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Randomized, Placebo-Controlled Trial of Atovaquone/Proguanil for the Prevention of *Plasmodium falciparum* or *Plasmodium vivax* Malaria among Migrants to Papua, Indonesia

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MAJOR ARTICLE

Randomized, Placebo-Controlled Trial of Atovaquone/Proguanil for the Prevention of *Plasmodium falciparum* or *Plasmodium vivax* Malaria among Migrants to Papua, Indonesia

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The increasing prevalence of resistance to antimalarial drugs reduces options for malaria prophylaxis. Atovaquone/proguanil (Malarone; GlaxoSmithKline) has been >95% effective in preventing *Plasmodium falciparum* malaria in lifelong residents of areas of holoendemicity, but data from persons without clinical immunity or who are at risk for *Plasmodium vivax* malaria have not been described. We conducted a randomized, double-blinded study involving 297 people from areas of nonendemicity in Indonesia who migrated to Papua (where malaria is endemic) ≤26 months before the study period. Subjects received prophylaxis with 1 Malarone tablet (250 mg of atovaquone and 100 mg of proguanil hydrochloride; $n = 148$) or placebo ($n = 149$) per day for 20 weeks. Hematologic and clinical chemistry values did not change significantly. The protective efficacy of atovaquone/proguanil was 84% (95% confidence interval [CI], 44%–95%) for *P. vivax* malaria, 96% (95% CI, 72%–99%) for *P. falciparum* malaria, and 93% (95% CI, 77%–98%) overall. Atovaquone/proguanil was well tolerated, safe, and effective for the prevention of drug-resistant *P. vivax* and *P. falciparum* malaria in individuals without prior malaria exposure who migrated to Papua, Indonesia.

Although malaria is one of the oldest known diseases among humans, it remains a global health threat, because the parasite and its vector continue to evade modern approaches to prevention and treatment. Malaria kills or debilitates nonimmune travelers, migrants, and returning emigres who do not receive adequate protection. Personal protective measures, such as insect repellents and bed nets, diminish risk and may be adequate where risk is low, but high risk demands chemoprophylaxis as well. The global resurgence of malaria and the increasing prevalence of resistance to standard antimalarial drugs increases the risk for travelers. Chloroquine-resistant *Plasmodium falciparum* is present throughout Africa, Asia, and South America, and

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multidrug-resistant *P. falciparum* is present in parts of Southeast Asia, including Indonesia [1–3]. Chloroquine-resistant *Plasmodium vivax* also poses a serious threat to public health in eastern Indonesia and perhaps other parts of Asia [1, 3–6]. Neuropsychiatric side-effects associated with mefloquine [7], severe cutaneous side-effects associated with pyrimethamine/sulfadoxine [8], and photosensitivity and adverse effects on tooth and bone development associated with doxycycline [9] preclude the use of these standard chemoprophylactic drugs for many individuals. Health care providers who advise travelers need broader options for chemoprophylaxis.

A fixed-dose combination of atovaquone and proguanil hydrochloride (Malarone; GlaxoSmithKline) has been approved by the US Food and Drug Administration for the prevention and treatment of malaria caused by *P. falciparum* [10]. Atovaquone is a hydroxynaphthoquinone that kills parasites via inhibition of mitochondrial electron transport and blockage of de novo pyrimidine synthesis [11]. Proguanil inhibits dihydrofolate reductase (via its metabolite cycloguanil) and is also directly synergistic with atovaquone in vitro [12, 13]. Randomized, double-blinded, placebo-controlled trials supporting the use of atovaquone/proguanil for prophylaxis for malaria caused by *P. falciparum* [14–17] were conducted in areas of holoendemicity in Africa, where clinical immunity to malaria may confound estimates of protective efficacy. To corroborate data from the studies in Africa and to estimate the drug's protective efficacy against *P. vivax* malaria, we conducted a randomized, placebo-controlled, double-blinded trial of atovaquone/proguanil for malaria prophylaxis in Indonesians who did not have sufficient clinical immunity to prevent febrile disease.

