

Amodiaquine, sulfadoxine/pyrimethamine, and combination therapy for treatment of uncomplicated falciparum malaria in Kampala, Uganda: a randomised trial

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Summary

Background Increasing *Plasmodium falciparum* resistance to chloroquine in sub-Saharan Africa necessitates use of alternative antimalarial agents. Affordable alternative treatments include sulfadoxine/pyrimethamine and amodiaquine. Combination of antimalarial agents can increase therapeutic efficacy and delay emergence of drug resistance. We compared the efficacy of sulfadoxine/pyrimethamine, amodiaquine, and an amodiaquine/sulfadoxine/pyrimethamine combination for treatment of uncomplicated malaria in a region of high chloroquine resistance.

Methods Patients with symptoms of uncomplicated falciparum malaria and confirmed disease in Kampala, Uganda, were randomly assigned to receive sulfadoxine/pyrimethamine (25 mg/kg sulfadoxine, and 1.25 mg/kg pyrimethamine) plus placebo; amodiaquine (25 mg/kg) plus placebo; or amodiaquine plus sulfadoxine/pyrimethamine. Patients were followed up for 14 days, and clinical and parasitological outcomes were assessed.

Findings 90% (400/445) of patients enrolled in the study successfully completed 14 days of follow-up. Treatment failure based on clinical criteria occurred in 13 of 131 (10%) patients on sulfadoxine/pyrimethamine, nine of 131 (7%) on amodiaquine, and four of 138 (3%) on amodiaquine/sulfadoxine/pyrimethamine. Based on parasitological criteria, treatment failed in 26%, 16%, and 10% of these patients, respectively. Amodiaquine/sulfadoxine/pyrimethamine was significantly more effective than sulfadoxine/pyrimethamine alone in children aged younger than 5 years (clinical failure in 3.5% vs 13.9%, respectively, risk difference 10.4% [95% CI, 1.6–19.3] $p=0.021$; parasitological failure in 12.8% vs 26.4%, risk difference 13.6% [1.2–26.0] $p=0.041$).

Interpretation Sulfadoxine/pyrimethamine, amodiaquine, and amodiaquine/sulfadoxine/pyrimethamine were all effective for treatment of uncomplicated falciparum malaria in Uganda. The amodiaquine/sulfadoxine/pyrimethamine combination was the most effective, and could be the optimum low-cost alternative to chloroquine in Africa.

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Introduction

Malaria control in Africa is threatened by widespread resistance of *Plasmodium falciparum* to chloroquine, the mainstay of antimalarial therapy for the past 50 years.¹ Sub-Saharan Africa, which bears the greatest burden of malaria morbidity and mortality, faces an impending catastrophe because of rising rates of chloroquine resistance and associated increases in childhood mortality.^{2,3} Thus, African countries are reassessing their antimalarial drug policies and examining alternative agents for first-line treatment of uncomplicated falciparum malaria.⁴ However, few effective, affordable alternatives to chloroquine are available.

The fixed combination of sulfadoxine and pyrimethamine (SP), which are inhibitors of two folate pathway enzymes, has been chosen to replace chloroquine as first-line therapy for uncomplicated falciparum malaria in several African countries.⁵ The advantages of sulfadoxine/pyrimethamine (SP) include low cost, simple dosing, and few toxic effects. However, the therapeutic lifespan of SP is limited by the rapid emergence of SP-resistant parasites. Resistance to SP developed rapidly in Southeast Asia and now seems to be rising in East Africa.

Amodiaquine, a 4-aminoquinoline antimalarial drug similar to chloroquine, was widely used until WHO withdrew its endorsement of the drug for malaria control programmes in 1990 as a result of reports of rare, but severe, toxic effects.¹⁰ Despite these safety concerns, the expanding issue of antimalarial drug resistance in Africa has renewed interest in amodiaquine as an alternative to chloroquine. Although potential cross-resistance between the 4-aminoquinolines has led to arguments against replacing chloroquine with amodiaquine,^{11,12} most data suggest that amodiaquine remains effective even in areas of substantial chloroquine resistance, with a side-effect profile similar to that of chloroquine and SP.^{9,10,13,14}

The strategy of combining drugs with different modes of action and mechanisms of resistance, a standard approach in the treatment of tuberculosis and HIV infection, is being advocated as a way to improve antimalarial therapeutic effectiveness and to delay the emergence of drug resistance.⁵ Findings of previous studies looking at the effectiveness of 4-aminoquinolines (chloroquine or amodiaquine) plus SP suggest that combination therapy might provide rapid resolution of symptoms and better cure rates than monotherapy.¹⁵

Although drug resistance has been slower to develop in Uganda than in neighbouring East African countries, high-level chloroquine resistance is now widespread, and resistance to SP is developing (Ugandan Ministry of Health, unpublished data). In Kampala, studies done in 1998 and 1999 documented clinical failure in 66% of children aged younger than 5 years who were given chloroquine, and 11% of those given SP.^{16,17} In a previous study of amodiaquine for treatment of uncomplicated malaria in western Uganda, no parasitological resistance was seen.¹⁸ To further investigate the efficacy of alternative antimalarial agents, and of combination therapy, we have

compared SP, amodiaquine, and the combination of amodiaquine and SP (AQ/SP), for treatment of uncomplicated falciparum malaria in Kampala.

