

Artemether-lumefantrine versus amodiaquine plus sulfadoxine-pyrimethamine for uncomplicated falciparum malaria in Burkina Faso: a randomised non-inferiority trial

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Summary

Background Artemisinin-based combination regimens are widely advocated for malarial treatment, but other effective regimens might be cheaper and more readily available. Our aim was to compare the risk of recurrent parasitaemia in patients given artemether-lumefantrine with that in those given amodiaquine plus sulfadoxine-pyrimethamine for uncomplicated malaria.

Methods We enrolled 521 patients aged 6 months or older with uncomplicated falciparum malaria in Bobo-Dioulasso, Burkina Faso. Patients were randomly assigned to receive standard doses of either artemether-lumefantrine (261) or amodiaquine plus sulfadoxine-pyrimethamine (260) for 3 days. Primary endpoints were the risks of treatment failure within 28 days, either unadjusted or adjusted by genotyping to distinguish recrudescence from new infection. The study is registered at controlled-trials.gov with the identifier ISRCTN54261005.

Findings Of enrolled patients, 478 (92%) completed the 28-day study. The risk of recurrent symptomatic malaria was lowest in the group given amodiaquine plus sulfadoxine-pyrimethamine (1.7% vs 10.2%; risk difference 8.5%; 95% CI 4.3–12.6; $p=0.0001$); as was the risk of recurrent parasitaemia (4.7% vs 15.1%; 10.4%; 5.1–15.6; $p=0.0002$). Nearly all recurrences were due to new infections. Recrudescences were four late treatment failures with artemether-lumefantrine and one early treatment failure with amodiaquine plus sulfadoxine-pyrimethamine. Both regimens were safe and well tolerated, with pruritus more common with amodiaquine plus sulfadoxine-pyrimethamine than with artemether-lumefantrine. Each regimen selected for new isolates with mutations that have been associated with decreased drug susceptibility.

Interpretation Amodiaquine plus sulfadoxine-pyrimethamine was more effective than was artemether-lumefantrine for the treatment of uncomplicated malaria. For regions of Africa where amodiaquine plus sulfadoxine-pyrimethamine continues to be effective, this less expensive and more available regimen should be considered as an alternative to blanket recommendations for artemisinin-based combination treatment for malaria.

Introduction

Antimalarial drug resistance is a severe and growing problem in Africa.¹ As older monotherapy regimens become less effective, a consensus has emerged for the use of combination treatments for malaria.² Artemisinin-based combination treatments have proved very effective against malaria in Asia and Africa,^{2,3} and most countries in Africa have now changed their national regimens to incorporate artemisinin-based combination regimens as first-line treatment for uncomplicated malaria.⁴

However, the implementation of artemisinin-based combination therapy has its difficulties. First, these regimens are much more expensive than previous treatments. Although funding for antimalarial treatment in Africa has been increased, available resources might not be adequate to fund all the necessary treatments. Second, supplies of artemisinin derivatives, although growing, remain inadequate for the estimated 1 billion malaria treatments given each year in Africa.⁵ Third, artemisinin-based combination treatments have not yet been widely studied in all epidemiological settings in Africa, and might not be as successful in high transmission regions as in other areas.

Antimalarial combination regimens that do not contain an artemisinin derivative remain of interest, since they can be much less expensive and they offer an alternative treatment if artemisinin use remains restricted by cost, supply, unexpected toxic effects, or a combination of such factors. The non-artemisinin combination treatment that has been best studied is amodiaquine with sulfadoxine-pyrimethamine. This regimen combines two inexpensive and readily available drugs, and has proved to be particularly effective in regions of Africa with low levels of resistance to each component, such as much of west Africa.^{6,7}

Amodiaquine plus sulfadoxine-pyrimethamine has been shown to lower the risk of new infections after treatment compared with artemisinin-based regimens, presumably because of the long half-lives of sulfadoxine-pyrimethamine and amodiaquine or its derivatives.⁸ However, the benefits of any long-acting drug might be offset if it is selected for parasites with mutations that confer resistance to important antimalarial agents.^{9–13}

Several countries in west Africa, including Burkina Faso, have changed their recommended first-line treatment for uncomplicated malaria to the artemisinin-based combination regimen, artemether-lumefantrine.⁴ However,

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few studies from Africa,¹⁴ and none from west Africa, have compared artemether-lumefantrine with non-artemisinin combination treatment. Our aim was to assess the efficacy of artemether-lumefantrine compared with amodiaquine plus sulfadoxine-pyrimethamine for treatment of patients with uncomplicated malaria in Burkina Faso.

