Malaria Prophylaxis Using Azithromycin: A Double-Blind, Placebo-Controlled Trial in Irian Jaya, Indonesia


New drugs are needed for preventing drug-resistant *Plasmodium falciparum* malaria. The prophylactic efficacy of azithromycin against *P. falciparum* malaria in malaria-immune Kenyans was 83%. We conducted a double-blind, placebo-controlled trial to determine the prophylactic efficacy of azithromycin against multidrug-resistant *P. falciparum* malaria and chloroquine-resistant *Plasmodium vivax* malaria in Indonesian adults with limited immunity. After radical cure therapy, 300 randomized subjects received azithromycin (148 subjects, 750-mg loading dose followed by 250 mg/d), placebo (77), or doxycycline (75, 100 mg/d). The end point was slide-proven parasitemia. There were 58 *P. falciparum* and 29 *P. vivax* prophylaxis failures over 20 weeks. Using incidence rates, the protective efficacy of azithromycin relative to placebo was 71.6% (95% confidence interval [CI], 50.3–83.8) against *P. falciparum* malaria and 98.9% (95% CI, 93.1–99.9) against *P. vivax* malaria. Corresponding figures for doxycycline were 96.3% (95% CI, 85.4–99.6) and 98% (95% CI, 88.0–99.9), respectively. Daily azithromycin offered excellent protection against *P. vivax* malaria but modest protection against *P. falciparum* malaria.

Malaria is a serious global public health problem. The World Health Organization estimates that there are 300–500 million cases of clinical malaria each year worldwide with 1.5 to 2.7 million deaths attributable to *Plasmodium falciparum* [1, 2].

Chemoprophylaxis for malaria is aimed at two distinct groups: nonimmune individuals of all ages who travel to areas where malaria is endemic [3] and pregnant women living in areas of endemicity [4]. Antimalarial drugs for prophylaxis and treatment are becoming increasingly ineffective because of the continuing rise of multidrug-resistant *P. falciparum* malaria in most areas where malaria is endemic [5, 6]. Malaria due to chloroquine-resistant *Plasmodium vivax* is now an emerging threat [7, 8].

Prophylactic drugs must have high efficacy and low toxicity. Mefloquine, doxycycline, and chloroquine/proguanil are currently recommended as prophylaxis for chloroquine-resistant *P. falciparum* malaria [3, 9, 10]. None of these drugs is ideal. Doxycycline is contraindicated in pregnancy [3, 10] and children younger than 8 years of age [9]. Mefloquine is contraindicated for patients with a history of epilepsy or serious psychiatric disease [9]. The World Health Organization [3] and the British authorities [10] recommend avoidance of mefloquine in the first trimester of pregnancy, but the Centers for Disease Control and Prevention support the use of mefloquine if travel to an area where chloroquine-resistant malaria occurs is unavoidable [9]. Chloroquine and proguanil are safe in pregnancy [10, 11], but this combination has low efficacy [12, 13].

Azithromycin, an azalide antibiotic similar to erythromycin, had good antimalarial activity in human malaria challenge studies [14, 15]. When azithromycin was used for treating Gambian children with trachoma, spleen rates, parasite counts, and the number of episodes of febrile parasitemia due to *P. falciparum* were coincidentally reduced [16]. In a malaria prophylaxis trial in Kenyan adults, 250 mg of azithromycin daily had a prophylactic efficacy against *P. falciparum* malaria based on crude incidence of 83% (95% CI, 68–91) [17].

Azithromycin can be used by pregnant and breast-feeding women and children older than 6 months of age [18]. If the measured prophylactic efficacy against *P. falciparum* malaria...
for a population with low or no immunity were high, then azithromycin would be a substantial addition to the present pool of prophylactic drugs.

We report the protective efficacy of daily azithromycin given to Indonesian adults with limited immunity to malaria who resided in an area where multidrug-resistant *P. falciparum* malaria and chloroquine-resistant *P. vivax* malaria occur.

