Comparison of artesunate–mefloquine and artemether–lumefantrine fixed-dose combinations for treatment of uncomplicated *Plasmodium falciparum* malaria in children younger than 5 years in sub-Saharan Africa: a randomised, multicentre, phase 4 trial


Summary

Background WHO recommends combinations of an artemisinin derivative plus an antimalarial drug of longer half-life as treatment options for uncomplicated *Plasmodium falciparum* infection. In Africa, artemether–lumefantrine is one of the most widely used artemisinin-based combination therapy, whereas artesunate–mefloquine is used infrequently because of a perceived poor tolerance to mefloquine. WHO recommends reconsideration of the use of artesunate–mefloquine in Africa. We compared the efficacy and safety of fixed-dose artesunate–mefloquine with that of artemether–lumefantrine for treatment of children younger than 5 years with uncomplicated *P. falciparum* malaria.

Methods We did this multicentre, phase 4, open-label, non-inferiority trial in Burkina Faso, Kenya, and Tanzania. Children aged 6–59 months with uncomplicated malaria were randomly assigned (1:1), via a computer-generated randomisation list, to receive 3 days’ treatment with either one or two artesunate–mefloquine tablets (25 mg artesunate and 55 mg mefloquine) once a day or one or two artemether–lumefantrine tablets (20 mg artemether and 120 mg lumefantrine) twice a day. Parasitological assessments were done independently by two microscopists who were blinded to treatment allocation. The primary outcome was the PCR-corrected rate of adequate clinical and parasitological response (ACPR) at day 63 in the per-protocol population. Non-inferiority was shown if the lower limit of the 95% CI for the difference between groups was greater than –5%. Early vomiting was monitored and neuropsychiatric status assessed regularly during follow-up. This study is registered with ISRCTN, number ISRCTN17472707, and the Pan African Clinical Trials Registry, number PACTR201202000278282.

Findings 945 children were enrolled and randomised, 473 to artesunate–mefloquine and 472 to artemether–lumefantrine. The per-protocol population consisted of 407 children in each group. The PCR-corrected ACPR rate at day 63 was 90·9% (370 patients) in the artesunate–mefloquine group and 89·7% (365 patients) in the artemether–lumefantrine group (treatment difference 1·23%, 95% CI –2·84% to 5·29%). At 72 h after the start of treatment, no child had detectable parasitaemia and less than 6% had fever, with a similar number in each group (21 in the artesunate–mefloquine group vs 24 in the artemether–lumefantrine group). The safety profiles of artesunate–mefloquine and artemether–lumefantrine were similar, with low rates of early vomiting (71 [15·3%] of 463 patients in the artesunate–mefloquine group vs 79 [16·8%] of 471 patients in the artemether–lumefantrine group in any of the three dosing days), few neurological adverse events (ten [2·1%] of 468 vs five [1·1%] of 465), and no detectable psychiatric adverse events.

Interpretation Artesunate–mefloquine is effective and safe, and an important treatment option, for children younger than 5 years with uncomplicated *P. falciparum* malaria in Africa.

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Introduction Since 2000, there has been substantial progress in the worldwide effort to control, and in some regions eliminate, malaria. However, the disease still caused an estimated 438 000 deaths worldwide in 2015, mostly in Africa (90%) and in children younger than 5 years (70%). The widespread deployment of artemisinin-based combination therapies (ACTs) for treating malaria
Artemether–lumefantrine. These findings should have important implications for health policy in Africa, where malaria remains a major public health problem, particularly in young children.

Implications of all the available evidence
Artesunate–mefloquine is one of five artemisinin-based combination therapies (ACTs) that are currently recommended by WHO as antimalarial treatments. However, this combination was not registered in Africa at the time of the start of the trial. WHO recommends deployment of multiple ACTs to reduce the risk of the development of drug resistance. Our data suggest that fixed-dose artesunate–mefloquine is safe and effective in treating young children with uncomplicated malaria in Africa and is as effective as artemether–lumefantrine. These findings should have important implications for health policy in Africa, where malaria remains a major public health problem, particularly in young children.

