Chloroquine versus Sulfadoxine-Pyrimethamine for Treatment of Plasmodium falciparum Malaria in Savannakhet Province, Lao People’s Democratic Republic: An Assessment of National Antimalarial Drug Recommendations

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The in vivo efficacies of the Lao People’s Democratic Republic (Laos) nationally recommended antimalarial agents—chloroquine and sulfadoxine-pyrimethamine—were assessed in a randomized, comparative trial that involved 100 patients with uncomplicated Plasmodium falciparum malaria who were followed for 42 days after starting treatment. Despite a shorter mean time to fever clearance associated with administration of chloroquine (mean time to clearance, 35.6 h; 95% confidence interval [CI], 26.3–45.0 h), compared with that associated with sulfadoxine-pyrimethamine (61.1 h; 95% CI, 50.9–71.3 h; \( P < .001 \)), treatment failures were twice as frequent among patients receiving chloroquine therapy than among those receiving sulfadoxine-pyrimethamine therapy (36% vs. 18%; \( P = .02 \)). Of 23 treatment failures, 10 (43%) were high grade. Treatment failure rates among children (age range, 5–15 years) were 4.9 times higher (95% CI, 2–12) than those among adults (\( P < .001 \)). Gametocytemia after antimalarial treatment was associated with receipt of sulfadoxine-pyrimethamine therapy and with treatment failure (\( P = .009 \)). The efficacy of both chloroquine and sulfadoxine-pyrimethamine in Laos is unsatisfactory.

The prevalence of malaria in the Lao People’s Democratic Republic (Laos) is \( \sim 14\% \) [1]. The nationally recommended drugs for the treatment of uncomplicated Plasmodium falciparum malaria—oral chloroquine and sulfadoxine-pyrimethamine—are no longer effective in all neighboring countries [2]. The current policy remains in place in Laos because, unlike in adjacent countries, there has been very little clinical research on the efficacy and effectiveness of antimalarial drugs. A recent study in Laos that included a 28-day follow-up period documented that 46% of patients with P. falciparum malaria who had received chloroquine did not respond to treatment [1]. There have been no assessments of sulfadoxine-pyrimethamine therapy in patients who have been followed-up for a sufficient duration.

We conducted recently a randomized, in vivo...
A comparative study of the use of oral chloroquine and sulfadoxine-pyrimethamine for the treatment of uncomplicated *P. falciparum* malaria with a 42-day follow-up. This was conducted in Fueng District (Vientiane Province, Laos; figure 1), an area with a low prevalence of malaria. We recorded unacceptably high rates of in vivo resistance among *P. falciparum* infections (n = 29) to each drug (80% were resistant to chloroquine, and 35% were resistant to sulfadoxine-pyrimethamine) (Maxay et al., unpublished data). We report here the results of a larger study conducted in the southeastern part of Laos, where the prevalence of malaria is higher.

**PATIENTS AND METHODS**

**Study site, patients, and clinical procedures.** The study was conducted from June 2001 through November 2001 in Phalanxay District (Savannakhet Province, Laos), which is located 605 km southeast of Vientiane. The patients, all of whom were members of the Lao Theung ethnic group, presented with symptoms and signs of acute uncomplicated malaria and had a blood smear positive for *P. falciparum*. Patients were enrolled into the study provided they (or their attending relatives) gave fully informed written consent, had asexual *P. falciparum* parasitemia of 5000–100,000 parasites/μL, were not pregnant, were ≥5 years old, had an axillary temperature of ≥37.5°C or a history of fever ≤3 days before enrollment, would complete a 42-day follow-up period, had not received a full course of chloroquine or sulfadoxine-pyrimethamine therapy in the previous 3 days, and did not have severe malaria [5] or a history of allergy to chloroquine or sulfadoxine-pyrimethamine. Ethical clearance was granted by the Ethics Committee of the Council of Medical Science, Ministry of Health (Vientiane).