Methods

Participants

The study was based in Bobo-Dioulasso, a city of about 450 000 inhabitants in western Burkina Faso, where malaria is holoendemic and transmission peaks during the rainy season (May to October). Patients were recruited from three government health centres (Colsama, Sarfalao, and Ouezzinville).

All patients who presented between August, 2005, and December, 2005, with high temperature or history of recent fever were referred to health-centre laboratories for initial screening of a thick blood smear (figure 1). Blood was also taken for a thin smear, a haemoglobin assessment, and storage on filter paper for future molecular studies. Consecutive patients for whom a thick blood smear was

positive for malaria were referred to study physicians for a standard baseline history and physical examination. Selection criteria were age 6 months or older; raised temperature ($>37.5^{\circ}\text{C}$ axillary) or history of fever in the previous 24 h; no history of serious side-effects from study drugs; weight of more than 5 kg; no evidence of a concomitant febrile illness in addition to malaria; provision of written informed consent by patient or guardian; ability to participate in 28-day follow-up; no history of treatment with any antimalarial other than chloroquine in the past 2 weeks; no danger signs or evidence of severe malaria;¹⁵ mono-infection with *P falciparum*; and haemoglobin concentration of greater than 50 g/L.

Treatment

At the time of presentation (day 0), consecutive patients who met the selection criteria were randomly assigned to artemether-lumefantrine (Novartis, China) or to amodiaquine (Aventis, France) plus sulfadoxine-pyrimethamine (Roche, South Africa). Patients assigned to artemether-lumefantrine were given tablets containing 20 mg artemether and 120 mg lumefantrine twice daily