One of the five WHO-recommended ACTs is artesunate–mefloquine. Available in loose or fixed-dose combination, artesunate–mefloquine showed high efficacy in treating uncomplicated *P. falciparum* malaria and has been used extensively over 20 years, mostly in Asia and Latin America. This combination is less commonly used in Africa, because of the availability of other affordable and already registered ACTs. Reports of mefloquine resistance in Asia, shortly after the drug’s introduction as monotherapy in the 1990s, had a negative effect on the introduction of artesunate–mefloquine in Africa. Furthermore, excessive vomiting associated with mefloquine seems the main reason for the restricted use of artesunate–mefloquine in African children. Early vomiting, shortly after treatment, is a reported cause of treatment failure in children. However, WHO has recommended that artesunate–mefloquine be reconsidered for treatment of uncomplicated malaria in Africa, particularly highlighting the paucity of data for this combination in children younger than 5 years.

A fixed-dose artesunate–mefloquine (containing 100 mg artesunate and 220 mg mefloquine hydrochloride) was, therefore, developed in Brazil by Farmanguinhos, through needs-driven initiative aiming to increase availability and reliable supply of fixed-dose ACTs of required quality.

is recognised as one key public health initiative for reducing malaria morbidity and mortality. Five ACTs are currently recommended by WHO for the treatment of uncomplicated *Plasmodium falciparum* infection, the predominant cause of malaria in Africa and, when untreated, the most deadly form of malaria worldwide.

Antimalarial drugs are used in combinations to prevent or delay the development of drug resistance and are now recommended in most malaria-endemic countries. Monotherapy with artemisinin or its derivatives is now strongly discouraged, especially after the emergence of artemisinin resistance in some regions. Deployment of multiple ACTs is regarded to be a further means to reduce development of drug resistance. Several effective ACTs are now available, many as fixed-dose formulations, which offer improved patient adherence. Artemether–lumefantrine was the first fixed-dose ACT to become available and is currently the most extensively used ACT.

The Drugs for Neglected Diseases initiative (DNDi), in partnership with the TDR (the Special Programme for Research and Training in Tropical Diseases) consortium, has collaborated with industry and academia for the development of two fixed-dose ACTs. This partnership formed the FACT (Fixed-dose Artesunate-based Combination Therapy) project consortium, which is a model
the FACT consortium, and registered there in 2008. A pivotal study in Thailand, involving 500 patients with uncomplicated malaria, including children aged <15 years, showed this fixed-dose combination to be better tolerated, with a lower incidence of vomiting, than equivalent loose tablet combinations. A randomised comparative trial in Burma showed that this fixed-dose artesunate–mefloquine had, with compared with other ACTs (loose artesunate–mefloquine, artemether–lumefantrine, artesunate–amodiaquine, dihydroartemisinin–piperaquine), the highest cure rate, the lowest rate of gametocyte carriage, and the most effective suppression of Plasmodium vivax malaria, and a large phase 4 trial (23845 patients) in Brazil confirmed its effectiveness as a treatment of uncomplicated P falciparum infection.

We did a randomised, multicentre, phase 4 trial with the aim of obtaining the most definitive evidence so far on the efficacy and safety of fixed-dose artesunate–mefloquine in children younger than 5 years with uncomplicated P falciparum malaria in Africa. The trial design was based on WHO guidelines and compared the efficacy and safety of fixed-dose artesunate–mefloquine with that of fixed-dose dispersible artemether–lumefantrine. Because of the long half-life of mefloquine, there was a prolonged follow-up (63 days), with an extensive safety assessment.

Methods

Study design and participants

This phase 4, multicentre, open-label, randomised, non-inferiority trial was done in six medical research centres across three African countries: Kilosa, Bagamoyo, and Korogwe (Tanzania); Balonghin and Banfora (Burkina Faso); and Ahero-Kisumu (Kenya).

Children were eligible for inclusion if they were aged 6–59 months, had an axillary temperature of 37·5°C or more, and had uncomplicated P falciparum monoinfection (2000–200000 asexual parasites per μL). Exclusion criteria were signs and symptoms of severe or complicated malaria; bodyweight less than 5 kg; inability to tolerate oral medication; mixed Plasmodium species infection; fever caused by non-malarial disease; hypersensitivity to mefloquine, quinine, quinidine, artesunate, or other artemisinins; antimalarial treatment within the previous 2 weeks (4 weeks for mefloquine or piperaquine); and participation in a clinical intervention trial within the previous 3 months. Informed consent was obtained from the child’s parent or legal guardian.