MATERIALS AND METHODS

Study sites and subjects. Individuals from areas of nonendemicity in Indonesia who reside in 3 villages in northeastern Papua formed the study population. Recruitment of volunteers occurred from April through December 1999. The villages (SP4, SP5, and SP6) were constructed as part of an Indonesian government program of sponsored migration from Java (transmigration). Each village was located in ~4 km^2 of cleared forest within 2 km of the coast. Homes of identical wood-plank and tin-roof construction were situated along a grid of unpaved roads at even intervals. Approximately 1500 people lived in each village, a mixture of people from Java, other islands of Indonesia, or the local area. Almost all residents engaged in agriculture as their primary economic activity. All 4 species of human malaria parasites occur in the region at a ratio of ~2:1:0.1:<.001 for *P. falciparum:P. vivax:Plasmodium malariae:Plasmodium ovale.* Malaria in the region is hyper- to holoendemic and highly resistant to chloroquine [3–6]. The *Anopheles punctulatus* complex *(A. punctulatus, Anopheles farauti,* and *Anopheles koliensis),* which feeds and breeds in the open, sunlit spaces provided by new settlements, is the only important vector of malaria [18]. Exposure to feeding anophelines occurs in and around homes rather than in association with occupational activity.

A government-operated health station in each village provided weekly chloroquine prophylaxis at no cost to transmigrants during the first 3 months of residence. Chloroquine prophylaxis appears to provide some relief from the symptoms of malaria, but it was no more effective than placebo for the prevention of patent parasitemia [19]. Compliance with chloroquine prophylaxis before study enrollment was not monitored. Subjects did not have access to chloroquine during the trial.

Eligible volunteers were aged 12–65 years and weighed ⩾40 kg. They had moved from Java or another area where malaria was not endemic 3–26 months before enrollment, and they had resided in these areas of nonendemicity for 2 years before moving. Exclusion criteria included pregnancy or unwillingness to use reliable contraception, lactation, glucose-6-phosphate dehydrogenase (G6PD) deficiency, or any medical condition that, in the physician's judgment, would compromise participation in the study. The study protocol and the process of informed consent were reviewed and approved by Indonesian and US committees for the protection of human subjects of medical research in accordance with US Navy regulations governing the use of human subjects of medical research (SECNAVINST 3900.39B). All participants in the study provided informed voluntary consent.

Sample size estimate. On the basis of incidence data collected in this region during 1997 and 1998, we estimated a 20-week *P. vivax* attack rate of 0.2 in the placebo group. In anticipation of 95% protective efficacy, the expected attack rate in the atovaquone/proguanil treatment arm during the 20-week period was therefore predicted to be 0.01. By use of the likelihood scores method [20] with power set at 80% and the lower 95% confidence limit set at 65% protective efficacy, we determined that 121 subjects were needed in each arm to detect differences between the atovaquone/proguanil and placebo groups. In anticipation of a 25% dropout rate during the prophylaxis period, we planned to randomize ~300 subjects (150 subjects per arm) to receive either atovaquone/proguanil or placebo.

Study design and procedures. The study consisted of 3 distinct phases: a 17-day period of radical cure treatment, 20 weeks of prophylaxis, and 4 weeks of postprophylaxis follow-up. Radical curative therapy eradicated preexisting malaria infection that could confound the interpretation of outcomes. This consisted of 1000 mg of atovaquone and 400 mg of proguanil hydrochloride (i.e., 4 Malarone tablets, each of which contains 250 mg of atovaquone and 100 mg of proguanil hy-

drochloride) given once daily with food for 3 days, followed by 2 primaquine phosphate tablets, each of which contained 15 mg of primaquine base (Sanofi-Winthrop), given once daily for 14 days. Details of the safety and efficacy of this radical curative regimen will be reported elsewhere.

After completing the radical cure regimen, subjects were randomized in a 3:1 ratio to continue or discontinue the trial. Those randomized to discontinue were offered the opportunity to volunteer for a parallel trial of primaquine for prophylaxis, which is reported elsewhere [21]. Subjects randomized to continue were further randomized in a 1:1 ratio to receive 1 Malarone tablet or 1 placebo tablet daily for 20 weeks. Study drugs (film-coated tablets of Malarone or placebo) were identical in appearance and packaging. Assignment to the active drug or placebo groups was accomplished off site using computer-generated codes randomly assigned to placebo or drug. Subjects were assigned blinded code numbers at enrollment. No subject or member of the research team knew the assignment code. The sealed key to the code was kept on site but was returned unopened to monitors at the conclusion of the study.

