Efficacy and safety of artemether–lumefantrine compared with quinine in pregnant women with uncomplicated \textit{Plasmodium falciparum} malaria: an open-label, randomised, non-inferiority trial

Patrice Piola, Carolyn Nabasumba, Eleanor Turyakira, Mehul Dhorda, Niklas Lindegardh, Dan Nyehangane, Georges Snounou, Elizabeth A Ashley, Rose McGeary, Francois Nosten, Philippe J Guerin

Summary

Background Malaria in pregnancy is associated with maternal and fetal morbidity and mortality. In 2006, WHO recommended use of artemisinin-based combination treatments during the second or third trimesters, but data on efficacy and safety in Africa were scarce. We aimed to assess whether artemether–lumefantrine was at least as efficacious as oral quinine for the treatment of uncomplicated falciparum malaria during the second and third trimesters of pregnancy in Mbarara, Uganda.

Methods We did an open-label, randomised, non-inferiority trial between October, 2006, and May, 2009, at the antenatal clinics of the Mbarara University of Science and Technology Hospital in Uganda. Pregnant women were randomly assigned (1:1) by computer generated sequence to receive either quinine hydrochloride or artemether–lumefantrine, and were followed up weekly until delivery. Our primary endpoint was cure rate at day 42, confirmed by PCR. The non-inferiority margin was a difference in cure rate of 5%. Analysis of efficacy was for all randomised patients without study deviations that could have affected the efficacy outcome. This study was registered with ClinicalTrials.gov, number NCT00495508.

Findings 304 women were randomly assigned, 152 to each treatment group. By day 42, 16 patients were lost to follow-up and 25 were excluded from the analysis. At day 42, 137 (99·3%) of 138 patients taking artemether–lumefantrine and 122 (97·6%) of 125 taking quinine were cured—difference 1·7% (lower limit of 95% CI –0·9). There were 290 adverse events in the quinine group and 141 in the artemether–lumefantrine group.

Interpretation Artemisinin derivatives are not inferior to oral quinine for the treatment of uncomplicated malaria in pregnancy and might be preferable on the basis of safety and efficacy.

Funding Médecins Sans Frontières and the European Commission.

Introduction

40% of all women are estimated to be exposed to malaria infection during the course of pregnancy,\textsuperscript{1} substantial proportions of maternal mortality have been attributed to malaria in Sudan (37·2%)\textsuperscript{2} and Zimbabwe (24%).\textsuperscript{3} Each year an estimated 75 000–200 000 deaths of infants are deemed to be safe in pregnancy,\textsuperscript{9,10} the three-times daily 7-day regimen is not ideal because of many adverse effects that lead to poor compliance.\textsuperscript{11} Few trials have investigated the efficacy of quinine treatment in Africa during pregnancy. In 2002, the findings of a study in Sudan\textsuperscript{12} showed reassuring quinine efficacy. WHO recommends artemisinin combination therapies (ACTs) in the second and third trimester, in agreement with recommendations in patients that are not pregnant.\textsuperscript{13} However, studies of treatment in pregnancy so far have been largely done in southeast Asia.\textsuperscript{14–16} PCR-adjusted ACT trials in Africa are scarce and have been limited mostly to non-fixed-dose combinations.\textsuperscript{17–20}

Artemether–lumefantrine is a fixed-dose combination that has proved safe and effective against infections with \textit{Plasmodium falciparum}, including one study in pregnancy in Asia,\textsuperscript{21} but there are no data from pregnant women in Africa. Our objective was to compare the efficacy of artemether–lumefantrine with that of quinine in the treatment of uncomplicated malaria in pregnancy in because of widespread resistance.\textsuperscript{22} Although quinine is deemed to be safe in pregnancy,\textsuperscript{23} the three-times daily 7-day regimen is not ideal because of many adverse effects that lead to poor compliance.\textsuperscript{11} Few trials have investigated the efficacy of quinine treatment in Africa during pregnancy. In 2002, the findings of a study in Sudan\textsuperscript{12} showed reassuring quinine efficacy. WHO recommends artemisinin combination therapies (ACTs) in the second and third trimester, in agreement with recommendations in patients that are not pregnant.\textsuperscript{13} However, studies of treatment in pregnancy so far have been largely done in southeast Asia.\textsuperscript{14–16} PCR-adjusted ACT trials in Africa are scarce and have been limited mostly to non-fixed-dose combinations.\textsuperscript{17–20}