Figure 1. Clinical trials of chloroquine (CQ) and sulfadoxine-pyrimethamine (SP) in the treatment of uncomplicated *Plasmodium falciparum* malaria in the Lao People's Democratic Republic (PDR). Data are from Pillai et al. [1], Mayxay et al. (unpublished data), Guthmann et al. [3], Schwobel et al. [4], and the present report. See Patients and Methods for definitions of adequate clinical response (ACR), early treatment failure (ETF), late treatment failure (LTF), and RI, RII, and RIII resistance. S, susceptible.
Blood from a fingerprick was obtained from each patient for measurement of the parasite count and assessment of the hematocrit. Three blood spots were collected on filter paper (3MM; Whatman) and stored in plastic bags containing silica gel. Patients were then randomized (in blocks of 10; the name of the treatment they were to receive was kept in a sealed envelope and opened only after enrollment) to receive either (1) oral chloroquine sulfate (Government Pharmaceutical Organization; Bangkok, Thailand), 10 mg base/kg immediately, followed by 10 mg base/kg 24 h later and 5 mg base/kg 48 h after initiation of therapy; or (2) a single dose of pyrimethamine, 1.25 mg/kg, and sulfadoxine, 25 mg/kg (Fansidar; Roche).

Drug administration was directly observed by study physicians. If vomiting occurred within 1 h of administration, the medication was administered again. Patients were assessed daily until parasite clearance and then weekly for 42 days or at other times if a patient felt unwell. At each visit, blood from a fingerprick was obtained to assess the \( P. falciparum \) count and hematocrit. Three additional blood samples obtained from patients with reappearance of asexual parasitemia were spotted onto filter paper for parasite genotyping [6]. Patients who had recurrent parasitemia were treated with the drug that was not used initially (i.e., if a patient was initially treated with chloroquine, he or she was treated with sulfadoxine-pyrimethamine and vice versa). Patients with a second reappearance of \( P. falciparum \) malaria or those who developed severe disease received rescue therapy with artesunate (Guilin Pharma), 4 mg/kg per day for 3 days, plus either mefloquine (Lariam; Roche), 15 mg/kg on day 1 and 10 mg/kg on day 2, or doxycycline (Medic Pharma), 4 mg/kg per day for 7 days. Those who received 2 or 3 courses of therapy were also followed-up for 42 days.

\textbf{Laboratory investigations and outcome measurements.}

Parasite counts were measured daily until parasites were undetectable for 2 consecutive days and then weekly beginning on day 7 of the follow-up period. The counts were calculated on the basis of the number of parasitized cells per 1000 erythrocytes detected on a thin film (by means of the measured hematocrit) or per 200 leukocytes (assuming a peripheral WBC count of 8000 cells per \( \mu L \) of blood) detected on a thick film stained with Field’s stain. Fifty percent of the slides (including those that were positive and those that were negative for \( P. falciparum \) parasites) were randomly selected for quality control by an expert microscopist who was blinded to clinical and treatment details (at Shoklo Malaria Research Unit; Mae Sot, Thailand). Urine specimens were obtained and analyzed for the presence of chloroquine, quinine, and pyrimethamine using immunochromatographic dipstick tests [7].

PCR amplification for parasite genotyping [6] was performed on paired samples of \( P. falciparum \) DNA to distinguish between reinfection and recrudescence. Three polymorphic loci—merozoite surface proteins 1 and 2 and the glutamate-rich protein, located on chromosomes 9, 2, and 10, respectively—were used as genetic markers. A parasite infection in which the same 3-locus genotype was found before and after treatment was considered to be an episode of recrudescence if the chance probability of a match was <0.05. This was determined using population genotype frequencies, which were calculated using data on 100 unambiguous 3-locus genotypes from pretreatment samples. Infections with \( P. falciparum \) parasites for which 3-locus genotype differed before and after treatment were considered to be reinfections.

Primary end points were the clinical [8] and parasitological [9] responses to treatment. Analysis was performed for each treatment either until day 42 after initiation of treatment or until the reappearance of malarial infection with \( P. falciparum \). Secondary end points were parasite clearance time (interval in days between the first treatment dose and the first thick film negative for \( P. falciparum \) parasites after checking \( \geq 200 \) oil fields), fever clearance time (interval in hours between the start of treatment and the time at which the axillary temperature was first <37.5°C and remained <37.5°C for 48 h), presence of gametocytemia, and change in hematocrit after antimalarial treatment.

