

## Artesunate and sulfadoxine–pyrimethamine combinations for the treatment of uncomplicated *Plasmodium falciparum* malaria in Uganda: a randomized, double-blind, placebo-controlled trial

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### Abstract

Drug-resistant malaria is spreading in Africa. The few available drugs might be safeguarded if combined with an artemisinin derivative. We investigated the efficacy, safety, and tolerability of 2 combinations of artesunate with sulfadoxine–pyrimethamine (SP) in a mesoendemic region in Uganda with SP resistance, from September 1999 to June 2000. In a randomized, double-blind, placebo-controlled trial, 420 children aged 6–59 months with uncomplicated *Plasmodium falciparum* malaria were assigned SP alone (25 mg/kg sulfadoxine, 1.25 mg/kg pyrimethamine) or combined with artesunate (AS; 4 mg/kg/d) for either 1 d (SPAS1) or 3 d (SPAS3). Children were followed-up for 28 d. Day 14 cure rates were 84.6% (99/117) with SPAS3 and 61.9% (73/118) with SPAS1 compared with 55.8% (86/154) with SP. Corresponding day 28 results were 74.4% (87/117) and 45.2% (52/115) compared with 40.5% (62/153). A significant improvement was obtained with the addition of 3 d, but not 1 d, of artesunate (risk ratio [RR] = 1.5, 95% CI 1.3–1.8 at 14 d and RR = 1.8, 95% CI 1.5–2.3 at 28 d). Both AS regimens achieved significantly faster parasite clearance and lower gametocyte carriage. All drug regimens were well tolerated, but SP alone was ineffective. Treatment efficacy improved with SPAS3 but the cure rate at day 28 was modest. The combinations were well tolerated and safe. In areas where SP resistance is prevalent other combinations should be considered.

**Keywords:** malaria, *Plasmodium falciparum*, chemotherapy, artesunate, sulfadoxine–pyrimethamine, Uganda

### Introduction

The increasing prevalence of drug-resistant *Plasmodium falciparum* malaria has created a serious global public health problem in terms of morbidity and mortality and complicates the choice of appropriate drugs for first-line treatment (White *et al.*, 1999). In Africa, where the malaria burden is the greatest, resistance to chloroquine has become widespread and resistance to sulfadoxine–pyrimethamine (SP) is spreading rapidly, especially in areas where it has replaced chloroquine as the first-line antimalarial (Brandling-Bennett *et al.*, 1988; Sexton *et al.*, 1988; Watkins *et al.*, 1988; Bayoumi *et al.*, 1989; Fowler *et al.*, 1993; Premji *et al.*, 1993; Wolday *et al.*, 1995; Kanya *et al.*, 2001; Staedke *et al.*, 2001; Legros *et al.*, 2002).

Current alternative therapies are few and expensive, and there is no immediate prospect for novel drugs. In order to safeguard and optimize the few available therapies, the most widely endorsed strategy is the combination of drugs with independent modes of action and resistance mechanisms, notably including an artemisinin derivative. The artemisinins, the most potent antimalarial drugs to date, produce a 10 000-fold reduction in the biomass of drug-resistant *P. falciparum* leaving the rest to be killed by high concentrations of the partner drug (White, 1997). An additional advantage is the marked reduction of gametocytes, the transmissible form of the parasite, which raises the possibility of reducing malaria transmission, at least in low transmission areas (Price *et al.*, 1996; White & Olliaro, 1996). Clinical resistance to artemisinin derivatives has not yet been recorded (White, 1999). They have an excellent safety and tolerability profile (White & Olliaro, 1998), which encourages compliance.

The spread of resistance to SP may be delayed by its combination with artesunate (AS), while increasing therapeutic efficacy, accelerating clinical recovery, and reducing malaria transmission. A study conducted in the Gambia showed that treatment with AS combined with SP for 3 d is highly effective in areas of SP

sensitivity (Von Seidlein *et al.*, 2000). However, it is important to establish the efficacy and safety of this combination in areas where SP resistance has already emerged, as well as in populations with lower immunity.

