Tropical Medicine and International Health

VOLUME 9 NO 11 PP 1184–1190 NOVEMBER 2004

Comparison of chloroquine, sulfadoxine/pyrimethamine, mefloquine and mefloquine-artesunate for the treatment of falciparum malaria in Kachin State, North Myanmar

Frank Smithuis[1], Maryam Shahmanesh[1], Moe Kyaw Kyaw[1], Olivia Savran[1], Saw Lwin[2] and Nicholas J. White[3,4]

1 *Medecins sans Frontieres – Holland, Yangon, Myanmar*
2 *Department of Health, Vector Borne Disease Control, Myanmar*
3 *Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand*
4 *Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, Churchill Hospital, Oxford, UK*

Summary Multi-drug resistant falciparum malaria is widespread in Asia. In Thailand, Cambodia and Vietnam the national protocols have changed largely to artesunate combined treatment regimens but elsewhere in East and South Asia chloroquine (CQ) and sulfadoxine-pyrimethamine (SP) are still widely recommended by national malaria control programmes. In Kachin State, northern Myanmar, an area of low seasonal malaria transmission, the efficacy of CQ (25 mg base/kg) and SP (1.25/25 mg/kg), the nationally recommended treatments at the time, were compared with mefloquine alone (M; 15 mg base/kg) and mefloquine combined with artesunate (MA; 15:4 mg/kg). An open randomized controlled trial enrolled 316 patients with uncomplicated *Plasmodium falciparum* malaria, stratified prospectively into three age-groups. Early treatment failures (ETF) occurred in 41% (32/78) of CQ treated patients and in 24% of patients treated with SP (18/75). In young children the ETF rates were 87% after CQ and 35% after SP. Four children (two CQ, two SP) developed symptoms of cerebral malaria within 3 days after treatment. By day 42, failure rates (uncorrected for reinfections) had increased to 79% for CQ and 81% for SP. ETF rates were 2.5% after treatment with M and 3.9% after treatment with MA ($P > 0.2$). Overall uncorrected treatment failure rates at day 42 following M and MA were 23% and 21%, respectively. Chloroquine and SP are completely ineffective for the treatment of falciparum malaria in northern Myanmar. Mefloquine treatment is much more effective, but three day combination regimens with artesunate will be needed for optimum efficacy and protection against resistance.

keywords malaria, *P. falciparum*, mefloquine, artesunate, Myanmar

Introduction

Although multi-drug resistant *Plasmodium falciparum* malaria is generally regarded as a South-east Asian problem (Singhasivanon 1999), recent results from Bangladesh (Rahman *et al.* 2001), Northeastern India (Medecins Sans Frontieres-Holland, personal communication, 2001), Pakistan (Rab *et al.* 2001), Southern China (Yang *et al.* 1997) and Western Myanmar (Smithuis *et al.* 1997) all indicate that the problem is much more widespread throughout the East and South Asian region. In Myanmar, low-grade resistance to chloroquine (CQ) appeared in the mid 1970s and resistance to both CQ and sulfadoxine-pyrimethamine (SP) has worsened since the 1980s (Aung-Than-Batu *et al.* 1975; Tin & Hlaing 1977; Tin *et al.* 1987). In the 1990s, high levels of resistance to CQ and SP were reported in West Myanmar (CQ; 82% failure by day 28 and SP; 67% failure by day 28; Smithuis *et al.* 1997). *In vitro* resistance to mefloquine (M) has been recorded in Eastern Myanmar (Wongsrichanalai *et al.* 2001) adjacent to the border with Thailand, where it has been deployed systematically since 1984, but mefloquine has remained effective in Western Myanmar (Smithuis *et al.* 1997). There are no recent data regarding the situation of drug resistance in Kachin State in the North of Myanmar bordering with India and China. In order to determine the efficacy of current treatment options for falciparum malaria in Northern Myanmar, to search for simple single administration alternatives, and thereby provide an evidence base to support policy change, we conducted a randomized prospective trial comparing CQ, sulfadoxine/pyrimethamine, mefloquine and a mefloquine-artesunate combination (MA).