Artemether–lumefantrine is a fixed-dose combination that has proved safe and effective against infections with \textit{Plasmodium falciparum}, including one study in pregnancy in Asia,\textsuperscript{21} but there are no data from pregnant women in Africa. Our objective was to compare the efficacy of artemether–lumefantrine with that of quinine in the treatment of uncomplicated malaria in pregnancy in
Uganda. Secondary objectives included establishing the safety profile of both treatments, comparison of fever and parasite clearance times, comparison of maternal, obstetric, and infant outcomes, and recording of lumefantrine blood concentrations at day 7.

Methods
Participants
Between October, 2006, and May, 2009, we did an open-label, randomised, non-inferiority efficacy trial at the antenatal clinics of the Mbarara University of Science and Technology Hospital in Uganda.

Women with positive blood smears during weekly antenatal follow-up were invited to participate in the study comparing the efficacy and tolerance of artemether–lumefantrine with quinine hydrochloride for the treatment of uncomplicated falciparum malaria. Women were eligible if they had a viable pregnancy with an estimated gestation of 13 weeks or longer and had malaria infection detected by microscopy (*P* falciparum mixed or monoinfection). Women were excluded if they had *P* falciparum parasitaemia of greater than 250 000 parasites per μL, severe anaemia (haemoglobin <7 g/dL), signs or symptoms of severe or complicated malaria needing parenteral treatment, known allergy to the study drugs, previous participation in the efficacy study, or an inability to attend follow-up. WHO inclusion criteria referring to fever or to a lower limit of parasitaemia were not used because they do not include the effect of low parasitaemia in pregnancy.

All patients provided written informed consent. Our study proposal was submitted and approved by four ethics committees: the Faculty Research Ethics Committee, the Institutional Review Board, the Uganda National Committee for Science and Technology, and the Comités de Protection des Personnes (Iles de France XI, France).

Procedures
After inclusion, eligible patients were randomly assigned (1:1) to the two intervention groups in computer-generated permuted blocks of eight. Each inclusion number corresponded to an opaque sealed envelope that contained a card with the concealed treatment group. The sealed envelope was opened by a clinical investigator after patients’ consent had been obtained; the clinical investigator was not involved in the generation of the allocation sequence. The allocation sequence was generated with a computerised system by a member of the research team who was not involved in the management of patient data. The different dosing schedules meant that the patients and the clinical investigators were aware of treatment allocation. Treatment allocation was masked from the laboratory that read the blood smears.

Participants received either quinine hydrochloride (300 mg of the base per tablet) given orally under supervision at 10 mg base per kg bodyweight every 8 h for 7 days, or artemether–lumefantrine (fixed-dose combination of 20 mg and 120 mg) given orally under supervision as four tablets at 0 h, 8 h, 24 h, 36 h, 48 h, and 60 h for 3 days with 200 mL of milk at each dose. We repeated doses if patients vomited within 30 min of administration, and gave the opposite intervention once if the patient vomited within 30 min after a repeat dose (the patient was then only followed up for safety).

Patients were followed up weekly until delivery. Baseline data on day 0 included a medical examination (bodyweight, blood pressure, and temperature), laboratory tests (blood smear, full blood count, liver function tests, and free plasma hormone levels), and a urine dipstick test. Blood smears were read at day 0 and patients were followed up weekly until delivery. Only patients with a patent parasitic infection on day 0 were included in the analysis. Patients with a patent parasitic infection on day 0 who did not consent to follow-up were not included in the analysis. Data were collected twice weekly until delivery by trained field staff, who were unaware of the intervention, and were stored in a laptop computer.

Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Quinine (n=152)</th>
<th>Artemether–lumefantrine (n=152)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range)</td>
<td>22·6 years (17–38)</td>
<td>22·5 years (15–38)</td>
</tr>
<tr>
<td>Median gravidity (range)</td>
<td>2 (1–7)</td>
<td>2 (1–8)</td>
</tr>
<tr>
<td>Mean weight (IQR)</td>
<td>58 kg (10)</td>
<td>58 kg (10)</td>
</tr>
<tr>
<td>Mean gestational age (range)</td>
<td>22·3 weeks (9–38)</td>
<td>24·7 weeks (10–39)</td>
</tr>
<tr>
<td>Proportion with history of fever</td>
<td>44·1%</td>
<td>33·6%</td>
</tr>
<tr>
<td>Proportion with fever (&gt;37·5°C)</td>
<td>20%</td>
<td>23%</td>
</tr>
<tr>
<td>Geometric mean <em>Plasmodium falciparum</em> density (IQR)</td>
<td>1995 parasites per μL (9771)</td>
<td>1418 parasites per μL (4727)</td>
</tr>
<tr>
<td>Median gametocyte carriage</td>
<td>9·2%</td>
<td>6·6%</td>
</tr>
<tr>
<td>Median haemoglobin (g/dL)</td>
<td>10·9 (10·9)</td>
<td>10·9 (10·9)</td>
</tr>
<tr>
<td>Median lymphocytes (10^9/L)</td>
<td>1·64×10^9/μL</td>
<td>1·76×10^9/μL</td>
</tr>
<tr>
<td>Median neutrophils (10^9/μL)</td>
<td>2·69×10^9/μL</td>
<td>2·66×10^9/μL</td>
</tr>
<tr>
<td>Median platelets (10^12/L)</td>
<td>138×10^12/L</td>
<td>148×10^12/L</td>
</tr>
<tr>
<td>Sickle cell trait</td>
<td>0/92</td>
<td>3/102 (3·1%)</td>
</tr>
<tr>
<td>QTc in baseline</td>
<td>368 ms</td>
<td>364 ms</td>
</tr>
</tbody>
</table>

Figure 1: Trial profile
Articles

and kidney function, urine analysis, sickle-cell electrophoresis, and PCR, 12-lead electrocardiogram (ECG; repeated on day 2), and an obstetric ultrasound. On a weekly basis, from day 0 to day 42 or delivery (whichever came last), we recorded medical history, medical and obstetric examination (bodyweight, fundal height, blood pressure, and temperature), blood smear, liver and kidney function (days 7, 14, and 42), lumefantrine plasma concentrations (day 7), full blood count (days 14 and 42), and adverse events. Intermittent preventive treatment in pregnancy was interrupted during this period. At delivery, mother, cord, placenta, and neonate blood smears were examined for parasites. Women in our study were not treated with sulfadoxine–pyrimethamine intermittent preventive treatment.

Thick and thin blood smears were prepared and stained with Giemsa. 200 high-power fields were read on the thick smear before declaring a slide negative. Parasitaemia was calculated by counting parasites against 200 white blood cells (or 500 if nine parasites or fewer were counted against 200 white blood cells) and with an assumed white blood cell count of 8000 cells per μL. External quality control was done at Shoklo Malaria Research Unit (Mae Sot, Tak, Thailand) on all slides collected at inclusion, at follow-up visits when recurrent parasitaemia was detected, and on an additional random selection of 5% of all slides collected for the study.

Peripheral blood samples for PCR genotyping were collected on Whatman 3MM paper strips (Whatman, Kent, UK) at baseline and reappearance. DNA was purified with commercial kits (Qiagen, Hilden, Germany). Differentiation of recrudescence from new infections was done on samples collected concurrently with a positive slide and was on the basis of three *P. falciparum* polymorphic markers: GLURP, MSP1, and MSP2. Parasitaemia during follow-up was classed as recrudescence when the parasites in the pretreatment and post-treatment samples shared at least one allelic variant for each of the three markers, and as a reinfection if the allelic variants for any one of the three markers were different for the pretreatment and post-treatment samples.22 An indeterminate result was reported if amplification of any one marker failed from either samples, except when the partial analysis was sufficient to class the episode as a reinfection. Internal quality control (ten sample pairs) and external quality control (five sample pairs) was done.