Methods

Study site

We undertook this study between September, 1999, and July, 2000, at the Mulago Hospital outpatient department in Kampala, Uganda, which serves a principally lower socioeconomic urban population. Malaria is mesoendemic in Kampala (25% palpable spleen rate, 25% parasitaemia rate), occurring perennially with peaks during the two rainy seasons (Ugandan Ministry of Health, unpublished data). The study was approved by the institutional review boards of the University of California, San Francisco and Makerere University, Kampala.

Patient recruitment

Patients presenting with symptoms suggestive of malaria and a positive screening thick blood smear were referred to the study clinic for further assessment. Consecutive patients were screened for the following inclusion criteria: (1) age 6 months or older; (2) weight over 5 kg; (3) tympanic temperature greater than or equal to 38.0°C, or febrile symptoms in the past 48 h; (4) absence of alternative diagnosis for febrile illness; (5) absence of severe malaria, including severe anaemia (packed-cell volume <15%),¹⁹ or danger signs (inability to stand or drink, lethargy, convulsions, persistent vomiting);²⁰ (6) willingness to remain in Kampala and participate in follow-up for the next 14 days; (7) written informed consent provided by patient or parent/guardian; (8) no participation in a clinical study in the past 3 months; and (9) no history of allergic reaction to SP or other sulfa drugs. All patients recruited for the study (or for children, the parent/guardian) were interviewed by a study physician about symptoms, duration of the illness, previous antimalarial therapy, and use of other medications. Core temperature (measured with an electronic tympanic thermometer), weight, and height were measured. Patients were examined for evidence of pallor or jaundice, and spleen size was ascertained by Hackett's classification system.

Randomisation and treatment

On day 0, patients were assigned a study number and treatment group on the basis of a computer-generated randomisation list (EpiInfo, version 6.04, Centers for Disease Control and Prevention, Atlanta, GA, USA). Patients were randomised to receive SP (Fansidar, Roche, 500 mg/25 mg tablets), amodiaquine (Camoquin, Parke-Davis, 200 mg tablets), or amodiaquine plus SP. Medications were dosed according to modified weight-based guidelines from WHO for administration of fractions of tablets (SP, 25 mg/kg sulfadoxine and 1.25 mg/kg pyrimethamine given orally as a single dose; amodiaquine, 25 mg/kg given orally as 10 mg/kg on days 0 and 1, and 5 mg/kg on day 2).²⁰ Personnel were not blinded to treatment group, but patients assigned to receive SP alone also received lactose placebo tablets in the same regimen as amodiaquine, whereas those assigned to amodiaquine alone received placebo tablets in the SP regimen. The appearance of the placebo tablet was not identical to study medications. Allocation and distribution of study medication was done in the clinic and all therapy was directly observed. Patients were observed for 30 min after administration of medication, and the dose was repeated if vomiting occurred. We provided patients with a 3-day supply of paracetamol for treatment of febrile symptoms. Patients with a packed-cell volume of less than 25% on day 0 were

given ferrous sulphate for 14 days and anthelmintic treatment if they were aged older than 1 year.

Patient follow-up

All patients who passed screening and were subsequently allocated to one of the treatment groups had blood removed by venepuncture on day 0 for thick and thin blood smears, packed-cell volume testing, and white blood cell (WBC) and neutrophil counts. Patients were enrolled in the study if they had *P. falciparum* mono-infection with at least 2000/μL asexual parasites on day 0. Follow-up appointments were scheduled for days 1, 2, 3, 7, and 14 and consisted of a physical examination and completion of a standardised history form. Blood was obtained (by fingerprick on days 3, 7, and any unscheduled day, and by venepuncture on day 14) to repeat thick blood smears for parasite density and gametocyte measurements. Repeat packed-cell volume, WBC, and neutrophil measurements were also done on day 14. Patients were encouraged to return to the clinic at any time if they felt ill. Patients who did not return for follow-up were visited at home.

Patients were excluded after enrolment for the following reasons: (1) self-administration of additional antimalarial drugs during follow-up; (2) emergence of any concomitant febrile illness that interfered with outcome classification; (3) withdrawal of informed consent; and (4) development of severe malaria or danger signs on day 0 after leaving the clinic.

Laboratory tests

Thick and thin blood smears were stained with 2% Giemsa for 30 min. All slides were read by a microscopist who was blinded to the treatment groups and clinical outcomes. Parasite density was calculated by counting the number of asexual parasites per 200 WBCs from the thick blood smear on the assumption of a WBC count of 8000/μL. A smear was regarded as negative if no parasites were seen after review of 100 high-powered fields. Gametocytaemia was also assessed from thick blood smears. Thin blood smears were reviewed for non-falciparum infection. Packed-cell volume was calculated with the micro-haematocrit method.²⁰ WBC and neutrophil counts were measured with a haemocytometer. Urine, collected on day 0, was tested for the presence of chloroquine and its metabolites with the Saker-Solomons test.²¹

Outcome measures

The primary endpoints of the study were clinical and parasitological outcome at 14 days. Patient outcomes were assessed by modifications of the WHO parasitological and clinical classification systems, as published.^{16,20,22} Parasitological responses were classified into success (S) or failure (RI, RII, RIII). Clinical outcomes were stratified into success (adequate clinical response) or failure (early treatment failure, late treatment failure). The WHO clinical classification system was slightly modified by the addition of reported fever in the past 48 hours on days 4–14 in the setting of rising parasitaemia as a criterion for late treatment failure. Patients who met criteria for early and late treatment failure in the SP and AQ/SP treatment groups were given quinine (10 mg/kg thrice daily for 7 days), whereas those in the amodiaquine group were given either SP (25 mg/kg sulfadoxine and 1.25 mg/kg pyrimethamine) or quinine at the discretion of the physician.