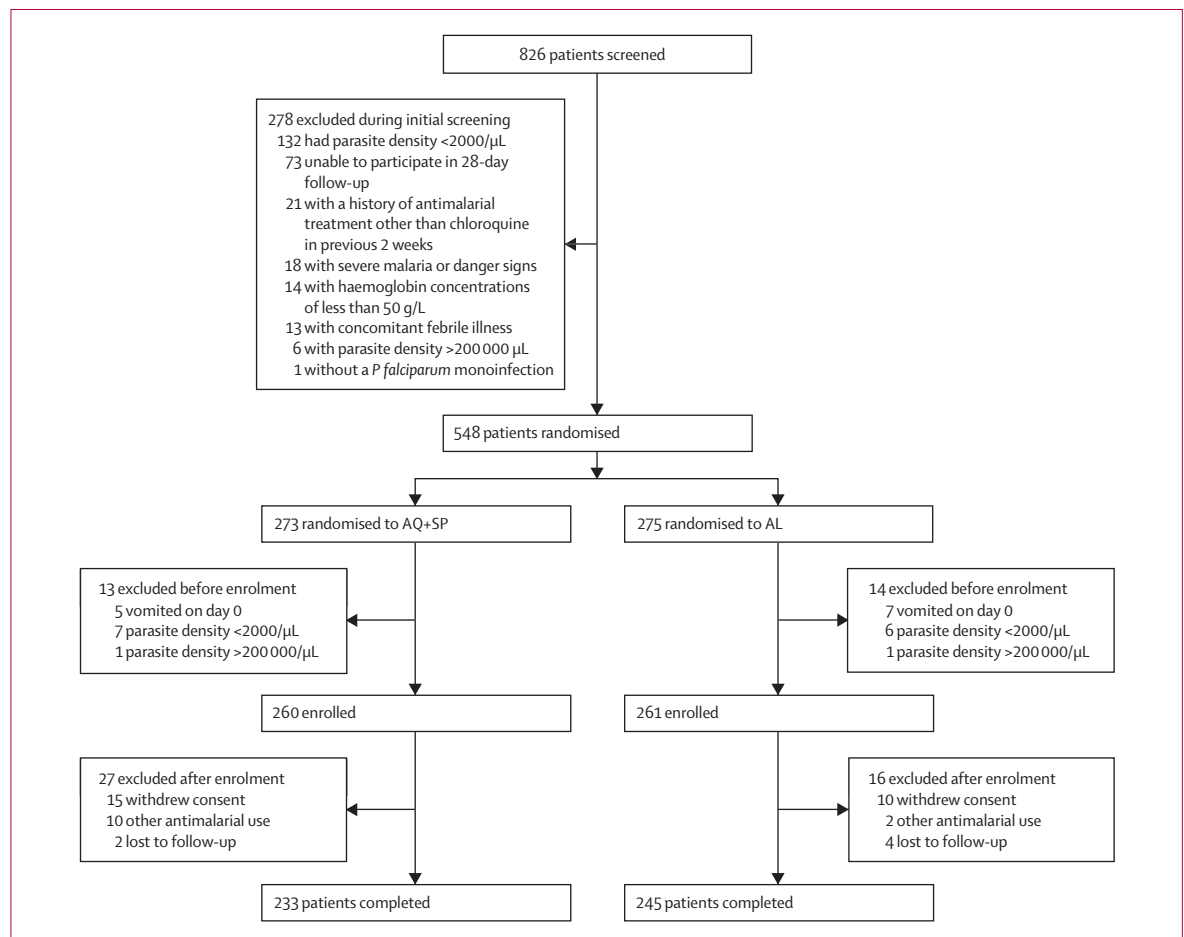


Figure 1: Trial Profile

AQ+SP=amodiaquine plus sulfadoxine-pyrimethamine. AL=artemether-lumefantrine.

for 3 days according to their weight: one tablet for patients weighing 5–14 kg, two for those weighing 15–24 kg, three for those weighing 25–34 kg, or four for those heavier than 35 kg. Patients assigned to the other group were given 200 mg tablets of amodiaquine (10 mg/kg on days 0 and 1, and 5 mg/kg on day 2) plus sulfadoxine-pyrimethamine (25 mg/kg of sulfadoxine and 1.25 mg/kg pyrimethamine, both on day 0). However, patients who repeatedly vomited the first dose of either treatment were excluded from enrolment and referred for appropriate care. Patients were also excluded at day 1 if parasite densities from screening of thick blood smears, which were not quantified until the day 1 visit, were less than 2000 parasites per μL or greater than 200 000/ μL .

Procedures

Nurses were responsible for treatment allocation, on the basis of computer-generated randomisation lists, which were stratified by the three clinic sites. These lists were provided by an off-site investigator who did not participate in administration of the trial. All doses were directly observed by investigators in the clinics or, for evening doses, in patients' homes. Food was not supplied with study drugs. Placebos, designed to simulate equal number of pills and doses in each treatment group, were given, but were not matched to the colour or taste of study drugs. Doses were readministered if patients vomited within 30 minutes of ingestion. Patients received a 3-day supply of paracetamol (10 mg/kg) for use every 8 h until the resolution of fever. Those with haemoglobin concentrations of less than 100 g/L were treated with ferrous sulphate according to WHO guidelines,¹⁶ and given anthelmintic treatments if they were older than 1 year and had not been treated in the previous 6 months. Investigators responsible for classification of treatment outcomes were unaware of treatment assignment. Patients were not informed of their treatment assignment. The study was approved by the institutional review boards of the University of California, San Francisco, USA and Centre Muraz, Bobo-Dioulasso.

Patients were asked to return to the clinic for follow-up on days 1, 2, 3, 7, 14, 21, 28, and on any unscheduled day that they felt ill. Those who did not return for scheduled follow-ups were visited at home on those days. Every visit included a standardised history and physical examination. Blood was obtained by finger prick on days 2, 3, 7, 14, 21, and 28, and on any unscheduled visit, to use for analysis of thick blood smears (for parasite density and gametocytes) and for storage on filter paper. Thin smears were examined for species of malaria parasites if clinical treatment failed after day 3. Haemoglobin concentrations were reassessed on day 28 or at the time of clinical treatment failure.

Patients were followed up for 28 days, and outcomes were assessed according to WHO guidelines for regions with intense malaria transmission: adequate clinical and parasitological response, early treatment failure, late

clinical failure, and late parasitological failure.¹⁵ Secondary outcomes were fever clearance, parasite clearance, change in haemoglobin concentration, presence of gametocytes, and adverse events. Patients in whom treatment failed were given quinine (10 mg/kg orally thrice daily for 7 days). Patients who developed severe malaria or danger signs¹⁵ were referred for treatment with parenteral quinine. Patients were excluded during follow-up if they had used antimalarial drugs outside the study; if they developed concomitant febrile illnesses that interfered with outcome assessment; if they withdrew informed consent; or if they could not be located within 24 h on days 1–3 or 48 h on days 4–28.

At every follow-up visit, adverse events (defined as any untoward medical occurrence) were assessed for severity and association with the drugs under study on the basis of guidelines from WHO and US National Institutes of Health.¹⁷ Serious adverse events were defined as death, life-threatening experience, hospital admission, persistent or clinically significant incapacity, or medical or surgical intervention to prevent serious outcomes.

Blood smears were stained with 2% Giemsa stain for 30 minutes. Thick blood smears were used to count asexual parasites per 200 white blood cells, and parasite densities were calculated on the basis of a presumed white blood cell density of 8000/ μL . A thick blood smear was regarded as negative for malaria if 100 high-power fields did not reveal parasites. Haemoglobin was measured from finger-prick blood samples with a portable spectrophotometer (HemoCue, Ängelholm, Sweden).

