07 ± 1.21	2.79 ± 0.86
Lymphocytes + monocytes, %	40.2 ± 8.9	41.3 ± 10.7	38.8 ± 8.7	36.3 ± 8.1	38.1 ± 10.6	35.9 ± 7.6
Total granulocytes × 10^9 cells/L	5.7 ± 2.0	5.36 ± 1.8	5.6 ± 1.8	5.57 ± 1.9	5.16 ± 2.1	5.11 ± 1.5
Granulocytes, %	59.8 ± 8.9	58.7 ± 10.8	61.3 ± 8.2	63.7 ± 8.1	61.6 ± 10.2	64.1 ± 7.6
Total WBCs × 10^9 WBCs/L	9.37 ± 2.7	8.99 ± 2.5	8.92 ± 2.4	8.64 ± 2.4	8.2 ± 2.6	7.9 ± 1.9
Hemoglobin, g/dL	13.4 ± 1.5	13.4 ± 1.8	13.6 ± 1.3	13.3 ± 1.5	13.5 ± 1.5	13.1 ± 1.4
Hematocrit level, %	41.1 ± 4.7	41.2 ± 5.4	43.8 ± 4.2	42.7 ± 4.4	42.4 ± 3.8	41.4 ± 3.5
Platelets × 10^9 platelets/L	264 ± 74	271 ± 91.3	271 ± 86	256 ± 75.2	254 ± 95	248 ± 77

yses were carried out using SPSS (version 9.0; SPSS) and Epi Info (version 6.04; Centers for Disease Control and Prevention).

RESULTS

Compliance. Fifteen (16%) of 97 subjects taking primaquine and 27 (18%) of 149 taking placebo withdrew from the study before reaching an end point. The week of withdrawal from the primaquine group ranged from 1 to 19 (median, week 10). The subjects contributed person-time at risk applied to tolerance, toxicity, and efficacy estimates up to point of withdrawal. Reasons cited for dropping subjects included withdrawal of consent (13) and failure to comply with protocol (2). One of the noncompliant subjects left the study site for >1 week, and he developed *P. falciparum* upon return. The other missed medication more than twice in 1 week. No subject cited adverse events as the basis of withdrawal. The 16% dropout rate (excluding malaria) was similar to the 18% rate among subjects receiving placebo ($P = .59$; table 1). Excluding dropped subjects, 12,233 doses were scheduled, and 12,201 (99.8%) were delivered.

Tolerability. No adverse event prompted withdrawal from the study, and no serious adverse events occurred. Table 2 lists the 20 most frequent adverse events. The only adverse events with statistically significant relative risk (primaquine compared to parallel placebo; $P < .05$) were headache ($RR = 0.62$), cough ($RR = 0.50$), and sore throat ($RR = 0.34$). $RR < 1.0$ indicates lesser risk in the primaquine group. Among the 17 other adverse events, no RR was significant. Among all 40 adverse event classifications evaluated with a total of 933 complaints registered, the RR in the primaquine group was 0.80 (95% CI 0.70–0.92; $P = .001$).

Hematological parameters. No hematological test outcome prompted withdrawal from the study in any subject taking prophylaxis. Table 3 summarizes hematological tests of subjects taking primaquine prior to radical cure, and at weeks 4 and 20 of prophylaxis. The difference between some values was statistically significant: mean total lymphocyte counts, mean % lymphocytes and monocytes, % granulocytes, and total WBC count. No difference was considered clinically significant, and all other comparisons showed no other statistically significant differences. The same was true for subjects receiving placebo, except statistically significant differences occurred with mean hematocrit level (%), total lymphocytes + monocytes, total WBCs, and platelet count. In the statistical comparison of these parameters between subjects taking primaquine and placebo at baseline, week 4 and week 20, significant differences appeared between mean total lymphocytes + monocytes, and mean total platelets. No difference was considered clinically significant.