“Early treatment failure” was defined by the presence of any of the following criteria: (1) the development of danger signs associated with malaria or the development of severe malaria on follow-up days 1, 2, or 3 in the presence of parasitemia; (2) a higher parasitemia level on day 2 than on day 0; and (3) a parasitemia level on day 3 that was >25% of the level on day 0. “Late treatment failure” was defined by the presence of any of the following criteria: (1) the development of danger signs associated with malaria or the development of severe malaria [5] after follow-up day 3 in the presence of parasitemia and (2) the presence of parasitemia on any scheduled follow-up day on or after day 7, regardless of the type and/or severity of malaria symptoms. “Adequate clinical response” was defined as the lack of criteria for early or late treatment failure and the lack of detection of \( P. falciparum \) parasites between day 7 and day 42. “Resistance” was defined as follows: RI, recrudescence of the infection between 7 and 42 days after starting treatment following initial resolution of symptoms and clearance of parasites; RII, reduction of parasite levels by >75% 48 h after starting treatment but failure to clear parasites within 7 days; and RIII, no reduction of parasite levels by >75% within 48 h of starting treatment [1].

\textbf{Statistical analysis.} Data were analyzed by SPSS software, version 8.0 (SPSS). Comparisons between the 2 treatment groups were made using the Mann-Whitney \( U \) test, Student’s \( t \) test, the \( \chi^2 \) test, and Fisher’s exact test, as appropriate. Parasite...
clearance time, fever clearance time, and hematocrits were analyzed using intent-to-treat analyses.

RESULTS

Blood smears from 1291 febrile patients were examined. Three hundred thirty-three smears (26%) were positive for Plasmodium species. In 297 cases (89%), the infecting organism was P. falciparum; in 28 (8.4%), Plasmodium vivax; in 1 (0.3%), Plasmodium malariae; and in 7 (2%), P. falciparum and P. vivax. Of the 297 patients with P. falciparum malaria, 120 were eligible for and willing to participate in the study. Of these, 20 were included in a separate study, and 100 were randomized to receive chloroquine \((n = 50)\) or sulfadoxine-pyrimethamine \((n = 50)\) treatment. The reasons for ineligibility were age <5 years (26% of patients with P. falciparum malaria), parasitemia <3000 parasites/µL (20%), parasitemia >100,000 parasites/µL or severe malaria (23%), unwillingness to consent to the study (15%), low probability of completing the 42-day follow-up period (13%), and pregnancy (3%).

There were no significant differences in the demographic characteristics and clinical features at study enrollment between the 2 study groups, except in the hematocrits, which were significantly lower in the chloroquine group (table 1). Among study patients, 42% (42 of 100) were ≤15 years old (24 patients in the chloroquine group and 18 in the sulfadoxine-pyrimethamine group). Only 2 (4.0%) of 50 patients in the chloroquine group and 1 (2.0%) of 50 in the sulfadoxine-pyrimethamine group vomited in the first hour after drug administration; treatment was successfully readministered in all 3 cases. Two patients in the sulfadoxine-pyrimethamine group were lost to follow-up on days 2 and 21 after starting treatment, and data for these patients were excluded from the analysis. Two patients developed severe jaundice within 48 h after sulfadoxine-pyrimethamine administration and subsequently received rescue therapy; 1 of these patients received a diagnosis of coincident leptospirosis. One patient in the chloroquine group developed coma 8 h after the first dose of chloroquine and received rescue therapy. No other adverse events potentially attributable to the study drugs were noted.

Antimalarial drugs were detected in urine specimens obtained from 35 (74%) of 47 patients in the chloroquine group (18 of whom had received chloroquine therapy only, 16 of whom had received quinine only, and 1 of whom had received chloroquine and quinine) and from 33 (72%) of 46 patients in the sulfadoxine-pyrimethamine group (16 of whom had received chloroquine therapy only, 11 of whom had received quinine only, 1 of whom had received pyrimethamine only, 4 of whom had received chloroquine and quinine, and 1 of whom had received chloroquine, quinine, and pyrimethamine). The