Secondary endpoints included resolution of fever (defined as core temperature of $\geq 38.0^\circ\text{C}$, equivalent to $\geq 37.5^\circ\text{C}$ axillary) and febrile symptoms, parasite clearance, change in packed-cell volume from day 0 to day 14, and presence of gametocytes on days 3, 7, and 14. Additionally,

patients were monitored for potential adverse drug events, including haematological toxic effects, hepatotoxicity, and dermatological abnormalities.

Statistical analysis

Estimates of clinical failure for each of the treatments were used to calculate the sample size so the study would have an 80% or greater power to detect a 15% difference in the proportion of clinical failures between any two of the treatment groups ($\alpha=0.05$). Because age younger than 5 years had been identified as the strongest predictor of chloroquine treatment failure in Kampala, an age stratified analysis (patients aged <5 years *vs* ≥ 5 years) was planned.¹⁶

Data were recorded on clinical and laboratory report forms, transferred into a database (EpiInfo, version 6.04), and verified with double entry. All patients with known outcomes were included in the analyses.

Proportions were compared with Fisher's exact test (SAS, version 8). A two-tailed p-value of less than 0.05 was judged significant. Analysis of variance (ANOVA) was used for normally distributed continuous data, and parasite densities were normalised by logarithmic transformation. The non-parametric Kruskal-Wallis test was used to analyse continuous data with skewed distribution. Risk differences, 95% CIs, and exact p-values were calculated with the SAS statistical analysis software package, version 8.

Results

Figure 1 shows the trial profile. Of the 1914 patients referred for evaluation, 1246 were excluded during screening (figure 1). Reasons for exclusion were residence outside of Kampala (356 [29%]), presence of danger signs or severe malaria (342 [27%]), concomitant febrile illness

