Supervised versus unsupervised intake of six-dose artemether-lumefantrine for treatment of acute, uncomplicated Plasmodium falciparum malaria in Mbarara, Uganda: a randomised trial.

Supervised versus unsupervised intake of six-dose artemether-lumefantrine for treatment of acute, uncomplicated *Plasmodium falciparum* malaria in Mbarara, Uganda: a randomised trial

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Summary

Background **The six-dose regimen of artemether-lumefantrine is effective and is among combination therapies prioritised to replace antimalarials that no longer work in Africa. However, its effectiveness has not been assessed in the field, and could be compromised by poor adherence, incorrect timing of doses, and insufficient intake of fatty foods with every dose. Our aim, therefore, was to assess the effectiveness of artemether-lumefantrine prescribed under routine outpatient conditions, compared with its efficacy when given under supervision to inpatients with acute uncomplicated falciparum malaria.**

Methods **We did a randomised trial to compare the efficacy, safety, and pharmacokinetics of artemether-lumefantrine when given in a supervised (all doses observed with fatty-food intake; n=313) or unsupervised (first dose supervised followed by outpatient treatment with nutritional advice; n=644) setting to patients of all ages (weight >10 kg) with acute, uncomplicated falciparum malaria in Mbarara, Uganda. Our primary endpoint was 28-day, PCR-adjusted, parasitological cure rate. Analysis was by intention to treat and evaluability analysis.**

Findings **38 patients were lost to follow-up and one withdrew consent. Day-28 cure rates were 97.7% (296 of 303) and 98.0% (603 of 615) in the supervised and unsupervised groups, respectively. We recorded 15 non-severe, drug-related adverse events, all of which resolved.**

Interpretation **Artemether-lumefantrine has a high cure rate irrespective of whether given under supervision with food or under conditions of routine clinic practice. If used as first-line treatment, artemether-lumefantrine could make a substantial contribution to malaria control in Africa, though cost is an issue.**

Introduction

With an estimated 500 million individuals affected every year, malaria is a leading cause of morbidity and mortality in sub-Saharan Africa along with HIV/AIDS.[1] Of the 1 million deaths caused by malaria worldwide, about 90% occur in African children, a situation compounded by the emergence of drug resistance.[2]

In Uganda, which had a population of 24·7 million in 2003, an estimated 9·8 million individuals are infected with malaria every year (John Bosco Rwakimari, Ugandan Ministry of Health, Uganda, personal communication; http://www.health.go.ug). To tackle malaria-related mortality and morbidity, the Ugandan Ministry of Health (MoH) is concentrating on early diagnosis and effective treatment of the disease. In the 1970s and the 1980s, high malaria awareness in the population and easy access to cheap and effective antimalarials such as chloroquine and sulfadoxine-pyrimethamine ensured the disease was reasonably well controlled. However, resistance to these drugs is now widespread in Uganda and in other parts of east Africa, with adverse consequences for malaria control.[3–7]

The MoH-recommended first-line antimalarial drug in Uganda is chloroquine combined with sulfadoxine-pyrimethamine,[6] though introduction of artemisinin-based combination treatments (ACTs) is planned for 2005.[8] Day-28 cure rates of 52%,[9] 65%,[7] and 77%[10] have been reported for this combination in different parts of Uganda. ACTs are judged effective in Africa, where they improve cure rates and reduce gametocyte carriage compared with presently used monotherapies.[11,12] To combat drug-resistant malaria in Africa, WHO advocates the adoption of ACTs as first-line treatment.[2] The use of the non-ACT combination of amodiaquine and sulfadoxine-pyrimethamine is considered by some as an interim measure while waiting for ACTs to become widely available. Day-28 efficacy rates of this combination were 84% and 90% in two studies in Uganda.[7,9]