On day 7, all patients from the artemether–lumefantrine group were sampled (2 mL) by venepuncture for lumefantrine concentration. Plasma was separated and stored at −30°C until it was analysed with a validated high-performance liquid chromatography method.23

The primary efficacy endpoint was the proportion of patients with PCR-corrected adequate clinical and parasitolological response (ACPR) at day 42—cure is defined as ACPR. The secondary efficacy endpoint was PCR-uncorrected ACPR on day 42 or delivery (whichever came last) to account for placental sequestration of malaria parasites. Treatment success or failures were classified according to WHO guidelines 2003.24

Safety outcomes were adverse events as defined by the International Conference on Harmonisation Good Clinical Practice guidelines.25 Safety outcome events documented during pregnancy were abnormal laboratory parameters (alanine aminotransferase, bilirubin, creatinine, and full blood count outside normal lab ranges); abnormal Fridericia corrected QT interval (QTc; >440 ms) on ECG; gestation at delivery including prematurity (<37 weeks); extreme prematurity (<28 weeks); congenital abnormalities; low birthweight (<2500 g); and perinatal, neonatal, and infant death. Gestational age was determined with ultrasound scan before 24 weeks of gestation and last menstrual period for later inclusions in the trial.

The independent data monitoring committee met twice during the trial and reviewed all serious adverse events.

### Statistical analysis

The non-inferiority margin for the difference in cure rates between the two treatments was δ=5%. The PCR-adjusted cure rate of quinine on day 42 was the chosen reference and estimated at 98%. The resulting number of

<table>
<thead>
<tr>
<th>PCR corrected</th>
<th>Quinine</th>
<th>Artemether–lumefantrine</th>
<th>Quinine</th>
<th>Artemether–lumefantrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage efficacy (range)</td>
<td>97.6% (93.1–99.5)</td>
<td>99.3% (96.0–99.9)</td>
<td>96.1% (90.2–98.9)</td>
<td>98.2% (93.5–99.7)</td>
</tr>
<tr>
<td>n/N</td>
<td>(122/125)</td>
<td>(137/138)</td>
<td>(98/102)</td>
<td>(108/110)</td>
</tr>
<tr>
<td>Difference (LLCI)</td>
<td>+1.7 (+0.9%)</td>
<td>+2.1 (+1.7%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Not PCR correction</th>
<th>Quinine</th>
<th>Artemether–lumefantrine</th>
<th>Quinine</th>
<th>Artemether–lumefantrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage efficacy (range)</td>
<td>96.1% (91.0–98.7)</td>
<td>99.3% (96.0–99.9)</td>
<td>83.8% (75.8–89.9)</td>
<td>87.8% (80.7–93.0)</td>
</tr>
<tr>
<td>n/N</td>
<td>(122/127)</td>
<td>(137/138)</td>
<td>(98/117)</td>
<td>(108/123)</td>
</tr>
<tr>
<td>Difference (LLCI)</td>
<td>+3.2 (+0.1%)</td>
<td>+4.0 (+3.4%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LLCI=lower limit of the one-sided 95% CI.

Table 2: Cure rates (modifed intention to treat) by day 42 and delivery in women with uncomplicated *Plasmodium falciparum* malaria treated with quinine or artemether-lumefantrine.

![Table 2: Cure rates (modified intention to treat) by day 42 and delivery in women with uncomplicated *Plasmodium falciparum* malaria treated with quinine or artemether-lumefantrine.](764)
patients needed in each treatment group was 152, to allow for a type 1 error (α) of 5%, a power of 80%, and a proportion of dropout of 10%.

The non-inferiority analysis used the proportion of ACPR. We analysed estimates of recrudescence and reinfection rates with Kaplan-Meier methods. Data were analysed for randomised patients except for those with protocol deviations that might affect the efficacy outcome; this adaptation of the intention-to-treat study population was made to account for the non-inferiority design. Participants who deviated from the protocol were excluded from the non-inferiority analysis and censored on the day of last available parasitaemia in the survival analysis. We also did a per-protocol analysis.

We compared continuous data between the groups with the Student’s t test. Data not normally distributed were log transformed or compared by use of the Mann-Whitney U test χ². Comparison of categorical data between groups was done with the χ² test or with Fisher’s exact test.

We double-entered data into Epitdata software 3.1 and analysed them with Stata (version 11). An independent data and safety monitoring board convened to review efficacy and safety data at yearly intervals as the trial progressed. This study was registered with ClinicalTrials.gov, number NCT00495508.

Role of the funding source
Médecins Sans Frontières and the European Commission funded the project but 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
304 patients were enrolled and 152 assigned to each treatment group (figure 1). The webappendix shows details of deviations from the protocol that led to exclusion from the analysis. Baseline characteristics were similar in the two groups (table 1), most participants had anaemia (haemoglobin <11 g/dL) at enrolment and a fifth were febrile.