**Methods**

**Study Design**

This was a randomized, double-blind, placebo-controlled study estimating the prophylactic efficacy of daily azithromycin against *P. falciparum* malaria and *P. vivax* malaria and assessing toxicity. Doxycycline served as a positive control because of its high prophylactic efficacy in a randomized control trial in the same area in 1994 [19].

**Study Site and Participants**

The study took place between July 1996 and January 1997 in Arso (a rural part of northeast Irian Jaya, close to Jayapura) where multidrug-resistant *P. falciparum* malaria [20–23] and chloroquine-resistant *P. vivax* malaria [8, 24] occur; the incidence rates (IRs) of *P. falciparum* and *P. vivax* infections have been documented as 3 cases per year [19, 25] and 2.5 cases per year [19], respectively. Entomological inoculation rates vary between 0.54 and 11.7 infective bites per person per month [25].

We recruited Indonesian Army soldiers from posts that were located near villages and housed ~12 men. They had arrived 6 months earlier from southern Sumatra and were taking doxycycline, chloroquine, or sulfadoxine pyrimethamine as malaria prophylaxis (the latter two drugs were changed to doxycycline after the arrival of our team). Civilians were immigrant farmers from Java who were residents in one village (Arso PIR V) for 15 months. They had received free chloroquine prophylaxis during the first 3 months after their arrival from the government clinic, which also provided free basic health care. Villagers could also buy antimalarial drugs in local shops. Soldiers and civilians used bed nets that were not insecticide-impregnated. The incidence of malaria is low in Java and the area of southern Sumatra where the soldiers were based (F. Laihad, unpublished data).

We obtained written informed consent from all study volunteers. The study was conducted according to the regulations of the Indonesian Ministry of Health, the Indonesian Army, and the U.S. Navy and Army that govern the protection of human subjects.

**Prestudy Assessment and Radical Cure Treatment**

The screening of potential subjects consisted of the following: obtaining a medical history; physical examination; examination of a blood smear for malaria; determination of complete blood count (Coulter Electronics, Hialeah, FL); biochemistry analysis: sodium, potassium, creatinine, aspartate aminotransferase, alkaline phosphatase, and total bilirubin (Kodak, Rochester, NY); determination of qualitative glucose-6-phosphate-dehydrogenase activity (G6PD spot test, Sigma, St. Louis); urine dipstick (Boehringer Mannheim, Mannheim, Germany); and urine pregnancy test (β HCG test pack, Abbott Laboratories, Chicago).

Eligible subjects were healthy males or nonpregnant females aged 18 to 55 years. Exclusion criteria included clinically significant disease, hepatic disease, history of splenectomy, hearing impairment (abnormal Rinne or Weber’s test), glucose-6-phosphate dehydrogenase deficiency, known study drug hypersensitivity, and residence for >18 months in Arso.

Enrolled subjects were given radical cure therapy to eliminate blood and liver forms of malaria. The regimen was concurrent quinine sulfate (10 mg/kg twice daily [thrice daily if there was toxicity]. Doxycycline served as a positive control because of its high prophylactic efficacy in a randomized control trial in the same area in 1994 [19].

**Randomization and Study Size**

After subjects had completed radical cure therapy, they were sequentially assigned a study number and the corresponding study drug code from a computer-generated randomization list. Blocked randomization with an average block size of four (computer-generated with a variable block size) was used to assign the three study drugs azithromycin, placebo, and doxycycline to achieve an expected 2:1:1 ratio after every four subjects were randomized. The statistical framework [26] for determining the sample size was based on the objective of estimating the protective efficacy of azithromycin to rule out a level of <70%. To reduce the number of subjects assigned to placebo and to increase power, we used an allocation of two azithromycin recipients to one placebo recipient. Assuming an attack rate of 60% over 20 weeks and an anticipated reduction in the number of prophylaxis failures of 85% with azithromycin, a total of 195 subjects (130 azithromycin recipients and 65 placebo recipients) would be required to have 80% power to rule out a protective efficacy of <70% (5% type I error; one-sided). The number of subjects receiving doxycycline was the same as the number of placebo recipients. To allow for dropouts, the final target number of volunteers to be randomized was 300.