A member of the research team visited each subject at home daily throughout the study. At each visit, the health care worker administered the study drug with sweet biscuits and asked "Do you have any complaints?" An affirmative response prompted recording of complaints as adverse events on a standard questionnaire. On-site physicians reviewed reports of adverse events each day. An adverse event was considered related to the drug if the reviewing physician thought the adverse event could have been caused by the study drug. An adverse event was considered serious if it was fatal, life threatening, or disabling, if it resulted in hospitalization, or if it otherwise seriously jeopardized the subject. Subjects were brought to the clinic for evaluation when indicated. In addition, a physician or nurse visited each participant every 2 weeks to assess general conditions and the use of nonstudy medications.

Subjects were discontinued from participation if they missed >2 doses of the study drug or placebo during any 7-day period. Urine pregnancy tests (Test Pack Plus; Abbot) were performed monthly for female subjects. All subjects were screened for G6PD deficiency using a commercial assay (G-6-PDH Deficiency Screen Kit 202; Sigma Diagnostics). Laboratory assays of hematology (QBC; Becton-Dickinson) and standard blood chemistry parameters (Ektachem DT II System; Kodak) were performed at enrollment and at weeks 4 and 20 of prophylaxis. Plasma samples were obtained at weeks 4 and 20 of prophylaxis to measure concentrations of atovaquone, proguanil, and cycloguanil [22, 23].

Efficacy. Blood films were obtained from subjects just before they received the radical cure regimen and again immediately before the start of prophylaxis. During prophylaxis, blood films were collected weekly or whenever subjects complained of symptoms consistent with malaria. Technicians stained blood films with Giemsa reagents, and expert microscopists read ⩾200 fields at 1000× oil immersion magnification. Positive blood films revealed ⩾2 asexual parasites confirmed by a second expert microscopist. A confirmed positive blood film regimen prompted immediate rescue therapy. Parasites per microliter of blood were calculated as the number of asexual parasites per 200 WBCs multiplied by 40 (the WBC count was assumed to be 8000 cells/μL).

Rescue therapy consisted of atovaquone/proguanil for *P. falciparum* or atovaquone/proguanil followed by primaquine for *P. vivax* infection, as for radical cure [24]. Subjects who developed parasitemia during the 4 weeks after completing prophylaxis received standard chloroquine, pyrimethamine/sulfadoxine, or quinine therapy, consistent with the Indonesian national malaria treatment policy.

Statistical analyses. The primary efficacy end point was the first occurrence of slide-proven *P. vivax* parasitemia. The secondary efficacy end point was the first occurrence of slide-proven *P. vivax* or *P. falciparum* parasitemia. Percentage of efficacy was calculated as $100 \times [1 - (\text{incidence density of malaria in atovaquone/proguanil recipients/incidence density of malaria in placebo recipients})]$. The 95% CI was calculated from the binomial distribution. Differences in the incidence density of adverse events were compared using Yates's corrected χ^2 test.

RESULTS

Study subjects and compliance. Eight hundred thirty-seven residents were screened, and 416 started receiving the radical cure regimen. Among the 402 who completed the radical cure regimen, 396 were randomized to receive either atovaquone/proguanil ($n = 150$) or placebo ($n = 149$) or to discontinue this study and to enter the parallel study of primaquine for prophylaxis ($n = 97$) [21]. Of the 299 randomized to continue, 90 did not complete the 20-week prophylaxis period because of withdrawal before they started the study drug regimen ($n = 2$), the presence of slide-confirmed malaria ($n = 40$), consent withdrawn while receiving study drug ($n = 28$), protocol violation ($n = 11$), loss to follow-up ($n = 5$), or an adverse event that prompted withdrawal from the study ($n = 4$) (figure 1).

At screening or immediately before commencement of the radical cure regimen, 43 subjects (11%) had *P. falciparum* parasitemia and 39 (10%) had *P. vivax* parasitemia. All subjects had negative blood smear results 15 days after they started receiving the radical cure regimen (2 days before randomization).