Blood chemistry parameters. No blood chemistry test result prompted withdrawal of study subjects taking prophylaxis. Table 4 summarizes blood chemistry findings among subjects taking primaquine at enrollment, week 4, and week 20. Among the 4 significant differences from baseline (2 at week 4 and 2 at week 20) in mean sodium, potassium, albumin, and creatinine, respectively, none appeared clinically significant. The same was true for the placebo group for mean potassium, bilirubin (week 4), and glucose (week 20). All other comparisons between means at enrollment and week 4 and 20 for either primaquine or placebo were not significant (P values ranged from .051 to .99). Comparisons of primaquine to placebo matched at baseline, week 4, and week 20 again showed no statistically significant differences, except between a minority of clinically insignificant distinctions (for sodium and bilirubin).

Methemoglobinemia. No subject complained of symptoms attributable to methemoglobinemia during the course of radical cure or prophylaxis. Figure 1 illustrates mean measurements of total, oxyhemoglobin, and methemoglobin among subjects taking primaquine beginning on the last day of prophylaxis. The graph reveals essentially normal levels of total and oxyhemoglobin through the 18 days of measurements and a mild methemoglobinemia (mean 3.5% of total hemoglobin, not exceeding

Table 4. Findings of blood chemistry assays (mean ± SD) among subjects taking primaquine or a parallel placebo.

Parameter	Enrollment		Week 4		Week 20	
	Placebo (n = 149)	Primaquine (n = 97)	Placebo (n = 137)	Primaquine (n = 92)	Placebo (n = 116)	Primaquine (n = 82)
Sodium, meq/L	138 ± 4.0	138 ± 3.6	140 ± 4.1	140 ± 6.3	137 ± 3.6	139 ± 3.2
Potassium, meq/L	3.69 ± 0.4	3.64 ± 0.5	3.83 ± 0.4	3.79 ± 0.4	3.79 ± 0.4	3.64 ± 0.30
Albumin, g/dL	4.15 ± 0.4	4.16 ± 0.4	4.21 ± 0.4	4.15 ± 0.3	4.06 ± 0.4	4.00 ± 0.40
Creatinine, mg/dL	1.12 ± 0.2	1.13 ± 0.2	1.08 ± 0.2	1.07 ± 0.2	1.1 ± 0.2	1.1 ± 0.20
Glucose, mg/dL	91.0 ± 20	91.9 ± 21	94.2 ± 22	94.6 ± 17	102 ± 24	96.5 ± 19
Total bilirubin, mg/dL	0.42 ± 0.2	0.47 ± 0.3	0.30 ± 0.2	0.53 ± 0.6	0.43 ± 0.3	0.42 ± 0.3
Alk phosphatase, U/L	84.1 ± 26	76.8 ± 23	87.9 ± 35	84.4 ± 35	84.1 ± 26	76.8 ± 24
ALT (SGPT), U/L	17.4 ± 10	18.8 ± 13	16.7 ± 12	18.6 ± 10	18.6 ± 10	18.5 ± 7.7

NOTE. Alk, alkaline; ALT (SGPT), alanine aminotransferase (serum glutamic pyruvic transaminase); meq, milliequivalents.

8.5%) on the last day of prophylaxis resolving by day 18. At day 28, the mean methemoglobinemia among 72 subjects was 0.5%, not exceeding 0.8%. The highest methemoglobin among any subject was 8.5% on the last day of prophylaxis.

Efficacy. Table 5 summarizes infections by plasmodia among study subjects. A total of 39 infections occurred among subjects taking placebo, 23 by *P. falciparum* and 16 by *P. vivax.* Two subjects had mixed infections by *P. falciparum* and *P. vivax,* and each infection counted among others of the same species. Two infections by *P. falciparum* occurred among compliant subjects taking primaquine prophylaxis. Protective efficacy against *P. falciparum* was estimated at 88% (95% CI 48%–97%). No infections by *P. vivax* occurred among primaquine-compliant subjects. The estimate of protective efficacy for *P. vivax,* >92% (95% CI >37%–99%) assumed a single infection. The protective efficacy against plasmodia of either species was 93% (95% CI 71%–98%).