Artemether-lumefantrine (Coartem, Novartis Pharma, Basel, Switzerland) is the only fixed-dose formulation ACT on the WHO essential drug list. However, the combination is not registered for use in pregnant women, and was not registered for children under 10 kg in weight when we did our trial. Results of studies[13–15] from southeast Asia show that the six-dose regimen of artemether-lumefantrine has cure rates of more than 96%, is well tolerated, and has a good safety profile when

given under supervision. However, a study[16] of the four-dose regimen done in Thailand resulted in a cure rate of only 83%. There are limited data on use of the six-dose regimen in Africa, though supervised administration of the combination had a 99% cure rate when assessed at day 14 in Burundian children.[17] Day-14 efficacy of the four-dose regimen was good in the Gambia (93%),[18] but modest in Tanzania (86%).[19]

Several factors could reduce considerably the effectiveness of artemether-lumefantrine under field conditions in Africa. Adherence to the complicated, twice-daily, three-day regimen might be suboptimum. To increase lumefantrine absorption, all doses should be correctly spaced and taken with food. The manufacturer recommends an interval of 8 h between the first and the second dose, 24 h between the first and the third dose, and 12 hourly intervals between doses thereafter. Lumefantrine absorption is greatly increased when taken with food, especially fatty foods. Plasma concentrations of the drug are low after initial doses, when patients are typically anorexic; levels increase in parallel with improved appetite.[20,21] The day-7 plasma concentration of lumefantrine is a predictor of therapeutic response. Concentrations of less than 280 μg/L were associated with an increased risk of treatment failure in Thailand.[22] This concentration is judged to be the in-vivo minimum inhibitory concentration for multidrug-resistant falciparum parasites.[23] Artemether-lumefantrine is expensive, with the WHO negotiated price ranging from US$0·9 in the smallest children to $2·40 for an adult course. This high cost could deter African Ministries of Health from recommending artemether-lumefantrine in the absence of donor funds.

In Mbarara, southwestern Uganda, the efficacies of chloroquine and sulfadoxine-pyrimethamine are low.[24] Furthermore, 3 days of treatment with artesunate plus sulfadoxine-pyrimethamine yield a day-28, PCR-corrected cure rate of only 74%.[25] A new treatment option is needed. Our aim, therefore, was to assess the effectiveness of artemether-lumefantrine prescribed under routine outpatient conditions, compared with the efficacy of the combination given under supervision to inpatients with acute uncomplicated falciparum malaria.

Methods

Participants

Between December, 2002, and January, 2004, we did an open-label, randomised trial at the Mbarara University Teaching Hospital, which is the regional referral hospital for the western region of Uganda. Mbarara town (population of about 69 000 in 2002) is in western Uganda, an area of perennial malaria transmission where the disease has two seasonal peaks that coincide with the rainy seasons (March–June and September–December). *Plasmodium falciparum* is the predominant species (95%, unpublished data) and is resistant to chloroquine and sulfadoxine-pyrimethamine.[24]

Potential participants were referred from the hospital outpatient clinic and local municipality dispensaries to the Epicentre clinic. Our inclusion criteria were: fever in the previous 24 h or confirmed fever (axillary temperature >37·5ºC); weight of 10 kg or more; monoinfection with *P falciparum*, parasitaemia of 500–100 000 trophozoites/μL, no danger signs (unable to drink or feed, repeated vomiting, convulsions during the present illness, lethargic or unconscious state, unable to sit or stand), and no signs of severe malaria;[26] no other clinically significant illnesses; not pregnant (confirmed by history and a negative urinary pregnancy test); and residence in Mbarara Municipality.

All patients or their guardians provided written informed consent. We wrote the study protocol following the principles of the Declaration of Helsinki, and it was approved by three ethics committees: the Mbarara Faculty of Medicine, the Mbarara University of Science and Technology, and the Uganda National Committee for Science and Technology.

Procedures

We stratified arbitrarily the study population so as to compare the efficacy of supervised and unsupervised treatment in three age groups: children younger than age 5 years; children aged 5–14 years; and patients aged 15 years or older. We used these age groups as surrogate markers of malaria-acquired immunity and possible adherence patterns.

