

A RANDOMIZED TRIAL OF ARTESUNATE–SULFAMETHOXYPYRAZINE–PYRIMETHAMINE VERSUS ARTEMETHER–LUMEFANTRINE FOR THE TREATMENT OF UNCOMPLICATED *PLASMODIUM FALCIPARUM* MALARIA IN MALI

ISSAKA SAGARA, ALASSANE DICKO, ABDOULAYE DJIMDE, OUSMANE GUINDO, MAMADY KONE, YOUSOUF TOLO, MAHAMADOU A. THERA, MOUSSA SOGOBA, MOUSSA FOFANA, AMED OUATTARA, MADY SISSOKO, HERWIG F. JANSEN, AND OGOBARA K. DOUMBO*

Malaria Research and Training Center, Department of Epidemiology of Parasitic Diseases, Faculty of Medicine, Pharmacy, and Odonto-Stomatology, University of Bamako, Bamako, Mali; Dafra Pharma, Turnhout, Belgium

Abstract. The choice of artemisinin-based combination that is being adopted for malaria treatment in sub-Saharan Africa may depend on several factors, including cost, efficacy, side effects, and simplicity of administration. We tested the hypothesis that artesunate–sulfamethoxy pyrazine–pyrimethamine is as efficacious as the four-dose regimen of artemether–lumefantrine for treatment of *Plasmodium falciparum* malaria. The study was carried out during two transmission seasons (2003 and 2004) in Sotuba, Mali. Participants at least 6 months of age with uncomplicated *P. falciparum* malaria were randomly assigned to receive artesunate–sulfamethoxy pyrazine–pyrimethamine or artemether–lumefantrine. Treatment efficacy was assessed using the World Health Organization 28-day protocol. A total of 606 (303 in each arm) patients were enrolled. The cure rate was higher for artesunate–sulfamethoxy pyrazine–pyrimethamine than for artemether–lumefantrine (98.7% versus 89.6%; $P < 0.0001$). After correction for cases of re-infection, the cure rates were 100% and 99.0%, respectively ($P = 0.08$). No serious adverse events occurred. Artesunate–sulfamethoxy pyrazine–pyrimethamine is well-tolerated and effective against *P. falciparum* malaria. It showed an additional benefit of preventing new infections.

INTRODUCTION

Several studies have been conducted or are currently under way to evaluate artemisinin-based combination malaria therapy. Studies comparing artemether–lumefantrine (AL), artesunate–sulfadoxine–pyrimethamine (AS plus SP), artesunate–amodiaquine, or artesunate–mefloquine combination therapy with sulfadoxine–pyrimethamine (SP), amodiaquine, or mefloquine monotherapy have shown that the combination therapies are safe and equally or more effective than monotherapy.^{1–4} The World Health Organization (WHO) has recommended the use of artemisinin-based combination therapies and called for their evaluation in various malaria-endemic areas. The artemisinin-based anti-malarial combination therapies differ in price, efficacy, side effects, and mode of administration. In the long term, the choice of artemisinin-based combination therapy in a specific malaria-endemic area needs to take into account the above criteria.

In Mali, although artemisinin-based combination therapy is being adopted, in practice, chloroquine and SP are still widely used to treat uncomplicated malaria. Unacceptable resistance of *Plasmodium falciparum* to chloroquine has developed in Mali, with more than a 25% failure rate in many areas (Djimde A, Diallo M, and Sogoba M, unpublished data).

We investigated whether artesunate–sulfamethoxy pyrazine–pyrimethamine (AS plus SMP) was efficacious and safe when compared with AL. Sulfamethoxy pyrazine (SM) or sulfalene is a well-characterized sulfonamide drug, which is chemically similar to sulfadoxine but biologically distinct with

a shorter half-life and less plasma protein binding.^{5,6} The efficacy of SMP in treating *P. falciparum* malaria has been demonstrated.^{7–11} Since SMP has not been used widely as an anti-malarial for more than 10 years, it is expected that the combination of this drug with artesunate will result in a highly efficacious treatment of *P. falciparum* malaria. Artemether–lumefantrine was used as a comparator because WHO has listed this drug as an essential anti-malarial drug.