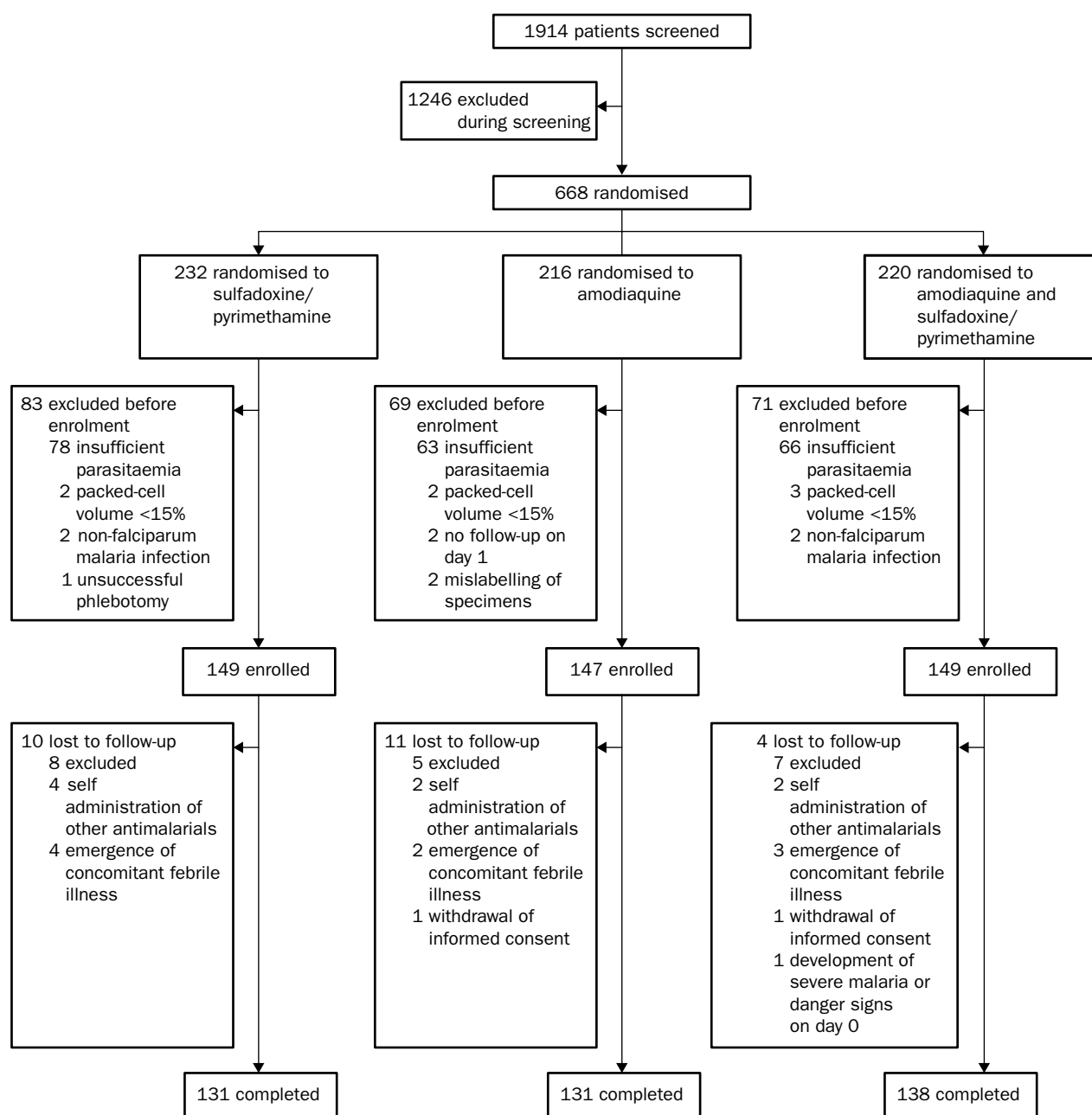


Figure 1: Trial profile

Characteristic	Sulfadoxine pyrimethamine (n=131)	Amodiaquine (n=131)	Amodiaquine/sulfadoxine pyrimethamine (n=138)
Sex (number female [%])	66 (50%)	76 (58%)	64 (46%)
Median (range) age (years)	4.0 (0.5–50.0)	4.0 (0.5–50.0)	3.25 (0.7–40.0)
Age < 5 years	72 (55%)	69 (53%)	87 (63%)
Antimalarial use in past 2 weeks*	71 (55%)	75 (59%)	91 (66%)
Chloroquine use in past 2 weeks*	52 (40%)	58 (45%)	64 (46%)
Sulfadoxine/pyrimethamine use in past 4 weeks*	4 (3%)	6 (5%)	9 (7%)
Mean (SD) number of treatments for malaria in past year*	3.9 (2.8)	4.0 (2.6)	4.1 (2.5)
Palpable spleen	35 (27%)	31 (24%)	38 (28%)
Mean (SD) duration of presenting symptoms (days)	5.7 (5.4)	5.5 (5.3)	5.3 (4.1)
Mean (SD) duration of presenting fever (days)	3.8 (2.6)	3.7 (3.0)	3.7 (2.3)
Mean (SD) initial temperature (°C)	38.1 (1.2)	38.0 (1.2)	38.0 (1.3)
Initial temperature ≥ 38.0°C	72 (55%)	70 (53%)	70 (51%)
Initial temperature ≥ 39.5°C	19 (15%)	15 (12%)	21 (15%)
Positive urine chloroquine test*	55 (62%)	63 (64%)	65 (65%)
Mean (SD) packed cell volume	27% (5.5)	27% (5.4)	27% (5.6)
Packed cell volume <30	87 (66%)	88 (67%)	90 (65%)
Geometric mean (95% CI) parasite density (per µL)	34 780 (3256–371 549)	29 975 (2244–400 388)	32 240 (2222–467 762)
Parasite density range (per µL)	2080–709 120	2000–1 028 000	2000–620 800
Parasite density >100 000/µL	23 (18%)	27 (21%)	28 (20%)

*Includes only patients in whom data were recorded.

Table 1: Baseline characteristics of patients who completed the study

(203 [16%]), no consent (109 [9%]), difficult follow-up (93 [7%]), no fever (71 [6%]), and other (64 [5%]). Of the 445 patients enrolled, 400 (90%) successfully completed the study and were evaluable.

Table 1 shows details of patients who completed the study: those who did not complete the study were more likely to be aged 5 years or younger than those who did (82% *vs* 57%, $p=0.001$). The age distribution of the 400 patients who completed the study was as follows: 228 (57%) younger than 5 years, 95 (24%) aged from 5 to 9 years, 45 (11%) aged from 10 to 14 years, and 32 (8%) older than 15 years.

The rate of clinical success was at least 90% in all three treatment groups (table 2). Compared with SP alone, AQ/SP significantly reduced the proportion of clinical failures (table 3). The AQ/SP combination was more effective than amodiaquine or SP monotherapy in both age groups (table 3), and AQ/SP gave significantly higher rates of clinical success than SP. In each treatment group, clinical success was more common in older patients (SP 95%, amodiaquine 97%, AQ/SP 98%) than in children aged younger than 5 years (SP 86%, amodiaquine 90%, AQ/SP 97%).

Success as measured by parasitological outcome was achieved in all three groups, but was greatest in patients given AQ/SP (table 2). Compared with SP monotherapy, treatment with AQ/SP significantly decreased the proportion of parasitological failures (table 3). In children

aged younger than 5 years, parasitological success was greater with AQ/SP than with SP (87% *vs* 74%, $p=0.041$). In patients aged older than 5 years, AQ/SP and amodiaquine were both more effective than SP in achieving parasitological success (94%, 90%, and 75%, respectively; $p=0.009$, AQ/SP *vs* SP; $p=0.030$, amodiaquine *vs* SP).