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### Table 1. Demographic and clinical characteristics at enrollment of 100 patients with Plasmodium falciparum malaria.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Chloroquine group</th>
<th>SP group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M/F</td>
<td>31/19</td>
<td>33/17</td>
<td>64/36</td>
</tr>
<tr>
<td>Age, years</td>
<td>22.9 (18.4–27.4)</td>
<td>24.1 (19.8–28.3)</td>
<td>23.5 (20.4–26.3)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>37.0 (32.5–41.5)</td>
<td>40.9 (37.2–44.5)</td>
<td>38.9 (36.0–41.8)</td>
</tr>
<tr>
<td>Previous malaria attacks, n/N (%) of patients</td>
<td>16/45 (35.5)</td>
<td>19/44 (43)</td>
<td>35/89 (39)</td>
</tr>
<tr>
<td>Duration of illness before admission, days</td>
<td>3.0 (2.5–3.4)</td>
<td>3.1 (2.7–3.6)</td>
<td>3.0 (2.7–3.4)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>105.4 (100.7–110.0)</td>
<td>108.6 (104.3–112.9)</td>
<td>107.1 (104.0–110.2)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>68.5 (64.2–72.7)</td>
<td>72.5 (68.7–76.3)</td>
<td>70.6 (67.8–73.4)</td>
</tr>
<tr>
<td>Pulse rate, beats/min</td>
<td>95.3 (91.1–99.5)</td>
<td>92.2 (87.9–96.5)</td>
<td>93.7 (90.8–96.7)</td>
</tr>
<tr>
<td>Temperature, °C (range)</td>
<td>38.1 (37.7–38.5)</td>
<td>38.0 (37.6–38.4)</td>
<td>38.0 (37.8–38.3)</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>25.2 (23.8–26.6)</td>
<td>25.3 (23.8–26.7)</td>
<td>25.2 (24.2–26.2)</td>
</tr>
<tr>
<td>Splenomegaly, n/N (%) of patients</td>
<td>3/50 (6.0)</td>
<td>1/48 (2.0)</td>
<td>4/98 (4.1)</td>
</tr>
<tr>
<td>Hepatomegaly, n/N (%) of patients</td>
<td>2/5 (4.0)</td>
<td>0/48 (0)</td>
<td>2/98 (2.0)</td>
</tr>
<tr>
<td>Parasites count, geometric mean parasites/µL (95% CI)</td>
<td>21,974 (18,176–26,564)</td>
<td>23,410 (18,531–29,573)</td>
<td>22,678 (19,561–26,297)</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>36.9 (35.1–38.6)a</td>
<td>39.2 (37.9–40.5)</td>
<td>38.0 (36.9–39.1)</td>
</tr>
</tbody>
</table>

**Urinalysis results, n/N (%) of patients**

<table>
<thead>
<tr>
<th>Antimalarial drugs detected</th>
<th>Chloroquine detected</th>
<th>Quinine detected</th>
<th>Pyrimethamine detected</th>
<th>Chloroquine and quinine detected</th>
<th>Chloroquine, quinine, and pyrimethamine detected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18/47 (38.3)</td>
<td>16/46 (34.8)</td>
<td>0/47</td>
<td>1/47 (2.1)</td>
<td>0/47</td>
</tr>
</tbody>
</table>

**NOTE.** Data are presented as mean values (95% CI), unless otherwise indicated. n/N, sample size/population size; SP, sulfadoxine-pyrimethamine.

* Significantly different from the other group \((P < .05)\).
proportion of patients from whom urine specimens were obtained that contained antimalarial drug(s) did not significantly differ between the 2 groups ($P = .8$).

Of 18 paired samples of *P. falciparum* DNA recovered from 13 patients who had recurrent parasitemia after day 7 of the follow-up period (RI resistance), PCR results showed matching genotypes consistent with recrudescent infection in 17 cases. In the remaining case, the recurrent parasitemia was due to *P. falciparum* parasites with a genotype different from that of the strain associated with the primary infection, which suggested a new infection. Findings from quality-control slide microscopy of 619 slides agreed well with the original field results ($k = 0.91; 95\% CI, 0.74–1.0$).