METHODS

Study site. The study was conducted in Sotuba, Mali. Sotuba is a peri-urban area of Bamako, Mali, with approximately 3,500 inhabitants. *Plasmodium falciparum* is the predominant infecting species, accounting for more than 95% of malaria cases. Previous studies found a failure rate of 25.5% for chloroquine and less than 5% for SP in 2000 and 2001 (Sogoba M, unpublished data).

Study population. Individuals at least six months of age who came to the local health center during the study period (September 2003 to January 2004 and then from August 2004 to October 2004) were included in the study if they satisfied the following criteria: weighed ≥ 5 kg, had a *P. falciparum* parasite density between 1,000 and 100,000/ μ L, had an axillary temperature $\geq 37.5^\circ$ or had a history of fever in the preceding 24 hours, were a resident of the study site, and could take oral medication. Individuals were excluded if they had symptoms or signs of severe malaria,¹² had a serious underlying disease, had an allergy to one or more study drugs, had used any component of the study drugs within 28 days of enrollment, or were pregnant (detected either clinically or with a urine β -human chorionic gonadotropin test).

Each participant or participant's guardian gave fully informed written consent prior to enrollment. The protocol was reviewed and approved by the ethical committee of the Faculty of Medicine, Pharmacy and Dentistry, University of Bamako.

* Address correspondence to Ogobara Doumbo, Malaria Research and Training Center, Department of Epidemiology of Parasitic Diseases, Faculty of Medicine, Pharmacy, and Odonto-Stomatology, University of Bamako PO Box 1805, Point G, Bamako, Mali. E-mail: okd@mrtcbko.org

Procedures. Enrolled patients were randomly assigned to receive either AS plus SMP (Co-arinat; Dafra Pharma, Turnhout, Belgium) or AL (Coartem®; Novartis, Basel, Switzerland). A simple complete randomization code with treatment arm was computer generated by the study statistician who was not involved in patients' enrollment or outcomes assessment. Study codes were sealed in individual opaque and sequentially numbered envelopes. Enrolled patients were assigned a treatment according to the envelope content. Although this was an open clinical trial, thick blood smear slide readers were kept from knowing the treatment arm until the end of the study; this aimed to minimize assessment bias because malaria parasite count was the key outcome used to define treatment failure.

All drugs were manufactured according to current Good Manufacturing Practice. Artemether-lumefantrine was packaged in fixed-dose combination tablets each containing 20 mg of artemether and 120 mg of lumefantrine. They were administered according to body weight (5–14 kg, one tablet; 15–24 kg, two tablets; 25–34 kg, three tablets; ≥ 35 kg, four tablets) in four consecutive doses: one dose administered at enrollment, one dose eight hours later, and one dose on the first day and one dose on the second day after initiation of treatment. The AS plus SMP treatment was supplied as two separate tablets in a single blister pack. The tablets were color-coded for ease of identification: pink for sulfamethoxy-pyrazine-pyrimethamine and white for artesunate. One dose was administered daily for three days. Dosage was determined by weight, with different blister packs for different weight arms. For a weight ≥ 40 kg, each blister contained a 200-mg tablet of artesunate plus a 500/25-mg tablet of sulfamethoxy-pyrazine-pyrimethamine. A tablet of each drug was administered each day. For a weight of 20–39 kg, each blister contained a 100-mg tablet of artesunate plus a 250/12.5-mg tablet of sulfamethoxy-pyrazine-pyrimethamine. A tablet of each drug was administered each day. For weights of 13–19 kg, 8–12 kg, and 5–7 kg, each blister contained a 50-mg tablet of artesunate plus a 125/6.25-mg tablet of sulfamethoxy-pyrazine-pyrimethamine. One and a half tablets, one tablet, and half of a tablet, respectively, of each drug were administered daily. For young children in both treatment arms, tablets were crushed and mixed with water. All drug doses were administered in the health center by a physician. A full dose was re-administered if a participant vomited the study drugs within 30 minutes of initial administration.

Study participants were examined in the study clinic 1, 2, 3, 7, 14, 21, and 28 days after enrollment or at any time if they did not feel well. A finger skin puncture was obtained to prepare a thick blood smear and a filter paper dot (for future parasite DNA extraction) at each follow-up visit except for the first day after enrollment. Study participants or their guardians were asked about drug use since the last visit to the clinic. Individuals for whom treatment failed were treated according to the treatment guidelines of the Malian National Malaria Control Program.