The trial was done in accordance with the Declaration of Helsinki and international and local national laws for protecting human rights and welfare. Ethical and regulatory approvals were obtained separately by each study centre: in Burkina Faso from the Ethics Review Committee of the Ministry of Health; in Tanzania from the National Health Research Ethics Review Committee and from the Tanzania Food and Drugs Authority; and in Kenya from the KEMRI Institutional Review Board and from the Kenyan Expert Committee on Clinical Trials/Pharmacy and Poisons Board.

An independent data safety monitoring committee was established to advise the sponsor if it was of the opinion that the ongoing trial had provided evidence that all or a specific subgroup(s) could either benefit from or be contraindicated for artesunate–mefloquine, on the basis of difference in the primary endpoint; evidence of drug-related toxic effects that outweighs the benefits of artesunate–mefloquine; or evidence that might reasonably be expected to influence patient management by clinicians who have become aware of any of the main trial results. The basis of any decision of the data safety monitoring committee was the content of any serious adverse event reports, all of which were received from the investigators without delay, and reviews of the study database done at regular intervals during the study.

Randomisation and masking

Eligible children were randomly assigned (1:1) to receive artesunate–mefloquine or artemether–lumefantrine. Treatment allocation was made using a computer-generated randomisation list and, for each patient, the allocated treatment was transmitted in a sealed envelope to the nurse or physician administering the treatment. This study was open label; however, laboratory technicians who did the parasitological assessments were masked to treatment allocation.

Procedures

The paediatric fixed-dose artesunate–mefloquine tablet (25 mg artesunate and 55 mg mefloquine hydrochloride, containing no flavouring [Farmanguinhos, Rio de Janeiro, Brazil]), is a round, smooth, biconvex, blue-coated tablet of 6·0 mm diameter; it was given once a day for 3 days, either as one tablet (for children aged 6–11 months) or two tablets (for children aged 12–59 months). The fixed-dose artemether–lumefantrine dispersible tablet (20 mg artemether and 120 mg lumefantrine, containing flavouring [Novartis Pharmaceuticals, Basel, Switzerland]), was dispersed in 200 mL milk (or breastmilk); it was given twice a day for 3 days, either as one tablet (for bodyweight ≥5 kg to <15 kg) or two tablets (for bodyweight ≥15 kg to <25 kg). Treatment was supervised and children observed for 60 min after treatment for possible vomiting. Test drug was readministered if vomiting occurred within 60 min. Patients with persistent vomiting and requiring more than a single repeat dose were excluded from the study and referred for further clinical management.

Children were followed up to day 63 after the start of treatment or to the first recurrence (first follow-up period). Patients with parasitaemia during follow-up were then switched to the alternative test treatment (except in Burkina Faso, where quinine was used for parasitaemia occurring within 28 days of the start of initial treatment, according to a national recommendation) and another 63 days of follow-up was started (second follow-up period).
945 randomly assigned to treatment  
390 Ilfunfo and Balinjhung, Burkina Faso  
113 Korogwe, Tanzania  
55 Bagamoyo, Tanzania  
40 Kilosa, Tanzania  
347 Kisuma, Kenya  

2339 patients screened for eligibility  
1394 ineligible  
555 low or no parasitaemia  
93 severe malaria or high parasitaemia  
49 mixed infection  
298 other disease present  
149 withdrew consent before randomisation  
175 antimalarial treatment within last 2 weeks  
77 other

472 assigned to artesunate–mefloquine (3-day treatment in hospital)  
472 assigned to artemether–lumefantrine (5-day treatment in hospital)

473 assigned to artesunate–mefloquine (3-day treatment in hospital)  
1 did not take study drug  

204 completed first 63-day follow-up period (assessments on days 7, 14, 21, 28, 35, 42, 49, 56, and 63)

202 completed first 63-day follow-up period (assessments on days 7, 14, 21, 28, 35, 42, 49, 56, and 63)

If recurrent parasitaemia, switch to the alternative treatment, but, in Burkina Faso and if before day 28, switch to quinine

62 completed second follow-up period (assessments on days 7, 28, and 63)

49 completed second follow-up period (assessments on days 7, 28, and 63)

472 (99.8%) included in intention-to-treat population

472 (100%) included in intention-to-treat population

65 excluded from per-protocol analysis  
31 major protocol violation*  
2 non-compliant with eligibility criteria  
17 last blood smear not performed  
5 treatment compliance of <80% or >120%  
5 PCR not done or missing  
5 took forbidden medication  
3 took wrong dose or failed to follow protocol  
4 discontinued study drug  
34 withdrew†  
7 parent’s decision  
1 investigator’s decision  
22 lost to follow-up  
2 took antibiotics with antimalarial activity  
2 took other antimalarial drug