After inclusion, we randomly assigned participants to receive either supervised or unsupervised artemether-lumefantrine, according to a computer-generated randomisation list designed in blocks of five. We used a one-to-one, a one-to-two, and a one-to-four (supervised-to-unsupervised) randomisation schedule for children aged younger than 5 years, those aged 5–14 years, and for patients aged 15 years or older, respectively. We randomly assigned patients in an unequal way in the different age groups to reduce to a minimum the time that patients would be away from school or work.

Treatment allocation was concealed. Every inclusion number corresponded to a sealed envelope, containing a card with the treatment allocation ("supervised" or "unsupervised") written on it. We prescribed artemether-lumefantrine in its blister pack. Tablets contained 20 mg of artemether and 120 mg of lumefantrine. The packs have in them pictures to show how tablets should be given, and contain two blisters for every day, containing one, two, three, or four tablets dependent on the weight group. The regimen consisted of one (10–14·9 kg), two (15–24·9 kg), three (25–34·9 kg), or four (>35 kg) tablets twice daily for 3 days. Tablets were crushed in water for young children unable to swallow them whole.

We admitted patients assigned to the supervised group to an observation ward for the duration of treatment. All doses were administered by a study nurse, and a fatty meal composed of about 300 mL of milk (10 g fat) and

30 g of peanuts (13 g fat) was given either before or just after drug administration. If the patient with malaria was being breastfed, mothers were encouraged to continue nursing. We administered doses at the times recommended by the manufacturer: 0 h, 8 h, 24 h, 36 h, 48 h, and 60 h. We repeated doses if patients vomited within 30 min of administration. Any prescribed concomitant drugs—eg, paracetamol—were administered and recorded. We gave patients in the unsupervised group their first dose at the clinic, observed them for vomiting, and then discharged them with their blister pack. We advised patients or their parents to combine the treatment with fatty meals or breastmilk. We emphasised the need to administer the second dose exactly 8 h after the first supervised dose.

We followed up patients for 28 days, according to a schedule of visits on days 3, 7, 14, 21, and 28 for clinical assessments and laboratory tests. We also saw and assessed the supervised patients daily for the first 3 days. At every visit, we prepared and read 3% Giemsa stained thick and thin smears to establish species (thin smear), quantify asexual parasitaemia (per μL), and detect gametocytaemia (number per 1000 white cells on a thick smear), according to WHO standard methods. We judged a slide negative after examination of 200 high-power fields. We collected capillary blood on Isocode kits (Schleicher and Schuell, Dassel, Germany) before treatment (day 0) and on the day of recurrent parasitaemia (in case this arose after day 3) for PCR genotyping. We distinguished reinfections from recrudescences by comparing the pretreatment and post-treatment genotypes of the *P falciparum* gene loci coding for the merozoite surface proteins 1 and 2 (MSP-1 and MSP-2) and the glutamate rich protein (GLURP).[27] We measured concentration of haemoglobin (capillary blood) with a Hemocue B-Hemoglobin apparatus (Hemocue, Angelholm, Sweden) on days 0 and 28.

We encouraged patients and their guardians to return to the clinic at any time if their health or that of their children deteriorated. Individuals who did not return for scheduled follow-up visits were traced the same day. Patients for whom artemether-lumefantrine was ineffective or who vomited persistently after treatment received rescue treatment with quinine hydrochloride (10 mg per kg every 8 h for 7 days).

Our primary endpoint was cure at 28 days. We considered the reasons some patients were not cured as either: parasitological in the case of PCR-confirmed recrudescent parasitaemia after day 3 (we recorded patients with indeterminate or missing PCR results as not having been cured, and patients reinfected as cured); or non-parasitological if the patient had taken any drugs with antimalarial activity during follow-up (other than rescue treatment), if treatment with artemether-lumefantrine had been interrupted because of an adverse event, or if a serious adverse event during follow-up arose, irrespective of whether there was an association with the study drug. Our secondary endpoints were the proportion of afebrile patients on days 1, 2, and 3, post-treatment gametocyte carriage, and haematological recovery.