The atovaquone/proguanil and placebo groups had no significant differences in age, sex, weight, or history of malaria (table 1). The mean age was 32 years, 105 subjects (35%) were

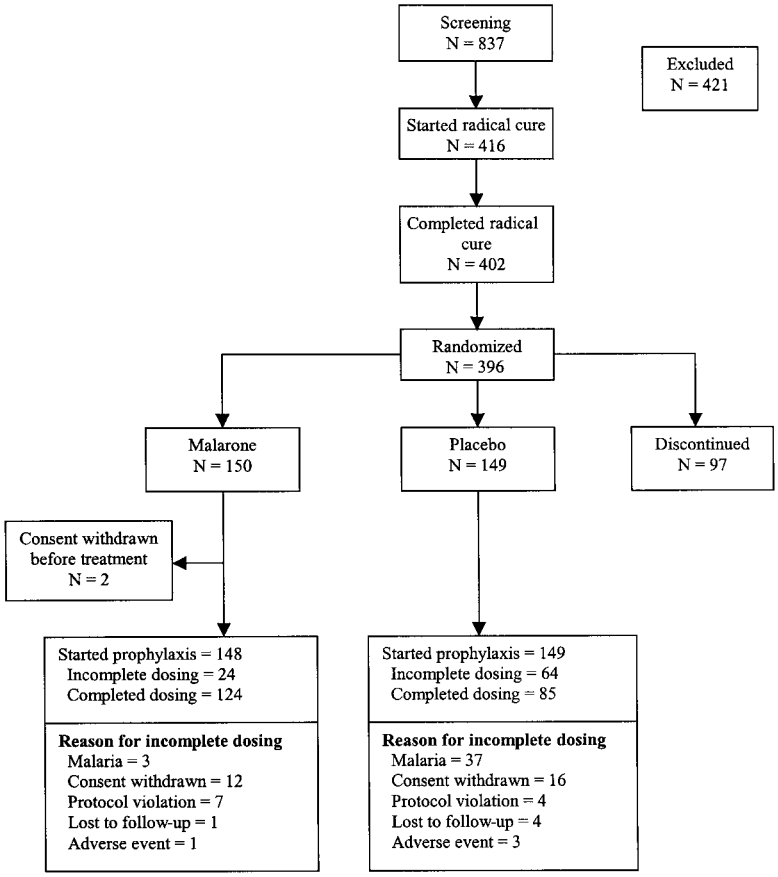

Figure 1. Flow diagram of subject accountability during the trial of atovaquone/proguanil for the prevention of *Plasmodium falciparum* or *Plasmodium vivax* malaria.

female, 122 (41%) had no knowledge of having been treated for malaria, and 112 (37%) said they had received no treatment for malaria before enrollment.

The mean (± SD) duration of exposure to study drug was 110 ± 42 days for placebo and 129 ± 29 days for atovaquone/proguanil. The duration of study drug exposure was 16–20 weeks for 100 placebo recipients (67%) and 128 atovaquone/proguanil recipients (86%). The numbers of doses of study drug missed or not witnessed were 55 (0.37%) in the placebo group and 72 (0.48%) in the atovaquone/proguanil group; 146 (98%) subjects in the placebo group and 144 (96%) in the atovaquone/proguanil group took >95% of prescribed doses.

Infection after the radical cure regimen. Malaria was diagnosed in 40 subjects during the prophylaxis phase of the study. Parasitemia occurred in 37 subjects in the placebo group (14 cases due to *P. vivax* alone, 21 due to *P. falciparum* alone, and 2 due to *P. vivax–P. falciparum*) and in 3 subjects in the atovaquone/proguanil group (2 cases due to *P. vivax* alone and 1 case due to *P. vivax–P. falciparum*; figure 2). The protective efficacy of atovaquone/proguanil was 84% (95% CI, 45%–95%) for *P. vivax,* 96% (95% CI, 71%–99%) for *P. falciparum,* and 93% (95% CI, 77%–98%) overall (table 2). During the 4-week follow-up period, parasitemia appeared in 5 subjects in the placebo group (3 cases due to *P. falciparum* and 2 due to *P. vivax*) and in 7 subjects in the atovaquone/proguanil group (2 cases due to *P. falciparum* and 5 due to *P. vivax*). Symptoms of malaria were present on the day of or the day after diagnosis in 95% of subjects with *P. falciparum* parasitemia and in 88% of subjects with *P. vivax* parasitemia. All had resolution of these symptoms after they received rescue treatment.