For episodes of recurrent parasitaemia more than 3 days after the initiation of treatment, DNA was isolated from filter-paper blood samples with chelex resin (Chelex X-100, Biorad Laboratories, Hercules, CA, USA).¹⁸ Paired samples from every patient, taken at initial enrolment and at time of recurrence, were genotyped in a stepwise fashion on the basis of polymorphisms in the genes for the merozoite surface proteins *m*sp-2 and *m*sp-1 and four microsatellites.¹⁹ If no alleles matched at any of the six loci between day 0 and day of recurrence, the infection was classified as new. If any allele was in common at each of the six loci, the infection was classified as a recrudescence.

To assess the effects of treatment on parasite mutations that might modulate treatment responses, we measured the prevalence of molecular markers associated with decreased sensitivity to amodiaquine, sulfadoxine-pyrimethamine, and lumefantrine. Mutations in the parasitic genes for dihydrofolate reductase (*dhfr*) and dihydropteroyl synthetase (*dhps*) mediate resistance to sulfadoxine-pyrimethamine;⁹ mutations in *Plasmodium falciparum* chloroquine resistance transporter (*pfcr*t) and *Pfalciparum* multidrug resistance (*pfmdr*1) mediate resistance to amodiaquine;^{10–12} and mutations in *pfmdr*1 affect sensitivity to halofantrine, and probably the related compound lumefantrine.¹³ We assessed the frequency of these mutations

in a random selection of 50 samples obtained before treatment, and in all samples from episodes of recurrent parasitaemia. The polymorphisms studied were *dhfr* N51I, C59R, and S108N; *dhps* A437G and K540E; *pfprt* K76T; and *pfmdr1* N86Y, Y184F, S1034C, and D1246Y. All mutations were identified with nested PCR, and then restriction enzyme digestion, as previously described.^{20,21} Digestion products were resolved by gel electrophoresis, and samples were classified as wild-type, pure mutant, or mixed. Investigators analysing these samples were not aware of the treatment group or outcome for each patient.

Statistical analysis

We designed a non-inferiority study to test the hypothesis that the risk of recurrent parasitaemia was not significantly worse with artemether-lumefantrine than with amodiaquine plus sulfadoxine-pyrimethamine. On the basis of an estimated risk of recurrent parasitaemia with amodiaquine plus sulfadoxine-pyrimethamine of 4%,⁷ an assumption of 10% loss of follow-up, and an expected difference in risk of recurrent parasitaemia between treatment arms of no greater than 3%, we calculated that 260 patients were needed in each treatment arm (80% power, two-sided type I error of 5%). Data were entered and verified with EpiInfo version 6.04 and analysed with SPSS version 12.0 and Stata version 8.0. Efficacy data were assessed with a per-protocol analysis that included all patients who completed the study. Primary outcomes included 28-day risks for recurrent malaria (early treatment failure or late clinical failure) and recurrent parasitaemia (early treatment failure, late clinical failure, or late parasitological failure). Primary outcomes were both adjusted by genotyping to distinguish recrudescence from new infection and unadjusted; all early treatment failures were classified as recrudescence. Risks of treatment failure (adjusted by genotyping) were estimated with the Kaplan-Meier product limit formula with censoring for patients with new infections. Other categorical variables were

compared with χ^2 or Fisher's exact test. A p value of less than 0.05 was regarded as statistically significant.

This study has been registered at controlled-trials.gov as ISRCTN54261005.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows that of the patients randomly assigned to a treatment group, 27 (5%) were excluded from enrolment either because they vomited their first dose of treatment twice or they had parasitaemias with densities that were outside of the inclusion criteria. Therefore, 521 patients were enrolled in the study. After 28 days of follow-up, 478 enrolled patients (92%) completed the study (figure 1). Table 1 shows the baseline characteristics of these study participants.

Table 2 shows results for 28-day treatment outcomes. Only one early treatment failure was seen: a child given amodiaquine plus sulfadoxine-pyrimethamine who failed on day 1 because of anaemia (haemoglobin concentrations fell from 60 to 34 g/L) despite diminished parasitaemia (100 285/ μ L to 24 653/ μ L). Recurrent symptomatic malaria and recurrent parasitaemia were more common with artemether-lumefantrine than with amodiaquine plus sulfadoxine-pyrimethamine (risk differences [RD] 8.5%; 95% CI 4.3–12.6; $p=0.0001$ and 10.4%; 5.1–15.6; $p=0.0002$, respectively). Differences in the risks of recurrent parasitaemia between the treatment groups were greater in patients younger than 5 years (26/145 [17.9%] vs 4/111 [3.5%]; 14.4%; 7.3–21.4%; $p<0.0001$) compared with patients 5 years and older (11/100 [11.0%] vs 7/122 [5.7%]; 5.3%; –2.1 to 12.7%; $p=0.16$). Genotyping using two polymorphic genes (*msh-2* and *msh-1*) and four microsatellites showed that nearly all recurrences were due to new infections, rather than recrudescence. The risk of recrudescence did not differ significantly between the treatment groups (table 2). The recrudescences included one patient given amodiaquine plus sulfadoxine-pyrimethamine who had early treatment failure, and three late clinical failures and one late parasitological failure after treatment with artemether-lumefantrine.