To explore a possible relation between lumefantrine concentrations and treatment failure, we took whole venous blood (4 mL) on days 3 and 7 from 70 patients in every treatment and age group. Patients were selected by simple random sampling with a computer-generated random-sampling list. We froze the serum at –80°C before shipping it to the Bioanalytics and Pharmacokinetics department of Novartis Pharma (Rueil Malmaison, France). Lumefantrine concentrations were ascertained by high performance liquid chromatography, according to a previously published method (minimum detectable lumefantrine concentration of 5 μg/L, within-day and day-to-day coefficients of variation of 1·8–4·0 and 1·8–4·2%, respectively),[28] and blinded to patients' endpoints.

During follow-up, we assessed patients clinically for the presence of adverse events (or any untoward medical occurrence from day 0 to day 28 in a participant who took at least one dose of artemether-lumefantrine) and serious adverse events, defined as an adverse event that was fatal, life threatening, permanently disabling, led to admission to hospital for treatment, or caused a congenital abnormality. We grouped adverse events and graded them by intensity with the Common Toxic Criteria (National Cancer Institute), before ordering them into six drug-event relation categories: none, unlikely, possible, probable, definite, and unknown. We monitored all patients with adverse events until their health improved.

Statistical analysis

We assessed our primary endpoint and all secondary endpoints by a modified intention-to-treat analysis in which participants without an ascertained study outcome (because of missed study visit or withdrawal of consent) were excluded. By way of comparison, we also did an evaluability analysis. In the evaluability analysis of the primary endpoint, we also excluded patients who were not cured for reasons other than parasitological factors, and for whom PCR data were missing or reinfection arose. We also excluded from the evaluability analysis patients who did not meet all of our inclusion criteria, were randomised to the wrong group, did not take all doses correctly (supervised group only), had non-falciparum parasitaemia during follow-up, or received unwarranted rescue treatment.

Based on limited published work, we assumed a day-28 cure rate in the supervised group of 96% among those younger than age 5 years, and of 97% among older patients. For the unsupervised group we assumed a cure rate of 85% in all age groups. We calculated the sample size to show an 11% and a 12% difference in cure rates for children aged younger than 5 years and for older age groups, respectively. We assumed a type 1 error of 5%, a power of 80%, and a 10% drop-out rate. As such, the required sample sizes were (supervised-to-