Drug concentrations in plasma among patients for whom atovaquone/proguanil failed. Among the 3 subjects who had parasitemia while receiving atovaquone/proguanil, the drug concentrations in plasma were consistent with normal absorption and good compliance (table 3). These subjects had missed just 0, 1, or 2 of the prescribed doses of atovaquone/proguanil during the 4 weeks before patency of parasitemia.

Adverse events. Among recipients of the placebo and active drug, 136 (91%) and 141 (94%), respectively, reported ⩾1 physical complaint during the prophylaxis period ($P = .25$). Figure 3 illustrates the incidence density of specific adverse events, either all such events (figure 3, *left*) or those considered possibly attributable to drug by the blinded supervising physicians (figure 3, *right*). In both analyses, stomatitis occurred

Table 1. Baseline characteristics of subjects randomized to receive chemoprophylaxis with atovaquone/proguanil or placebo, Papua, Indonesia.

Characteristic	Atovaquone/ proguanil group (n = 150)	Placebo group (n = 149)
Age, years		
Mean ± SD	31.1 ± 10.0	33.3 ± 10.9
Range	13–63	12–60
Sex		
Male	93 (62)	101 (68)
Female	57 (38)	48 (32)
Asian race	150 (100)	149 (100)
Height, mean cm ± SD	157 ± 8.5	157 ± 7.2
Weight, mean kg ± SD	50.9 ± 6.6	51.2 ± 6.1
Duration of residence in Papua, mean months ± SD	21.0 ± 3.4	20.5 ± 3.7
History of malaria treatment before arrival in Papua	6 (4)	3 (2)
History of malaria treatment after arrival in Papua		
Never	65 (43)	57 (38)
Once	38 (25)	42 (28)
Twice	14 (9.3)	17 (11)
More than twice	33 (22)	33 (22)

NOTE. Data are no. (%) of patients, unless otherwise indicated.

more frequently in the atovaquone/proguanil group than it did in the placebo group ($P < .001$ and $P = .009$), and abdominal pain ($P = .02$ and $P = .04$) and malaise ($P = .01$ and $P = .02$) occurred more frequently in the placebo group. Back pain appeared more frequently among atovaquone/proguanil recipients ($P = .009$), but the blinded supervising physicians did not attribute most of these complaints to the study drug. Most adverse events were mild (77.0% of events) or moderate (22.6% of events) in intensity. Four subjects had adverse events that were classified as severe and considered by the blinded supervising physicians to be possibly drug related (3 patients had abdominal pain and 1 had an exfoliative skin rash). The skin rash was considered to be serious, and, although it was possibly drug related, a similar rash occurred during the same period in 2 other residents of the same village who were not study subjects. Thus, we considered a viral etiology to be a more likely explanation for the rash in the study subject.

Laboratory safety samples were obtained at baseline, week 4, and week 20 from 150, 143, and 121 subjects who received atovaquone/proguanil and from 149, 137, and 116 subjects who received placebo, respectively. For both men and women, there were no significant differences between the treatment groups at baseline or during follow-up with regard to any hematologic and clinical chemistry test result, and no clinically important laboratory abnormalities were identified.

DISCUSSION

Daily administration of atovaquone/proguanil provided safe, well-tolerated, and effective protection against *P. falciparum* and *P. vivax* malaria in nonimmune migrants to Papua, Indonesia. In studies reported elsewhere, atovaquone/proguanil taken daily for 10 or 12 weeks by lifelong residents of countries where malaria is endemic [14–16] or for an average of 4 weeks in nonimmune travelers [26, 27] was safe and well tolerated. We used atovaquone/proguanil for 20 weeks in the present study and observed no evidence of toxicity, either clinically or in longitudinal evaluations of hematologic and blood chemistry parameters. This corroborates the reported experience of others