**Cure rates.** The overall proportions of treatment failures that occurred after receipt of initial and second treatments combined, with chloroquine and sulfadoxine-pyrimethamine (parasitological: 20 [36\%] of 55 vs. 11 [18\%] of 62 patients [$P = .02$]; and clinical: 20 [36\%] of 55 vs. 12 [19\%] of 63 patients [$P = .02$]), were significantly higher in the chloroquine than in the sulfadoxine-pyrimethamine group (tables 2 and 3). There was no significant difference in the early treatment failure rates associated with receipt of initial treatment between the chloroquine and sulfadoxine-pyrimethamine groups, assessed either parasitologically or clinically. The frequency of RIII treatment failures after receipt of initial treatment was 14\% (7 of 50 patients) in the chloroquine group and 6\% (3 of 50 patients) in the sulfadoxine-pyrimethamine group; 43\% of all treatment failures were high-grade (i.e., RIII) failures. The majority of the patients (15 [88\%] of 17) with a parasitological outcome associated with RI resistance had recurrent parasitemia between days 14 and 28 of the follow-up period (mean interval, 22.9 days; 95\% CI, 19.7–26.1 days). Only 2 patients experienced recurrence of malaria after day 28 or before day 14 (on days 39 and 12, respectively).

Of the 15 patients whose illness failed to respond to chloroquine, 12 (80\%) were treated successfully with sulfadoxine-pyrimethamine, but only 29\% (2 of 7) of the patients whose illness failed to respond to sulfadoxine-pyrimethamine were treated successfully with chloroquine during the 42-day follow-up period ($P = .05$). Of the 22 patients whose illness failed to respond to 1 drug, 8 (36\%) had illness that failed to respond to both chloroquine and sulfadoxine-pyrimethamine. However, these patients were all cured after receipt of 3 days of mefloquine or 7 days of doxycycline.

The patients treated with chloroquine had significantly shorter mean time to fever clearance (35.6 h; 95\% CI, 26.3–45.0 h), compared with those treated with sulfadoxine-pyrimethamine (61.2 days; 95\% CI, 50.7–71.6 days; $P < .001$). However, the mean times to parasite clearance were similar in the chloroquine group (3.0 days; 95\% CI, 2.8–3.2 days) and the sulfadoxine-pyrimethamine group (3.2 days; 95\% CI, 2.9–3.5 days; $P = .2$). Treatment response did not differ between patients with and without antimalarial drugs detected in their urine ($P > .7$).

The mean hematocrit was significantly higher in the sulfadoxine-pyrimethamine group than in the chloroquine group on day 14 (35.1\% [95\% CI, 33.8%–36.4\%] vs. 33.2\% [95\% CI, 32.0%–34.5\%]; $P = .04$) and on day 21 (35.8\% [95\% CI, 34.7%–36.9\%] vs. 34.0\% [95\% CI, 32.8%–35.2\%]; $P = .03$) (figure 2). The proportion of patients who received ferrous sulfate and folate supplements was similar between the groups (3 [6\%] of 50 patients in the sulfadoxine-pyrimethamine group vs. 6 [12\%] of 50 patients in the chloroquine group; $P = .50$).

**Gametocyte carriage.** The proportion of patients with gametocytemia after receipt of treatment was significantly higher in the sulfadoxine-pyrimethamine group (17 [34\%] of 50) than in the chloroquine group (6 [12\%] of 50; $P = .009$) (figure 3). The mean duration of gametocytemia for all patients was 2.04 patient-weeks (95\% CI, 1.5–2.5 patient-weeks), with a mean duration of 2.3 patient-weeks (95\% CI, 1.7–2.9 patient-weeks) in the sulfadoxine-pyrimethamine group and 1.3 patient-weeks (95\% CI, 0.8–1.9 patient-weeks) in the chloroquine group ($P = .07$). The geometric mean gametocyte counts were similar in the sulfadoxine-pyrimethamine group ($P = .36$).
failures among patients

The proportion of treatment failures were treated successfully (mean age, 26.1 years; 95% CI, 9.4–20.6 years) than those whose infections failed to respond to treatment were younger (mean age, 15.0 years; 95% CI, 9.4–20.6 years). The mean duration of gametocytemia did not differ between patients who were successfully treated (1.9 patient-weeks; 95% CI, 1.5–2.3 patient-weeks) and patients for whom treatment failure (2.3 days; 95% CI, 1.8–2.7 days) than among patients who were cured (2.9 days; 95% CI, 2.8–3.1 days; P < .001).