Giemsa-stained thick blood smears were read by experienced microscopists who were blinded to treatment allocation. Parasite densities were calculated by counting the number of asexual *P. falciparum* parasites until 300 leukocytes were observed and then converting that to parasites per microliter of blood, assuming an average leukocyte count of 7,500/μL. For quality control, 10% of the slides selected at

random were re-read by another microscopist who was unaware of the results of the first reading.

A complete blood count plus serum alanine aminotransferase (ALT) and serum creatinine assessments were performed among the first enrolled on approximately 20% of the total participants at baseline and 14 days after initiation of treatment. Tests were also performed if clinically indicated or if a significant abnormality was detected on day 14. In addition, hemoglobin levels were measured using a Hemocue machine (Hemocue, Ängelholm, Sweden) at baseline and on day 28.

For participants with recurrent parasitemia after day 7, paired polymerase chain reaction (PCR) blots (from day 0 and the day of parasitemia recurrence) were analyzed for parasite merozoite surface proteins (MSP1 and MSP2) and for glutamate-rich protein (GLURP), to distinguish between re-infection and recrudescence. The MSP1 gene was amplified using nested PCR.^{13,14} The MSP1 outer primers (MSP1-1: 5'-TAG AAG ATG CAG TAT TGA CAG GTT A-3' and MSP1-2: 5'-ATT CTA ATT CAA GTG GAT CAG TAA ATA A-3') were used in the first step under conditions described below. Allotype-specific primers (MAD20-1: 5'-GTA TTA AAT GAA GGA ACA AGT GGA ACA G-3' and MAD20-2: 5'-TAT CTG AAG GAT TTG TAC GTC TTG AAT T-3'; RO33-1: 5'-ATT AAA GGA TGG AGC AAA TAC TCA AGT TGT-3' and RO33-2: 5'-TCT GAA GGA TTT GCA GCA CCT GGA GA-3'; K1-1: 5'-CTT AAA TGA AGA AGA AAT TAC TAC AAA AGG TGC-3' and K1-2: 5'-GAG GGC TTG CAC CAG ATG AAG T-3') were used in the second step under the same conditions. Five microliters of DNA was used in a total volume of 45 μL of reaction mixture. A total of 30.5 μL of mixture 1 composed of 0.2 mM dNTPs, 1× phosphate-buffered saline (PBS), 1.5 mM MgCl₂, distilled water and 1 μL of each primer (40 ng/μL) was dispensed into 0.6-mL tubes. Paraffin beads were added to the tubes and melted at 73°C for 3 minutes. A total of 14.5 μL of mixture 2 composed of distilled water (12 μL), 1× PBS (2 μL) and 0.5 units of *Taq* polymerase was then added. The DNA (5 μL) was added last. The cycling conditions were one cycle at 95°C for 2 minutes followed by 35 cycles at 94°C for 30 seconds, 57°C for 40 seconds, and 72°C for 70 seconds using a Robocycler (Stratagene, La Jolla, CA). The amplified product was identified by electrophoresis on 2% agarose (Gibco-BRL, Gaithersburg, MD) gels containing 1 mg/mL of ethidium bromide (Sigma, St. Louis, MO) and photography using ultraviolet light. Sizes of amplified products were estimated using molecular marker VI (Boehringer-Mannheim, Mannheim, Germany).

A single round of PCR was used with the above mixture and amplification parameters to amplify the GLURP gene with the pair GLURP-1: 5'-CAG AAC TAC ATG AAA ATG AAG TGG CTC A-3' and GLURP-2: 5'-CAT TGT TAT TTG TTT GTG ATG GTA CTT CTT CA-3'.¹⁵ Previously described methods were used to extract DNA¹⁶ and measure polymorphisms of MSP2.¹⁷

Initial determination of recrudescence versus re-infection was made with MSP1. Those samples that failed to yield results or were recrudescence with MSP1 were analyzed using GLURP primers. Only samples that gave no result or were classified as recrudescence with GLURP were analyzed with MSP2. A sample was classified as a true failure if it was recrudescence with all three markers. No case of indeterminate or mixed infection was encountered.