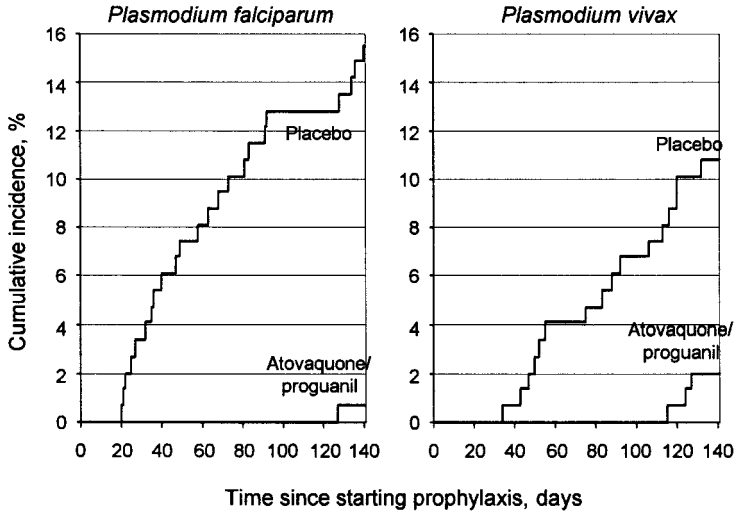

Figure 2. Cumulative incidence of parasitemia due to *Plasmodium falciparum* or *Plasmodium vivax*

Table 2. Efficacy of atovaquone/proguanil for the prevention of *Plasmodium falciparum* and *Plasmodium vivax* parasitemia.

Variable	Placebo group (n = 149)	Atovaquone/ proguanil group (n = 150)	Efficacy,[a] % (95% CI)	P
Person-weeks	2354	2723		
Incident cases				
P. falciparum	23	1	96 (72–99)	<.001
P. vivax	16	3	84 (44–95)	<.001
Either species	37	3	93 (77–98)	<.001

[a] Efficacy rate = 100 × [1 − (incidence density in atovaquone/proguanil group/incidence density in placebo group)].

who have administered atovaquone alone for up to 30 months [28] or proguanil alone for many years [29]. Except for stomatitis, which is an established side-effect of proguanil [30], and back pain, no adverse events occurred at a higher rate in atovaquone/proguanil recipients compared with placebo recipients. The blinded supervising physicians did not attribute most complaints of back pain to the study drug, but recipients of atovaquone/proguanil were more likely to report that complaint. Placebo recipients were more likely to report abdominal pain or malaise.

Naturally acquired immunity to malaria may confound the findings of trials evaluating the protective efficacy of drugs intended for use in nonimmune individuals. For example, randomized, double-blinded, placebo-controlled trials of azithromycin for the prevention of *P. falciparum* malaria showed reasonable efficacy (83% [95% CI, 68%–91%]) among African adults [31] but somewhat lower efficacy (72% [95% CI, 50%–84%]) among nonimmune Indonesian soldiers and migrants to Indonesian New Guinea [32], which suggests that acquired immunity in African adults might have contributed to higher drug efficacy. In our study, we corroborated the excellent protective efficacy (>95%) of atovaquone/proguanil against *P. falciparum* malaria reported from trials in Africa [14–17] and demonstrated good protective efficacy against *P. vivax* (84% [95% CI, 45%–95%]).

Although not all subjects in our study population were completely naive to malaria, the vast majority had no clinically significant acquired immunity. Malaria has been exceedingly rare on Java since the 1950s, when a campaign of DDT (dichlorodiphenyltrichloroethane) spraying eradicated endemic malaria from East and West Java and dramatically reduced transmission in Central Java [33–35]. Surveillance data from 1993 are typical for the period of 1960–1996 and reveal an islandwide incidence of ~1 infection per 10,000 persons per year [36]. Because most infections have occurred within a few well-known foci of chronic hypoendemicity in Central Java,

Table 3. Drug concentrations in plasma for subjects who developed parasitemia while receiving atovaquone/proguanil.

Subject number, study week	Time since last dose, h	Drug concentration in plasma[a]		
		Atovaquone, μg/mL	Proguanil, ng/mL	Cycloguanil, ng/mL
2398				
Week 4	31.8	7.59	QNS	QNS
Week 19	9.3	2.79	113	16.1
2472				
Week 4	25.5	4.32	6.72	5.18
Week 18	3.8	1.54	7.06	BQL
2485: week 4[b]	6.8	10.4	104	57.1

NOTE. Subject 2398 had mixed *Plasmodium vivax* and *Plasmodium falciparum* parasitemia at week 19. The other 2 subjects had *P. vivax* parasitemia at week 18. BQL, below the limits of quantification; QNS, sample insufficient to perform assay.

