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Comparison of Two Mefloquine Regimens for Treatment of *Plasmodium falciparum* Malaria on the Northeastern Thai-Cambodian Border

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In 1991 and 1992, a prospective randomized trial was conducted on the northern Thai-Cambodian border. That trial compared the efficacy and tolerance of two mefloquine regimens for the treatment of uncomplicated *Plasmodium falciparum* malaria in an area with multi-drug-resistant *P. falciparum*. The resolution of fever and other symptoms was faster with high-dose mefloquine (25 mg/kg of body weight [M25 group; $n = 68$]) than with the conventional 15-mg/kg dose (M15 group; $n = 71$). There were no early treatment failures (days 7 to 9) in the M25 group, but there were 5 (7%) treatment failures in the M15 group ($P = 0.03$). The incidences of treatment failures by day 28 were 40% with the M15 group and 11% with the M25 group ($P = 0.0004$). By day 42, these values had risen to 50 and 27%, respectively ($P = 0.01$). The risk of treatment failure was highest in children (relative risk, 2.1; 95% confidence interval, 1.3 to 3.4) and patients with posttreatment diarrhea (relative risk, 2.0; 95% confidence interval, 1.3 to 3.1). Over half of the recrudescences in the M25 group occurred between days 28 and 42, whereas 17% of the recrudescences in the M15 group occurred between days 28 and 42 ($P = 0.02$). Thus, the sensitivity of assessment was significantly increased with longer follow-up. Treatment failure was associated with a delayed parasite clearance and an inadequate hematological recovery. Upper gastrointestinal side effects and dizziness were significantly more common in the M25 group, but overall, the high dose was relatively well tolerated, in particular by children. An increase in the dose to 25 mg/kg can prolong the therapeutic use of mefloquine in areas with multi-drug-resistant *P. falciparum* malaria where high-grade resistance to mefloquine is still rare.

The resistance of *Plasmodium falciparum* to mefloquine is a rapidly increasing problem in Thailand, particularly in its border regions (3, 5). In a recent study on the border between Thailand and Myanmar (Burma) (8), it was found that the efficacy of mefloquine could be markedly enhanced by increasing the conventional dosage (15 mg/kg of body weight) to 25 mg/kg. However, on the southeastern part of the Thai-Cambodian border, higher doses resulted only in a decrease in the proportion of RIII failures, but not in an additional efficacy overall (2). This is the worst area in the world for mefloquine resistance; in 1991, 24% of the patients failed to respond to mefloquine (25 mg/kg) by days 7 to 9 after treatment had begun (2). We report here the results of a study comparing the efficacy and tolerance of these two regimens in an area along the northeastern Thai-Cambodian border where high-grade mefloquine resistance (RII and RIII types) is still relatively rare.

MATERIALS AND METHODS

Study site. The present study was conducted in site B, a camp for 60,000 displaced persons of the Khmer ethnic group situated in the northeastern Thai province of Surin, which is 10 km from the Thai-Cambodian border. Health care in this camp is provided by the aid organization Médecines sans Frontières (MSF-Holland) under the auspices of the United Nations Border Relief Operations. Malaria is an important imported medical problem in this camp. In 1990 and 1991, respectively, 12,000 and 6,500 patients with malaria were referred to the hospital and the outpatient clinic of MSF, with a peak between August and November of each year. Most patients were adult males and contracted malaria in northwest Cambodia. Although detailed epidemiological data are not available, it is generally believed that malaria transmission does not occur inside the camp. There have been no documented cases of malaria acquired in the camp, and regular entomological surveys in site B found that none of the collected mosquitoes were infected with *Plasmodium* species.

Study procedure. The study was designed to detect a reduction in the failure rate from 50 to 25% with 80% power and a 95% confidence limit. Symptomatic patients reporting to the MSF clinics with uncomplicated *P. falciparum* malaria were enrolled in the study if they gave fully informed consent and agreed to remain in the camp during the follow-up period. Patients with a history of recent antimalarial treatment (mefloquine within 9 days or quinine within 7 days of admission), a history of psychiatric disorders, or signs of severe malaria (10) and pregnant women and neonates were excluded. On admission and follow-up, a routine clinical examination was performed and a history of symptoms, side effects, and recent travel to malarious areas was recorded. All patients enrolled in the study were admitted to the hospital, and daily smears for malaria and hematocrits