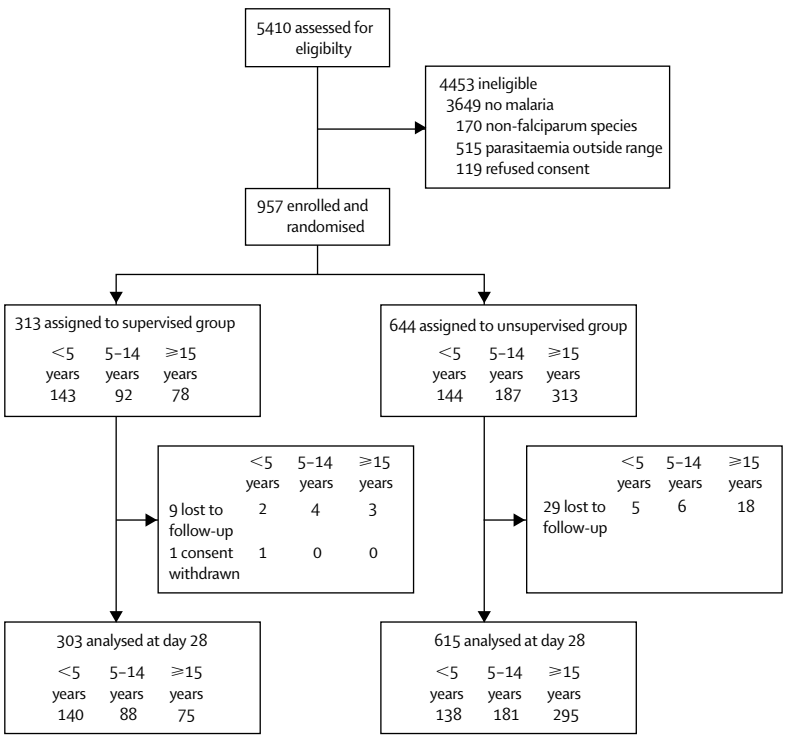

Figure: **Trial profile (intention-to-treat analysis)**

unsupervised): 141-to-141 (<5 years), 91-to-183 (5–14 years), and 78-to-312 (≥15 years).

We double-entered data with EpiData 3.0 software (EpiData Association, Odense, Denmark), and cleaned and analysed the data with Stata 8.2 (StataCorp, College Station, Texas, USA). We compared categorical variables with a χ^2 test. To compare continuous data between groups, we used the Mann-Whitney *U* test for the day 0 asexual parasite counts and lumefantrine concentrations (not normally distributed by Kurtosis test) and the unpaired *t* test for age, weight, temperature, and haemoglobin concentrations.

Role of the funding source

Médecins Sans Frontières (MSF) funded the project and participated in protocol development, but had no subsequent role in undertaking the study or in this publication. Novartis Pharma funded and did the pharmacokinetics analysis, but had no role in any other trial-related activity or this publication, and had no access to study data.

Results

The figure shows the trial profile. We screened 5410 patients for eligibility, of whom 957 (18%) were enrolled. Baseline characteristics were comparable across groups (table 1), with the exception of asexual

	<5 years		5–14 years		≥15 years	
	Supervised (n=143)	Unsupervised (n=144)	Supervised (n=92)	Unsupervised (n=187)	Supervised (n=78)	Unsupervised (n=313)
Age (years)	2·8 (1·5)	2·7 (1·0)	8·5 (2·8)	8·3 (2·8)	27·7 (10·4)	28·5 (11·1)
Male (number [%])	83 (58%)	80 (56%)	44 (48%)	86 (46%)	35 (45%)	126 (40%)
Female (number [%])	60 (42%)	64 (44%)	48 (52%)	101 (54%)	43 (55%)	187 (60%)
Weight (kg)	13·2 (3·4)	13·0 (2·5)	24·4 (7·2)	25·0 (7·9)	56·3 (9·1)	56·5 (9·3)
Haemoglobin (g/dL)	9·6 (1·9)	9·5 (1·9)	11·2 (1·7)	11·4 (1·6)	13·2 (1·9)	12·9 (2·0)
Temperature (°C)	37·4 (1·2)	37·5 (1·2)	37·3 (1·1)	37·0 (1·1)	36·7 (1·0)	36·6 (1·0)
Median (range) parasite density per µL	11 421 (125–140 278)	18 551 (350–130 521)	15 668 (676–94 205)	10 017 (597–128 264)	6250 (662–115 214)	5909 (394–97 657)
Splenomegaly (number [%])	49 (34%)	29 (20%)	27 (29%)	51 (27%)	10 (13%)	30 (10%)
Hepatomegaly (number [%])	8 (6%)	1 (1%)	4 (4%)	4 (2%)	0	8 (3%)
Gametocyte carriage (number [%])	19 (13%)	17 (12%)	3 (3%)	14 (8%)	1 (1%)	18 (6%)

Data are mean (SD) unless otherwise stated.