All enrolled patients were febrile on day 0 or had reported fever in the 48 hours before presentation. Most (91% [385 of 423]) patients had a normal temperature by day 3. However, the rate of fever resolution differed between the treatment groups (figure 2). Patients given amodiaquine, either alone or in combination with SP, were less likely to be febrile or report febrile symptoms by day 2, than were patients who received SP monotherapy.

Most patients (87%) had parasite clearance by day 3, irrespective of treatment group (table 4). However, significantly more patients given SP remained parasitaemic on day 3 than those given AQ/SP or amodiaquine alone. On day 14, fewer patients given AQ/SP were parasitaemic than those given either amodiaquine or SP.

The WHO clinical classification scheme categorises patients in whom fever and other symptoms resolve as an adequate clinical response, even if parasitaemia persists. In patients with an adequate clinical response, there was a lower proportion with parasitaemia on day 14 for AQ/SP treatment than amodiaquine or SP (2% [three of

	Sulfadoxine/pyrimethamine (n=131)		Amodiaquine (n=131)		Amodiaquine/sulfadoxine/pyrimethamine (n=138*)	
	Number	95% CI	Number	95% CI	Number	95% CI
Clinical						
Success (ACR [†])	118 (90%)	84–95	122 (93%)	87–97	134 (97%)	93–99
Failure	13 (10%)	5–16	9 (7%)	3–13	4 (3%)	1–7
ETF [‡]	4 (3%)	1–8	0 (0%)	0–0.02	1 (1%)	0–4
LTF [§]	9 (7%)	3–13	9 (7%)	3–13	3 (2%)	1–6
Parasitological						
Success (S)	97 (74%)	66–81	110 (84%)	77–90	123 (90%)	83–94
Failure	34 (26%)	19–34	21 (16%)	10–24	14 (10%)	6–17
RI	17 (13%)	8–20	11 (8%)	4–15	6 (4%)	2–9
RII	15 (11%)	7–18	10 (8%)	4–14	8 (6%)	3–11
RIII	2 (2%)	0–5	0 (0%)	0–0.02	0 (0%)	0–0.02

*n=137 for parasitological outcome because of exclusion of one patient who met criteria for early treatment failure (danger signs) on day 1 and was not classifiable by our parasitological outcome criteria. [†]ACR=adequate clinical response. [‡]ETF=early treatment failure. [§]LTF=late treatment failure.

Table 2: Clinical and parasitological outcomes

	Clinical outcome risk difference for failure*			Parasitological outcome risk difference for failure*		
	Risk difference	95% CI	p-value	Risk difference	95% CI	p-value
All ages						
SP† vs AQ/SP	7%	1.2 to 12.9	0.023	16%	6.7 to 24.8	0.0008
AQ‡ vs AQ/SP	4%	-1.2 to 9.1	0.160	6%	-2.3 to 13.9	0.204
SP vs AQ	3%	-3.7 to 9.8	0.505	10%	0.13 to 19.7	0.068
Age <5						
SP vs AQ/SP	10%	1.6 to 19.3	0.021	14%	1.2 to 26.0	0.041
AQ vs AQ/SP	7%	-1.4 to 14.8	0.109	9%	-3.1 to 21.0	0.194
SP vs AQ	4%	-7.0 to 14.5	0.608	5%	-9.4 to 18.7	0.559
Age ≥5						
SP vs AQ/SP	3%	-3.7 to 9.9	0.622	20%	6.7 to 32.4	0.009
AQ vs AQ/SP	1%	-4.6 to 7.1	1.00	4%	-6.0 to 13.6	0.510
SP vs AQ	2%	-5.3 to 9.0	0.675	16%	2.4 to 29.1	0.030

*Risk difference is the proportion failure in the first comparison group minus the proportion failure in the second. †Sulfadoxine/pyrimethamine. ‡Amodiaquine.

Table 3: Pairwise comparison of treatment efficacy

	Sulfadoxine/pyrimethamine (SP)	Amodiaquine (AQ)	(AQ/SP)
Positive thick blood smears			
Day 0	131 (100%)	131 (100%)	138 (100%)
Day 3*	30/130 (23%)	14/131 (11%)	7/137 (5%)
Day 7	13/127 (10%)	9/130 (7%)	8/137 (6%)
Day 14†	21/123 (17%)	12/126 (10%)	4/135 (3%)
Gametocyte positive smears			
Day 0	2/131 (2%)	0/131 (0%)	2/138 (1%)
Any follow-up day‡	43/131 (33%)	9/131 (7%)	9/138 (7%)

*SP vs AQ/SP, $p < 0.0001$; SP vs AQ, $p = 0.008$; †SP vs AQ/SP, $p = 0.0002$; AQ vs AQ/SP, $p = 0.037$; ‡SP vs AQ/SP, $p < 0.0001$; SP vs AQ, $p < 0.0001$.

Table 4: Parasitological results

134], 7% [eight of 122], and 14% [16 of 118], respectively). Patients with an adequate clinical response who had been given AQ/SP had significantly fewer circulating parasites on day 14 ($p = 0.0007$) than those given SP alone. Of the 400 patients who completed the study, circulating gametocytes were seen on day 0 in only four (table 4). However, 61 patients (15%) had gametocytes on a follow-up thick blood smear. The presence of gametocytes during follow-up was

significantly more common in patients given SP than in those given amodiaquine or AQ/SP.