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TABLE 1. Admission variables and treatment response

Variable[a]	Age, ≤15 years		Age, >15 years		P value[b]
	Mefloquine, 15 mg/kg	Mefloquine, 25 mg/kg	Mefloquine, 15 mg/kg	Mefloquine, 25 mg/kg	
No. of patients enrolled	12	15	59	53	
Age (yr [mean ± SD])	9.3 ± 4.2	9.3 ± 3.5	29.0 ± 9.7	30.3 ± 8.7	NS
Sex (no. [%] of males)	6 (50)	7 (47)	56 (95)	49 (92)	NS
Parasitemia/mm^3 (geometric mean [range])	7,918 (720–42,158)	4,905 (1,480–74,720)	6,152 (1,040–48,160)	5,952 (720–44,528)	NS
Hematocrit (% [mean ± SD])	29.3 (6.4)	30.4 (4.1)	35.6 (6.4)	34.7 (6.1)	NS
Palpable spleen (no. [%])	6 (50)	5 (33)	21 (36)	17 (32)	NS
Palpable liver (no. [%])	6 (50)	5 (33)	9 (15)	9 (17)	NS
PCT (days [median (range)])	2.3 (1–>9)	1.9 (1–4)	1.9 (1–>9)	1.9 (1–4)	NS
No. (%) parasitemic on day 4	2 (17)	0	5 (8)	1 (2)	0.03
FCT (days [median (range)])	4.4 (1–>9)	3.3 (1–>9)	1.4 (1–>9)	0.8 (1–>9)	0.055
Cumulative failure rates (no. who failed therapy/total no. tested [%])					
Day 28	6/11 (55)	5/15 (33)	18/49 (37)	2/48 (4)	0.0004[c]
Day 42	8/11 (73)	8/15 (53)	21/47 (45)	8/44 (18)	0.01[c]

[a] PCT and FCT, parasite and fever clearance times, respectively.
[b] *P* value for overall difference between mefloquine at 15 and 25 mg/kg. NS, not significant.
[c] By Mantel-Haenszel summary chi-square statistic adjusted for age and posttreatment diarrhea.

were taken until parasites were undetectable for 2 consecutive days. Patients were then seen weekly until day 42 or on any day up to day 42 if they developed fever. Parasites were counted against 200 leukocytes on Giemsa-stained blood smears and are expressed per cubic millimeter, assuming a leukocyte count of 8,000/mm^3. Patients were randomly allocated into pairs to receive a single dose of mefloquine at either 15 mg/kg of body weight (M15 group) or 25 mg/kg of body weight (M25 group). All febrile patients received acetaminophen (paracetamol) before treatment and tepid sponging until the axillary temperature was below 37.5°C. Drug administration was supervised, and if vomiting occurred within 1 h following drug administration in the M15 group or within 30 min following drug administration in the M25 group, the full dose was repeated. If vomiting occurred between 30 and 60 min in the M25 group, a repeat dose of only 15 mg/kg was given. Patients who vomited more than two times were omitted from the study and were treated with quinine and tetracycline. Treatment was considered to have failed in all symptomatic patients with blood smears positive for *P. falciparum* on day 7 or 8 and all patients positive on day 9 and onward (also when the patients were asymptomatic) (5). Infections which recrudesced within 14 days following primary treatment with the 25-mg/kg dose were retreated with a 7-day course of quinine (30 mg/kg/day) combined with tetracycline (20 mg/kg/day) or with a repeat dose of 25 mg of mefloquine per kg if recrudescence occurred after day 14. All failures in the M15 group were retreated with mefloquine at 25 mg/kg. Any further recrudescent infections were treated with a 10-day course of quinine-tetracycline.

Statistical analysis. The data were analyzed by using Epiinfo and SPSS software. Dichotomous variables were compared by the Fisher exact test or the chi-square test. The relative risks (RRs) and probability of recrudescent infection were calculated by using Mantel-Haenszel stratified cross-tabulations with allowance for the risk factors age and diarrhea. Normally distributed variables were compared by one-way analysis of variance. The time needed for 50% of the patients to become afebrile or aparasitemic (median) were compared by the Mann-Whitney U test. The median times presented were calculated by fitting a sigmoid E_{max} model to the data by using NFIT software (University of Texas).