Table 1: **Baseline characteristics**

	Supervised				Unsupervised			
	<5 years	5-14 years	≥15 years	Total	<5 years	5-14 years	≥15 years	Total
No cure	5	2	0	7	4	6	2	12
Parasitological recrudescence	0	0	0	0	0	0	0	0
Recurrent parasites, no PCR result	1	1	0	2	1	2	1	4
Other antimalarial intake	2	1	0	3	2	3	1	6
AL interrupted by severe adverse event	2	0	0	2	1	1	0	2
Cure	135	86	75	296	135	175	293	603
Absence of parasites after day 3	130	85	74	289	122	169	291	582
Reinfection detected by PCR	5	1	1	7	13	6	2	21
Cure rate (%, 95% CI)	135 of 140 (96·4%, 91·4–98·7)	86 of 88 (97·7%, 91·2–99·6)	75 of 75 (100·0%, 93·9–100)	296 of 303 (97·7%, 95·1–99·0)	135 of 139 (97·1%, 92·3–99·1)	175 of 181 (96·7%, 92·6–98·6)	293 of 296 (99·0%, 96·8–99·7)	603 of 615 (98·0%, 96·5–98·9)

AL=artemether-lumefantrine.

Table 2: **Modified intention-to-treat analysis day-28 cure rates**

	<5 years		5–14 years		≥15 years	
	Supervised	Unsupervised	Supervised	Unsupervised	Supervised	Unsupervised
Day 3						
Number of patients	69	58	85	83	74	73
Mean (SD) concentration (μg/L)	7050 (3560)	4064 (3609)	6906 (3683)	4389 (3155)	5596 (2691)	4090 (3080)
Day 7						
Number of patients	68	59	85	83	74	73
Mean (SD) concentration (μg/L)	376 (217)	249 (245)	526 (556)	307 (208)	460 (288)	317 (190)
Number (%) below 280 μg/L	25 (37%)	42 (71%)	24 (28%)	47 (57%)	18 (24%)	33 (45%)

Table 3: **Mean lumefantrine concentrations on days 3 and 7**

parasitaemia in children younger than age 5 years. Day 0 gametocytaemia declined with increasing age. During follow-up, we withdrew 69 patients (7%) from the evaluability analysis, of whom: 19 did not meet all inclusion criteria, three were randomised in error, four interrupted treatment, seven had recurrent non-falciparum parasitaemia, nine took other antimalarials, 24 had a reinfection, and three had an indeterminate PCR result. 38 patients (4%) defaulted (two of these were among those withdrawn from the evaluability group) and one withdrew consent, leaving a sample of 918 (96%) for the intention-to-treat analysis and 851 (89%) for the evaluability analysis.

Cure rates were high with both forms of analysis. In the intention-to-treat analysis, the overall cure rates were 97·7% in the supervised group and 98·0% in the unsupervised group (table 2). In the evaluability analysis, the cure rate was 100% in both groups (95% CI 98–100 and 99–100 for supervised and unsupervised, respectively). None of the differences between treatment groups and age groups were significant ($p>0·20$ for all comparisons).

Of the 918 patients included in the intention-to-treat analysis, 296 (32%) had a fever on day 0. In the supervised group, 79% (92 of 116) and 100% (116 of 116) were afebrile on days 1 and 3, respectively. In the unsupervised group, these proportions were 97% (175 of 180) on day 3 and 100% on day 7. The proportion of patients with gametocytes declined from: 8% (69 of 918) on day 0 to 2% (17 of 898) on day 7 for the entire cohort; from 16% (35 of 279) to 4% (12 of 273) in children younger than age 5 years; from 6% (16 of 269) to 1% (two of 263) in children aged 5–14 years; and from 5% (18 of 370) to 1% (three of 362) in individuals aged 15 years or older. Only three (0·3%) patients (≥15 years) were still gametocytaemic on day 14 (two unsupervised, one supervised) and only one had gametocytes after day 14. By day 28, mean haemoglobin concentrations had increased in all age groups with no significant difference between the supervised and unsupervised patients (*t* tests for <5 years: p=0·53; for 5–14 years: p=0·98; and for ≥15 years: p=0·91). The mean (SD) fractional change was significantly higher in the two younger age groups compared with the adults ($p<0·0001$): 2·1 (1·70) g/dL (<5 years), 1·3 (1·64) g/dL (5–14 years), and 0·3 (1·58) g/dL (≥15 years).