We investigated the efficacy, safety, and tolerability of the AS + SP combination in Mbarara, Uganda. This study was part of a WHO/TDR-initiated multicentric trial to assess several AS-based combinations for the treatment of *P. falciparum* malaria.

### Methods

The randomized, double-blind, placebo-controlled trial compared the AS + SP combination in 2 dosing regimens (AS for 1 d and 3 d) with SP alone.

#### Study site

The study was conducted between September 1999 and June 2000 in Mbarara Hospital, the referral hospital for south-western Uganda. Mbarara is a city of 54 000 inhabitants in a mostly rural (94%) and densely populated (98.1 inhabitants/km<sup>2</sup>) district where malaria is mesoendemic with 2 annual peaks. In a 14 d *in vivo* test conducted in 1998, the level of clinical resistance to chloroquine was 81% and to SP 25% (Legros *et al.*, 2002). The protocol was approved by the Uganda National Council for Science and Technology and the Mbarara University Ethics Committee. The study was conducted to Good Clinical Practice standards.

#### Patients

All children presenting at the outpatient department with clinically suspected malaria were screened at the study clinic for the following inclusion criteria: aged 6–59 months; weight  $\geq$  5 kg; *P. falciparum* mono-infection with 500 to 100 000 asexual parasites/ $\mu$ L; febrile (axillary temperature  $\geq$  37.5 °C) or history of fever in the preceding 24 h; absence of severe malaria (WHO criteria, 1990) or danger signs (unable to sit/stand or drink, persistent vomiting, convulsions, impaired consciousness); no severe underlying diseases; no other major infectious diseases; no history of allergy to study drugs; no history of adequate treatment with antimalarials in the preceding 72 h excluding chloroquine; and

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residence within the Mbarara municipality. Parents or guardians were informed of the study purpose and procedures in the local language. Written informed consent was obtained.

#### Randomization and treatment

Eligible patients were randomly assigned to receive standard-dose generic SP (25 mg/kg sulfadoxine, 1.25 mg/kg pyrimethamine; International Dispensary Association, Amsterdam, The Netherlands) alone (reference group), or combined with either AS (4 mg/kg/d; Sanofi-Synthelabo, Gentilly, France) for 3 d (SPAS3) or AS for 1 d followed by placebo for 2 d (SPAS1). Placebo and AS tablets were identical. The AS manufacturer generated block-randomized codes (block-size 12) and packaged the drugs in numbered sachets. All investigators and patients were blinded to the randomization codes. The treatment was administered daily by a nurse, and patients were kept under observation for 30 min thereafter. If vomiting occurred, the dose was repeated once. Children vomiting replacement doses were withdrawn and given rescue treatment (parenteral quinine).

#### Assessment and follow-up

Subjects were asked to return to the clinic on days 1, 2, 3, 7, 14, 21, and 28. Any patient failing to come was actively traced. Patients were encouraged to return to the clinic at any time they felt ill. At each visit children were clinically assessed, thick and thin blood films were made and Giemsa-stained. Asexual forms were counted against 200 leucocytes and the density was calculated using measured white blood cell (WBC) counts. Gametocytes were counted against 500 leucocytes. A blood slide was declared negative after examining 200 thick fields. All slides were submitted to systematic, blinded quality control. A senior microscopist reviewed all discrepant results.

Antimalarial drugs in urine were investigated at entry using the Saker-Solomons test to detect chloroquine and its metabolites, and to a lesser extent quinine, proguanil, mefloquine, and pyrimethamine (Mount *et al.*, 1989).

Biochemistry and routine haematology measurements were performed in a subsample of 89 successive patients on days 0, 7, and 28. Haematological analysis was performed for all patients on days 0 and 28. Haematocrit, haemoglobin, and total WBC were measured by an automatic haemoanalyser (Sysmex, Kobe, Japan). Differential counts were done manually. Alanine aminotransferase (ALT), total bilirubin, glucose, and creatinine were measured by a colorimetric method (Randox, Crumlin, Co. Antrim, UK). Blood filter-paper samples were also collected for parasite genotyping by polymerase chain reaction (PCR) to distinguish recrudescence from newly acquired infections. The PCR was performed at the Ifakara Health Research Centre in Tanzania. Analysis of polymorphic genes (*msp1*, *msp2*, and *glurp*) was carried out on baseline and reappearance samples according to previously published methods (Irion *et al.*, 1998; Snounou & Beck, 1998). A recrudescence (treatment failure) was defined as the presence of identical patterns of *msp2*, *glurp* and any of the 3 blocks of trimorphic *msp1*. When a baseline sample was polyclonal, if any of the clones matched the reappearance sample it was considered a recrudescence. Mismatching genotypes were considered new infections (treatment success).