[a] For comparison, the mean (± SD) plasma drug concentrations in 100 adults who received the recommended prophylactic dose of atovaquone/proguanil were 2.1 ± 1.2 μg/mL for atovaquone, 26.8 ± 14.0 ng/mL for proguanil, and 10.9 ± 5.6 ng/mL for cycloguanil [25].

[b] For subject 2485, a plasma sample at the onset of parasitemia was not available.

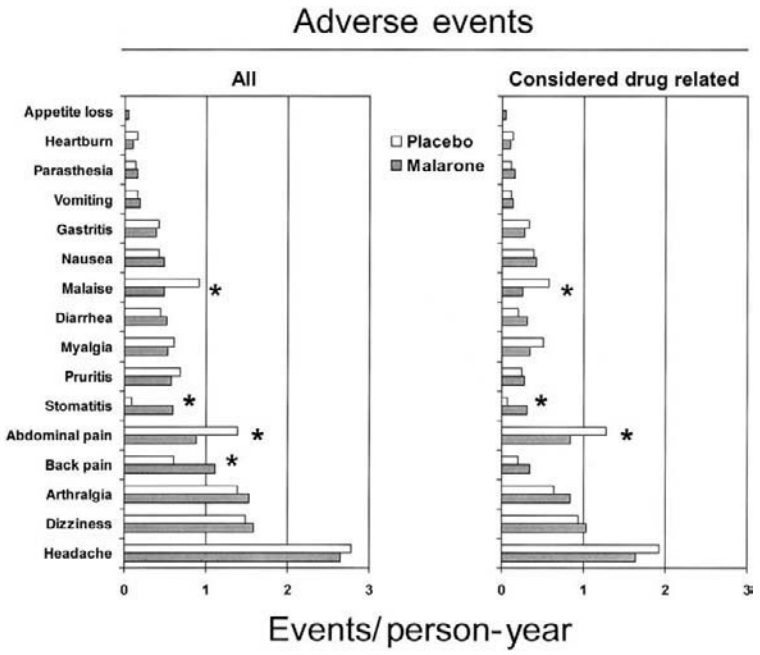

Figure 3. Incidence density of all adverse events *(left)* and those considered by blinded supervising physicians to be possibly drug related *(right).* Complaints are ordered from most to least frequent among recipients of atovaquone/proguanil (Malarone; GlaxoSmithKline). *Statistically significant difference between treatment groups (i.e., $P < .05$).

the risk on most of the island is ~1 infection per 100,000 persons per year. Thus, chronic exposure to malaria on Java and attendant clinical immunity was virtually nonexistent in our transmigrant population. Previous studies of malaria in Javanese migrants to Indonesian New Guinea have indicated that ⩾3 episodes of infection within 12 months are required for the onset of clinical immunity to *P. falciparum* malaria in adults [37–39]. Only 21% of the subjects in this study reported receiving treatment for malaria on >2 occasions, during an average of 21 months' residence in Indonesian New Guinea before study entry. The fact that 95% of subjects with *P. falciparum* parasitemia had symptomatic malaria affirmed the lack of clinical immunity to malaria among subjects in our study.

Atovaquone/proguanil kills blood stages of *P. falciparum* and *P. vivax* [40, 41]. In addition, atovaquone and proguanil have causal prophylactic activity directed against the liver stages of *P. falciparum* [42, 43]. This property allows a person to discontinue use of atovaquone/proguanil 7 days after leaving an area of risk [17, 44]. However, atovaquone/proguanil apparently does not eradicate hypnozoites of *P. vivax* [41]. Although it is possible that atovaquone/proguanil might prevent the formation of hypnozoites, our study design did not address this possibility by observing subjects for months after completion of prophylaxis, because they continued to be at risk for new infections. Until additional information is available, atovaquone/proguanil should be considered to provide only suppressive prophylaxis for *P. vivax.*

In summary, atovaquone/proguanil was safe, well tolerated, and effective for prevention of *P. falciparum* and *P. vivax* malaria in clinically nonimmune persons exposed in Papua, Indonesia. Our findings support the view that atovaquone/proguanil is an important new option for nonimmune individuals, especially those traveling to Southeast Asia, where infection with multidrug-resistant *P. falciparum* and chloroquine-resistant *P. vivax* often occurs.

NAVAL MEDICAL RESEARCH UNIT 2 CLINICAL TRIAL TEAM

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