Patients and methods

Study site and population

The trial was carried out in the village Sinbo located in the township of Myitkyina in Kachin State. Kachin State is the most northern state of the Union of Myanmar, situated between China (Yunnan) and India (Assam). Sinbo is a small isolated village on the bank of the Irrawaddy river with a stable population of 6000 people. The village is accessible only by boat. The area consists of low mountainous forest and sparsely populated plains, cultivated mainly for rice. The monsoon season lasts from May to October. Malaria transmission of *P. falciparum* (±80%) and *P. vivax* (±20%) is low and seasonal. Although detailed entomological data are unavailable, by comparison with adjacent areas, the entomological inoculation rate is unlikely to exceed 1 inoculation/person/year. The first line treatment protocol for falciparum malaria was CQ or sulfadoxine/pyrimethamine (SP) in accordance with National Malaria Control Programme guidelines at the time of this study (the first line treatment subsequently changed in 2002, see Discussion), although artesunate and to a lesser extent mefloquine were available through the private sector.

From July to October 1998, all people with complaints of fever attending the Station Hospital (SH) of Sinbo were invited to participate in a randomized prospective study before taking drugs. This was conducted by doctors and microscopists from *Artsen zonder Grenzen* (*Medecins Sans Frontieres*-Holland) in co-operation with the SH staff. The study protocol was approved by the health authorities of Kachin State.

Study procedures

A blood smear was prepared from all patients presenting with an axillary temperature ≥37.5 °C or a history of fever within the past 2 days. To avoid enrolling patients with asymptomatic parasitaemia, patients were included only if they had fever or history of fever and a parasite density of more than 1000 asexual *P. falciparum* parasites per mm^3. Parasite density was calculated relative to 500 leucocytes in the thick blood smear stained with Giemsa (pH 7.2), assuming a standard whole blood leucocyte count of 8000/mm^3. Children with a body weight of less than 5 kg, pregnant women, patients with signs and symptoms suggestive of complicated malaria (World Health Organization and Control of Tropical Diseases 1990) or suggestive of another cause for fever, and patients with a recent history of mefloquine use were excluded from entering the study. Patients with a parasite count >250 000/mm^3 or with a mixed infection were also excluded.

Patients were enrolled in the study only after full informed consent was obtained from them or from their parents or guardians. The patient was then interviewed and examined and a symptom questionnaire was completed in each case. The patients were stratified prospectively in three age groups (<5, 5–14 and ≥15 years) and were allocated randomly to one of four treatment arms:

- CQ: chloroquine (Pharmamed, Valetta Malta) 10 mg base/kg on day 0 and 1, 5 mg/kg on day 2.
- SP: sulfadoxine/pyrimethamine (Pharmamed); single dose: 25 and 1.25 mg/kg, respectively.
- M: mefloquine (Eloquine; Medochemie Ltd, Limassol, Cyprus); single dose: 15 mg base/kg.
- MA: mefloquine 15 mg base/kg + artesunate (Guilin Pharmaceutical Works, Guangxi, China); single dose: 4 mg/kg.

All dosages were single and supervised, except for patients from the CQ group, who had to return on day 1 and 2 for supervised drug administration to complete the 3 day treatment regimen. Patients with an axillary temperature over 38 °C were given paracetamol (15 mg/kg). If the patient vomited within 30 min the full dose was repeated. If vomiting occurred after 30 min but within the hour, half the dose was repeated.

Patients were seen on day 0, 3, 7, 14, 21, 28, 35 and 42 and they were invited to come at any other time they felt sick and/or when fever developed. In the first 2 weeks of follow-up clinical symptoms and temperature were recorded, and on all follow-up dates a malaria blood film was prepared. On day 0 and day 3 the parasite density was also checked. The haemoglobin concentration was measured on enrollment and on day 14.

Therapeutic response was defined using a combination of clinical and parasitological criteria: *Early treatment failure ≤ day 3*: persistent fever on day 3 plus presence of *P. falciparum* in the blood smear, or a parasite density on day 3 ≥25% of parasite density on day 0, or clinical deterioration up to day 3 in the presence of parasites.