Patients whose illness failed to respond to treatment had a significantly shorter mean time to fever clearance (62.4 h; 95% CI, 41.5–83.4 h) than did patients who were cured (46.8 h; 95% CI, 38.6–54.9 h), but this difference was not statistically significant (P = .1). The mean time to parasite clearance was significantly longer among patients whose illness failed to respond to treatment (3.9 days; 95% CI, 3.3–4.5 days) than among patients who were cured (2.9 days; 95% CI, 2.8–3.1 days; P < .001).

Patients whose illness failed to respond to treatment had significantly lower hematocits at admission and at days 7, 14, and 21 after starting therapy than did those whose illness responded successfully to treatment (P = .01, P = .002, P = .003, and P = .04, respectively). The mean duration of illness before admission was significantly shorter among patients with treatment failure (2.3 days; 95% CI, 1.8–2.7 days) than among patients with treatment success (3.2 days; 95% CI, 2.8–3.6 days; P = .01).

Table 3. Responses to second treatment regimen, according to parasitological and clinical outcomes at day 42 of follow-up, among patients in the chloroquine and sulfadoxine-pyrimethamine (SP) groups who were treated with the other drug after failure of initial treatment.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Chloroquine group, n/N (%) of patients</th>
<th>SP group, n/N (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parasitological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Susceptible</td>
<td>2/7 (29)a</td>
<td>12/16 (75)b</td>
</tr>
<tr>
<td>RI</td>
<td>5/7 (71)</td>
<td>2/16 (13)</td>
</tr>
<tr>
<td>RIIL</td>
<td>0/7 (0)</td>
<td>0/16 (0)</td>
</tr>
<tr>
<td>RIII</td>
<td>0/7 (0)</td>
<td>1/16 (6)</td>
</tr>
<tr>
<td>Resistant</td>
<td>5/7 (71)</td>
<td>3/16 (19)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>0/7 (0)</td>
<td>1/16 (6)</td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACR</td>
<td>2/9 (22)</td>
<td>12/16 (75)</td>
</tr>
<tr>
<td>ETF</td>
<td>0/9 (0)</td>
<td>1/16 (6)</td>
</tr>
<tr>
<td>LTF</td>
<td>5/9 (56)</td>
<td>2/16 (13)</td>
</tr>
<tr>
<td>Resistance (ETF and LTF)</td>
<td>5/9 (56)</td>
<td>3/16 (19)</td>
</tr>
<tr>
<td>Lost to follow-up or excluded</td>
<td>2/9 (22)c</td>
<td>1/16 (6)</td>
</tr>
</tbody>
</table>

NOTE. See Patients and Methods for definitions of adequate clinical response (ACR), early treatment failure (ETF), late treatment failure (LTF), and RI, RIIL, and RIII resistance. n, No. of patients who responded to treatment with other drug; N, no. of patients who received treatment with other drug.

a One patient who did not respond to initial SP therapy declined consent to further follow-up after chloroquine treatment.

b One patient disappeared after 2 days of initial chloroquine therapy and was later found with Plasmodium falciparum parasitemia but could not be defined as RI, RIIL, or RIII. He was treated with SP.

c These 2 patients received artesunate rescue therapy; data for these patients were, therefore, excluded from analysis.

The frequency of gametocytemia after receipt of treatment was also significantly higher among patients with treatment failure (9 [38%] of 24 patients) than among patients with cured infections (13 [18%] of 72 patients; P = .05). However, the mean duration of gametocytemia did not differ between patients who were successfully treated (1.9 patient-weeks; 95% CI, 1.5–2.3 patient-weeks) and patients for whom treatment failed (2.2 patient-weeks; 95% CI, 0.9–3.5 patient-weeks; P = .6). The geometric mean gametocyte counts were also similar in both groups (136 gametocytes/μL [95% CI, 94–196 gametocytes/μL] vs. 128 gametocytes/μL [95% CI, 83–196 gametocytes/μL]; P = .8).