RESULTS

Between August 1991 and February 1992, 141 patients entered the study. Two patients who were randomized to receive mefloquine at 25 mg/kg did not tolerate mefloquine and were excluded from the study. Of the remaining 139 patients, 71 received mefloquine at 15 mg/kg and 68 received mefloquine at 25 mg/kg. Their clinical and laboratory characteristics on admission to the study were comparable (Table 1). Overall, 16 patients (12%) were withdrawn from the study by day 28 because they had left the camp for more than 2 weeks (M15 group, 11 patients [15%]; M25 group, 5 patients [7%]; $P > 0.1$), and 22 (16%) were withdrawn from the study by day 42 (M15 group, 13 patients [18%]; M25 group, 9 patients [13%]; $P > 0.4$). Their characteristics at the time of admission to the study were similar to those who completed the follow-up.

Initial clinical and parasitological responses. The resolution of symptoms was faster in the high-dose group. Patients in

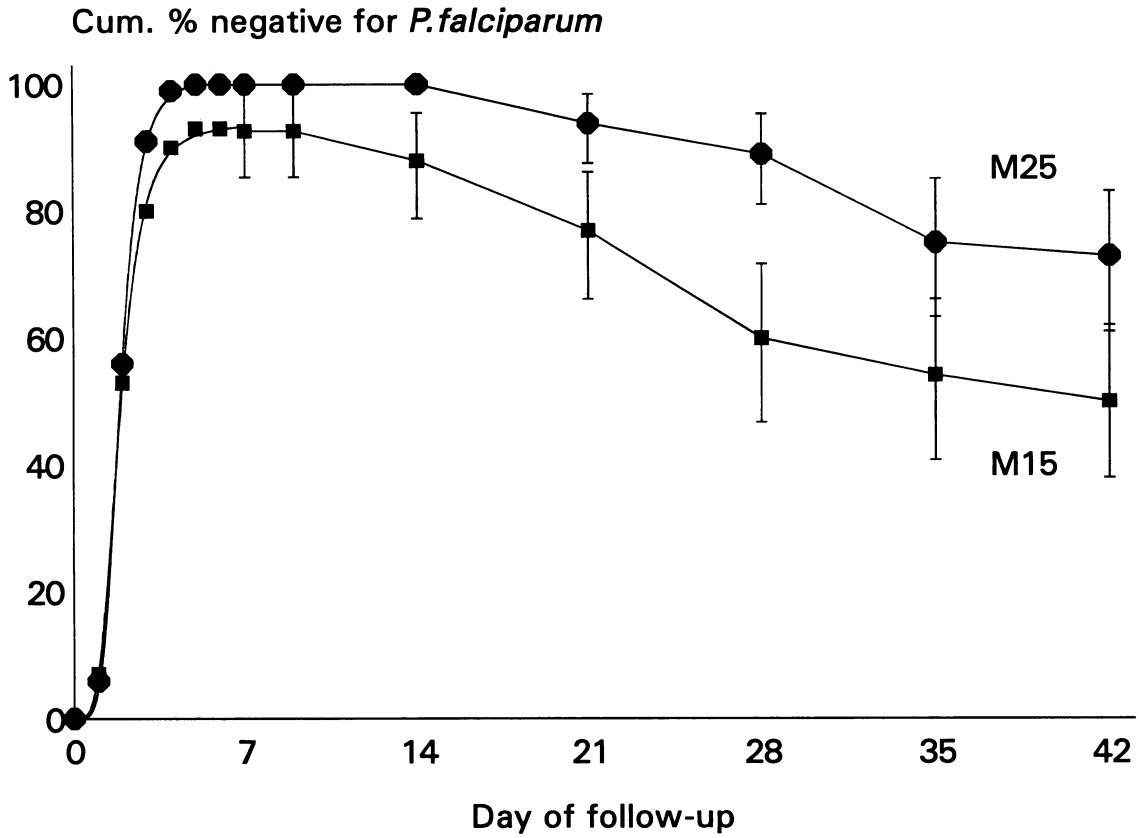

FIG. 1. Cumulative proportion (95% CI) of patients who became blood smear negative for *P. falciparum* between days 1 and 9 and who remained without recrudescence of infection during the 42-day follow-up period.