Intermediate treatment failure day 4–14: reappearance of fever on any day between day 4 and day 14 plus a positive blood film for *P. falciparum*.

Late treatment failure day 15–42: positive blood film for *P. falciparum* between day 15 and day 42, with or without fever. This includes both recrudescences and reinfections, but given the low transmission in the area, less than 15% of recurrent parasitaemias within the 42-day follow-up period would be expected to be new infections even taking into account seasonality of transmission.

Retreatment

All patients with treatment failures following CQ or SP received MA (15 and 4 mg/kg, respectively) in a single dose. Patients with treatment failures after M or MA were given treatment with artesunate (2 mg/kg/day) for 7 days.

Statistical analysis

With a sample size of 78 patients per treatment arm, a difference in treatment failure rate of 50% *vs.* 25% could be detected with 80% power and 95% confidence, taking into account a drop out rate of up to 20%.

Data were analysed using SPSS for Windows (SPSS Software, Gorinchem, The Netherlands) and EpiInfo, version 6 (CDCP, Atlanta, GA, USA). Continuous data were analysed by Student's *t*-test or ANOVA. Proportions and categorical data were compared by chi-square test with Yates', correction or by two-tailed Fisher's exact test.

Results

Between July and August 1998, 317 patients with uncomplicated falciparum malaria were recruited. One patient withdrew after day 0 and was excluded from the analyses. Ten patients withdrew during follow-up. All of them had initially cleared their parasitaemias. Twelve patients (4%) became positive for *P. vivax* during the follow up period, all after day 14 (CQ, 1; SP, 5; MQ, 2; MA, 4). Nine of these were withdrawn from further follow-up as they received CQ treatment again before day 42. The other three presented with *P. vivax* infections on day 42. All data of patients are included in the analysis for the period they participated (Figure 1).

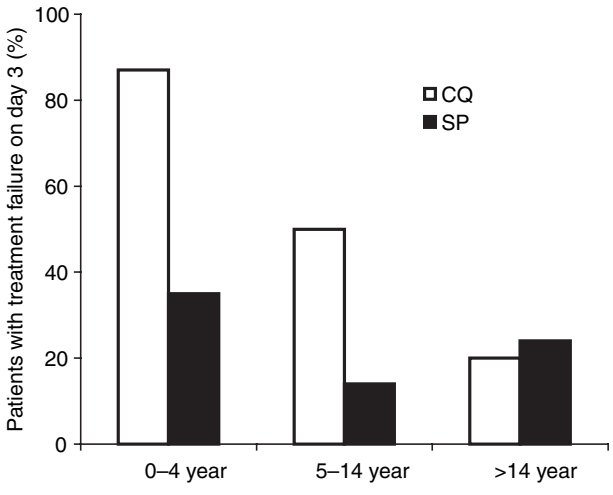

Figure 1 Comparison of failure rates on day 3 stratified by age.

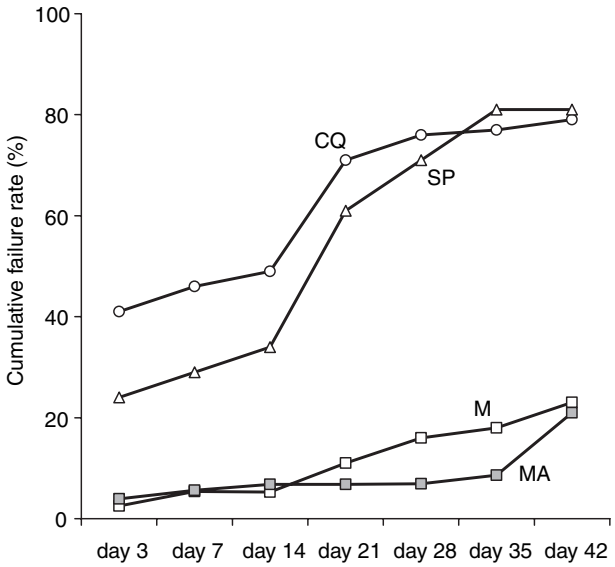

Figure 2 Comparison of responses to treatment of falciparum malaria with chloroquine (CQ), sulfadoxine/pyrimethamine (SP), mefloquine (M) and mefloquine plus artesunate (MA).