Objectives. The primary objective was to test the hypothesis that AS plus SMP is as efficacious as AL in the treatment of uncomplicated *P. falciparum* malaria. The secondary objectives were to assess and compare the following outcomes in the two treatment arms: parasite and fever clearances, re-infection rate, gametocyte carriage rate, anemia correction rate, and clinical and biologic adverse events.

Therapeutic outcomes were classified according to the current WHO protocol¹⁸ (in areas of low-to-moderate malaria transmission). The primary endpoint was an adequate clinical and parasitologic response, or cure rate, after 14 days of follow-up. Secondary endpoints were incidence of adverse events (clinical and laboratory abnormalities), re-infection rate, anemia correction rate (anemia was defined as a hemoglobin level < 11 g/dL), fever (temperature $\geq 37.5^{\circ}\text{C}$), parasitemia clearance rate, and gametocyte carriage rate. Fever clearance was assessed on days 1, 2, and 3; parasite clearance was assessed on days 2 and 3; and gametocyte carriage was assessed on days 0, 3, 7, 14, 21, and 28. The anemia correction rate was determined by subtracting the anemia rate for day 28 from the anemia rate for day 0 for each treatment arm. An adverse event was defined as any sign, symptom, or abnormal laboratory value not present on day 0 but that occurred during follow-up, or one that was present on day 0 but became worse during follow-up. A serious adverse event was defined according to the International Conference on Harmonization (ICH E6, Glossary 1.50).

Statistical methods. The required sample size was calculated using the assumption that the two study drugs were equally effective in terms of the primary endpoint, with a two-sided $\alpha = 0.05$ and a power of 80%. The maximum accepted difference in efficacy between the two study treatments was set at 6%. Based on a study from The Gambia in which a 93% 14-day cure rate was reported for AL,² 606 participants (303 in each treatment arm, including a 10% attrition rate) were deemed necessary. The intention-to-treat analysis for adverse events included all randomized participants, and that for the primary endpoint excluded participants who withdrew from the study or were lost to follow-up.

Data were double-entered, validated using Microsoft Access® (Microsoft Corporation, Redmond, WA), and analyzed with STATA version 8.2 software (Stata Corporation, College Station, TX). For the baseline and the primary endpoint, the binary data were analyzed by estimation of differences in proportions with corresponding 95% confidence intervals (CIs). Exact 95% CIs were calculated when the proportions were close to 0 or 1; otherwise, normal estimations were used. For secondary endpoints, the chi-square test or Fisher exact test was used as appropriate to compare categorical variables. Student's unpaired *t*-test was used to assess differences between groups in mean for continuous variables. The McNemar paired chi-square test was used to compare the prevalence of anemia before and after treatment in each treatment arm. A *P* value < 0.05 was considered statistically significant.

RESULTS

Participant characteristics. Six hundred six of 2,685 patients who were screened for malaria symptoms were enrolled. Figure 1 shows detailed enrollment and follow-up information. Of the 606 enrolled participants, 303 were randomized to

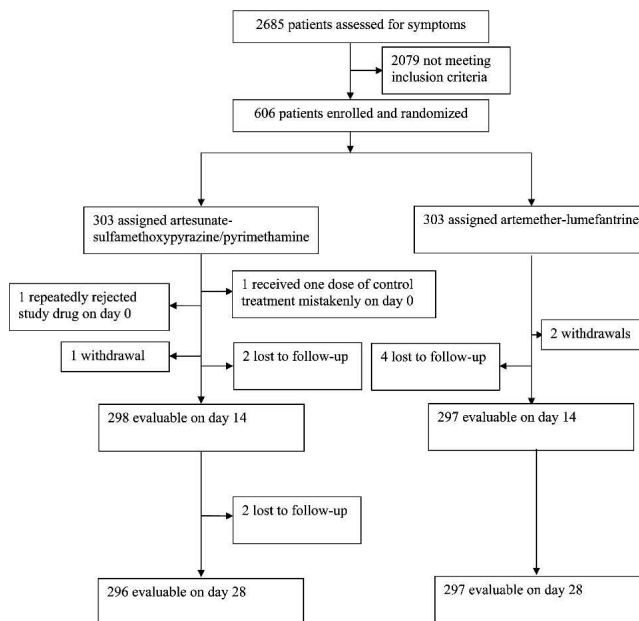


FIGURE 1. Trial profile.