**Blinding and Drug Packaging**

No field-based investigator knew the randomization code. It was securely stored in individually sealed envelopes and was
broken only if a subject had a serious adverse event necessitat- 
ing study withdrawal.

Study drugs and identical placebo (azithromycin and pla- 

cebo, red tablets; doxycycline and placebo, white capsules) 

were supplied in blister packs (Pfizer Central Research, Groton 

CT). Labeled drug packs containing a 1-week supply of both 

azithromycin or placebo and doxycycline or placebo were 

made; two extras of each drug were included in case of emesis 

within 1 hour of drug administration.

Conduct of Clinical Trial

Radical cure therapy was initiated over a 7-week period. 

Administration of study drugs commenced the day after radical 

cure (day 0). All doses were given using the double-dummy 

method—the simultaneous administration of an active drug 

and placebo. On day 0, all subjects received one doxycycline 

(100 mg) or placebo capsule and a loading dose (three tablets) 

of azithromycin (750 mg) or placebo; based on a computer-

simulated model, the loading dose ensured the attainment of 

90% of steady-state serum and tissue levels by day 1. Thereaf-

ter, one azithromycin (250 mg) or placebo tablet and one doxy-

cycline (100 mg) or placebo capsule were given daily over a 

follow-up period of 20 weeks. Drinking water and sweet 

biscuits were provided with each dose.

Drug administration and consumption were witnessed and 

signed for by a health worker and the subject. If a soldier 

was absent, his post commander was given study drugs, sweet 

biscuits, and a record book. The post commander was responsi-

ble for administering and recording drug administration. Sol-

diers away on patrol were given a 2-week supply of study 

drugs. Drug forms were inspected daily, supplemented by peri-

odic drug counts and supervisory field visits.

Thick and thin blood smears were made weekly, or sooner 

if clinically indicated. Giemsa-stained slides were read by mi-

croscopists who were unaware of the symptom status of the 

subject. A positive slide was defined as two or more asexual 

malarial parasites seen after reading 200 thick smear fields at 

×1,000 magnification. All positive slides were confirmed by 

a second microscopist in a blinded fashion. Parasitemia was 

quantified as the number of thick smear asexual parasites per 

200 WBCs × 40 [27].

All subjects with parasitemia were interviewed by a study 

doctor. One or more of the following defined symptomatic 

parasitemia: fever, chills, sweating, myalgia, headache, an-

orexia, nausea, vomiting, abdominal pain, and/or diarrhea.

End Points

The primary efficacy end point was the first occurrence of 

slide-proven parasitemia (prophylaxis failure). Follow-up time 

for efficacy analysis was defined as the time from day 0 to the 

date of prophylaxis failure or the date of study completion. For 

those subjects not completing scheduled follow-up (i.e., study 

withdrawals or protocol violations), follow-up time was mea-

sured to the date of the last negative slide. Nonmalaria reasons 

for withdrawal from the study were as follows: serious adverse 

event, unsupervised drug administration for >14 days, con-

sumption of a nonstudy antimalarial drug, two doses of study 

drug or placebo missed within 7 days, and voluntary dropout.

Assessment of Study Drug Tolerance

Tolerance was assessed by interviewing subjects with a 

26-symptom questionnaire on day 0 and day 1 (tolerance to 

loading dose) and by recording symptoms every day in answer 

to the open question ‘‘Any symptoms?’’. Blood samples were 

obtained for determination of complete blood counts and bio-

chemistry at enrollment, 1 month into the study, and at study 

end. All safety and tolerance data for volunteers who were 

removed from follow-up for efficacy (those with protocol viola-

tions) but who continued to receive study drug or placebo were 

included in the analyses of drug safety and tolerance.