Baseline admission clinical and laboratory variables are shown in Table 1 and did not differ significantly among the four treatment groups. The geometric mean parasite density on admission was significantly lower in the younger age groups than in the older age group ($P < 0.001$).

Clinical and parasitological responses

Early failures (≤ 3 days). No patient died, but four patients, all aged under 5 years, developed cerebral malaria within 3 days. Two had received CQ and the other two had received SP as initial treatment. All survived after treatment with intramuscular artemether. On day 3, 32% (24/76) of patients in the CQ group and 27% (20/74) of patients in the SP group were still febrile. These rates were much lower for patients from the M (9%) and MA (12%) groups ($P < 0.0001$, RR = 2.8, 95% CI 1.7–4.8) (Figure 2). Of the 76 patients who received CQ and 73 patients who received SP 41 (54%) and 27 (37%), respectively, had not cleared their parasites by day 3. These rates were 13% (10/80) and 5% (4/76), respectively, after receiving M and MA ($P < 0.0001$, RR = 5.1 95% CI 3.0–8.6). Early failure rates (within 3 days) were 32 of 78 (41%), 18 of 75 (24%), two of 80 (3%), and three of 76 (4%) in the CQ, SP, M and MA groups, respectively ($P < 0.0001$). The early failure rate of the CQ group was

Table 1 Admission characteristics of patients with falciparum malaria

	CQ	SP	M	MA
Number of patients	79	79	80	78
Age <5 years	15 (19%)	19 (24%)	16 (20%)	15 (19%)
5–14 years	22 (28%)	21 (27%)	24 (30%)	26 (33%)
≥15 years	42 (53%)	39 (49%)	40 (50%)	37 (47%)
Mean age (range)	16.1 (1–54)	17.2 (1–64)	18.2 (1–64)	16.7 (1–51)
Male (%)	61	53	54	47
Haemoglobin (SD) (g/dl)	10.9 (1.8)	10.9 (1.7)	10.8 (1.9)	10.8 (1.7)
Parasite density[a] (range)	12 465 (1100–175 000)	13 444 (1200–200 000)	15 837 (1700–230 000)	11 609 (1100–210 000)
Temperature[b] (range)	38.4 (36.0–41.1)	38.4 (35.5–41.0)	38.2 (36.0–40.6)	38.2 (35.5–40.5)

[a] Geometric mean; [b] mean.
CQ, chloroquine (25 mg/kg); SP, sulphadoxine-pyrimethamine (1.25/25 mg/kg); M, mefloquine (15 mg/kg); MA, mefloquine/artesunate (15/4 mg/kg).

Table 2 Clinical and parasitological outcome indicators on day 3 after treatment

	CQ	SP	M	MA
Total	79	79	80	78
Parasitaemic on day 3	41/76 (54%)	27/73 (37%)	10/80 (13%)	4/76 (5%)
Temperature >37.5 °C on day 3	24/76 (32%)	20/74 (27%)	7/78 (9%)	9/76 (12%)
Failure rate at day 3	32/78 (41%)	18/75 (24%)	2/80 (3%)	3/76 (4%)
(a) Clinical deterioration	2/78 (3%)	2/75 (3%)	0	0
(b) Parasitaemia >25% of day 0	18/78 (23%)	11/75 (15%)	1/80 (1%)	3/76 (4%)
(c) Fever >37.5 °C and parasitaemia	22/78 (28%)	11/75 (15%)	1/80 (1%)	2/76 (3%)
Success on day 3	46/78 (59%)	57/75 (76%)	78/80 (98%)	73/76 (96%)