Table 3 shows secondary outcomes. Clearance of fever was more rapid in patients given amodiaquine plus sulfadoxine-pyrimethamine than in the other treatment group. 1 day after the initiation of treatment, 34/260 (13%) of patients given amodiaquine plus sulfadoxine-pyrimethamine and 66/261 (25%) of those given artemether-lumefantrine remained febrile (RD 12%; 6–19; $p=0.0004$; figure 2). By day 2, nearly all fevers had resolved, and the two regimens did not differ in prevalence of fever ($p=0.32$). Parasites were cleared more

	Treatment group	
	AQ+SP (n=260)	AL (n=261)
Study site		
Colsama	78 (30%)	77 (29%)
Ouezzinville	119 (46%)	119 (46%)
Sarfalao	63 (24%)	65 (25%)
Female (%)	142 (55%)	134 (51%)
Age in years [% under 5]*	5.0 (2.6–10)[48%]	4.0 (2.0–7.0) [59%]
Temperature (°C)†	38.5 (0.9)	38.6 (0.9)
Parasite density (per μ L)‡	27 237 (2050–199 980)	27 689 (2000–200 000)
Haemoglobin (g/L)†	99 (23)	93 (23)
Chloroquine use in previous 2 weeks (%)	27 (10%)	24 (9.2%)

AQ+SP=amodiaquine plus sulfadoxine-pyrimethamine. AL=artemether-lumefantrine. Data are number (%), unless otherwise indicated. *Median (IQR) †Mean (SD). ‡Geometric mean (SD).

Table 1: Baseline characteristics of enrolled patients

	AQ+SP (n=260)	AL (n=261)	RD (95% CI)	p value
WHO treatment outcomes for patients completing follow-up				
Early treatment failure (ETF)	1	0
Late clinical failure (LCF)	3	25
Due to recrudescence	0	3
Due to new infection	3	22
Late parasitological failure (LCF)	7	12
Due to recrudescence	0	1
Due to new infection	7	11
Adequate clinical and parasitological response	222	208
Comparative results				
Recurrent malaria PCR unadjusted*	4/233 (1.7%)	25/245 (10.2%)	8.5% (4.3% to 12.6%)	0.0001
Recurrent malaria PCR adjusted†	0.4%¶	1.2%¶	0.8% (-0.8% to 2.4%)	0.62
Recurrent parasitaemia PCR unadjusted‡	11/233 (4.7%)	37/245 (15.1%)	10.4% (5.1% to 15.6%)	0.0002
Recurrent parasitaemia PCR adjusted§	0.4%¶	1.6%¶	1.2% (-0.6% to 3.0%)	0.37

AQ+SP=amodiaquine plus sulfadoxine-pyrimethamine. AL=artemether-lumefantrine. RD=risk difference. *ETF or LCF. †Any ETF or LCF due to recrudescence. ‡ETF, LCF, or LPF. §Any ETF, LCF or LPF due to recrudescence. ¶Adjusted values were estimated with the Kaplan-Meier product limit formula, and therefore actual numbers cannot be provided. 27 (10%) in AQ+SP and 16 (6%) in AL groups were excluded after enrolment; 233 (90%) and 245 (94%), respectively, completed follow-up.

Table 2: Primary treatment outcomes

often by day 2 with artemether-lumefantrine than with amodiaquine plus sulfadoxine-pyrimethamine. By day 3 parasites had cleared in more than 96% of patients in both treatment groups. Haemoglobin concentrations improved equally in both groups during the 28 days after treatment. Gametocytaemia was rare; gametocytes were detected during follow-up in seven of 261 patients (3%) given amodiaquine plus sulfadoxine-pyrimethamine and none in the other group ($p=0.007$).

Adverse events did not differ between treatment groups, apart from pruritus, which was more common with amodiaquine plus sulfadoxine-pyrimethamine 44/260 (16%) than with artemether-lumefantrine 7/261 (3%, $p<0.0001$). Serious adverse events were seen in two patients: both had drops in haemoglobin below 50 g/L. In one of these patients, early treatment failure happened after amodiaquine plus sulfadoxine-pyrimethamine, and the other had late clinical failure after artemether-lumefantrine.