65 excluded from per-protocol analysis  
22 major protocol violation*  
11 last blood smear not performed  
10 treatment compliance <80% or >120%  
5 PCR not done or missing  
1 took forbidden medication  
1 randomisation error  
11 study drug discontinued  
43 withdrew†  
16 parent’s decision  
22 lost to follow-up  
2 took antibiotics with antimalarial activity  
3 took other antimalarial drug

407 (86%) included in per-protocol population

407 (86%) included in per-protocol population

468 (98.9%) included in safety population

465 (98.5%) included in safety population

Figure 1: Trial profile
The intention-to-treat population consisted of all randomly allocated patients who received at least one dose of study drug. The per-protocol population consisted of all patients without a major protocol deviation, who were fully treatment compliant (defined as ≥80% and <120% intake of study drug), who had a primary endpoint at day 63, and who did not withdraw from study treatment (except for those who withdrew because of adverse events or an absence of efficacy). The safety analyses included all randomly allocated patients who took at least one dose of study drug and had at least one exploitable safety measure. *Some patients had more than one protocol violation. †Reason for withdrawal was other than recurrences or adverse event during follow-up.

Articles

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Outcomes

Treatment outcomes (classified using standard definitions and adjusted to the 63 days of follow-up) were adequate clinical and parasitological response (ACPR), early treatment failure, late parasitological failure, and late clinical failure. At intervals after the start of treatment, we calculated the gametocyte carriage (percentage of patients with gametocytes) and the parasite reduction ratio (baseline parasite count/parasite count at the specific interval).

The primary efficacy endpoint was PCR-corrected ACPR rate at day 63 (in the per-protocol population). The secondary efficacy endpoints were non-PCR-corrected ACPR rate at day 63; Kaplan-Meier analysis of number of patients with ACPR after PCR correction; proportion of patients with early treatment failure, late treatment failure, and late parasitological failure; proportion of patients with recrudescence or re-infection; PCR-corrected and non-PCR-corrected ACPR rates on days 28 and 42; proportion of patients with parasitaemia on days 1, 2, and 3; rate of gametocyte carriage; and proportion of patients with fever on days 1, 2, and 3. Pharmacokinetic analyses were also included as a secondary endpoint and will be presented elsewhere. The safety endpoints were proportion and severity of adverse events, time of any vomiting relative to and within 60 min of treatment, and proportions of serious adverse events and adverse events that led to treatment discontinuation.

Statistical analysis

The main features of the statistical methods were described in the protocol and detailed in the statistical analysis plan. The final version of the statistical analysis plan was signed before database lock and any analyses of results. The statistical analyses were done independently (Venn Life Sciences, Paris, France). The primary analysis tested the non-inferiority of artesunate–mefloquine over artemether–lumefantrine, using the per-protocol analysis of PCR-adjusted ACPR at day 63. The per-protocol population consisted of all patients without a major...
Table 2: Rates of adequate clinical and parasitological response (ACPR)