the M25 group reported 23% fewer episodes of headache or muscle or abdominal pain between days 1 and 3 than those in the M25 group (P = 0.006 and 0.045, respectively). The median (range) times by which 50% of the patients had become afebrile (axillary temperature, ≤37.3°C) were 2.4 days (1 to >9 days) in the M15 group and 1.0 day (1 to >9 days) in the M25 group (P = 0.055) (Table 1). There were no differences between the treatment groups in the rates at which hepatosplenomegaly or anemia resolved. The median parasite clearance times were the same in both groups; however, persistence of parasitemia until day 4 or after was significantly more common in the M15 group (Table 1).

Treatment failures. There were five early treatment failures in the M15 group, i.e., 7% (5 of 68 patients), but there no treatment failures in the 66 patients in the M25 group who were followed up successfully for 7 to 9 days (P = 0.03). The overall cumulative failure rates by day 28 were 11% (7 of 63 patients) in the M25 group and 40% (24 of 60 patients) in the M15 group. The RR of failure by day 28 when adjusted for the risk factors age and posttreatment diarrhea (see below) was 0.27; the 95% confidence interval (CI) was 0.13 to 0.59 (P = 0.0004). By day 42, the cumulative failure rate had increased to 27% (16 of 59 patients) in the M25 group versus 50% (29 of 58 patients) in the M15 group (RR, 0.52; 95% CI, 0.32 to 0.86; P = 0.01). Thus, whereas in the M25 group, 56% (9 of 16 patients) of the failures occurred after day 28, this was only 17% (5 of 29 patients) in the M15 group (P = 0.02). The median (range) times to recrudescence were 22.9 days (7 to 42 days) in the M15 group and 30.2 days (17 to 42 days) in the M25 group (P = 0.02). All patients who completed the study denied having visited a malarious area in between the weekly follow-up visits. The temporal relationship between the parasitological efficacy and mefloquine dose is illustrated in Fig 1.

Recrudescence rates were highest in children under 16 years of age, i.e., 73% in the M15 group (8 of 11 patients) and 53% in the M25 group (8 of 15 patients); this is in comparison with recrudescence rates of 45% (21 of 47 patients) and 18% (8 of 44 patients), respectively, in adults (RR, 2.14; 95% CI, 1.36 to 3.36; P = 0.007, adjusted for treatment group and diarrhea). Diarrhea (loose, watery stools [1]) on day 1 or 2 posttreatment was also associated with an increased risk of treatment failure; 86% (6 of 7 patients) of the patients with posttreatment diarrhea (days 1 or 2) had a subsequent recrudescence of infection, but only 36% (39 of 110 patients) of the patients who did not have posttreatment diarrhea had a recrudescence of infection (RR, 1.99; 95% CI, 1.29 to 3.05; P = 0.09, adjusted for treatment group and age).

Parasite clearance was slower in treatment failures (median parasite clearance time, 2.4 days; range, 2 to >9 days) than in treatment successes (median parasite clearance time, 1.7 days; range, 1 to 4 days; $P < 0.0001$). The sensitivity of a positive blood smear on day 3 for predicting a treatment failure was 36% (16 of 45 failures; M15 group, 13 of 29 patients; M25 group, 3 of 16 patients with a 94% specificity; 68 of 72 successes; M15 group, 2 of 29 patients; M25 group, 2 of 43 patients). All patients with persistent parasitemias until day 4 (n = 7; all in the M15 group) had a subsequent recrudescence of infection.