Statistical Analysis

Data for all 300 randomized volunteers were included in the 

analyses of efficacy and drug safety and tolerance. Data were 

entered twice, discrepancies resolved, and end points finalized 

before the databases were locked and the randomization code 

was broken. Epi Info Version 6.02 (Centers for Disease Control 

and Prevention), Minitab 11 for Windows (Minitab, State Col-

lege, PA), and Statxact 3 for Windows (CYTEL Software, 

Cambridge, MA) were used for data management and analysis.

Efficacy. IRs (density) were calculated as the number of 
malaria cases divided by the total person-years of follow-up. 
The protective efficacy (PE) was defined as the percent reduc-

tion (drug relative to placebo) in the IRs of malaria and was 
calculated as 1 

0 

ratio of two Poisson variables) were calculated 

subject. A positive slide was defined as two or more asexual 
malarial parasites seen after reading 200 thick smear fields at 

×1,000 magnification. All positive slides were confirmed by 
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those subjects not completing scheduled follow-up (i.e., study
**Drug safety and tolerability.** Reported symptoms in the drug and placebo groups were compared in terms of the proportion of subjects with a new symptom 1 day after the loading dose and the IR of daily symptoms reported (total number of symptoms/total person-time for drug safety and tolerance follow-up). Symptoms reported within 7 days of a positive malaria slide were discounted because they may have been due to malaria. Differences in proportions were compared, and confidence intervals for relative risks were obtained as mentioned above.

### Results

#### Enrollment and Withdrawals

Of the 364 registered volunteers, 48 did not meet the criteria for study enrollment, and 16 failed to complete radical cure therapy (figure 1). Three hundred volunteers were randomized to the three drug arms: azithromycin (148), doxycycline (75), and placebo (77).

Characteristics of the subjects at enrollment and baseline laboratory values were similar between the three study groups (table 1). Male subjects (median age, 27 years) predominated. All reported malaria within 1 year of study enrollment was based on history and had occurred since the subject’s arrival in Irian Jaya. Certain markers of recent malaria exposure were significantly higher in the civilians than in the soldiers (see below under Subgroup Analysis of Civilians and Soldiers).

#### Parasitemia End Points

There were 87 cases of parasitemia (table 2): 55 *P. falciparum*, 29 *P. vivax*, and 3 cases of mixed infection that were counted as *P. falciparum*, the dominant species in each case. The number (%) of cases of parasitemia per the total number of randomized subjects in each treatment arm was as follows: placebo, 56 (72.7%) of 77; azithromycin, 28 (18.9%) of 148; and doxycycline, 3 (4%) of 75.

Most subjects (66 [75.9%] of 87) had symptomatic parasitemia. By species, these symptomatic infections were due to *P. falciparum* in 47 (81%) of 58 cases and *P. vivax* in 19 (65.5%) of 29 cases and occurred in 45 (27 *P. falciparum*, 18 *P. vivax*; 80.4%) of 56 placebo recipients, 20 (19 *P. falciparum*,

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### Table 1. Baseline characteristics of volunteers in a trial of prophylaxis for malaria in Indonesia.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Azithromycin recipients (n = 148)</th>
<th>Doxycycline recipients (n = 75)</th>
<th>Placebo recipients (n = 77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of males</td>
<td>142</td>
<td>72</td>
<td>72</td>
</tr>
<tr>
<td>No. of females</td>
<td>6</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Median age in y (range)</td>
<td>27 (18–52)</td>
<td>27 (21–54)</td>
<td>26 (20–50)</td>
</tr>
<tr>
<td>Median weight in kg (range)</td>
<td>60 (43–75)</td>
<td>58 (39–83)</td>
<td>59 (42–75)</td>
</tr>
<tr>
<td>Reported malaria illnesses* (SD)</td>
<td>3.8 (3.7)</td>
<td>3.8 (4.4)</td>
<td>3.2 (3.2)</td>
</tr>
<tr>
<td>No. (%) with splenomegaly</td>
<td>19 (12.8)</td>
<td>6 (8)</td>
<td>8 (10.4)</td>
</tr>
<tr>
<td>No. (%) positive malaria slides</td>
<td>38 (25.7)</td>
<td>21 (28)</td>
<td>23 (29.9)</td>
</tr>
<tr>
<td>Mean hemoglobin level in g/dL (SD)</td>
<td>14.3 (1.5)</td>
<td>14.2 (1.2)</td>
<td>14.1 (1.7)</td>
</tr>
<tr>
<td>Mean platelet count ×1,000/µL (SD)</td>
<td>195 (54)</td>
<td>195 (55)</td>
<td>190 (52)</td>
</tr>
<tr>
<td>Mean creatinine level in mg/dL (SD)</td>
<td>1.1 (0.2)</td>
<td>1.1 (0.1)</td>
<td>1.1 (0.1)</td>
</tr>
<tr>
<td>Mean AST level in IU/L (SD)</td>
<td>29 (10)</td>
<td>28 (10)</td>
<td>28 (10)</td>
</tr>
<tr>
<td>Mean total bilirubin level in mg/dL (SD)</td>
<td>0.6 (0.2)</td>
<td>0.6 (0.1)</td>
<td>0.7 (0.2)</td>
</tr>
</tbody>
</table>