<table>
<thead>
<tr>
<th></th>
<th>Artesunate–mefloquine (per-protocol n=407; intention-to-treat n=472)</th>
<th>Artemether–lumefantrine (per-protocol n=407; intention-to-treat n=472)</th>
<th>Difference, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 63</strong></td>
<td></td>
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<tr>
<td>Per-protocol population</td>
<td>370 (90·9%)</td>
<td>365 (89·7%)</td>
<td>1·23 (-2.84 to 5.29)</td>
</tr>
<tr>
<td>Non-PCR-corrected ACPR</td>
<td>203 (49·4%)</td>
<td>203 (49·4%)</td>
<td>0·25 (-6.62 to 7.11)</td>
</tr>
<tr>
<td>Intention-to-treat population</td>
<td>376 (79·7%)</td>
<td>367 (77·8%)</td>
<td>1·91 (-3.31 to 7.13)</td>
</tr>
<tr>
<td>Non-PCR-corrected ACPR</td>
<td>203 (43·0%)</td>
<td>201 (42·6%)</td>
<td>0·42 (-5.89 to 6.74)</td>
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<tr>
<td><strong>Day 42</strong></td>
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<tr>
<td>Per-protocol population</td>
<td>381 (93·6%)</td>
<td>375 (92·1%)</td>
<td>1·47 (-2.06 to 5.01)</td>
</tr>
<tr>
<td>Non-PCR-corrected ACPR</td>
<td>253 (62·2%)</td>
<td>234 (57·5%)</td>
<td>4·67 (-2.06 to 11·4)</td>
</tr>
<tr>
<td>Intention-to-treat population</td>
<td>397 (84·1%)</td>
<td>384 (81·4%)</td>
<td>2·75 (-2.06 to 7.57)</td>
</tr>
<tr>
<td>Non-PCR-corrected ACPR</td>
<td>266 (56·4%)</td>
<td>243 (51·5%)</td>
<td>4·87 (-1.48 to 11·22)</td>
</tr>
<tr>
<td><strong>Day 28</strong></td>
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<tr>
<td>Per-protocol population</td>
<td>397 (97·5%)</td>
<td>385 (94·6%)</td>
<td>2·95 (0.29 to 5.61)</td>
</tr>
<tr>
<td>Non-PCR-corrected ACPR</td>
<td>331 (81·3%)</td>
<td>289 (71·0%)</td>
<td>10·12 (4.51 to 16·13)</td>
</tr>
<tr>
<td>Intention-to-treat population</td>
<td>422 (89·4%)</td>
<td>402 (85·2%)</td>
<td>4·24 (0.00 to 8.48)</td>
</tr>
<tr>
<td>Non-PCR-corrected ACPR</td>
<td>355 (75·2%)</td>
<td>306 (64·8%)</td>
<td>10·38 (4.57 to 16·19)</td>
</tr>
</tbody>
</table>

Data are n (%), unless otherwise indicated. The non-inferiority of artemesunate–mefloquine over artemether–lumefantrine is shown when the lower limit of the 95% CI for the difference between groups is greater than -5%.

Table 2: Rates of adequate clinical and parasitological response (ACPR)
–2.84% to 5.29%; table 2), showing non-inferiority of artesunate–mefloquine for the primary endpoint. Findings were similar when the intention-to-treat population was used in the analysis (difference in PCR-corrected ACPR rate at day 63 of 1.91%, 95% CI –3.31% to 7.13%; table 2).

Additional by-site analysis prespecified in the statistical analysis plan showed that the PCR-corrected ACPR rates at day 63 (per-protocol population) were similar between groups at each of the individual trial centres (Kilosa, Tanzania: 15 [88.2%] of 17 patients in the artesunate–mefloquine group vs 17 [89.5%] of 19 patients in the artesunate–mefloquine group vs 17 [89.5%] of 19 patients in the artesunate–mefloquine group; Bagamoyo, Tanzania: 21 [100%] of 21 vs 18 [85.7%] of 21; Korogwe, Tanzania: 41 [100%] of 41 vs 50 [98.0%] of 51; Kisumu, Kenya: 121 [81.8%] of 148 vs 108 [79.4%] of 136; Balonghin, Burkina Faso: 120 [97.6%] of 123 vs 117 [95.9%] of 122; Banfora, Burkina Faso: 52 [91.2%] of 57 vs 55 [94.8%] of 58). The small sample sizes prevented meaningful statistical analysis.

The non-PCR-corrected ACPR rates at day 63 were very similar in the two treatment groups, with 15 cases in the artesunate–mefloquine group and 17 cases in the artemether–lumefantrine group (0.4% of 472 patients); both patients were two early treatment failures, both in the artesunate–mefloquine group. At 72 h, no patients in either group had parasitaemia (none of 324 in the artesunate–mefloquine group vs none of 329 in the artemether–lumefantrine group. At 48 h, the proportions were 20 (6.3%) of 320 in the artemether–lumefantrine group and 24 (7.2%) of 332 in the artemether–lumefantrine group. At 72 h, no patients in either group had parasitaemia (none of 324 in the artesunate–mefloquine group and none of 329 in the artemether–lumefantrine group; per-protocol population). In both the per-protocol and intention-to-treat analyses, the mean time to similar proportions in the two treatment groups (table 2).
parasite clearance did not differ between treatment groups (analyses exclude those with missing data).