Of the 400 patients who completed the study, repeat packed-cell volume results on day 14 were available for 373 (93%). In all treatment groups, the mean packed-cell volume increased between day 0 and day 14 (SP from 26.6 to 29.4%; amodiaquine from 27.3 to 30.0%; AQ/SP from 27.2 to 29.9%), with no significant differences between the three treatment groups. Additionally, the proportion of anaemia (packed-cell volume $< 30\%$) fell during the 2 weeks of follow-up in all groups (SP from 66% to 50%, $p = 0.010$; amodiaquine from 67% to 42%, $p < 0.0001$; AQ/SP from 65% to 41%, $p = 0.00013$). Although anaemia after treatment was more common in patients on SP than in those on amodiaquine or AQ/SP, this difference was not significant ($p = 0.250$, SP vs amodiaquine; $p = 0.202$, SP vs AQ/SP).

No severe adverse events were recorded during the course of the study in any treatment group. The most commonly reported symptoms at the time of presentation were fever, malaise, anorexia, cough, vomiting, and headache. Because many potential adverse effects of the antimalarial drugs are similar to symptoms of malaria, we had difficulty attributing symptoms to treatment. However, the frequency of commonly reported symptoms (cough, vomiting, anorexia, pruritis, and diarrhoea) presenting after day 0 was not different between the treatment groups. Pruritis after day 0 was reported more in patients given amodiaquine (amodiaquine 14% [16 of 116], AQ/SP 15% [18 of 122]) than those on SP (8% [nine of 113]) ($p = 0.116$). No patient developed jaundice after day 0. No serious dermatological disorders were seen. Between days 0 and 14, mean WBC count remained stable, and the mean neutrophil count decreased in all treatment groups (SP from 3457/ μL to 2588/ μL ; amodiaquine from 3633/ μL to 2511/ μL ; AQ/SP from 3396/ μL to 2476/ μL), the counts did not differ significantly between the groups.

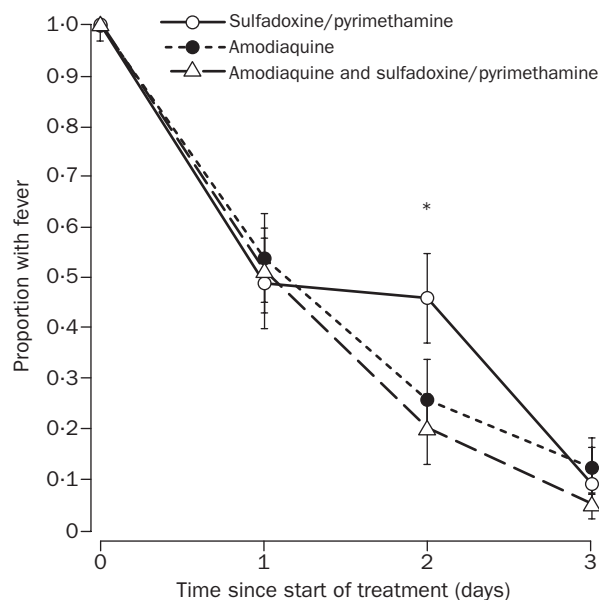


Figure 2: Fever resolution after antimalarial therapy

Percentage of patients with fever ($\geq 38.0^\circ\text{C}$ tympanic, or reported as a symptom within 48 h of day 0 or 24 h of each subsequent visit) is plotted over time. Error bars represent 95% CIs. * $p = 0.0001$, sulfadoxine/pyrimethamine vs amodiaquine/sulfadoxine/pyrimethamine; $p = 0.0012$, sulfadoxine/pyrimethamine vs amodiaquine

Discussion

In this trial, SP, amodiaquine, and AQ/SP, were all effective in the treatment of uncomplicated falciparum malaria in Kampala, Uganda, an area where high-level chloroquine resistance has been documented.^{16,17} Clinical and parasitological success was seen in a higher proportion of patients given amodiaquine than SP, and optimum success was achieved by combining amodiaquine and SP. These results are consistent with reports that amodiaquine is a suitable alternative to chloroquine and that the combination of a 4-aminoquinoline with SP might improve the effectiveness of treatment.^{9,10,13-15} Our findings suggest that the combination of amodiaquine and SP, both of which are available at low cost in Africa, offers a highly effective regimen for the treatment of falciparum malaria in areas with high chloroquine resistance.