*NOTE. AST = aspartate aminotransferase.
*Reported number of malaria illnesses per subject (not microscopically confirmed) within 1 year of study enrollment.

One hundred fifty-four subjects (51.3%) completed the study as per protocol without acquiring parasitemia. Eighty-seven subjects (29%) developed parasitemia, and 59 (19.7%) withdrew from the study for other reasons (figure 1). The median follow-up time for all subjects in each arm was as follows: doxycycline, 16.1 weeks (range, 2.4–20.1 weeks); azithromycin, 15.8 weeks (range, 1.1–20.1 weeks); and placebo, 7.6 weeks (range, 0–18.6 weeks). The differences in these follow-up times were due to the different rates of parasitemia acquisition (figure 2).
Of the 26,857 intended doses, 25,181 (93.8%) were administered under direct observation by our team, 860 (3.2%) were witnessed by a post commander, 781 (2.9%) were taken unwitnessed, and 35 (0.1%) were not taken.

Overall, the study drugs were well tolerated (further details will be reported elsewhere). One azithromycin recipient who developed an erythematous, maculopapular rash was withdrawn from the study. There were seven other serious adverse events that were all considered unrelated to the study drugs: azithromycin group—ureteric stone, possible dengue fever, and motor cycle accident; doxycycline group—acute bronchitis with hyperventilation and subarachnoid hemorrhage; and placebo group—headache with photophobia and severe malaria. Three of these subjects were withdrawn from the study.

The loading dose was well tolerated by the azithromycin group; there were no significant differences in the proportions of subjects with a new symptom on day 1 between all three drug groups. The daily symptoms in the azithromycin and placebo groups were compared; azithromycin recipients reported a higher frequency of heartburn, paresthesia, and itching, whereas placebo recipients complained more often of fever, diarrhea, severe headache, tinnitus, and blurred vision. No reported symptom exceeded 3.6 complaints per person-year. Hematologic and biochemistry values did not significantly differ over time within or between study groups.

### Subgroup Analysis of Civilians and Soldiers

We compared certain civilian data with soldier data (table 3). At enrollment, the four malarialometric indices showed that, since their arrival in Irian Jaya, the civilians had significantly more prestudy malaria exposure than the soldiers. However, the outcomes for civilians and soldiers who received placebo were not significantly different with respect to overall attack rate, occurrence of symptomatic parasitemia, and levels of parasitemia (P. falciparum or P. vivax). Although the estimated protective efficacy of azithromycin against P. falciparum was higher for the civilians (88.4% [95% CI, 56.6–97.4]) compared

### Table 2. Malaria incidence rates and prophylactic efficacies for azithromycin and doxycycline.

<table>
<thead>
<tr>
<th>Malaria species</th>
<th>Azithromycin (148, 38.88)*</th>
<th>Doxycycline (75, 22.15)*</th>
<th>Placebo (77, 11.83)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>IR¹</td>
<td>PE² (95% CI)</td>
</tr>
<tr>
<td>All malaria</td>
<td>28</td>
<td>0.72</td>
<td>84.7 (75.6–90.7)</td>
</tr>
<tr>
<td>P. falciparum</td>
<td>27</td>
<td>0.69</td>
<td>71.6 (50.3–83.8)</td>
</tr>
<tr>
<td>P. vivax</td>
<td>1</td>
<td>0.03</td>
<td>98.9 (93.1–99.9)</td>
</tr>
</tbody>
</table>

NOTE. IR = incidence rate; PE = prophylactic efficacy.