No evidence of rebound parasitemia appeared among subjects finishing the 20 weeks of primaquine. Postprophylaxis follow-up for 4 weeks revealed 1 parasitemia (*P. falciparum* during week 4) among the 77 at risk in the primaquine group. This was not significantly different from the 3 postprophylaxis parasitemias occurring in the 85 subjects completing placebo.

Illness on the day of parasitemia documented the nonimmune status of study subjects. Among the 37 subjects with slide-proven malaria, 21 (57%) had documented fever (axillary temperature >37.5°C), and 33 (89%) complained of fever, chill, headache, nausea, vomiting, myalgia, or malaise (table 6).

DISCUSSION

A 30-mg daily adult regimen of primaquine provided well-tolerated, safe, and efficacious protection against *P. falciparum* and *P. vivax* for 20 weeks in G6PD-normal people living in northeastern Papua. No serious adverse events occurred, and no subject was removed from the study because of intolerance or evidence of toxicity. Subjects taking primaquine registered complaints of adverse events less often than did subjects in a parallel placebo group (RR = 0.80; 95% CI 0.70–0.92; P = .001). Most hematological and blood chemistry parameters before prophylaxis were indistinguishable from those measured after 4 or 20 weeks. The few differences noted were between means within normal ranges. The same was true of hematological values (tables 3 and 4). Mild methemoglobinemia on the last day of prophylaxis resolved within 18 days. Methemoglobinemia after 52 weeks [15] or 20 weeks of 30 mg primaquine daily was no more pronounced than in subjects receiving standard 15 mg daily for 14 days [21]. The risk of methemoglobinemia did not increase with duration of dosing. Methemoglobin levels observed in this study did not approach the 20%–30% level considered the threshold at which symp-

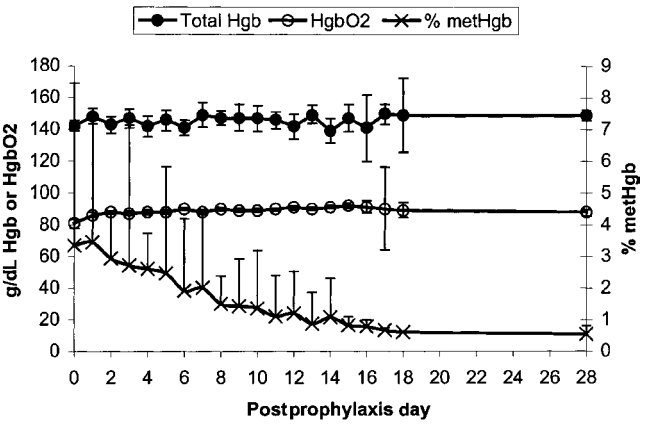

Figure 1. Mean levels of total hemoglobin (Hgb g/dL [●]), oxyhemoglobin (HgbO2 g/dL [○]) and methemoglobin (metHgb; % of total Hgb [×]) among a median of 22 measurements per data point (range, 2–72). Bars indicate 95% confidence limits for mean total Hgb and HbgO2 and mean % metHgb with upper range shown in the bar.

Table 5. Protective efficacy of 30 mg of primaquine given daily for 20 weeks.

Variable	Person-years at risk	*Plasmodium falciparum*	*Plasmodium vivax*	Any species
Primaquine	33.7	2	0	2
Placebo	45.3	23	16	39
Efficacy, % (95% CI)	—	88 (48–97)	>92[a] (>37–99)	93 (71–98)

[a] Assumes a single infection by *P. vivax*.

toms such as dyspnea or nausea occur [22]. Contrary to often-cited reports [11, 23], primaquine caused no more stomach upset than did placebo (table 2). We attributed this to administration of drug with food. Clayman et al. [24] demonstrated relief from even severe stomach upset with extraordinary doses of primaquine (≤240 mg) by administration with food.