Patients were withdrawn from the study after enrolment if (i) the parent/guardian withdrew the consent, (ii) they consumed an antibiotic with antimalarial activity (e.g. co-trimoxazole, tetracycline, erythromycin), (iii) they vomited the treatment twice on day 0, or (iv) severe anaemia or other exclusion criteria were discovered to have been present at the time of enrolment.

#### Outcome measures

The primary endpoints for efficacy testing were the cure rates, defined as the clearance of parasites without reappearance, at days 14 and 28. The criteria for treatment failure were: parasitaemia on day 2  $\geq$  day 0; parasitaemia on day 3  $\geq$  25% of day 0; parasites on day 7; parasitaemia clearance but recurrence at any time during follow-up; emerging danger signs of severe malaria; adverse events requiring study withdrawal; and self-medication with antimalarials during the follow-up period. Treatment failure after day 14 was reclassified as cured if the baseline and reappearing genotypes were different. Cases with missing PCR data or ambiguous results were regarded as treatment failures. We also classified parasitological failures as RI/RII/RIII resistance (WHO, 1973).

Secondary efficacy endpoints were: proportion of patients parasitaemic on days 1–3; proportion of patients febrile (axillary temperature  $\geq$  37.5°C) on days 1–3; presence of gametocytes during follow-up; proportional changes of anaemic children from day 0 to day 28 (anaemia defined as haemoglobin (Hb) < 11 g/dL [aged 6–12 months]; Hb < 12 g/dL [aged 13–24 months]; and Hb < 12.5 g/dL [aged 25–60 months]). Drug safety and tolerability were assessed clinically and by laboratory tests.

#### Statistical analysis

Based on expected cure rates of 85% and 95% respectively in the groups receiving SP monotherapy or AS + SP combination therapy, with a risk  $\alpha$  of 0.05 (one-sided test), and power of 80%, the sample size was calculated at 111 children per group. Because the SP group was used for 2 comparisons, a correction ( $N = n\sqrt{\text{no. of comparisons}}$ ) was applied (Lellouch & Lazar, 1974), bringing that group to 157. Allowing for a dropout rate of 10%, the total sample size was 420.

Data were recorded on individual patient files and in specific registers. They were then transferred to the Case Report Form by the clinical investigators, who verified all entries against the source documents. Data were double-entered, validated using Epi-Info 6.04b (CDC, Atlanta, GA USA) and analysed with SPSS 10.0.5 (SPSS Inc., Chicago, IL, USA).

The intention-to-treat analysis excluded patients who were enrolled in error (not meeting entry criteria, e.g. severe anaemia or low parasitaemia) and lost to follow-up. Continuous variables were compared by parametric (Student's *t*) and non-parametric (Mann-Whitney *U*) tests for means, and categorical variables by  $\chi^2$ , Fisher's exact, and McNemar's tests. Parasite counts were normalized by logarithmic transformation.

#### Results

Of 1381 children screened, 420 were enrolled and randomized (Fig. 1). The main reason for non-eligibility was a negative slide for *P. falciparum* (41.3%). The groups were similar with respect to their baseline demographic, biological, and clinical characteristics (Table 1) except for weight ( $P = 0.03$ ). The total dropout rate at 28 d, including 21 lost-to-follow-up and 14 exclusions, was 8.3%.