significantly higher than in the SP group ($P = 0.04$, RR = 1.71, 95% CI 1.1–2.8). Patients from the M and MA groups had significantly less early failures than patients from the CQ ($P < 0.0001$, RR = 12.8, 95% CI 5.2–31.6) and the SP group ($P < 0.0001$, RR = 7.5, 95% CI 2.9–19.4) (Table 2). Children under 5 years of age had an early failure rate of 87% (13/15) after CQ and 33% (6/18) after SP ($P = 0.006$), while after the M and MA group there were no early failures in this age group. Early failure was closely related to age in the CQ group (Figure 1). The youngest children had higher failure rates after CQ treatment than the older children ($P = 0.052$, RR = 1.73, 95% CI 1.09–2.75), and the older children had significant higher failure rates than the adults ($P = 0.026$, RR = 2.56, 95% CI 1.21–5.42) (Figure 3).

Intermediate failures (4–14 days). Between day 4 and day 14, 35 patients presented again with recurrent parasitaemia, of whom 17 also had fever and were defined as failures. Of the remaining 18 patients with parasitaemia without fever, who continued regular follow-up, only three patients were a treatment success at day 42 (two CQ and one M), and 15 failed treatment (six CQ, seven SP, one M and one MA). Of these 11

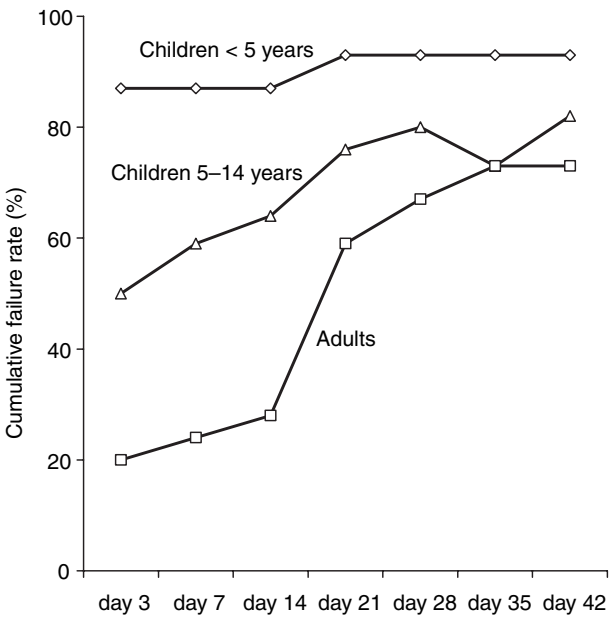

Figure 3 Comparison of cumulative failure rates for young children, older children and adults, after treatment of falciparum malaria with chloroquine.

Table 3 Cumulative failure rates stratified by age

	Failure rates			
	Day 3	Day 14	Day 28	Day 42
Chloroquine				
Age <5 years	13/15 (87)	13/15 (87)	14/15 (93)	14/15 (93)
Age 5–14 years	11/22 (50)	14/22 (64)	16/20 (80)	18/22 (82)
Age ≥15 years	8/41 (20)	11/40 (28)	24/36 (67)	29/40 (73)
Total	32/78 (41)	38/77 (49)	54/71 (76)	61/77 (79)
Sulfadoxine/pyrimethamine				
Age <5 years	6/17 (35)	8/17 (47)	13/17 (76)	15/18 (83)
Age 5–14 years	3/21 (14)	5/21 (24)	13/19 (68)	17/20 (85)
Age ≥15 years	9/37 (24)	12/35 (34)	23/33 (70)	27/35 (77)
Total	18/75 (24)	25/73 (34)	49/69 (71)	59/73 (81)
Mefloquine				
Age <5 years	0/16 (0)	1/15 (7)	4/15 (27)	4/14 (29)
Age 5–14 years	2/24 (8)	3/23 (13)	5/22 (23)	10/23 (44)
Age ≥15 years	0/40 (0)	0/37 (0)	2/33 (6)	3/37 (8)
Total	2/80 (3)	4/75 (5)	11/70 (16)	17/74 (23)
Mefloquine-artesunate				
Age <5 years	0/15 (0)	1/14 (7)	1/14 (7)	1/14 (7)
Age 5–14 years	0/26 (0)	1/26 (4)	1/25 (4)	7/25 (28)
Age ≥15 years	3/35 (9)	3/34 (9)	3/33 (9)	7/34 (21)
Total	3/76 (4)	5/74 (7)	5/72 (7)	15/73 (21)

Percentage values are given in parenthesis.

patients had failed by day 21. Overall failure rates at day 42 were similar for CQ (79%) and SP (81%). M and MA had comparable overall failure rates (23 and 21%, respectively) and were significantly better than both CQ and SP ($P < 0.0001$, RR = 3.7, 95% CI 2.7–5.0) (Table 3).