The hematological recovery was also worse in treatment

TABLE 2. Patients with symptoms and adverse events

Age group and day of follow-up[a]	No. (%) of patients with:											
	Vomiting		Nausea		Anorexia		Diarrhea		Mild dizziness[b]		Moderate-severe dizziness[b]	
	M15	M25	M15	M25	M15	M25	M15	M25	M15	M25	M15	M25
5–15 yr[c]												
0 (9, 13)	2 (22)	6 (46)	3 (33)	3 (23)	5 (56)	3 (23)	2 (22)	2 (15)	5 (56)	4 (33)	4 (44)	1 (8)
1 (9, 13)	0	3 (23)	1 (11)	0	3 (33)	1 (8)	1 (11)	2 (15)	4 (44)	5 (39)	6 (67)	1 (14)[d]
2 (9, 13)	0	2 (15)	0	0	0	2 (15)	1 (11)	2 (15)	2 (22)	4 (31)	2 (22)	0
>15 yr												
0 (59, 53)	18 (31)	15 (28)	18 (31)	13 (25)	38 (64)	37 (70)	13 (22)	3 (6)[d]	46 (78)	36 (68)	17 (29)	15 (28)
1 (56, 53)	7 (13)	7 (13)	7 (13)	7 (13)	27 (48)	24 (45)	9 (16)	7 (13)	38 (68)	35 (66)	12 (21)	16 (30)
2 (58, 53)	6 (10)	4 (8)	3 (5)	9 (17)[d]	11 (19)	20 (38)[d]	4 (7)	0	36 (62)	30 (57)	7 (12)	15 (28)[d]

[a] Values in parentheses are numbers of patients in the M15 group and numbers of patients in the M25 group.
[b] A feeling of light-headedness was classified as mild dizziness, feelings of swaying or rotation were classified as moderate dizziness, and dizziness associated with inability to walk unaided was classified as severe dizziness.
[c] Children aged ≤5 years who were unable to answer the questions were excluded (n = 5).
[d] P value, <0.05.

failures. The maximum fall (geometric mean [95% CI]) in hematocrit relative to the admission value was 6.3% (95% CI, 4.4 to 9.2%) in patients who were treatment failures and 4.7% (95% CI, 3.7 to 5.9%) in those who were treatment successes (P = 0.04). The lowest hematocrits recorded during follow-up were 28.9% (mean; 95% CI, 27.0 to 30.6%) in treatment failures and 32.3% (mean; 95% CI, 31.1 to 33.5%) in treatment successes (P = 0.004). This effect was independent of the hematocrit level at the time of admission to the study and age. The subsequent hematological recovery was compared by determining the proportions of initially anemic patients (hematocrit, <35%) who were still anemic at the day of treatment failure or by day 42. These were 49% (19 of 39 patients) in treatment failures and 22% (13 of 58 patients) in treatment successes (P = 0.007). There was no relationship between treatment outcome and the time needed for fever to resolve or for the liver or spleen to become impalpable.

Retreatment. The overall risk of recrudescence was higher when mefloquine at 25 mg/kg was given as retreatment than when it was given as primary treatment. Of the 45 patients who were treatment failures who received mefloquine at 25 mg/kg as retreatment, 36 (80%) were followed up for 28 days and 34 (76%) were followed up for 42 days. Parasites recurred in 12 patients by day 28 (33%), which was higher (not significant) than the 11% failure rate when mefloquine at 25 mg/kg was used as the primary treatment (RR adjusted for age, 2.11; 95% CI, 1.00 to 4.46; P = 0.09). The retreatment failure rate by day 42 was 44% (15 of 34 patients), whereas it was 27% in those who received mefloquine at 25 mg/kg as the primary treatment (RR, 1.34; 95% CI, 0.79 to 2.28; P = 0.4). The 15 patients who twice failed therapy with mefloquine were retreated with a strictly supervised 7-day course of quinine combined with tetracycline. Three patients (20%) had a third recrudescence by day 28 and 4 of 14 patients (29%) had a third recrudescence by day 42. They were all successfully treated with a 10-day course of quinine in combination with tetracycline.

Adverse effects. Five (7%) of the 70 patients randomized to receive mefloquine at 25 mg/kg vomited within the first hour and received a repeat dose. Two vomited again and were excluded from the study. None of the patients who received mefloquine at 15 mg/kg vomited within the first hour (P = 0.03), although one adult vomited at 60 min (and was not retreated). Posttreatment anorexia, nausea, and dizziness were common and occurred more frequently in the high-dose group (Table 2). Diarrhea occurred significantly more often in the M15 group (22%) than in the M25 group (8%) at the time of enrollment in the study (P = 0.02), but the proportions of patients with posttreatment diarrhea were similar between the two treatment groups (Table 2). It is difficult to determine the relative contributions of malaria and mefloquine in causing posttreatment diarrhea. We therefore separated the analysis for patients with diarrhea at the time of enrollment in the study and those without diarrhea (1). The proportions of patients who either developed diarrhea after the start ofs treatment or whose diarrhea upon admission to the study had resolved by day 1 or 2 posttreatment were similar in both treatment groups (M15 group, 13 and 60%, respectively; M25 group, 10 and 50%, respectively) and in both age groups (children, 9 and 60%, respectively; adults, 12 and 56%, respectively). Thus, as in a previous study (8), diarrhea was associated with acute *P. falciparum* malaria, but there was no evidence that mefloquine-induced diarrhea (if any) was dose related in our study population.