At 14 d follow-up, the cure rate with SP was 55.8% (95% CI 47.6–63.8). The addition of 3 d, but not 1 d, of AS resulted in significantly higher cure rates (84.6%, 95% CI 76.5–90.4) (Table 2). By day 28, the crude cure rates with SP, SPAS1, and SPAS3 were 36.6%, 29.6%, and 58.1%, respectively. Of 95 cases of recurrent parasitaemia seen after day 14, 92 pairs were genotyped. There was genetic discordance in 43 pairs (47%) which were considered to be new infections and reclassified as cured: 66% (19/29) of those on SPAS3, 53% (18/34) on SPAS1, and 21% (6/29) on SP alone. Concordant pairs (recrudescence,  $n = 24$ ) and uninterpretable results ( $n = 25$ ) were classified as failures.

By day 28, the PCR-adjusted cure rate with SP alone

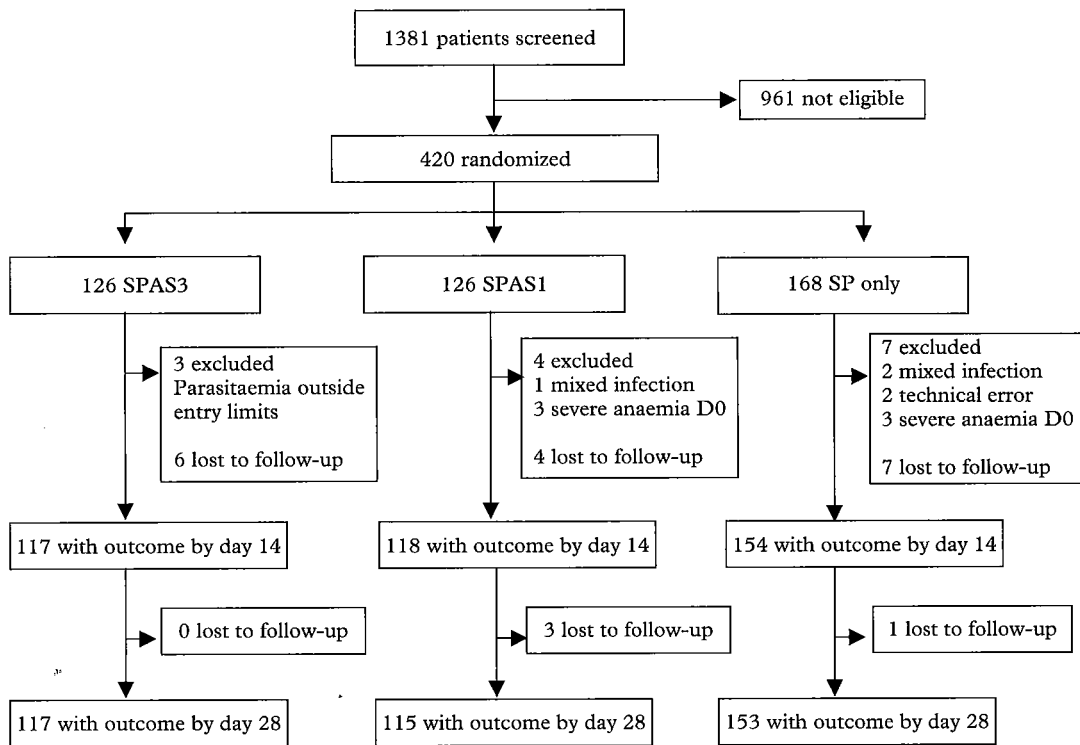


Fig. 1. Trial profile of children presenting at the outpatient department of Mbarara Hospital, Uganda with clinically suspected malaria, September 1999–June 2000. SP, sulfadoxine–pyrimethamine alone; SPAS1, SPAS3, SP combined with artesunate for 1 d and 3 d (see Methods).