Late failures (day 15–42). Failure rates at day 42 were similar for children under 5 years (56%) and children aged between 5 and 14 years (58%) but compared with adults, children had more treatment failures ($P = 0.056$, RR = 1.3, 95% CI 1.0–1.6). This difference was only significant for the mefloquine group ($P = 0.006$, RR = 4.7, 95% CI 1.5–14.9). In the SP group and the MA group there was no clear relationship between failure rates and age (Table 3). In this study, we could not differentiate between recrudescent parasitaemia and new infections but transmission intensity is low (estimated EIR < 1 per year) and so the majority of recurrent infections were probably recrudescences. In order to estimate the conditional probability of late recurrent parasitaemia during each week after receiving treatment, we calculated the proportion of patients with recurrent parasitaemia per week for patients who still remained in the study, excluding patients who failed, became positive for *P. vivax*, or who dropped out of the study during previous weeks (Table 4).

Table 4 The conditional probability of late recurrent parasitaemia after four treatment regimens

	Day 15–21	Day 22–28	Day 29–35	Day 36–42
Chloroquine	9/29 (31)	4/21 (19)	3/21 (14)	4/20 (20)
Sulfadoxine/ pyrimethamine	12/40 (30)	6/24 (25)	8/21 (38)	2/16 (13)
Mefloquine	3/65 (5)	3/62 (5)	2/61 (3)	4/61 (7)
Mefloquine-artesunate	0/68 (0)	0/67 (0)	1/65 (2)	9/67 (13)
CQ/SP pooled	21/69 (30)	10/45 (22)	11/42 (26)	6/36 (17)

Percentage values are given in parenthesis.

Of the patients in the CQ group who were still followed up during the fifth week, 14% (3/21) had recurrent parasitaemias, and of the patients who were still followed-up during the sixth week 20% (four of 20) developed recurrent parasitaemias. These figures were 38% (8/21) and 13% (2/16), respectively, for the SP group.

Anaemia

As a result of the high number of early treatment failures among patients who received CQ or SP, many patients could not be assessed for change in haemoglobin on day 14. Of the patients who had not yet failed on day 14, the haemoglobin concentration increased on average 0.49 g/dl after CQ, 0.52 g/dl after SP, 0.55 g/l after M and 0.64 after MA ($P = 0.78$).

Results of re-treatment

All clinical failures within 14 days after treatment with CQ or SP, who had no signs of complicated malaria, were retreated with Mefloquine (15 mg/kg) and Artesunate (4 mg/kg) as a single dose and followed-up for another 6 weeks. All these patients (60) cleared their parasitaemia before day 7. Of the 57 patients who could be followed-up weekly for 42 days, 10 (18%) patients had a recurrence of parasitaemia within 3–6 weeks after retreatment. This failure rate was similar to the original first line MA treatment group.

Discussion

This study revealed very high levels of clinical and parasitological resistance to CQ and SP on the northern Myanmar border. Early failure rates were alarmingly high, particularly in young children who received CQ (87%). These findings are similar to a study done in Western Myanmar in 1995 (Smithuis *et al.* 1997), and they confirm that CQ and SP are not appropriate for the treatment of

falciparum malaria in this region. Indeed there are no convincing recent reports that these drugs continue to work well anywhere from Pakistan across Northern India and Bangladesh through to Vietnam.