receive AS plus SMP and 303 to receive AL. Of the 606, 13 (2.1%) withdrew or were lost to follow-up. Reasons for withdrawal included withdrawal of consent (one in the AS plus SMP arm and two in the AL arm), receiving the wrong treatment drug on day 0 (one in the AS plus SMP arm who mistakenly received a dose of AL), repeated rejection (spit out) of study drug (one in the AS plus SMP arm), and lost to follow-up (four in the AS plus SMP arm and four in the AL arm). As shown in Table 1, the participants in the two treatment arms had similar demographic, clinical, and laboratory characteristics at enrollment.

Cure rates. No early treatment failures were observed in either treatment arm. As shown in Table 2, the 14-day cure (adequate clinical and parasitologic response) rates before adjusting for cases of re-infection were 100% (298 of 298) and 98% (291 of 297) for participants receiving AS plus SMP and AL, respectively ($P = 0.036$); the difference was statistically significant. When adjusted for cases of re-infection, the 14-day cure rate for the AL arm was 100%.

As shown in Table 3, the 28-day cure rates were 98.6% (292 of 296) and 89.6% (266 of 297) for participants receiving AS plus SMP and AL, respectively ($P < 0.001$). After adjusting for cases of re-infection, the 28-day cure rates were 100% (296 of 296) and 99% (294 of 297) for those receiving AS plus SMP and AL, respectively. This difference between treatment arms was not statistically significant ($P = 0.08$). Twenty-eight-day re-infection rates were 1.3% (4 of 296) and 9.4% (28 of 297) for participants receiving AS plus SMP and AL, respectively ($P < 0.001$).

Fever and parasite clearance and gametocyte carriage. As shown in Figure 2, the proportion of participants without fever was similar on days 2 and 3. However, on day 1, the fever clearance rate was higher in the AS plus SMP arm (90.6%, 184 of 203) than in the AL arm (78.4%, 163 of 208) ($P = 0.001$).

Both treatments resulted in rapid clearance of parasites (Figure 3). The proportion of participants who were apar-

TABLE 1
Demographic, clinical, and laboratory characteristics of patients at enrollment*

Characteristic	AS + SMP (n = 303)	AL (n = 303)
Mean age, years (range)	12.47 (0.6–63)	12.08 (0.6–58)
% < 5 years of age	17.82	17.16
% ≥ 5 years of age	82.18	82.84
Male/female	156/147	160/143
% temperature ≥ 39.0°C	18.81	18.48
Mean parasite count, μL (range)†	13,981 (1,025–99,875)	13,143 (1,000–99,100)
Mean hemoglobin level, g/L (SD)	11.9 (1.8)	11.8 (2.1)
Mean leukocyte count, ×10 ⁹ /L (SD)‡	7.9 (3.5)	7.9 (3.0)
Mean ALT level, IU/L (SD)‡	18.4 (14.4)	16.8 (9.9)
Mean creatinine level, μmol/L (SD)‡	54.1 (11.4)	60.3 (11.4)

* AS + SMP = artesunate-sulfamethoxyprazine-pyrimethamine; AL = artemether-lumefantrine; ALT = alanine aminotransferase.

† Geometric mean.

‡ Biochemical analysis and hemograms were performed among the first 20% of the participants.

sitemic was similar between the two treatment arms: 99.3% (299 of 301) and 97.4% (295 of 303) for those receiving AS plus SMP and AL, respectively, on day 2 ($P = 0.11$) and 99.3% (299 of 301) and 100% (301 of 301) for those receiving AS plus SMP and AL, respectively, on day 3 ($P = 0.3$).

Gametocyte carriage rates decreased gradually from day 0 to day 28 (Figure 4). No gametocytes were observed by day 28 for any treatment arm. No statistically significant differences were detected between the arms at any follow-up day ($P > 0.05$).

Anemia. In the AS plus SMP arm, 38 (12.7%) of 299 participants had anemia on day 0 compared with 7 (6.5%) of 107 on day 28. For the AL arm, 48 (16.1%) of 299 and 13 (13.8%) of 94 had anemia on day 0 and day 28, respectively. Using the McNemar paired chi-square test, we found that treatment with AS plus SMP significantly lowered the prevalence of anemia 28 days after treatment initiation ($P = 0.0003$), but this difference was not statistically significant for the AL arm ($P > 0.8$).