We measured blood concentrations of lumefantrine in 228 supervised patients and in 214 unsupervised individuals. The mean lumefantrine concentrations (μg/L) were significantly lower ($p<0·0001$) on days 3 (4210 *vs* 6512) and 7 (319 *vs* 461) in the unsupervised versus supervised group; this pattern was seen for every age group (table 3). On day 7, all age groups had a significantly higher proportion of patients with lumefantrine concentrations of less than 280 μg/L in the unsupervised group than in the supervised group (table 3). Detailed findings on predictors of lumefantrine concentration, and on the effect on varying weight-adjusted lumefantrine doses on both lumefantrine and reinfection risk will be presented elsewhere.

We mistakenly included four pregnant women in the study and treated them with full courses of artemether-lumefantrine during the first trimester. They were followed up closely and all had normal deliveries. All newborn babies were healthy and subsequent follow-up for 1 year has not revealed any developmental delays. Overall, there were 521 reported adverse events, the most common of which were cough (12%), upper respiratory tract infection (11%), abdominal pain (7%), headache (6%), fever (4%), diarrhoea (3%), rash (3%), dizziness (3%), anorexia (2%), and vomiting (2%). The breakdown of drug-event associations was: three (0·6%) definite, 12 (2%) probable, 33 (6%) possible, 360 (69%) unlikely, and 113 (22%) not related to artemether-lumefantrine. There were no differences between the groups (data not shown). All of the 15 definitely or probably drug-related adverse events were of mild or moderate severity, and resolved: three vomiting (0 mild/3 moderate), three diarrhoea (1/2), three anorexia (2/1), two abdominal pain (0/2), two palpitations (0/2), one nausea (0/1), and one pruritus (0/1). There were eight severe adverse events, which were all malaria-related or intercurrent illnesses unrelated to the study drug: convulsions 5 min after first drug intake, severe malaria on day 0, measles, seizure with febrile semiconsciousness, ectopic pregnancy, pelvic inflammatory disease, obstructed inguinal hernia, and death due to pneumonia in an HIV-positive man.

Discussion

Our results indicate that artemether-lumefantrine has a high cure rate—exceeding 96%–irrespective of whether given under supervision with food or under conditions of

routine clinic practice. This finding confirms the efficacy of the six-dose regimen reported by investigators in southeast Asia and Burundi.[13–15,17] Our results are also consistent with an earlier study done at the same clinic as this one and showing 90% adherence to outpatient treatment with artemether-lumefantrine.[29] Provision of a short explanation about how to take a drug to patients at the point of prescription is, seemingly, a simple but important intervention to enhance adherence. Although this research clinic might over-rate population adherence to artemether-lumefantrine, our encouraging data should facilitate a decision on whether to introduce this drug as first-line treatment for *P falciparum* malaria in Uganda.

Our underlying hypothesis was that a trial of artemether-lumefantrine efficacy alone, done under ideal conditions of drug and food administration, was likely to yield an overly optimistic estimate of the actual cure rate and ignore the possible negative effect of factors such as poor lumefantrine absorption under normal conditions of food intake, poor adherence to the obligatory 8-h delay between the first and the second dose, and early interruption of treatment because of rapid symptomatic relief. Nevertheless our findings suggest that artemether-lumefantrine would be highly effective in an African clinic provided that clear explanations on how to take the drug are given. It is noteworthy, however, that no matter how closely we have tried to mimic the real-life situation, study procedures always impose an artificial environment that indirectly promotes adherence, and therefore overestimates the true drug efficacy in the unsupervised group.