Seven participants did not finish their treatment or withdrew consent before the end of treatment (six in the quinine group and one in the artether–lumefantrine group). Of those that interrupted treatment in the quinine group, three withdrew consent after 1 day of treatment and never returned, two refused to take the treatment and received a rescue treatment, and one delivered and discontinued treatment.

Of the 29 patients who had recurrent falciparum parasitaemia between day 7 and delivery (or day 42 whichever was last), PCR genotyping confirmed that 22 (76%; 12 on quinine and 10 on artether–lumefantrine) were new infections, three (10%; two on quinine on day 14 and 138 and one on artether–lumefantrine on day 119) were recrudescent, and four (14%; three on quinine and one on artether–lumefantrine) were indeterminate. The median time to first P falciparum reappearance was 65 days (range 34–138) for quinine and 70 (49–154) for artether–lumefantrine (p=0.4).

Of the 13 patients with recurrent non-falciparum infections (six Plasmodium vivax, six Plasmodium ovale, and one Plasmodium malariae) by delivery (or day 42 whichever was last), seven were on artether–lumefantrine and six were on quinine. The median time to first non-falciparum detection was 63 days (range 35–133) in the artether–lumefantrine group and 38 (28–70) in the quinine group (p=0.1).

Cure rates were high and the lower limit of the one-sided 95% CI was never lower than –5% (table 2). The PCR-uncorrected results also seemed to show non-inferiority (table 2), and the per-protocol analysis concluded the non-
inferiority of artemether–lumefantrine (data not shown). No significant difference between the two treatments was noted with Kaplan-Meier analysis of recurrence or recrudescence (figure 2).

Fever clearance was rapid in both groups (table 3). On day 2, parasite clearance was lower in the quinine group than in the artemether–lumefantrine group (p<0·0001; table 3) but increased on day 3. Artemether–lumefantrine was more effective than quinine in gametocyte clearance by day 2 (p=0·03) and day 7 (p=0·04; table 3). Four women without gametocytes at inclusion had gametocytes on day 7 (three taking quinine and one taking artemether–lumefantrine), and one on day 42 (quinine).

Placenta blood smears were obtained for 214 (76%) of 281 births. Ten smears (4·7%), five per group, were positive for *P falciparum* (figure 3). In six cases, both mother and placenta were positive: five were still under initial treatment (three on quinine and two on artemether–lumefantrine) and one (artemether–lumefantrine) with a new infection at the time of delivery. Of the four women with a negative peripheral blood smear, three had their primary treatments (two had quinine and one had artemether–lumefantrine) 132, 118, and 8 days before delivery. The fourth woman was in the quinine group and was treated with artemether–lumefantrine 182 days before delivery and she had a new infection 63 days later—ie, 119 days before delivery (figure 3).

235 (87%) of 281 newborns were screened for malaria within 24 h of birth, none of whom were positive for malaria.

There was a gain in haemoglobin of 0·8 g/dL in both groups 42 days after treatment, after an initial mean decrease at day 7 in the artemether–lumefantrine group: decrease of 0·5 g/dL in artemether–lumefantrine vs gain of 0·3 g/dL in quinine (p<0·0001; figure 4).

At delivery, mean haemoglobin was 12·1 g/dL (range 7·4–16·8) in the quinine group compared with 11·9 g/dL (8·0–15·7) in the artemether–lumefantrine group (p=0·45). Of the women from whom we could obtain blood at the moment of delivery, three (3%) of 107 had severe anaemia in the quinine group and one (1%) of 122 in the artemether–lumefantrine group (p=0·24). Laboratory tests did not show any clinically significant adverse event. 14 days after treatment there was no neutropenia recorded in either group. We noted four cases of lymphopenia in the artemether–lumefantrine group (one reached 0·75×10^9 cells per L) and none in the quinine group. In both groups, by day 42, platelets increased by about 50% and eosinophils doubled (11 adverse events in the quinine group and five in the artemether–lumefantrine group). No substantial difference in alanine amino-transferase, bilirubin, creatinine, and full blood count were noted between the groups.