When compared with SP monotherapy, treatment with amodiaquine, either alone or in combination with SP, was associated with more rapid resolution of fever, as has been reported with 4-aminoquinoline therapy.^{10,15,23,24} Additionally, AQ/SP therapy promoted rapid parasite clearance, which was sustained over the 2-week follow-up. The standard 14-day follow-up recommended by WHO for areas of intense transmission, and used in this study, might not have been sufficient to detect late emergence of resistant parasites, and thus, some resistant outcomes could have been missed.²⁰ However, the 14-day follow-up restricted the misclassification of new infections presenting more than 2 weeks after therapy as treatment failures.²⁵

The life cycle of *P. falciparum* depends on the transmission of the sexual gametocyte stage of the parasite from the human host to the mosquito vector. We noted fewer gametocytes in follow-up thick blood smears of patients given amodiaquine or AQ/SP than in those of patients given SP alone. In Thailand, a decrease in the frequency of falciparum malaria was attributed to lower gametocyte carriage rates associated with the introduction of therapy with artemisinin derivatives.²⁶ Although it remains to be seen whether decreasing gametocyte carriage rates could substantially affect malaria transmission in Africa, a reduction in gametocytaemia might be a further advantage of amodiaquine or AQ/SP therapy over SP alone.

We recorded no major adverse drug events. Chemoprophylaxis with amodiaquine has been associated with agranulocytosis, hepatotoxicity, and aplastic anaemia, with a total estimated death rate of one in 15 650.²⁷ When used for chemoprophylaxis, SP has been associated with serious dermatological reactions, and an estimated case fatality rate of 1 in 11 100.²⁷ Although treatment with amodiaquine and SP seems safer than chemoprophylaxis, and no serious adverse events have been reported with amodiaquine at doses up to 35 mg/kg per treatment course, use of this drug has been limited by concerns about toxic effects.¹⁰ Since, in areas of high transmission, repeated dosing can increase the risk of serious toxic effects,¹⁰ additional assessment of AQ/SP pharmacokinetics and larger studies of drug safety, preferably longitudinal in design, are needed to further assess the risk associated with routine use of these drugs.

Combining antimalarial agents that have independent mechanisms of action and patterns of resistance should delay the development of resistance to either agent. Drug pressure and exposure of parasites to subtherapeutic drug concentrations selects for drug-resistant parasites that have spontaneously acquired mutations resulting in

reduced drug susceptibility.²⁸ This selection can occur with incomplete or delayed eradication of parasites, or when new infections are acquired during the elimination phase of a drug.^{29,30} However, the probability that parasites will develop resistance after exposure to two effective antimalarials, calculated by multiplying the parasite mutation rates for the individual drugs by the number of parasites present during infection, is very low.²⁸ Because amodiaquine, its metabolites, and SP have similar terminal elimination half-lives (amodiaquine from 7 to 21 days, sulfadoxine from 5 to 8 days, pyrimethamine from 3 to 4 days) there might be an additional advantage to the use of a combination of these agents in areas of high transmission.^{30,31}

P. falciparum resistance to chloroquine has reached severe levels in much of Africa, but the optimum replacement for chloroquine as first-line therapy of uncomplicated falciparum malaria is not clear. SP, amodiaquine, and AQ/SP are effective therapies for treatment of uncomplicated malaria in Kampala, Uganda. Both SP and amodiaquine are widely available in that country at a cost similar to that of chloroquine, and much lower than potential alternatives. However, SP resistance has already emerged in Uganda, and can be expected to spread rapidly as high rates of chloroquine resistance fuel increased reliance on SP. The use of amodiaquine and SP in combination would likely delay development of *P. falciparum* resistance to both drugs, thereby prolonging the lifespan of this highly effective regimen.

Contributors

Sarah Staedke, Moses Kamya, Grant Dorsey, Grace Ndeezi, and Philip Rosenthal designed and coordinated the study. Sarah Staedke, Moses Kamya, and Grant Dorsey supervised the enrolment and follow-up of patients with the help of Anne Gasasira and Grace Ndeezi. Sarah Staedke analysed and interpreted the data, with assistance from Moses Kamya, Grant Dorsey, Anne Gasasira, Edwin Charlebois, and Philip Rosenthal. All investigators contributed to the preparation of the report.

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References

- Campbell CC. Challenges facing antimalarial therapy in Africa. *J Infect Dis* 1991; **163**: 1207-11.
- Marsh K. Malaria disaster in Africa. *Lancet* 1998; **352**: 924.
- Trape JF, Pison G, Preziosi MP, et al. Impact of chloroquine resistance on malarial mortality. *C R Acad Sci III* 1998; **321**: 689-97.
- Bloland PB, Ettling M. Making malaria-treatment policy in the face of drug resistance. *Ann Trop Med Parasitol* 1999; **93**: 5-23.
- White NJ, Nosten F, Looareesuwan S, et al. Averting a malaria disaster. *Lancet* 1999; **353**: 1965-67.
- Pinichpongse S, Doberstyn EB, Cullen JR, Yisunsri L, Thongsombun Y, Thimasarn K. An evaluation of five regimens for the outpatient therapy of falciparum malaria in Thailand 1980-81. *Bull World Health Organ* 1982; **60**: 907-12.
- Ronn AM, Msangeni HA, Mhina J, Wernsdorfer WH, Bygbjerg IC. High level of resistance of *Plasmodium falciparum* to sulfadoxine-pyrimethamine in children in Tanzania. *Trans R Soc Trop Med Hyg* 1996; **90**: 179-81.
- Wolday D, Kibreab T, Bukenya D, Hodes R. Sensitivity of *Plasmodium falciparum* in vivo to chloroquine and pyrimethamine-sulfadoxine in Rwandan patients in a refugee camp in Zaire. *Trans R Soc Trop Med Hyg* 1995; **89**: 654-56.
- van Dillen J, Custers M, Wensink A, et al. A comparison of amodiaquine and sulfadoxine-pyrimethamine as first-line treatment of falciparum malaria in Kenya. *Trans R Soc Trop Med Hyg* 1999; **93**: 185-88.