Table 1. Baseline characteristics of study children at enrolment, Mbarara, Uganda, September 1999–June 2000

|                                     | SPAS3<br>(n = 126)   | SPAS1<br>(n = 126)   | SP alone<br>(n = 168) |
|-------------------------------------|----------------------|----------------------|-----------------------|
| Age (months) <sup>a</sup>           | 29.0 (15.9)          | 25.3 (13.4)          | 26.0 (15.4)           |
| Gender ratio (M/F)                  | 0.7                  | 0.9                  | 1.0                   |
| Ethnic group                        |                      |                      |                       |
| Nyankole                            | 62.7%                | 70.6%                | 63.1%                 |
| Baganda                             | 27.0%                | 24.6%                | 28.6%                 |
| Other                               | 10.3%                | 4.8%                 | 8.3%                  |
| Weight (kg) <sup>a</sup>            | 11.7 (2.8)           | 10.9 (2.6)           | 11.1 (2.9)            |
| Temperature (°C) <sup>a</sup>       | 37.8 (1.2)           | 37.8 (1.3)           | 37.8 (1.3)            |
| Asexual parasites/μL <sup>b</sup>   | 21 373 (909–302 817) | 17 078 (504–121 111) | 16 143 (531–117 280)  |
| Gametocyte carriage rate            | 23.8%                | 22.2%                | 25.6%                 |
| Gametocytes/1000 WBC <sup>b,c</sup> | 7.2 (1.0–176)        | 6.5 (2.0–90.0)       | 4.7 (1.0–34.0)        |
| Haemoglobin (g/dL) <sup>d</sup>     | 9.1 (5.0–14.9)       | 8.8 (3.2–15.4)       | 8.7 (4.1–14.0)        |
| Antimalarial use                    |                      |                      |                       |
| Urine test <sup>e</sup>             | 42.9%                | 47.2%                | 61.9%                 |
| Self-reported <sup>f</sup>          | 14.0%                | 26.9%                | 19.3%                 |
| Combined data <sup>g</sup>          | 28.5%                | 36.7%                | 29.1%                 |

SP, sulfadoxine–pyrimethamine; SPAS1, SPAS3, SP combined with artesunate for 1 d or 3 d.

<sup>a</sup>Mean (SD).

<sup>b</sup>Geometric mean (range).

<sup>c</sup>Calculated among patients with gametocytes.

<sup>d</sup>Mean (range).

<sup>e</sup>Saker–Solomons test (n = 127).

<sup>f</sup>History of antimalarial use within the preceding 72 h in insufficient dosage or chloroquine at any dose (n = 401).

<sup>g</sup>Saker–Solomons test or antimalarial use within preceding 72 h or both is true (n = 408).

was 40.5% (95% CI 32.8–48.8), again significantly higher with 3-d (74.4%, 95% CI 65.3–81.1), but not 1-d, AS. The probability of cure with SPAS3 was increased 1.5 and 1.8-fold at 14 and 28 d, respectively (Table 2).

By day 3, the proportion of parasitaemic patients was significantly lower in both AS groups compared with SP alone: 3.5% (95% CI 1.1–9.4) on SPAS3 and 36.8% (95% CI 28.1–46.4) on SPAS1 compared with

68.9% (95% CI 60.7–76.1) on SP monotherapy ( $P < 0.001$  in both comparisons). A significant difference ( $P < 0.01$ ) was also demonstrated at days 1 and 2 (Fig. 2). Gametocytes were detected in 24% (94/385) of all children at enrolment. By day 7 the proportion increased markedly to 84% (119/142) in the SP monotherapy group (Fig. 3) while it remained at 26% (60/227) in both AS groups combined ( $P < 0.001$ ). This significant difference was sustained throughout

**Table 2. Parasitological efficacy at days 14 and 28, corrected by polymerase chain reaction in study patients, Mbarara, Uganda, September 1999–June 2000**