Figure 3 shows the prevalence of relevant mutations (*dhfr* N51I, C59R, and S108N; *dhps* A437G and K540E; *pfprt* K76T; and *pfmdr1* N86Y, Y184F, S1034C, and D1246Y) in a random sample of 50 patients at baseline and in all isolates obtained at presentation with new infections after treatment. For patients assigned to receive amodiaquine plus sulfadoxine-pyrimethamine, new isolates after treatment had significantly higher prevalences of *pfprt* 76T, which is associated with resistance to chloroquine;²² *pfmdr1* 86Y and 184F, which are associated with altered sensitivity to several antimalarial agents;¹³ and mutations in *dhfr* that are associated with resistance to sulfadoxine-pyrimethamine.⁹ For patients given artemether-lumefantrine, new isolates had decreased prevalence of *pfmdr1* 86Y, which shows a reversion to wild-type as seen previously with use of

artemether-lumefantrine.^{23,24} The *dhps* 540E and *pfmdr1* 1034C mutations were not seen in any isolates; for *pfmdr1* 1246Y, no pure mutants were detected, but mixed genotypes were seen in 14% of pretreatment samples,

	Treatment group		p value
	AQ+SP (n=260)	AL (n=261)	
Parasite clearance			
Parasitaemia on day 2 (%)	68 (27%)	12 (4.6%)	<0.0001
Parasitaemia on day 3 (%)	9 (4%)	4 (1.6%)	0.15
Gametocytes on			
Day 0 (%)	1 (0%)	0%	0.50
Day 2 (%)	2 (1%)	0%	0.24
Day 3 (%)	3 (1%)	0%	0.12
Day 7 (%)	3 (1%)	0%	0.12
Day 14 (%)	2 (1%)	0%	0.24
Day 21 (%)	0%	0%	1.0
Day 28 (%)	1 (0%)	0%	1.0
Increase in haemoglobin (g/L)	10.1 (2)	11.8 (1.9)	0.36
Adverse events of any severity (%)			
Cough	42 (16%)	57 (22%)	0.08
Pruritus	42 (16%)	7 (2.7%)	<0.0001
Coryza	20 (8%)	25 (9.6%)	0.44
Vomiting	19 (7%)	16 (6.1%)	0.59
Abdominal pain	18 (7%)	11 (4.2%)	0.13
Anorexia	17 (7%)	16 (6.1%)	0.85
Headache	14 (5%)	10 (3.8%)	0.40
Weakness	7 (3%)	10 (3.8%)	0.46
Diarrhoea	5 (2%)	11 (4.2%)	0.13
Patients with serious adverse events (%)	1 (0%)	1 (0.4%)	1.0

AQ+SP=amodiaquine plus sulfadoxine-pyrimethamine. AL=artemether-lumefantrine. Data are number (%) or mean (SD).

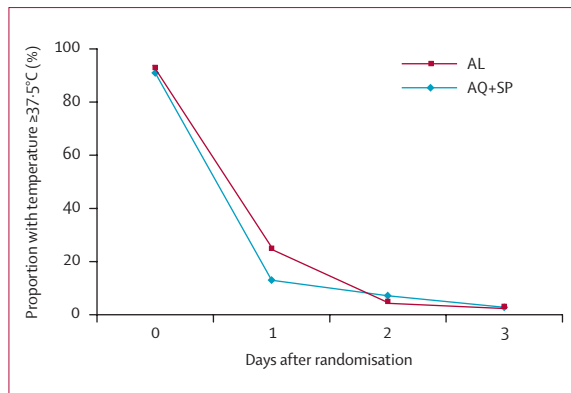


Figure 2: Fever clearance during the first 3 days of follow-up
AQ+SP=amodiaquine plus sulfadoxine-pyrimethamine. AL=artemether-lumefantrine.