Adverse events. Artesunate-sulfamethoxyprazine-pyrimethamine and artemether-lumefantrine were both well tolerated. No serious adverse events occurred (0 [0%]) of 303 participants in each arm). One of the 303 participants randomized to the AS plus SMP arm repeatedly rejected the study drug on day 0. This participant received alternative treatment of malaria and was withdrawn from the study. As shown in Table 4, the number reporting any symptom or sign within the first week after treatment was similar between the arms ($P > 0.05$), as was the total number of reported adverse events: 125 in the AS plus SMP arm versus 122 in the AL arm ($P = 0.80$). Fourteen participants reported diarrhea (3 in the AS plus SMP arm versus 11 in the AL arm) ($P = 0.03$).

Two (2.9%) and 1 (1.5%) of 68 participants in the AS plus SMP arm compared with 0 (0%) of 54 and 1 (1.8%) of 56 in the AL arm had mild and transient elevation of ALT and creatinine levels, respectively, on day 14 ($P > 0.5$). These abnormal values were not associated with clinical illness and resolved spontaneously within three weeks of day 14.

DISCUSSION

This study demonstrates that both AS plus SMP and AL are highly effective for treating uncomplicated *P. falciparum* malaria in Sotuba, Mali. The 14-day cure rates were 100% in both arms. The 28-day cure rates were 100% in the AS+SMP arm and 99.0% in the AL arm ($P < 0.08$).

After several studies were conducted using either four-dose or six-dose regimens of AL in malaria-endemic areas (both with and without multi-drug anti-malarial resistance),^{2,19–25} a recommendation was made by the drug manufacturer, and the product was registered as such to adopt the four-dose regimen for use in areas without multidrug resistance and the six-dose regimen for use in areas with multidrug resistance. High 28-day cure rates (> 92.0%) with the four-dose regimen of AL have previously been demonstrated in trials performed in The Gambia and India.^{2,25} However, in areas with multi-drug resistance, the four-dose regimen has demonstrated poor efficacy (cure rates < 85%) compared with other treatments.²⁵ The WHO has recently recommended using the six-dose regimen of AL in all malaria-endemic areas, and the drug manufacturer has agreed to avoid confusion and ensure the highest efficacy and reliability of this combination.^{26,27} However, the adoption of the six-dose regimen may have a negative impact on treatment and on the cost of treatment in malaria-endemic areas of Africa.

The high cure rates we found for AS plus SMP were ex-

TABLE 2
Clinical and parasitologic response at day 14*

Treatment arm outcome	AS + SMP (n = 298)	AL (n = 297)	Δ (95% CI)	P
	No. (%)	No. (%)		
ETF	0 (0)	0 (0)	–	–
ACPR	298 (100)	291 (98.0)	2.0 (0.4–3.6)	0.036
Corrected ACPR†	–	297 (100)	–	–

* AS + SMP = artesunate-sulfamethoxyprazine-pyrimethamine; AL = artemether-lumefantrine; CI = confidence interval; ETF = early treatment failure; ACPR = adequate clinical and parasitologic response.

† Adjusted for re-infection using polymerase chain reaction.

TABLE 3
Clinical and parasitologic response at day 28*

Treatment arm outcome	AS + SMP (n = 296)	AL (n = 297)	Δ (95% CI)	P
	No. (%)	No. (%)		
ACPR	292 (98.7)	266 (89.6)	9.1 (5.4–12.8)	< 0.001
Corrected ACPR†	296 (100)	294 (99.0)	1.0 (–0.1–2.1)	0.08

* For definitions of abbreviations, see Table 2.

† Adjusted for re-infection using polymerase chain reaction.