*P. falciparum* gametocytes were detected (thick blood smears) in few patients at baseline (intention-to-treat population: 22 [4·7%] of 471 patients in the artemether–lumefantrine group and 25 [5·3%] of 469 in the artesunate–mefloquine group; per-protocol population: 21 [5·2%] of 406 vs 22 [5·4%] of 404; analyses exclude those with missing data). At 48 h and 72 h (approximately 20% with missing data), the gametocyte carriage rates were 14 (4·4%) of 318 patients and seven (2·2%) of 319 patients in the artemether–lumefantrine group and 17 (5·2%) of 329 patients and 12 (3·8%) of 317 patients in the artemether–lumefantrine group, respectively (per-protocol population). No patient at days 28, 42, and 63 had detectable gametocytes.

Between 24 h and 48 h after the start of treatment, axillary temperatures of more than 37·5°C were significantly less frequent in patients in the artemether–mefloquine group (45 [11·1%] of 406) than in patients in the artemether–lumefantrine group (85 [20·9%] of 404; per-protocol population; p=0·0002; Fisher’s exact test). After 48 h, the proportions declined and were similar in both treatment groups. The mean time to attain an axillary temperature of 37·5°C or lower was slightly shorter with artemether–mefloquine (6·5 h) than with artemether–lumefantrine (7·5 h). These findings were unaffected by the number of patients taking paracetamol, which was similar between groups (between 24 h and 48 h: 302 patients in the artemether–mefloquine group vs 300 in the artemether–lumefantrine group). 21 (4·8%) of 436 patients in the artemether–mefloquine group had fever 72 h after the start of treatment versus 24 (5·4%) of 444 in the artemether–lumefantrine group.

Table 4 lists adverse events that occurred in more than 5% of patients, by study period and treatment group. The second follow-up of patients receiving, as rescue treatment, the alternative investigated drug; and the second follow-up of patients receiving, as rescue treatment, an antimalarial drug other than the alternative investigated drug. (analyses exclude those with missing data).

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### Table 4: Adverse events occurring in more than 5% of patients, by study period and treatment group.

<table>
<thead>
<tr>
<th>Event</th>
<th>Artesunate–mefloquine</th>
<th>Artemether–lumefantrine</th>
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</thead>
<tbody>
<tr>
<td>First 63-day follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>468</td>
<td>465</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
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<tr>
<td>Anaemia</td>
<td>130 (27·8%)</td>
<td>104 (22·4%)</td>
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<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
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<tr>
<td>Diarrhoea</td>
<td>57 (12·2%)</td>
<td>43 (9·2%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>69 (14·7%)</td>
<td>77 (16·6%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>34 (7·3%)</td>
<td>22 (4·7%)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td>56 (12·0%)</td>
<td>52 (11·2%)</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>27 (5·8%)</td>
<td>19 (4·1%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>24 (5·1%)</td>
<td>21 (4·5%)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>41 (8·5%)</td>
<td>48 (10·3%)</td>
</tr>
<tr>
<td>Tinea capitis</td>
<td>38 (8·1%)</td>
<td>19 (4·1%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>93 (19·9%)</td>
<td>87 (18·2%)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>34 (7·3%)</td>
<td>23 (4·9%)</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>98 (20·9%)</td>
<td>92 (19·8%)</td>
</tr>
<tr>
<td>Rhinorrhoea</td>
<td>40 (8·5%)</td>
<td>30 (6·5%)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>32 (6·8%)</td>
<td>22 (4·7%)</td>
</tr>
<tr>
<td>Second 63-day follow-up after treatment with the alternative test treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>192</td>
<td>171</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>10 (5·2%)</td>
<td>4 (2·3%)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td>6 (3·1%)</td>
<td>9 (5·3%)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>5 (2·6%)</td>
<td>12 (7·0%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>19 (9·9%)</td>
<td>16 (9·4%)</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>18 (9·4%)</td>
<td>15 (8·8%)</td>
</tr>
<tr>
<td>Second 63-day follow-up after treatment with antimalarial other than artemether–mefloquine or artemether–lumefantrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>33</td>
<td>48</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>2 (6·1%)</td>
<td>1 (2·1%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1 (3·0%)</td>
<td>3 (6·3%)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malaria</td>
<td>4 (12·1%)</td>
<td>3 (6·3%)</td>
</tr>
<tr>
<td>Data are n (%). Data show adverse events occurring in more than 5% of patients during the first follow-up (up to day 63) or until the day before start of rescue treatment, the second follow-up of patients receiving, as rescue treatment, the alternative investigated drug; and the second follow-up of patients receiving, as rescue treatment, an antimalarial drug other than the alternative investigated drug.</td>
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</tr>
</tbody>
</table>
During the first follow-up period, nervous system disorders were infrequent overall but more frequent in the artesunate–mefloquine group than in the artemether–lumefantrine group (ten [2·1%] of 468 patients vs five [1·1%] of 465). Six patients in the artesunate–mefloquine group had convulsions or febrile convulsions and two patients in the artemether–lumefantrine group had convulsions, with two patients in each treatment group having such events during the 3 days of treatment. The frequencies of the other CNS adverse events, headache and lethargy, were similar between groups: three (0·6%) patients in the artesunate–mefloquine group and two (0·4%) patients in the artemether–lumefantrine group had headache; one (0·2%) patient in each group had lethargy. However, none of the CNS adverse events were deemed related to study treatment by the investigator or led to study treatment discontinuation or were serious adverse events. No psychiatric disorders were reported in any patient.