* No. of randomized subjects, total follow-up time in person-years.

¹ No. of cases per person-year.

² Based on percent reduction in IRs relative to placebo.
Table 3. Subgroup analysis of civilian and soldier subjects in a malaria prophylaxis trial in Indonesia.

<table>
<thead>
<tr>
<th>Variable, finding</th>
<th>Civilians</th>
<th>Soldiers</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enrollment characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of subjects</td>
<td>75</td>
<td>225</td>
<td></td>
</tr>
<tr>
<td>Reported malaria illness*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%) with at least one</td>
<td>74 (98.7)</td>
<td>170 (75.6)</td>
<td>&lt;.001²</td>
</tr>
<tr>
<td>Median (range)</td>
<td>10 (0–20)</td>
<td>2 (0–16)</td>
<td></td>
</tr>
<tr>
<td>No. (%) with splenomegaly</td>
<td>24 (32)</td>
<td>9 (4)</td>
<td>&lt;.001²</td>
</tr>
<tr>
<td>No. (%) positive malaria slides</td>
<td>29 (38.6)</td>
<td>53 (23.5)</td>
<td>.02²</td>
</tr>
<tr>
<td>Mean hemoglobin level in g/dL (SD)</td>
<td>13.5 (1.7)</td>
<td>14.5 (1.3)</td>
<td>&lt;.001²</td>
</tr>
<tr>
<td><strong>Outcomes for placebo group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of subjects</td>
<td>18</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>No. (%) with malaria</td>
<td>15 (83.3)</td>
<td>41 (69.5)</td>
<td>.36³</td>
</tr>
<tr>
<td>No. (%) with symptomatic cases</td>
<td>13 (86.7)</td>
<td>32 (78)</td>
<td>.70³</td>
</tr>
<tr>
<td>Median Plasmodium falciparum count in /µL (range)</td>
<td>940 (80–20,640)</td>
<td>1,600 (60–32,920)</td>
<td>.53³</td>
</tr>
<tr>
<td>Median Plasmodium vivax count in /µL (range)</td>
<td>200 (80–500)</td>
<td>400 (100–1,880)</td>
<td>.10³</td>
</tr>
<tr>
<td><strong>Prophylactic efficacy</strong>³ in % (95% CI) against</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P. falciparum malaria</td>
<td>88.4 (56.6–97.4)</td>
<td>62.9 (29.5–80.4)</td>
<td>.08³³</td>
</tr>
<tr>
<td>P. vivax malaria</td>
<td>100 (83.9–100)</td>
<td>98.3 (89.4–99.9)</td>
<td>.68³³</td>
</tr>
</tbody>
</table>

* Reported no. of malaria illnesses per subject (not microscopically confirmed) within 1 year of study enrollment.

² Fisher’s exact test.

³ Unpaired t-test.

§ Mann-Whitney U test.

Based on percent reduction in incidence rates relative to that for placebo.

³³ Exact (conditional) test.

Discussion

Daily azithromycin demonstrated excellent efficacy against *P. vivax* (98.9% [95% CI, 93.1–99.9]) but only modest efficacy against *P. falciparum* (71.6% [95% CI, 50.3–83.8]) in Irian Jaya.