Factors affecting treatment responses. Patients whose infections failed to respond to treatment were younger (mean age, 15.0 years; 95% CI, 9.4–20.6 years) than those whose infections were treated successfully (mean age, 26.1 years; 95% CI, 22.4–29.7 years; P = .002). The proportion of treatment failures among patients ≤15 years old was 45% (19 of 42 patients), compared with 9% (5 of 54 patients) among those >15 years old (relative risk, 4.9; 95% CI, 2–12; P < .001). For those treated with chloroquine, the treatment failure rate among patients ≤15 years old was 50% (12 of 24 patients), compared with 16% (4 of 25 patients) among those >15 years old (P = .01). For those treated with sulfadoxine-pyrimethamine, the failure rate among patients ≤15 years old was 39% (7 of 18 patients), compared with 3.4% (1 of 29 patients; P = .003) among patients >15 years old. Thus, there was no difference in treatment failure rates among children between the 2 groups (P = .07).

Patients whose illness failed to respond to treatment had a longer mean time to fever clearance (62.4 h; 95% CI, 41.5–83.4 h) than did patients who were cured (46.8 h; 95% CI, 38.6–54.9 h), but this difference was not statistically significant (P = .1). The mean time to parasite clearance was significantly longer among patients whose illness failed to respond to treatment (3.9 days; 95% CI, 3.3–4.5 days) than among patients who were cured (2.9 days; 95% CI, 2.8–3.1 days; P < .001).

Patients whose illness failed to respond to treatment had significantly lower hematocits at admission and at days 7, 14, and 21 after starting therapy than did those whose illness responded successfully to treatment (P = .01, P = .002, P = .003, and P = .04, respectively). The mean duration of illness before admission was significantly shorter among patients with treatment failure (2.3 days; 95% CI, 1.8–2.7 days) than among patients with treatment success (3.2 days; 95% CI, 2.8–3.6 days; P = .01).

DISCUSSION

This study demonstrated a high proportion of treatment failures associated with chloroquine (36%) and sulfadoxine-pyrimethamine (18%) therapy, the 2 drugs locally recommended for the treatment of P. falciparum malaria in Laos. The presence of high-grade (RIII) resistance after initial treatment (14% in the chloroquine group and 6% in the sulfadoxine-pyrimethamine group) and the very high failure rates of therapy in children suggest that patients’ background immunity was a very important contributor to the treatment response. This may explain why the results of the current study appear to be better than the results of our previous investigation in north central Laos (Maxay et al., unpublished data)—the frequency of malaria transmission is higher in southeastern Laos. The differences in responses between the 2 drugs were found only in semi-immune adults. Thus, although the parasites were highly resistant to the drugs, their host defenses often controlled the infection. Drug assessments in semi-immune adults overestimate antimalarial efficacy and are often used to sustain ineffective drug regimens in national policy [10]. In addition, the proportion of patients with antimalarial drugs detected in urine...
Treatment of P. falciparum Malaria in Laos

Figure 2. Hematocrit (mean % ± SD) before and after administration of study drug in the chloroquine group (solid circles) and sulfadoxine-pyrimethamine group (open circles). *Significant difference between values in the sulfadoxine-pyrimethamine and chloroquine groups (P < .05).

specimens obtained at admission was significantly higher in Phalanxay (73%) than in Fueng (46%; P = .01), probably because the availability of oral antimalarial drugs was greater at the former site. The high prevalence of antimalarial drug(s) in urine specimens obtained from patients in each group suggests that the treatment failure rate is underestimated in this study.

The proportion of chloroquine- and sulfadoxine-pyrimethamine–resistant cases in this study was comparable to that in previously published reports in Laos with a >28-day follow-up period [1, 3]. A recent study with a 14-day follow-up period in Attapeu (figure 1) found early treatment failure or late treatment failure among 45% and 18% of patients, respectively, treated with chloroquine and sulfadoxine-pyrimethamine [4]. Taken together, these studies demonstrate that chloroquine and sulfadoxine-pyrimethamine have unacceptably high rates of treatment failure, particularly in the most vulnerable non-immune children, and that the national policy in Laos for the treatment of uncomplicated P. falciparum malaria urgently needs to be reviewed. Antimalarial treatment should be provided as a combination of drugs. Combined oral chloroquine and sulfadoxine-pyrimethamine treatment, if it were effective, would be likely to have a short period of usefulness in Laos, because resistance to both drugs is well established. Other, more effective combination regimens to be considered include artemesunate-mefloquine, artemether-lumefantrine, and dihydroartemisinin-piperaquine [11, 12].