|                                      | Outcome | <i>n</i> | Rate (%) | RR <sup>a</sup> (95% CI) | <i>P</i> |
|--------------------------------------|---------|----------|----------|--------------------------|----------|
| Efficacy at day 14                   |         |          |          |                          |          |
| SPAS3 ( <i>n</i> = 117)              | Cure    | 99       | 84.6     | 1.5 (1.3–1.8)            | <0.001   |
|                                      | Failure | 18       | 15.4     |                          |          |
| SPAS1 ( <i>n</i> = 118)              | Cure    | 73       | 61.9     | 1.1 (0.9–1.4)            | 0.32     |
|                                      | Failure | 45       | 38.1     |                          |          |
| SP alone ( <i>n</i> = 154)           | Cure    | 86       | 55.8     | –                        | –        |
|                                      | Failure | 68       | 44.2     |                          |          |
| Efficacy at day 28, corrected by PCR |         |          |          |                          |          |
| SPAS3 ( <i>n</i> = 117)              | Cure    | 87       | 74.4     | 1.8 (1.5–2.3)            | <0.001   |
|                                      | Failure | 30       | 25.6     |                          |          |
| SPAS1 ( <i>n</i> = 115)              | Cure    | 52       | 45.2     | 1.1 (0.8–1.5)            | 0.44     |
|                                      | Failure | 63       | 54.8     |                          |          |
| SP alone ( <i>n</i> = 153)           | Cure    | 62       | 40.5     | –                        | –        |
|                                      | Failure | 91       | 59.5     |                          |          |

SP, sulfadoxine–pyrimethamine; SPAS1, SPAS3, SP combined with artesunate for 1 d or 3 d.  
<sup>a</sup>Risk ratio (SPAS3 vs. SP alone and SPAS1 vs. SP alone).

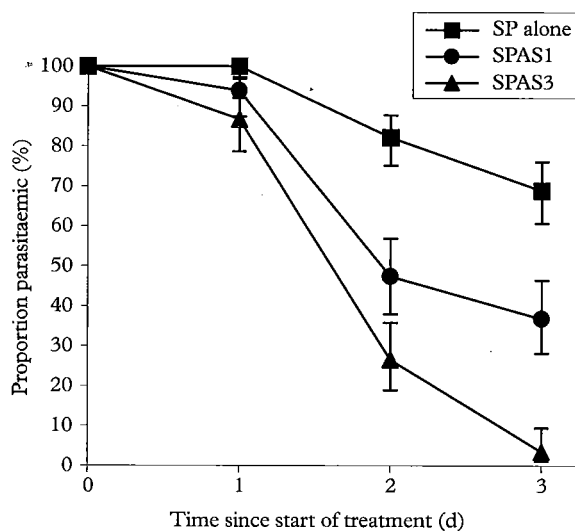


Fig. 2. Proportion of study patients with asexual parasitaemia, Mbarara, Uganda, September 1999–June 2000. Key: SP, sulfadoxine–pyrimethamine; SPAS1, SPAS3, SP combined with artesunate for 1 d or 3 d. Vertical bars represent 95% CI.

follow-up. By day 28, 40% (27/68) of SP recipients were still gametocytaemic. Among 375 subjects with analysable parasitological data (10 cases classified by non-parasitological criteria were excluded from this analysis), RIII resistance was observed only with SP monotherapy, and RI/RII resistance was less common with SPAS3 than with the other 2 regimens (Table 3).

At entry, all children were either febrile (54%) or

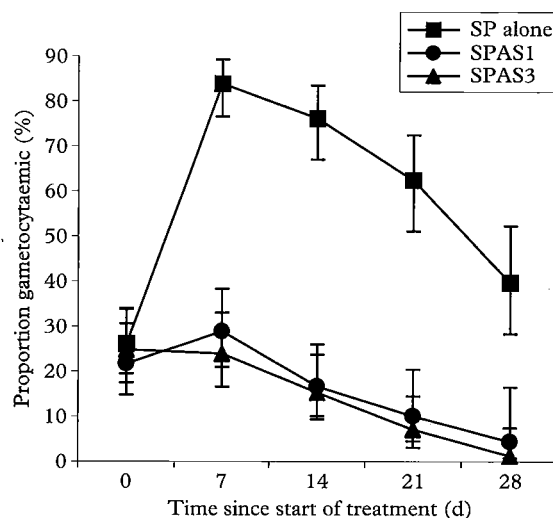


Fig. 3. Proportion of study patients with gametocytes, Mbarara, Uganda, September 1999–June 2000. Key: SP, sulfadoxine–pyrimethamine; SPAS1, SPAS3, SP combined with artesunate for 1 d or 3 d. Vertical bars represent 95% CI.

reported fever in the preceding 24 h. By day 1, 5.3% had fever in both AS groups combined, compared with 12.5% in the SP group ( $P=0.01$ ). By day 2 the difference was even greater: 1.8% in both AS groups compared with 21.1% in the SP group ( $P<0.001$ ). By day 3 the proportions were similar ( $P=0.91$ ) in all groups: 2.6% (AS groups) and 3.4% (SP alone). Antipyretic use was evenly distributed in the 3 groups.