The proportion of patients presenting with early vomiting was similar between groups (71 [15·3%] of 463 patients in the artesunate–mefloquine group vs 79 [16·8%] of 471 in the artemether–lumefantrine group in any of the three dosing days), when considering the two artemether–lumefantrine daily doses together (appendix). The overall proportion per day decreased from 10·5% (98 of 930 patients) to 3·5% (32 of 933 patients) over the 3 days and most (>90%) children had at least one adverse event; a non-significant greater proportion of patients in the artesunate–mefloquine group had at least one serious adverse event, which were all possibly related to treatment. The frequency of serious adverse events was generally lower than in the first 63-day follow-up period and proportions were similar between the two treatment groups (appendix), possibly influenced by the lower frequency of visits during the second follow-up period. During this follow-up, the relation of adverse events to rescue treatment was only recorded in the centres in Burkina Faso, where no patient had an adverse event that was at least possibly related to treatment. The frequency of serious adverse events was also lower in the second 63-day follow-up period than in the first 63-day follow-up. Five patients treated with artesunate–lumefantrine as rescue treatment and two patients treated with artesunate–mefloquine as rescue treatment had at least one serious adverse event, which were all infections. Four and two patients in the respective groups of patients receiving rescue treatment other than artesunate–mefloquine or artemether–lumefantrine had at least one serious adverse event (either anaemia or infection).

**Discussion**

Our study provides important findings on the use of artesunate–mefloquine in the treatment of children younger than 5 years with uncomplicated *P falciparum* infection in Africa. It included a 63-day follow-up and an extensive safety assessment, and provides much-needed additional data on the use of artesunate–mefloquine in young African children. To our knowledge, this is the first trial of artesunate–mefloquine with a design compliant with current WHO guidelines in this especially vulnerable population.

The primary outcome, the rate of PCR-corrected ACPR at day 63 in the per-protocol population, was very similar in the artesunate–mefloquine and artemether–lumefantrine groups, with a percentage difference that had a lower bound of the 95% CI (−2·84%) greater than −5%. Thus, the criterion for the non-inferiority of artesunate–mefloquine to artemether–lumefantrine was met in young African children. The cure rates were similar to, although a little below, published rates for the two ACTs in mixed-aged populations in non-African countries, including trials with the fixed-dose artesunate–mefloquine tablet. We found no published data on 63-day cure rates for artesunate–mefloquine and artemether–lumefantrine in young children. All our...
patients were admitted to hospital for treatment and compliance was 100%, or just less, at all sites during the 3 days of treatment.

Previously, in studies in populations of mixed age in Senegal, Nigeria, Mali, and Kenya, artesunate–mefloquine was reported to be effective and well tolerated. These trials each used a follow-up of just 28 days, which might be too short to fully assess accurate cure rates and safety of artesunate–mefloquine because of mefloquine’s slow elimination. The low deployment of artesunate–mefloquine in Africa might result from the early vomiting and neuropsychiatric effects reported with mefloquine monotherapy, and also from the absence of a fixed-dose paediatric formulation. In this study we tested a fixed-dose artesunate–mefloquine tablet, designed to optimise the compliance of a 3-day combination treatment and to improve the tolerability of mefloquine by dividing the dose into three equal daily doses. We found that the fixed-dose artesunate–mefloquine tablet has a good safety profile that is similar to that of artemether–lumefantrine, with a low risk of repeated early vomiting during the treatment period and a low incidence of neuropsychiatric adverse events, which were deemed unrelated to study treatment.