Of the women that did not have a prolonged QTc at inclusion, two (1%) of 149 developed a prolonged QTc at day 2 in the quinine group (highest QTc 530 ms) and three (2%) of 151 in the artemether–lumefantrine group (highest QTc 590 ms; p=0·66).

The most common symptoms reported before treatment were headache, abdominal pain, dizziness, and weakness (table 4). In the quinine group 142 (93%) of 152 patients presented at least one adverse event compared with 94 (61·8%) in the artemether–lumefantrine group (highest QTc 590 ms; p=0·66).

<table>
<thead>
<tr>
<th>Quinine</th>
<th>Artemether–lumefantrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afebrile at day 0</td>
<td>121/151 (80%)</td>
</tr>
<tr>
<td>Afebrile at day 1</td>
<td>128/129 (99%)</td>
</tr>
<tr>
<td>Afebrile at day 2</td>
<td>127/128 (99%)</td>
</tr>
<tr>
<td>Afebrile at day 3</td>
<td>146/146 (100%)</td>
</tr>
<tr>
<td>Gametocyte free at day 2</td>
<td>133/143 (93%)</td>
</tr>
<tr>
<td>Gametocyte free at day 7</td>
<td>135/143 (94%)</td>
</tr>
<tr>
<td>Parasite free at day 2</td>
<td>123/143 (86%)</td>
</tr>
<tr>
<td>Parasite free at day 3</td>
<td>141/144 (98%)</td>
</tr>
</tbody>
</table>

Data are number/total number (%).

![Figure 3: Results of placental blood smears](image-url)

![Figure 4: Variation of haemoglobin](image-url)
common, happening between a median delay of 21 days and 14 days after start of treatment and not substantially different between groups. Common adverse events in the artemether–lumefantrine group were abdominal pain (5 days), headaches (4 days), and influenza-like syndrome (21 days). The one serious adverse event was a maternal death in a woman in the quinine group with her first pregnancy. Death was caused by sepsis 5 days after a caesarean section for obstructed labour in a term pregnancy.

Birth outcomes were documented in 137 (90%) of 152 women in the quinine group and in 144 (95%) of 152 in the artemether–lumefantrine group. There were a few spontaneous abortions and neonatal deaths, all proportionally lower (non-significant) in the artemether–lumefantrine than in the quinine group (table 5).

Malformations detected at birth included two neonates with polydactyly in each group, which was a family trait in both, and one with acyanotic heart disease in a woman treated with artemether–lumefantrine at 19 weeks of gestation. 181 (65%) of 280 women on whom we could obtain the date of delivery, had their gestational age defined by ultrasound, the remainder being included after 24 weeks of pregnancy. No significant difference in mean birthweight, proportion of low birthweight, mean gestational age, or premature or severely premature infants was noted (table 6).

Of the 152 women in the artemether–lumefantrine group, plasma lumefantrine concentrations at day 7 were available for 97 women (64%) who had completed their treatment (median 481 ng/mL; range 15–3246). 31 (32%) of 97 had a lumefantrine concentration of less than 280 ng/mL. In six women, the reappearance of malaria was non-inferior to quinine for the treatment of uncomplicated malaria in the second and third trimesters of pregnancy. This confirmation of efficacy of both drugs in this region of Africa is reassuring. Most pregnant women included in this study were asymptomatic with low parasitaemia, which is sufficient to complicate a pregnancy and fetal growth.7 The poor tolerability of quinine caused patients to interrupt treatment (data not shown).

Placental infection at delivery in all women in Africa has been estimated at 26% (range 5–52%).9 In our study, in which all women had slide-confirmed malaria, effective treatment during pregnancy, and active weekly detection, only four (2%) of 214 women that finished their treatment had an apparent microscopic infection at delivery. This rate is similar to findings from the low-transmission site in Thailand.21 Our study suggests that active detection and treatment by weekly malaria smear substantially decreases the risk of patients having parasites in the peripheral and placental blood at the time of delivery. Active antenatal screening rather than passive case management should be encouraged in all areas where malaria is endemic.