In this study, we included 'patients with persistent fever on day 3 together with *P. falciparum* in the bloodsmear' in the definition of early failure. This was a precaution based on a previous finding in Myanmar that patients with parasites in the blood on day 3 after CQ or SP, respectively, 97 and 98% would eventually fail (Smithuis *et al.* 1997). This policy of caution could have led to overestimation of the early failure rates. There was a strong correlation between age and treatment failure after treatment with CQ and to a lesser extent after mefloquine. As in our earlier study, the early failure rate was significantly higher in children in the CQ treatment group than in adults (RR = 3.3, 95% CI 1.7–6.5, $P = 0.0001$). This was not evident for the other treatment groups. However, mefloquine treated children had significantly more late treatment failures than adults (RR = 4.7, CI 1.5–14.9, $P = 0.006$). The higher rate of therapeutic failure in children is a common finding in endemic areas (ter Kuile *et al.* 1992; Smithuis *et al.* 1997) and presumably reflects the lower level of acquired immunity in children compared with adults (Mayxay *et al.* 2001). This emphasizes the importance of assessing the efficacy of antimalarials in all age groups (stratified for age). It would be very misleading to study the efficacy of an ineffective drug such as CQ in adults only. The duration of follow-up is also critical. A short follow-up period of the treated patients would have seriously underestimated the seriousness of resistance. Resistance to both CQ and SP would have been underestimated by almost half, if the follow-up period had been limited to the WHO 14-day test (World Health Organization 1996), which, although recommended in high transmission settings, is also widely used in low transmission settings such as this. For the more efficacious mefloquine regimen, a 14-day follow-up would have missed nearly all failures, and even 28 days surveillance was insufficient for this slowly eliminated drug. Almost 50% of the recurrent infections appeared after 28 days. Some of the apparent treatment failures will be new infections and not recrudescences. This would be more likely among the patients with a late recurrence of parasitaemia. However, as the study area was a low transmission setting (estimated EIR < 1), a significant proportion of the recurrent parasitaemias probably resulted from recrudescent parasitaemias. Mefloquine treatment was much more effective than either CQ or SP, but already significant levels of mefloquine resistance are prevalent in this area. Even a combination of mefloquine (15 mg/kg) and artesunate (4 mg/kg), which has had very good cure rates in western Myanmar (Smithuis *et al.* 1997), was associated with a failure rate of 21%. In contrast to our experience in western Myanmar, in this study, the addition of a single dose of artesunate, did not increase efficacy (21% *vs.* 23%). As the trial did not include parasite genotyping and most of the mefloquine-artesunate recurrences occurred in the sixth week of follow-up, we cannot draw definitive conclusions. But these results do suggest that the higher dose mefloquine (25 mg/kg) – 3 day artesunate treatment protocols that have proved highly effective in Thailand (Nosten *et al.* 2000) should be adopted to ensure high cure rates and to protect these drugs from further selection of resistant strains. Such an approach is likely to be cost-effective in the long-term despite a higher initial outlay on drug costs. The findings of this study provided an evidence base to support a proposal to change to a new first line antimalarial treatment regimen in Myanmar. In 2002, a Committee on the Development of National Antimalarial Treatment Policy (for Myanmar) was formed by the Department of Health to discuss the national protocol for malaria. This committee endorsed a 3 day mefloquine – artesunate combination regimen (mefloquine 15 mg/kg on day 1 and 10 mg/kg on day 2 + artesunate 4 mg/kg on day 0, 1 and 2) as the first line treatment for falciparum malaria.

When poor countries do not have enough money for an effective first line treatment for all patients, hard choices have to be made. In this light, taking into account the significant difference in treatment outcome in different age groups, it might be an unsatisfactory but pragmatic compromise to consider different treatment regimens for different age groups. The failure rate to CQ (and to a lesser extent to SP) is much higher among children, while they are more likely to progress to severe malaria. The combination treatment of mefloquine and artesunate is much less expensive for a child than for an adult.

Acknowledgements

We are grateful to the staff of the Sinbo Station Hospital and the staff of the Vector Borne Disease Control (DOH) for their support, and we thank all the clinical and laboratory staff of Medecins sans Frontieres Holland for their hard work. This study was financed by the private foundation of Medecins sans Frontieres Holland. NJ White is a Wellcome Trust Principal Fellow.