This double-blind, placebo-controlled trial measured the prophylactic efficacy of azithromycin against vivax and falciparum malaria in a clinically susceptible population. Such trials provide the best evidence for drug efficacy and tolerance [10]. We followed a large number of subjects with 6–15 months of malaria exposure who lived under basic field conditions, akin to those experienced by backpackers, missionaries, refugees, and deployed soldiers. They suffered moderately intense malaria transmission, confirmed by the crude attack rate of just under 73% among the placebo group during the course of the study. The high prophylactic efficacy of the doxycycline positive control excludes poor drug compliance as a cause of the low falciparum result.

To recommend a drug for malaria prophylaxis, that drug must have low toxicity and offer good protection comparable with that of the current first-line drugs. There is no generally accepted minimum efficacy. This trial adopted a priori a minimum acceptable protective efficacy of 70% (lower 95% CI, ≥70%). The lower 95% confidence interval for azithromycin against falciparum malaria was 50.3%. This compares poorly with the lower 95% confidence interval for doxycycline in this trial (85.4%) and those of mefloquine (93%) and doxycycline (88%) obtained in a similar trial in 1994 [19].

In our study, the soldiers (who had only 6 months of malaria exposure) resembled malaria-naive individuals more closely than did the civilians (who had 15 months of malaria exposure). The prophylactic efficacy against *P. falciparum* for the soldiers was 62.9% (95% CI, 29.5–80.4), which was lower than that for the civilians (88.4% [95% CI, 56.6–97.4]) and similar to that of chloroquine/proguanil for Kenyan adults (54% [95% CI, 25–72], which was measured prospectively [13]). The difference between soldiers and civilians was not statistically significant, but we believe that the prophylactic efficacy for the soldiers approximates that of a malaria-naive population. Therefore, for nonimmune populations (a major group receiving prophylaxis), 250 mg of azithromycin daily cannot be recommended as a first-line drug against *P. falciparum*, the species causing severe malaria and high mortality [2].

Comparable data evaluating azithromycin for malaria prophylaxis are limited. In Kenyan adults, daily azithromycin (250 mg; no loading dose) had a prophylactic efficacy (based on crude incidence) of 83% (95% CI, 68–91) against falciparum malaria [17]; the entomological inoculation rate in Kenya (30 infective bites per month) is higher than that in Irian Jaya, and the subjects of the Kenyan study were lifelong residents. None of the subjects to the soldiers (62.9% [95% CI, 29.5–80.4]), there was overlap in the respective confidence intervals.
failing prophylaxis had symptoms attributable to malaria, indicating a high degree of clinical immunity [17, 32].

In contrast, our soldiers and civilians had less clinical immunity because most were symptomatic. However, the similarity of the efficacy results between our civilians and the Kenyans suggests that, after only 15 months of malaria exposure, the immunity acquired was enough to enhance parasite suppression by azithromycin. This is an important finding suggesting that results of studies conducted in populations with even limited immunity to malaria cannot be reliably applied to nonimmune populations.

The marked difference in protective efficacy between falciparum malaria and vivax malaria was an unexpected result. The mechanisms underlying this finding are speculative but might be similar to those of bacterial resistance to macrolide antibiotics—e.g., inhibition of binding to the 50S ribosome or drug extrusion via an ATP pump [33].

Azithromycin, administered for up to 20 weeks, was well tolerated and did not adversely affect standard hematologic and biochemical measurements. One subject was withdrawn for possible azithromycin-induced cutaneous toxicity. Other side effects were mild and reported infrequently. This study was of insufficient size to detect rare side effects.

We conducted this trial in predominantly healthy young men and a small number of women. Pregnant women and children, two potentially vulnerable groups, were excluded from the study. Our results of efficacy and tolerance are primarily applicable to men and not to women and children.

In summary, azithromycin (250 mg/d) should not be used as first-line prophylaxis for falciparum malaria in nonimmune individuals. Azithromycin might be useful as a second choice for patients with absolute contraindications or unacceptable toxicity due to mefloquine and doxycycline. Patients should be warned that no prophylactic drug confers absolute protection against malaria and that compliance is essential [10].

Azithromycin may have a future role in combination with other antimalarial drugs for malaria treatment or prophylaxis.

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