In southeast Asia,21 PCR confirmed efficacy of artemether–lumefantrine (intention to treat) in pregnant women was lower (82–0%; range 74–8–89·3) at delivery (or day 42 if later) than in our study (98·2%; 93·5–99·7%). Several factors might explain this difference: in Thailand,
less than 60% of pregnant women are cured when treated with 7 days supervised quinine.39 probably related to the high background prevalence of pfmdr1 in the population.28 In a mesoendemic area like Mbarara, pregnant women have a higher level of background immunity suggested by the lower proportion of women with febrile presentation and lower baseline parasitaemia (about three-times lower) than in the Thailand study. The longer parasite reappearance time in this study compared with that in the Thailand study might also be explained by a difference in immunity. Drug absorption could also have a role, as shown in our study by the higher risk of recurrent parasitaemia in women with lower concentrations of blood lumefantrine at day 7. However, a third of women without recurrent parasitaemia had lumefantrine concentrations on day 7 lower than 280 ng/mL, suggesting that drug concentrations alone might not explain the difference in efficacy between sites. Although non-falciparum infections are not widely reported from Africa, 30% of the reappearances in our study were non-falciparum infections. The prophylactic effect of antimalarials in pregnancy is important, as even a single P vivax parasite has been associated with low birthweight and anaemia.29 Another factor that could contribute to a difference in results is the method of analysis,30 mainly the allocation of efficacy endpoints to different deviations.

Although, our study was done at a single site, the results should be interpreted in the epidemiological context of the study site. Scaling up of ACTs in pregnancy will need further assessment of their efficacy and safety in other regions. We used sealed envelopes because it suited our setting, although central mechanisms ensure better randomisation.

Our study also provides supportive safety data for the use of artemisinin derivatives in pregnant women. The rise in platelets over time can be interpreted as a sign of recovery from malaria and is known to cause thrombocytopenia.31 The transitory fall in haemoglobin, mostly in the artemether–lumefantrine group, might be related to a haematological effect of artemisinins32 or directly related to the pathophysiology of malaria infection. Early Chinese studies of artemether and oral dihydroartemisinin treatments33 recorded low reticulocyte counts in 10–20% of patients during the first week after treatment. More women in the quinine group and in the artemether–lumefantrine group had severe anaemia at delivery, but the study was not powered to detect a significant difference for this comparison. However, the sample size of our study was not calculated for the detection of rare adverse events.

The day 7 lumefantrine plasma concentration is deemed to be the main determinant of efficacy in non-pregnant patients, and concentrations below 280 ng/mL is the threshold associated with increased risk of treatment failure.34 A similar proportion of women in the Thailand study (35%) and in our Uganda study (32%) had day 7 plasma lumefantrine concentrations below this threshold. The kinetics of lumefantrine are altered in pregnancy, and in our trial women with recurrent infections had lower than expected lumefantrine concentrations. Our findings confirm those in Thailand and the importance of pharmacokinetic and pharmacodynamic studies in trials of malaria treatment.35 Although cure rates were adequate, the substantial proportion of pregnant women with lumefantrine concentrations below the threshold might have serious ramifications on the development of resistance: wide deployment of artemether–lumefantrine in Africa might result in high numbers of women receiving subtherapeutic concentrations, which increase the chance of failure for the individual patient and potentially threaten the long-term therapeutic life of the drug. Sulfadoxine-pyrimethamine and mefloquine both have a history of subtherapeutic doses and the subsequent loss of the drug as monotherapy.36 More detailed pharmacokinetic data is being assessed.

Prices of ACTs, and in particular artemether–lumefantrine, have dropped substantially in recent years and therefore make treatment costs comparable to those for quinine. Additionally, large funding agencies such as the Global Fund to Fight AIDS, Tuberculosis and Malaria or the President’s Malaria Initiative are now largely subsidising ACTs. This improves the cost-effectiveness of ACTs compared with that of quinine.

Our study suggests that artemisinin derivatives, depending on the companion drug, could be preferable to oral quinine for the treatment of uncomplicated malaria in pregnancy, because they are better tolerated with reassuring safety results and not inferior to quinine in efficacy.

Contributors
PP, EA, RMG, FN, and PG made substantial contributions to the concept and design of the study, CN, ET, MD, and DN were involved in the acquisition of data. PP, ET, NL, GS, EA, RMG, FN, and PG contributed to the analysis and interpretation of data. All authors critically reviewed the report and approved the final version of the report for submission.

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Conflicts of interest
We declare that we have no conflicts of interest.

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