**Table 3. Results classified by degree of resistance, corrected by polymerase chain reaction in study patients, Mbarara, Uganda, September 1999–June 2000**

|                   | SPAS3 ( <i>n</i> = 112) |           | SPAS1 ( <i>n</i> = 113) |           | SP alone ( <i>n</i> = 150) |           |
|-------------------|-------------------------|-----------|-------------------------|-----------|----------------------------|-----------|
|                   | <i>n</i> (%)            | 95% CI    | <i>n</i> (%)            | 95% CI    | <i>n</i> (%)               | 95% CI    |
| RI <sup>a</sup>   | 23 (20.5)               | 13.8–28.8 | 46 (40.7)               | 31.7–50.4 | 51 (34.0)                  | 26.8–41.4 |
| RII <sup>a</sup>  | 2 (1.8)                 | 0.3–5.8   | 15 (13.2)               | 7.9–21.5  | 22 (14.7)                  | 9.7–21.0  |
| RIII <sup>a</sup> | 0                       | –         | 0                       | –         | 16 (10.7)                  | 6.4–16.4  |
| Total failures    | 25 (22.3)               | 15.3–30.7 | 61 (54.0)               | 44.4–63.3 | 89 (59.3)                  | 51.3–67.0 |

SP, sulfadoxine–pyrimethamine; SPAS1, SPAS3, SP combined with artesunate for 1 d or 3 d.

<sup>a</sup>See WHO (1973).

Mean Hb at enrolment was 8.9 g/dL. The proportion of anaemic children fell during follow-up in all groups (SPAS3, 94% to 76%; SPAS1, 94% to 83%; SP alone, 95% to 83%), but the day 28 proportions were not significantly different across the three groups. Paired Hb results at days 0 and 28 were available for 189 patients. The mean increment with SPAS3 after 28 d (2.3 g/dL) was larger than with SPAS1 (1.9 g/dL) and SP alone (1.7 g/dL); the difference was significant ( $P=0.046$ ) only between SPAS3 and SP monotherapy.

No serious drug-related adverse events occurred and there were no deaths. Treatment-emergent signs and symptoms by day 7 were less frequent in both AS groups, though without significant differences. At entry, serum total bilirubin was raised in 57% (51/89) of the children, bilirubin in 15% (13/89), and ALT in 7% (6/89). By day 7, ALT values were normal in 79 children, marginally raised in 2 and raised over twice the normal limit in 1 case (SP monotherapy arm). No other clinically relevant abnormality in biochemical values was recorded during follow-up.

## Discussion

We have demonstrated the superior efficacy of the 3-dose AS + SP regimen in terms of parasite clearance, cure rate, gametocyte carriage, and haematological recovery compared with SP monotherapy. The failure rate with SP monotherapy was extremely high. The addition of 1 d of AS to SP did not produce a significant benefit in cure rate but did improve the parasite clearance time, clinical recovery, and gametocyte carriage. The drug combination treatments were well tolerated, although our sample size was too small to detect rare toxic effects.

The adjustment of outcome by PCR analysis has some known limitations (Brockman *et al.*, 1999) that may misclassify a small number of cases. Our study was conducted in a hospital-based, predominantly urban population that may not be representative of the general population. Levels of drug resistance tend to be higher in urban areas because of easier drug access and higher drug pressure (Wernsdorfer & Payne, 1991). Nevertheless, these factors alone are not sufficient to explain the high rates of parasitological treatment failures demonstrated, and the rate of resistance in the general population can be assumed to be unacceptably high.