The parasite clearance rate was rapid with both ACTs, with most children showing complete parasite clearance within 2 days. The parasite reduction ratios for both artesunate–mefloquine and artemether–lumefantrine are high compared with published values. Artesunate–mefloquine was marginally superior to artemether–lumefantrine in the rapidity of parasite clearance and the slightly more rapid decline in fever. Although these differences might be chance findings, the high parasite reduction ratios serve to strengthen our evidence of the efficacy of artesunate–mefloquine in African children by comparison with artemether–lumefantrine. Rapid parasite clearance and fever reduction are essential to ensure compliance with antimalarial treatment.

There were only two early treatment failures overall. By day 63, the rates of late treatment failure were similar for artesunate–mefloquine and artemether–lumefantrine, and mostly caused by re-infection. We detected that, up to day 49, the cumulative rates of recrudescence and of re-infection were each delayed by about 7 days with artesunate–mefloquine relative to those with artemether–lumefantrine. A similar finding was reported by Sagara and colleagues in their trial of artesunate–mefloquine versus artemether–lumefantrine in Mali. These findings suggest that artesunate–mefloquine provides longer protection against malaria than artemether–lumefantrine, possibly because of the longer half-life of mefloquine compared with lumefantrine, with reported median terminal clearance half-lives of about 20 days and 5 days, respectively. By day 63, the comparative efficacy is unaffected by the different clearance rates.

We found the safety profiles of artesunate–mefloquine and artemether–lumefantrine to be similar, with low frequencies of nervous system disorders and no psychiatric disorders. Our investigators were instructed to look for possible neuropsychiatric disorders, but no active neurological testing was done. Relevant neuropsychiatric adverse events are difficult to identify in young children and are consequently under-reported. Another study of artesunate–mefloquine (fixed dose of 50 mg artesunate and 125 mg mefloquine per day for 3 days) in 213 young children in Africa, with a 63-day follow-up, actively tested for neuropsychiatric effects (using standard infant neurological tests) and reported mild-to-moderate, spontaneously resolving neuropsychiatric adverse events, with sleeping disorders being the most common (2–3% of patients). Notably, because of the risk of serious psychiatric side-effects, the latest WHO antimalarial treatment guideline recommends an interval of 60 days between consecutive periods of mefloquine treatment.

In children younger than 5 years, mefloquine has been associated with early vomiting causing impaired absorption, but studies, including in young children, show that the incidence of early vomiting is substantially reduced by splitting the mefloquine dose across successive days and by coadministration with artesunate. In a mixed-aged population, early vomiting was reported in only 3% of patients treated with fixed-dose artesunate–mefloquine. Dividing the mefloquine dose across 2 or 3 days does not affect efficacy because of its slow clearance. In our study population, about 10% had early vomiting but less than 10% of these patients vomited after readministration. Lower rates were measured in mixed-aged populations in large trials in Brazil and in Burma, with the same fixed-dose artesunate–mefloquine tablet that we tested here.

Our study has limitations. It is an open-labelled study and was not powered for safety. However, to our knowledge, it is the largest randomised controlled trial providing efficacy and safety data for artesunate–mefloquine in children in Africa. We conclude that fixed-dose artesunate–mefloquine is safe and effective in treating young African children with uncomplicated malaria. This combination is shown to be as effective as artemether–lumefantrine, which is recognised as a safe and efficacious antimalarial drug in children. Our data are derived from a large trial, optimally designed for testing an ACT, such as artesunate–mefloquine, with a slowly cleared active component. We believe our results support the deployment of fixed-dose artesunate–mefloquine in young children in Africa. Our findings should have important implications for health policy in sub-Saharan Africa.

Contributors
SBS, BO, JPAL, AM, and ZM supervised the execution of the study at the different sites. AO, JBY, KOO, SG, EM, and JSN supported the field trial coordination and were involved in data collection. IA coordinated the data management and data analyses activities. FA supported the data analyses plan, data analyses, was involved in the interpretation of the results, and co-authored the clinical study report. JV participated in the database cleaning and data analyses plan, and contributed to the clinical study report and the manuscript. NS participated in study design and protocol.