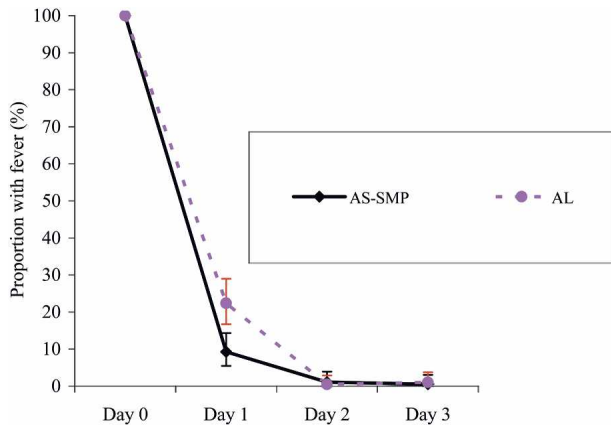


FIGURE 2. Proportion of participants with fever during the first three days of treatment. Error bars show 95% confidence intervals. AS-SMP = artesunate-sulfamethoxy-pyrazine-pyrimethamine; AL = artemether-lumefantrine. This figure appears in color at www.ajtmh.org.

pected because of the high efficacy of artesunate; the low-level resistance of *P. falciparum* to SP in Mali, as in most west African countries; and potentially because of the non-wide use of SMP as an anti-malarial more than 10 years ago.⁷⁻¹⁰ The mechanism of action of this drug is the same as that of SP. Some differences between the two drugs are protein binding (65% for SMP versus 99% for SP) and elimination half-life. The shorter half-life of sulfamethoxy-pyrazine compared with that of sulfadoxine favors its combination with artesunate, while sulfadoxine combined with artesunate would be a great pharmacokinetic mismatch.

In our study, AS plus SMP showed an additional benefit of preventing new infections; the 28-day re-infection rates were 1.3% and 9.4%, respectively ($P < 0.001$). A multi-center study conducted in Africa²⁸ found that a six-dose regimen of AL resulted in a high cure rate (93.9%), but the cure rate for the four-dose AL regimen in our study was even higher (99%). Differences in elimination half-life may not explain the advantage of AS plus SMP over AL in preventing re-infection because artemether and artesunate have similar half-lives (approximately two hours each) and the elimination half-life of lumefantrine is comparable^{29,30} to that of sulfamethoxy-pyrazine or pyrimethamine⁵ (3-6 days, 3-4 days, and 2-6

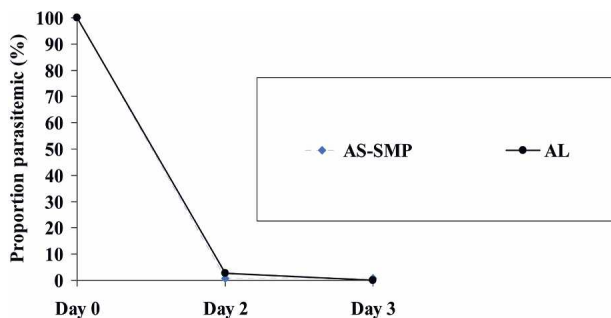


FIGURE 3. Proportion of participants with asexual *Plasmodium falciparum* parasitemia during the first three days of treatment. AS-SMP = artesunate-sulfamethoxy-pyrazine-pyrimethamine; AL = artemether-lumefantrine. This figure appears in color at www.ajtmh.org.

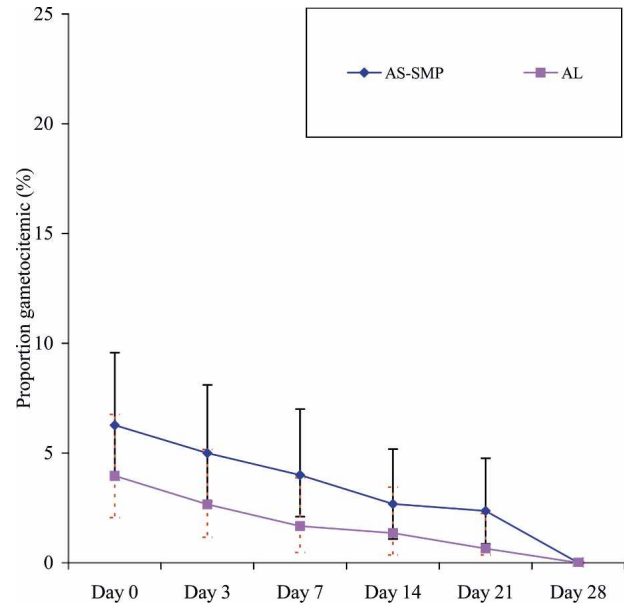


FIGURE 4. Proportion of participants with gametocytes at baseline and follow-up. Error bars show 95% confidence intervals. AS-SMP = artesunate-sulfamethoxy-pyrazine-pyrimethamine; AL = artemether-lumefantrine. This figure appears in color at www.ajtmh.org.