- 10 Olliaro P, Nevill C, LeBras J, et al. Systematic review of amodiaquine treatment in uncomplicated malaria. *Lancet* 1996; **348**: 1196–201.
- 11 Bloland PB, Ruebush TK. Amodiaquine. *Lancet* 1996; **348**: 1659–60.
- 12 White NJ. Can amodiaquine be resurrected? *Lancet* 1996; **348**: 1184–85.
- 13 Brasseur P, Guiguemde R, Diallo S, et al. Amodiaquine remains effective for treating uncomplicated malaria in West and Central Africa. *Trans R Soc Trop Med Hyg* 1999; **93**: 645–50.
- 14 Gorissen E, Ashruf G, Lamboo M, et al. *In vivo* efficacy study of amodiaquine and sulfadoxine/pyrimethamine in Kibwezi, Kenya and Kigoma, Tanzania. *Trop Med Int Health* 2000; **5**: 459–63.
- 15 McIntosh HM, Greenwood BM. Chloroquine or amodiaquine combined with sulfadoxine-pyrimethamine as a treatment for uncomplicated malaria - a systematic review. *Ann Trop Med Parasitol* 1998; **93**: 265–70.
- 16 Dorsey G, Kanya MR, Ndeezi G, et al. Predictors of chloroquine treatment failure in children and adults with falciparum malaria in Kampala, Uganda. *Am J Trop Med Hyg* 2000; **62**: 686–92.
- 17 Kanya MR, Dorsey G, Gasasira A, et al. The comparative efficacy of chloroquine and sulfadoxine-pyrimethamine for the treatment of uncomplicated falciparum malaria in Kampala, Uganda. *Trans R Soc Trop Med Hyg* 2001; **95**: 50–55.
- 18 Kamugisha J, Kipp W, Burnham G. *In vivo* sensitivity of *Plasmodium falciparum* to chloroquine, amodiaquine, and sulfadoxine-pyrimethamine in Western Uganda. *Trop Geogr Med* 1994; **46**: 364–65.
- 19 Warrell DA, Molyneux ME, Beales PF. Severe and complicated malaria. World Health Organization, Division of Control of Tropical Diseases. *Trans R Soc Trop Med Hyg* 1990; **84** (suppl 2): 1–65.
- 20 World Health Organization. Assessment of therapeutic efficacy of antimalarial drugs for uncomplicated falciparum malaria in areas with intense transmission. Geneva; WHO, 1996.
- 21 Mount DL, Nahlen BL, Patchen LC, Churchill FC. Adaptations of the Saker-Solomons test: simple reliable colorimetric field assays for chloroquine and its metabolites in urine. *Bull World Health Organ* 1989; **67**: 295–300.
- 22 World Health Organization. Antimalarial drug policies: data requirements, treatment of uncomplicated malaria and management of malaria in pregnancy. Geneva; WHO, 1994.
- 23 Muller O, Boele van Hensbroek M, Jaffar S, et al. A randomized trial of chloroquine, amodiaquine and pyrimethamine-sulfadoxine in Gambian children with uncomplicated malaria. *Trop Med Int Health* 1996; **1**: 124–32.
- 24 Onyiorah E, Boele van Hensbroek M, Jah MS, Greenwood B. Early clinical failures after pyrimethamine-sulfadoxine treatment of uncomplicated falciparum malaria. *Trans R Soc Trop Med Hyg* 1996; **90**: 307–08.
- 25 von Siedlein L, Bojang K, Jones P, et al. A randomized controlled trial of artemether/benflumetol, a new antimalarial and pyrimethamine/sulfadoxine in the treatment of uncomplicated falciparum malaria in African children. *Am J Trop Med Hyg* 1998; **58**: 638–44.
- 26 Price RN, Nosten F, Luxemburger C, et al. Effects of artemisinin derivatives on malaria transmissibility. *Lancet* 1996; **347**: 1654–58.
- 27 Phillips-Howard PA, West LJ. Serious adverse drug reactions to pyrimethamine-sulfadoxine, pyrimethamine-dapsone and to amodiaquine in Britain. *J R Soc Med* 1990; **83**: 82–85.
- 28 White N. Antimalarial drug resistance and combination chemotherapy. *Philos Trans R Soc Lond B Biol Sci* 1999; **354**: 739–49.
- 29 Wernsdorfer WH. Epidemiology of drug resistance in malaria. *Acta Trop* 1994; **56**: 143–56.
- 30 Watkins WM, Mosobo M. Treatment of *Plasmodium falciparum* malaria with pyrimethamine-sulfadoxine: selective pressure for resistance is a function of long elimination half-life. *Trans R Soc Trop Med Hyg* 1993; **87**: 75–78.
- 31 Krishna S, White NJ. Pharmacokinetics of quinine, chloroquine, and amodiaquine: clinical implications. *Clin Pharmacokinet* 1996; **30**: 263–99.