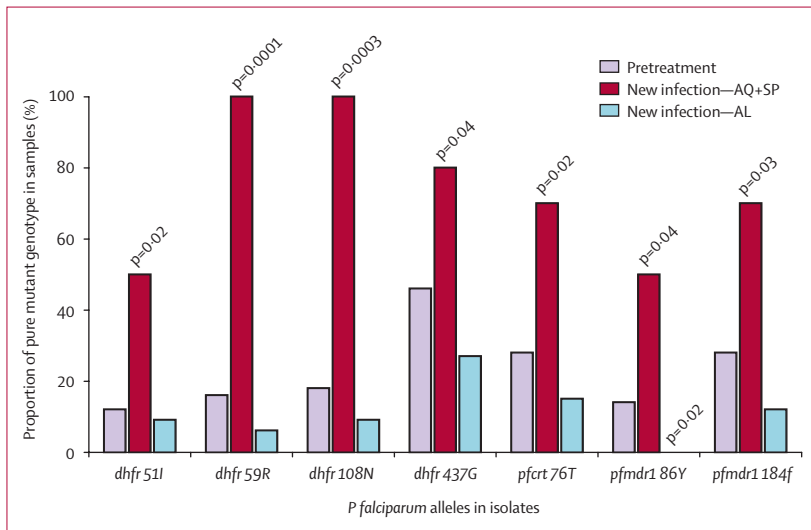


Figure 3: Prevalence of pure mutant genotypes in pretreatment samples and samples from subsequent new infections

AQ+SP=amodiaquine plus sulfadoxine-pyrimethamine. AL=artemether-lumefantrine. DHFR=dihydrofolate-reductase. DHPS=dihydropteroate-synthase. PFCRT=*P falciparum* chloroquine resistance transporter. PFMDR1=*P falciparum* multidrug resistance 1. P values are shown for statistically significant difference.

10% of new infections after amodiaquine plus sulfadoxine-pyrimethamine, and 6% of new infections after artemether-lumefantrine.

Discussion

We have shown that both artemether-lumefantrine and amodiaquine plus sulfadoxine-pyrimethamine were effective for clearance of uncomplicated malaria infections. However, in high transmission settings characteristic of much of sub-Saharan Africa, effects of therapy on subsequent infections should also be considered. Indeed, recurrent illnesses due to recrudescence and those caused by new infections are generally clinically indistinguishable.⁸ Therefore, the effects of treatment on the overall risk of subsequent recurrent malaria might be regarded as the most important outcome for comparison between potential antimalarial regimens. Amodiaquine

plus sulfadoxine-pyrimethamine was more effective for reduction of the overall incidence of malaria after treatment than was artemether-lumefantrine, with significantly lower risks of recurrent symptomatic malaria and parasitaemia.

Artemisinin offer potent antimalarial activity but short-course monotherapy is often followed by recrudescence, which necessitates combination with long-acting agents. Artemisinin-based combination regimens have been proven to clear parasites for 28 or more days of follow-up.² In Africa, the six-dose regimen of artemether-lumefantrine that is now standard consistently clears more than 90% of malaria infections over 28 days.²⁵⁻²⁷ However, artemisinin-based regimens offer little protection against recurrent malaria infections after treatment. Thus, in a very high transmission region of Uganda, treatment with artemether-lumefantrine or artesunate and amodiaquine was followed by recurrent parasitaemia within 28 days in 51% and 66% of patients, respectively.²⁸

Of non-artemisinin combination regimens, amodiaquine plus sulfadoxine-pyrimethamine has shown excellent antimalarial efficacy in most African studies, even in those from regions, such as east Africa, where levels of resistance to each component drug are high.^{29,30} In several comparative trials, amodiaquine plus sulfadoxine-pyrimethamine offered similar or better efficacy than that of artemisinin-based combinations.^{27,31,32} Amodiaquine plus sulfadoxine-pyrimethamine was more efficacious than artesunate and sulfadoxine-pyrimethamine in Uganda and Rwanda in east Africa because of decreased rates of recrudescence.^{31,32} The efficacy of this combination was also greater than that of artesunate and amodiaquine in Uganda because of decreased rates of new infection.²⁷ In one trial in coastal Tanzania, amodiaquine plus sulfadoxine-pyrimethamine was less effective than either artemether-lumefantrine or artesunate and amodiaquine, perhaps because of unusually high resistance to both component drugs in that region.²⁸ Amodiaquine plus sulfadoxine-pyrimethamine might be especially useful in west Africa, where resistance to both amodiaquine and sulfadoxine-pyrimethamine is low. This combination treatment had more than 94% efficacy against uncomplicated malaria in Nigeria,³³ Ghana,⁶ and Burkina Faso.⁷

Our study shows that, in Burkina Faso, the efficacy of treatment with amodiaquine plus sulfadoxine-pyrimethamine was equal to that of artemether-lumefantrine in clearance of infections; with the exception of one early treatment failure due to progressive anaemia, no recrudescences were seen after 260 treatments. The efficacy of amodiaquine plus sulfadoxine-pyrimethamine was greater than that of artemether-lumefantrine for prevention of recurrent symptomatic malaria or parasitaemia during the month after treatment. Additionally, fever was cleared faster in patients given amodiaquine plus sulfadoxine-pyrimethamine than in those given artemether-lumefantrine, which was probably because of the antipyretic properties of 4-aminoquinolines.