The protective efficacy of 30 mg daily primaquine against infection by plasmodia was 93% (95% CI 71%–98%). An earlier trial in 43 subjects for 52 weeks in the same region [15] showed 92% efficacy (95% CI 79%–99%). Soto et al. [16] reported 89% protective efficacy (95% CI 75%–96%) against infection of 167 Colombian soldiers for 16 weeks. Weiss et al. [14] evaluated 15 mg daily in 32 Kenyan children and measured a protective efficacy against *P. falciparum* of 85% (95% CI 67%–94%). Randomized, placebo-controlled clinical trials of daily primaquine in 339 subjects living in Southeast Asia, South America, and Africa demonstrate consistently excellent protective efficacy. Corroboration of the earlier trials by our findings confirms the excellent protective efficacy and good safety and tolerability of daily primaquine for preventing *P. falciparum* and *P. vivax* in travelers. Moreover, Schwartz and Regev-Yochay [17] reported superior effectiveness of the 30 mg daily primaquine regimen compared to mefloquine or doxycycline in Israeli travelers.

Available data demonstrate the necessity of 30 mg daily as the adult dose for good protective efficacy. When Arnold et al. [10] tried a daily 15-mg dose against challenge by *P. vivax*, the protective efficacy was 80% (8 of 10 subjects protected) compared to 100% (10 of 10 protected) for 30 mg daily. When they gave a single 15-mg dose the day following challenge with *P. falciparum*, the protective efficacy was 40% (4 of 10 protected) compared to 100% (10 of 10 protected) for the single 30-mg dose [9]. When Powell et al. [25] challenged 3 subjects taking daily 30 mg primaquine, none became parasitemic; however, 1 of 3 subject taking 15 mg daily became parasitemic. When we evaluated a 30-mg regimen on alternate days in Indonesia ($n = 45$), the protective efficacy was just 74% (95% CI 21%–94%) against *P. falciparum* [12]. A similar alternate day regimen evaluated by Weiss et al. [14] showed 0% (95% CI 0%–50%) protective efficacy against *P. falciparum* in 39 Kenyan children.

Table 6. Illness with slide-proven malaria.

Group, report of illness	Infection		
	Plasmodium falciparum	*Plasmodium vivax*	Mixed
Primaquine			
Reported	1	0	0
Not reported	1	0	0
Placebo			
Reported	19	11	2
Not reported	2	3	0
Either			
Reported	20	11	2
Not reported	3	3	0
Ill, %	87	79	100

Primaquine substantially improves the range of chemoprophylactic options for preventing malaria in travelers. The primary advantage over currently available suppressive prophylactics such as mefloquine or doxycycline is freedom from the necessity of 4 weeks of postexposure prophylaxis. Travelers often fail to comply with a lengthy postexposure dosing regimen [26–29]. This may be especially true of travelers who have had relatively brief periods of exposure to risk of infection. Travelers facing risk of infection spanning just a few days may be unlikely to accept and comply with a regimen of 4 weeks of postexposure dosing. Primaquine offers these travelers a dosing regimen that spans the period of exposure and just 2–6 days after returning home. Finally, a loading regimen of primaquine is not necessary.

The safe limit of duration of prophylaxis using primaquine has not been firmly established. Randomized trials of daily primaquine for prophylaxis have ranged from 12 to 52 weeks [13–16]. No complaint became more frequent as the cumulative dose increased. Methemoglobinemia did not increase after 20 (figure 1) to 52 weeks [15] of daily dosing compared to the standard 14-day treatment regimen [19]. Except for the 42 subjects taking daily primaquine for 52 weeks, all other studies have spanned 12–20 weeks of daily dosing. Therefore, the safe duration of primaquine dosing may be estimated between 12 and 20 weeks.

In summary, a 30-mg daily adult regimen of primaquine provided well-tolerated, safe, and efficacious prophylaxis against *P. falciparum* and *P. vivax* for 20 weeks among nonimmune people

living in endemic Papua. The findings corroborate trials in a nearby area, in mesoendemic South America, and in holoendemic Africa [13–17]. Primaquine offers health care providers an excellent option to standard suppressive prophylactics for travelers exposed to malaria. Primaquine should not be used by pregnant women, because of the risk to the fetus of hemolysis with G6PD deficiency, and prescribing primaquine for prophylaxis should only follow laboratory ascertainment of a normal G6PD phenotype.

NAMRU-2 CLINICAL TRIALS TEAM

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