Our findings are broadly consistent with those of Von Seidlein *et al.* (2000). However, despite a similar trend of superiority of SPAS3, our absolute cure rates were much lower. In The Gambia, SP monotherapy is still highly effective (92.7% day 28 cure rate) while in Mbarara it has become ineffective and is no longer of use. In 1998 the clinical treatment failure rate at day 14 with SP was 25% ( $n=64$ ), measured in the same hospital population, using WHO criteria (1996). The parasitological failure rate, a more sensitive measure of resistance, in our study reached 44.2% at 14 d and 59.5% at 28 d. This accentuates the need to monitor closely the evolution of drug efficacy and to conduct, where feasible, *in vivo* tests over 28 d to more accurately define resistance levels. With such a poor efficacy, SP is not a suitable companion drug for AS in this and other settings of high SP resistance.

In East Africa, SP resistance has emerged rapidly over the last years, as documented in Uganda in Mbarara (Legros *et al.*, 2002) and Kampala (Staedke *et al.*, 2001); in Tanzania in Tanga region (Rønn *et al.*, 1996; Trigg *et al.*, 1997; Mutabingwa *et al.*, 2001) and Kigoma (Gorissen *et al.*, 2000); in Kenya in Kilifi (Nzila *et al.*, 2000) and Kibwezi (Gorissen *et al.*, 2000); and in Rwanda/RDC near Goma (Wolday *et al.*, 1995). The need to test combinations of AS with other inexpensive antimalarial drugs is therefore urgent. Unfortunately, countries in need of drug policy change have

very limited options, which are mostly dictated by financial constraints. Some countries have opted for interim policies, in an attempt to replace chloroquine monotherapy, while waiting for new data on the efficacy, tolerability, and feasibility of artemisinin-based combinations. Malawi, Kenya, and Tanzania have adopted SP monotherapy as first-line treatment while Uganda and Rwanda are either considering or have already adopted a chloroquine + SP combination. Results of AS + amodiaquine combinations have recently been published and show promise (Adjuik *et al.*, 2002).

Artemisinin + mefloquine has been extensively studied in Thailand (Nosten *et al.*, 2000) and is another potential option, though high cost and early vomiting in young children pose problems.

New antimalarials tend to be out of reach for resource-limited African countries where the malaria burden is greatest. Artemether + lumefantrine is available as a fixed-dose combination, having proved effective in Thailand when administered at 6 doses over 3 d (Lefèvre *et al.*, 2001), but its high cost and cumbersome regimen remain important obstacles. The synergistic antifolate combination chlorproguanil + dapsone (LAPDAP) is being developed as a low-cost replacement for SP with superior efficacy and anticipated lower potential for resistance. It is currently awaiting regulatory review. The development of the triple combination including AS (CDA) is at an early stage (Winstanley, 2001). The Chinese synthetic drug pyronaridine is also a candidate for co-administration with AS (WHO, 2001).

We believe that a new strategy of treatment of uncomplicated malaria with artemisinin-based combinations is necessary in Africa. Access to effective treatment is crucial if we want to successfully control malaria. Further studies to assess the public health and economic impact of AS-based combinations as well as the optimal way of deploying them are now needed.

## Acknowledgements

We thank the clinical field team members Alex Ahabwe, Jeninah Atwebembeire, Peruth Mwesigwa Komuccera, Juliet Kyomuhendo, James Mugeni, Alex Muhumuza, Joy Musabe, Proscovia Namiro, and Enid Ngaanzi Nuwagaba. Joseph Ndarubweine, James Kiguli, Godfrey Masette, and Lwasa Lukyamuzi Bakaluba carried out laboratory analysis. Laurence Bonte provided technical support on laboratory analysis.

Important facilitators and advisers were Frederic I. B. Kayanja, E. K. Mutakooha, Nery Saez-Pozas, and Vincent Tukei (Mbarara University of Science and Technology, Uganda); Amooti Kaguna (Uganda Ministry of Health). Technical advice on statistical treatment was kindly provided by François Belanger, Catherine Com-Nougé, and Thierry Moreau. We thank the participation of members of the Drug Safety Monitoring Committee, B. Greenwood, R. Peto, and N. White. This research was funded mainly by Médecins Sans Frontières, with a complement from the Embassy of France in Uganda and the World Health Organization.

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Received 11 September 2002; revised 30 October 2002; accepted for publication 6 November 2002