Artemether-lumefantrine had a profound effect on gametocyte carriage; only one patient had gametocytes after day 14. This factor might confer additional benefit to the community by reducing transmission of the disease if the drug were widely deployed in our setting. Other ACTs also inhibit gametocyte development.[11] By contrast, sulfadoxine-pyrimethamine monotherapy is associated with high gametocyte carriage rates, a major disadvantage of its use.[25] As with other efficacious antimalarials, there was good haematological recovery especially in the youngest and most vulnerable age group. Artemether-lumefantrine was well tolerated and there were no drug-induced serious adverse events, which is consistent with other trials.[30] Additionally, four babies were born to pregnant women who had been exposed inadvertently to artemether-lumefantrine in the first trimester of pregnancy. They showed no abnormality at birth and are well after a year of monthly follow-up visits.

We measured blood lumefantrine concentrations on days 3 and 7. A day-7 concentration of less than 280 μg/L has been used as a pharmacokinetic marker of treatment failure in western Thailand, an area of highly drug-resistant *P falciparum*.[23,31] Although day-7 lumefantrine concentrations were significantly lower and more frequently less than 280 μg/L in the unsupervised group, a fairly high proportion of the supervised patients also had concentrations below this marker. These data indicate that supervised drug administration results in improved lumefantrine concentrations, but does not guarantee high day-7 concentrations. However, in this area of Uganda, low day-7 lumefantrine concentrations did not affect the day-28 cure rate. Our fairly short follow up could nonetheless have missed late recrudescent infections, and extending the follow up of artemether-lumefantrine to 42 days is recommended.[32] Malaria-acquired immunity is a probable contributing factor in our high cure rates, but another important issue is the intrinsic sensitivity of local *P falciparum* parasites to lumefantrine. Although we did not measure this factor in Mbarara, African isolates have considerably lower IC50 values than those from western Thailand, where the high IC50 values are probably explained by the in-vitro cross-resistance between lumefantrine and mefloquine and halofantrine.[31,33,34] A day-7 lumefantrine concentration of less than 280 μg/L as a pharmacokinetic predictor that treatment will not work might not be applicable to all regions, and further research should be done to assess the appropriate threshold as a function of parasite sensitivity.

If, as we believe, parasites in this area are highly sensitive to lumefantrine and artemether, then now is the best time for the Ugandan MoH to introduce the study combination to reduce the likelihood that resistance will develop.[23] Every effort should be made to ensure full adherence to this valuable ACT to maximise protection from resistance and realise the possibility of a reduction in malaria transmission. We could not show to what extent high effectiveness was attributable to the improved, sealed-blister design of the packaging of artemether-lumefantrine, consisting of visual depictions of when to take each dose appropriate for non-literate users; nevertheless, our findings do strongly suggest that such a mode of packaging favours high adherence and should be standard for all ACT combinations. In a previous study,[29] we showed high (90%) adherence to artemether-lumefantrine in our clinic setting. One major drawback of the combination remains its cost. Many African countries will not be able to afford artemether-lumefantrine for public-sector use without external support, such as from the Global Fund. This factor could also compromise adherence, since African patients and caregivers often use incomplete doses, keeping the remaining tablets for the next attack of malaria.[35]

The six-dose regimen of artemether-lumefantrine is a promising option as a replacement for antimalarial therapies that no longer work in Uganda and other African countries. Deployment on a wide scale should be undertaken in parallel with research into effectiveness, pharmacovigilance, and resistance monitoring.

Contributors

P Piola was the main investigator. P Piola and J-P Guthmann cowrote the first draft of this paper; all coauthors contributed to the final version. F Checchi designed the study protocol with the support of the Protocol Development Team. C Fogg, F Bajunirwe, S Biraro, F Grandesso, E Ruzagira, J Babigumira, I Kigozi, J Kiguli, and J Kyomuhendo were in

charge of trial recruitment and follow-up, and contributed to data analysis. L Ferradini implemented and supervised PCR analysis. W Taylor assisted with protocol design and was the Good Clinical Practice adviser.

Conflict of interest statement

We declare that we have no conflict of interest. The opinions expressed in this article are not to be construed as representing those of WHO.

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