Any benefit of a long-acting drug might be offset by selection for a population of parasites that are resistant to important antimalarial agents. Use of the drug could therefore lead to a higher incidence of complicated malaria. Therefore, antimalarial regimens should be chosen, in part, on the basis of their potential effects on the selection of drug-resistant parasites. Mutations in *dhfr* and *dhps* mediate resistance to sulfadoxine-pyrimethamine,⁹ mutations in *pfcr* and *pfmdr1* mediate resistance to amodiaquine,^{10–12} and mutations in *pfmdr1* affect sensitivity to halofantrine, and probably the related compound lumefantrine.¹³ The drugs trialled in our study showed the expected selective pressure (figure 3); amodiaquine plus sulfadoxine-pyrimethamine selected for *dhfr*, *dhps*, *pfcr*, and *pfmdr1* mutations associated with resistance. Artemether-lumefantrine selected for the *pfmdr1* N86 allele, which (although classified as wild-type) might be associated with diminished in-vitro responsiveness to halofantrine.³⁴ Thus, both amodiaquine plus sulfadoxine-pyrimethamine and artemether-lumefantrine probably select for parasites with diminished drug sensitivity. However, the clinical relevance of these findings is uncertain. In particular, we do not know whether amodiaquine plus sulfadoxine-pyrimethamine will be effective against parasites that are resistant to sulfadoxine-pyrimethamine, but that do not have high-level resistance mediated by mutations (eg, *I164L*) that are rarely seen in Africa. Indeed, the protective action of amodiaquine plus sulfadoxine-pyrimethamine against new infections after treatment,^{6,8,31} and the benefits of sulfadoxine-pyrimethamine as intermittent preventive treatment³⁵ in east Africa, suggest that amodiaquine plus sulfadoxine-pyrimethamine will continue to be effective in west Africa, where resistance to both drugs is low, and where the *dhps* 540E mutation, which has a key role in mediation of resistance to sulfadoxine-pyrimethamine,³⁶ remains rare.³⁷

Both amodiaquine and sulfadoxine-pyrimethamine have been associated with severe toxic effects when used chronically,³⁸ but seem well tolerated for short-term antimalarial treatment. Both our study regimens were well tolerated; only pruritus, which is a well known consequence of aminoquinoline treatment, was more common with amodiaquine plus sulfadoxine-pyrimethamine. Serious adverse events were rare. However, cost limitations prevented full haematological or biochemical analysis, and the frequency of sub-clinical toxic effects caused by the study drugs is unknown.

How should efficacy data inform the treatment of malaria in Africa? Unless unforeseen difficulties develop, the introduction of artemisinin-based regimens for the treatment of malaria in regions with resistance to other available drugs will remain an urgent goal. However, since new treatment goals have not been fully implemented, serious consideration of alternative treatments is warranted. WHO recommendations list four artemisinin-based regimens as first-line treatments for malaria:

artesunate-mefloquine, which is unaffordable in Africa, artesunate plus sulfadoxine-pyrimethamine, which has not done well in comparative trials,^{31,32} and the two regimens that have been adopted by most African countries: artemether-lumefantrine and artesunate with amodiaquine. Treatment with amodiaquine plus sulfadoxine-pyrimethamine has proved more effective than artesunate and amodiaquine in high-transmission regions of east Africa,⁸ and in our study amodiaquine plus sulfadoxine-pyrimethamine showed better efficacy than artemether-lumefantrine in west Africa. In both studies, this regimen was best at prevention of new infections.

Amodiaquine plus sulfadoxine-pyrimethamine is advocated by WHO only for circumstances in which artemisinin-based combination regimens are unavailable. We suggest that the proven efficacy of amodiaquine plus sulfadoxine-pyrimethamine in west Africa, together with its lower cost and greater availability, make it a viable first-line treatment for uncomplicated malaria in west Africa. We believe that ineffective antimalarial monotherapies should be abandoned immediately, and, in the absence of adequate supplies and distribution of artemisinin combinations, this goal will most readily be achieved by replacement of monotherapies with amodiaquine plus sulfadoxine-pyrimethamine.

Contributors

I Zongo, N Rouamba, R T Guiguemde, H Tinto, and J Ouedraogo contributed to the design and coordination of the study, supervised the enrolment and follow-up of patients, assisted with data entry and interpretation, and prepared the manuscript. G Dorsey, C Dokomajilar, and P Rosenthal contributed to the design of the study, participated in analysis and interpretation of data, and participated in the preparation of the manuscript. All authors have seen and approved the final version.

Conflict of interest statement

We declare that we have no conflict of interest

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