Overall, children tolerated mefloquine better than did adults. There were no serious neuropsychiatric or cutaneous adverse events.

DISCUSSION

Results of the present study confirm the fact that mefloquine efficacy has declined dramatically along the Thai-Cambodian border since it was first introduced as the treatment of choice for uncomplicated *P. falciparum* malaria in 1985. In 1983, mefloquine (15 mg/kg in combination with sulfadoxine and pyrimethamine as MSP) cured over 98% of the infections in this area when assessed by day 28 posttreatment (4). This cure rate has fallen to 60% for assessments done by day 28 posttreatment and 50% for assessments done by day 42 posttreatment. The incidence of high-grade resistance, indicated by the proportion of patients who failed to respond by days 7 to 9, was 7%. These early failure rates are worrying, but they were less than expected and considerably lower than the 24% high-grade failure rate reported from the eastern border with Cambodia (≈300 km to the south), where an increase in the dose of mefloquine did not enhance efficacy (2). In contrast, we found that by increasing the dose to 25 mg/kg, the rates of clinical recovery could be significantly improved and early failures could effectively be

prevented. Furthermore, there was a 73% reduction (P = 0.0004) in the overall failure rate by day 28 and a 42% reduction by day 42 (P = 0.01). These results are very similar to those reported from a comparative trial conducted on the border between Thailand and Myanmar, where the majority of cases of mefloquine resistance were also low grade (8). An increase in the dose in this area prolonged the therapeutic use of mefloquine for a period of 2 years (7). It can be concluded from the results of the three studies that the level of mefloquine resistance varies considerably on the borders of Thailand and that increasing the dose of mefloquine can markedly increase efficacy, but only in areas where high-grade resistance is not yet common. An increase in the dose was also associated with an increase in reported upper gastrointestinal side effects and dizziness, but overall, high-dose mefloquine was relatively well tolerated, in particular by children.

The treatment of recrudescent infections is becoming a problem of increasing magnitude in Thailand. In the present study, mefloquine (25 mg/kg), when given as retreatment to those who had failed primary mefloquine treatment, proved inadequate and was associated with a 44% failure rate by day 42, i.e., 1.6-fold higher than the primary failure rate of 27%. This stresses the need for an adequate history of previous antimalarial drug use when prescribing mefloquine. A similar high failure rate (29%) was found when these patients with multiple recrudescences were retreated with a 7-day course of supervised quinine combined with tetracycline.

As in previous studies, young age (≤15 years), posttreatment diarrhea, and prolonged parasite clearance times were associated with an increased risk of recrudescent infections (1, 6, 8). Patients who were treatment failures were also more likely to experience persistent anemia; the rate and magnitude of the decrease in hematocrit during the first week were greater in patients with a subsequent recrudescence, and their subsequent hematological recovery (if any) was significantly worse.

The duration of follow-up was an important determinant of antimalarial efficacy. The conventional length of follow-up is 28 days, but infections may recrudesce up to 10 weeks (and probably more) after treatment with mefloquine (3, 9). We used a 42-day follow-up as a practical compromise. The sensitivity of detection of treatment failures was markedly increased with longer follow-up. This was particularly evident in the group that received the higher dose, in which over half of the recrudescences occurred after 28 days. These infections would thus have been erroneously classified as susceptible to treatment with a shorter follow-up. Reinfections could not be ruled out completely, but it is unlikely that this was an important bias. Malaria transmission in the camp, if any, is minimal and all patients denied having visited a malarious area during the weekly follow-up period.

In conclusion, high-dose mefloquine was relatively well tolerated and proved superior to the conventional 15-mg/kg regimen for the treatment of multi-drug-resistant *P. falciparum* malaria. An increase in the dose may prolong the therapeutic use of mefloquine in areas where the incidence of high-grade mefloquine resistance is still low.

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