References

Aung-Than-Batu H, Nyun R, Tin F, Myint T & Kyi KK (1975) Chloroquine-resistant malaria in Burma. *Journal Tropical Medicine and Hygiene* **78**, 186–189.

ter Kuile F, Nosten F, Thieren M *et al.* (1992) High dose mefloquine in the treatment of multidrug resistant falciparum malaria. *Journal of Infectious Diseases* **166**, 1393–1400.

Mayxay M, Chotivanich K, Pukrittayakamee S, Newton P, Looareesuwan S & White NJ (2001) Contribution of humoral immunity to the therapeutic response in falciparum malaria. *American Journal of Tropical Medicine and Hygiene* **65**, 918–923.

Nosten F, van Vugt M, Price R *et al.* (2000) Effects of artesunate-mefloquine combination on incidence of *Plasmodium falciparum* malaria and mefloquine resistance in western Thailand; a prospective study. *Lancet* **356**, 297–302.

Rab MA, Freeman TW, Durrani N, de Poerck D & Rowland MW (2001) Resistance of *Plasmodium falciparum* malaria to chloroquine is widespread in eastern Afghanistan. *Annals of Tropical Medicine and Parasitology* **95**, 41–46.

Rahman MR, Paul DC, Rashid M *et al.* (2001) A randomized controlled trial on the efficacy of alternative treatment regimens for uncomplicated falciparum malaria in a multidrug-resistant falciparum area of Bangladesh–narrowing the options for the National Malaria Control Programme. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **95**, 661–667.

Singhasivanon P (1999) Mekong malaria. Malaria, multi-drug resistance and economic development in the greater Mekong subregion of Southeast Asia. *Southeast Asian Journal of Tropical Medicine and Public Health* **30** (Suppl. 4), 1–101.

Smithuis FM, Monti F, Grundl M *et al.* (1997) In vivo sensitivity of *Plasmodium falciparum* to chloroquine, sulfadoxine/pyrimethamine and mefloquine in Rakhine State, Western Myanmar. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **91**, 468–472.

Tin F & Hlaing N (1977) Resistance to antimalarials by *Plasmodium falciparum* in Burma. *Southeast Asian Journal of Tropical Medicine and Public Health* **8**, 104–112.

Tin F, Hlaing N, Lim MA, Win S & Lasserre R (1987) Double-blind trial to find dose range using a fixed combination of mefloquine, sulfadoxine and pyrimethamine in falciparum malaria: a field study on adults in Burma. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **81**, 910–912.

Wongsrichanalai C, Lin K, Pang LW *et al.* (2001) In vitro susceptibility of *Plasmodium falciparum* isolates from Myanmar to antimalarial drugs. *American Journal of Tropical Mededicine and Hygiene* **65**, 450–455.

World Health Organization (1996) Assessment of therapeutic efficacy of antimalarial drugs for uncomplicated falciparum malaria in areas with intense transmission. WHO/MAL/96.1077.

World Health Organization, Control of Tropical Diseases (1990) Severe and complicated malaria, 2nd edn. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **84** (Suppl. 2): 1–65.

Yang HL, Liu DQ, Yang YM *et al.* (1997) In vitro sensitivity of *Plasmodium falciparum* to eight antimalarials in China–Myanmar and China–Lao PDR border areas. *Southeast Asian Journal of Tropical Medicine and Public Health* **28**, 460–464.

Authors

Frank Smithuis, Maryam Shahmanesh, Moe Kyaw Kyaw and **Olivia Savran**, Medecins sans Frontieres – Holland, Yangon, Myanmar.
Saw Lwin, Vector Borne Disease Control, Department of Health, Yangon, Myanmar
N.J. White, Faculty of Tropical Medicine, Mahidol University, 420/6 Rajvithi Road, Bangkok 10400, Thailand. Tel: (66) 2 354 9172; Fax: (66) 2 354 9169; E-mail: nickw@tropmedres.ac (corresponding author)