Most cases of late treatment failure in this study were associated with recurrence of parasitemia after day 14. If the World Health Organization 14-day test had been used, 94% of RI cases (16 of 17) would have been missed, and, thus, the study would have substantially underestimated the true resistance rate [10]. The overall treatment failure rate after the initial and second treatments in this study, as assessed using the World Health Organization 14-day test, would have been only 22% (12 of 55 cases) for chloroquine and 5% (3 of 62 cases) for sulfadoxine-pyrimethamine. Prolonged 42-day follow-up was conducted as we had expected, with the long half-life of the antimalarial drugs used, to find late treatment failures after day 28. However, only 1 of the cases of RI resistance occurred after day 28, suggesting that P. falciparum resistance to chloroquine and sulfadoxine-pyrimethamine is serious. The profile of therapeutic responses in this study—in which there were nearly as many RIII as RI parasitological responses, a failure rate that was 5 times greater among children than among adults, and very few late treatment failures—is reminiscent of studies conducted in Africa with ineffective chloroquine or sulfadoxine-pyrimethamine regimens. It reflects a high level of intrinsic resistance in P. falciparum, malaria that is not controlled by drug therapy and public health measures, and acquisition of significant antiparasitic immunity by the time of adulthood.

The high rate of potentially dangerous early treatment failures indicates that, in the most vulnerable group, young children, death may occur. If this study had been conducted in adults only, the treatment failure rate might have been considered too low to justify changing from sulfadoxine-pyrimethamine therapy to another therapy.

In the present study, although chloroquine treatment failure rates were higher than those associated with sulfadoxine-pyrimethamine, fever subsided significantly more quickly in the patients treated with chloroquine than in those treated with sulfadoxine-pyrimethamine. If only the patients with treatment success were included, the mean time to fever clearance was also significantly shorter among patients treated with chloroquine (30.7 h; 95% CI, 22.9–38.5 h) than among those treated with sulfadoxine-pyrimethamine (60.5 h; 95% CI, 48.5–72.5 h; P < .001). This has been observed in previous studies and reflects the malaria-stage specificity of chloroquine and its pharmacokinetic profile [13].

Hematocrits improved significantly more quickly after re-

Figure 3. Percentage of patients with gametocytemia after administration of study drug in the chloroquine (CQ) group and sulfadoxine-pyrimethamine (SP) group and the overall percentage of patients with gametocytemia, according to treatment failure or success.
cept of treatment in the sulfadoxine-pyrimethamine group than in the chloroquine group. The mean hematocrit in patients treated with sulfadoxine-pyrimethamine reached ≥35% by day 14 of follow-up, whereas the mean hematocrit in those treated with chloroquine reached ≥35% by day 28 (figure 2). These results, together with the lower rate of treatment failure, confirm that sulfadoxine-pyrimethamine currently has greater efficacy than chloroquine in Laos. However, patients treated with sulfadoxine-pyrimethamine produced significantly more gametocytes than did those treated with chloroquine, which potentially increases malaria transmission, consistent with previous reports [14–16]. Patients whose illness failed to respond to treatment produced significantly more gametocytes than did those whose infections were cured, supporting previous findings that recrudescence infections are more likely to produce gametocytes than primary infections [17]. Thus, if ineffective antimalarial drugs, especially sulfadoxine-pyrimethamine, are used, the transmission of resistant parasites is enhanced.

In conclusion, these results demonstrate high treatment failure rates associated with both chloroquine and sulfadoxine-pyrimethamine, suggesting that the national strategy in Laos for treating uncomplicated *P. falciparum* malaria needs to be reviewed urgently. We are conducting a clinical trial comparing artesunate plus mefloquine, chloroquine plus sulfadoxine-pyrimethamine, and artemether plus lumefantrine as a first step in determining the optimum combination treatment regimen.

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