days, respectively). Lumefantrine absorption or minimum inhibitory concentration may account for the difference; lumefantrine absorption is greatly improved with the intake of fatty food.^{29,30} During our study, all drugs were administered in the clinical center by the physician using only water. Therefore, doses may have been taken in the fasting state because the participants may have been anorectic during their symptomatic malaria episodes.

Both treatments were similar regarding the secondary endpoints of parasite clearance rate, fever clearance rate (except for day 1 when the fever clearance was greater in the AS plus SMP arm), gametocytes carriage rate, and clinical (except for diarrhea, which was more prevalent in AL arm) and laboratory adverse events. However, the study was not empowered to detect true differences that may exist between these variables in the two treatment arms.

Administered in a single dose, a three-day course of AS plus SMP is as effective and well tolerated as a four-dose

TABLE 4
Observed adverse events after treatment administration *

Adverse event	AS + SMP (n = 303)	AL (n = 303)	P
Abdominal pain	31 (10.2)	21 (7.0)	0.19
Vomiting	25 (8.3)	20 (6.6)	0.54
Headaches	19 (6.3)	15 (5.0)	0.60
Weakness	18 (5.9)	26 (8.6)	0.27
Dizziness	12 (4.0)	12 (4.0)	1.0
Body aches	10 (3.3)	7 (2.3)	0.62
Malaise	5 (1.7)	2 (0.7)	0.45
Diarrhea	3 (1.0)	11 (3.6)	0.03
Icterus	1 (0.3)	0	1.0
Pruritus	1 (0.3)	7 (2.3)	0.07
Skin rash	0	1 (0.3)	1.0
Total	125	122	0.80

* Values are no. (%) of participants with the sign or symptom from day 1 to day 7 after treatment. For definitions of abbreviations, see Table 2.

course of AL for treating *P. falciparum* malaria. Artesunate-sulfamethoxyprazine-pyrimethamine showed an additional benefit of preventing new infections. Since sulfamethoxyprazine and sulfadoxine are both sulfonamides (although quite different) and because of the insufficient data regarding cross-resistance of *P. falciparum* to sulfonamides,³¹ studies are ongoing in other malaria-endemic areas with different transmission patterns and different levels of *P. falciparum* resistance to SP to assess the efficacy and safety of AS plus SMP.

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Authors' addressees: Issaka Sagara, Alassane Dicko, Abdoulaye Djimde, Ousmane Guindo, Mamady Kone, Youssouf Tolo, Mahamadou A. Thera, Moussa Sogoba, Moussa Fofana, Amed Ouattara, Mady Sissoko, and Ogobara K. Doumbo, Malaria Research and Training Center, Department of Epidemiology of Parasitic Diseases, Faculty of Medicine, Pharmacy, and Odonto-Stomatology, University of Bamako PO Box 1805, Point G, Bamako, Mali, Telephone 223-222-8109, Fax: 223-222-4987, E-mails: isagara@mrtcbko.org, adicko@mrtcbko.org, adjimde@mrtcbko.org, guindous@mrtcbko.org, tolo@mrtcbko.org, mthera@mrtcbko.org, msogoba@mrtcbko.org, moussaf@mrtcbko.org, amed@mrtcbko.org, mady@mrtcbko.org, and okd@mrtcbko.org. Herwig F. Jansen, Dafra Pharma, NV Slachthuisstraat 30/7, 2300 Turnhout, Belgium, Telephone: 32-1-461-7820, Fax: 32-1-461-7859, E-mail: fhj@dafra.be.

Reprint requests: Ogobara K. Doumbo, Malaria Research and Training Center, Department of Epidemiology of Parasitic Diseases, Faculty of Medicine, Pharmacy, and Odonto-stomatology, University of Bamako PO Box 1805, Point G, Bamako, Mali. E-mail: okd@mrtcbko.org.

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