Efficacy of 3-day low dose quinine plus clindamycin versus artemether-lumefantrine for the treatment of uncomplicated *Plasmodium falciparum* malaria in Kenyan children (CLINDAQUINE): an open-label randomized trial

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**Abstract**

**Background:** The World Health Organization recommends quinine plus clindamycin as first-line treatment of malaria in the first trimester of pregnancy and as a second-line treatment for uncomplicated falciparum malaria when artemisinin-based drug combinations are not available. The efficacy of quinine plus clindamycin was compared with that of artemether-lumefantrine in the treatment of uncomplicated *Plasmodium falciparum* malaria in children below 5 years of age.

**Methods:** An open-label, phase 3, randomized trial was conducted in western Kenya. Children aged 6–59 months with uncomplicated falciparum malaria were randomly assigned (1:1) via a computer-generated randomization list to receive 3 days of twice a day treatment with either oral quinine (20 mg/kg/day) plus clindamycin (20 mg/kg/day) or artemether-lumefantrine (artemether 20 mg, lumefantrine 120 mg) as one (for those weighing 5–14 kg) or two (for those weighing 15–24 kg) tablets per dose. The primary outcome was a PCR-corrected rate of adequate clinical and parasitological response (ACPR) on day 28 in the per-protocol population.

**Results:** Of the 384 children enrolled, 182/192 (94.8%) receiving quinine plus clindamycin and 171/192 (89.1%) receiving artemether-lumefantrine completed the study. The PCR-corrected ACPR rate was 44.0% (80 children) in the quinine plus clindamycin group and 97.1% (166 children) in the artemether-lumefantrine group (treatment difference −53.1%, 95% CI −43.5% to −62.7%). At 72 h after starting treatment, 50.3% (94 children) in the quinine plus clindamycin group were still parasitaemic compared with 0.5% (1 child) in the artemether-lumefantrine group. Three cases of severe malaria were recorded as serious adverse events in the quinine plus clindamycin group.

**Conclusions:** The study found no evidence to support the use of a 3-day low dose course of quinine plus clindamycin in the treatment of uncomplicated falciparum malaria in children under 5 years of age in Kenya, where artemether-lumefantrine is still effective.

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Background
Malaria is a major public health problem in sub-Saharan Africa. In 2018, malaria caused 405,000 deaths, globally, out of whom 67% were children below 5 years of age and 94% were residents of sub-Saharan Africa [1]. Universal implementation of artemisinin-based combination therapy (ACT) for malaria treatment and insecticide-treated bed nets for vector control comprises the main strategies for reducing malaria-related morbidity and mortality [2]. The World Health Organization (WHO) currently recommends five artemisinin-based combinations for the first-line treatment of uncomplicated Plasmodium falciparum infection, the most virulent and predominant malaria parasite in sub-Saharan Africa [2]. ACT is known to rapidly clear parasitaemia, delay the development of drug resistance, and reduce gametocyte carriage [3]. However, a high proportion of malaria cases in sub-Saharan Africa do not receive ACT due to factors associated with stock-out of drugs or poor access to healthcare providers [4]. In some settings, widespread deployment of ACT for malaria treatment has already resulted in significant reductions in malaria-related morbidity, mortality and admissions [5–8]. Artemisinin resistance (defined as delayed parasite clearance) has been reported in Southeast Asia and most recently in sub-Saharan Africa [9–11]. Safe and effective alternatives to ACT are necessary.

In 2010, the WHO recommended second-line anti-malarial drug combinations with either an alternative ACT or a combination of quinine or artesunate with an antibiotic with anti-malarial activity (clindamycin, tetracycline, or doxycycline) [12]. However, data on the comparative efficacy between first-line and second-line anti-malarial combinations are scarce, as most research into anti-malarial drug efficacy has focused on comparing the efficacy of first-line treatments with an alternative artemisinin-based combination. The 2010 version of the WHO guidelines for the treatment of malaria recommended seven days of quinine plus clindamycin as a first-line treatment for malaria in the first trimester of pregnancy and as a second-line anti-malarial drug when ACT is not available [12]. The same guidelines recommended quinine for the treatment of severe falciparum malaria, uncomplicated malaria in pregnant women and drug-resistant malaria. Clindamycin is a lincosamide antibiotic with anti-malarial activities, used for the treatment of anaerobic and gram-positive bacterial infections, babesiosis, toxoplasmosis, and Pneumocystis jirovecii pneumonia [13]. Clindamycin is effective against P. falciparum, but it is a slow-acting drug with a mean parasite clearance time of four to six days and a mean fever clearance time of three to five days [14, 15]. In combination, the relatively fast action of quinine overcomes the drawback arising from the slow-action of clindamycin.

One systematic review of seven randomized trials found inconclusive evidence on the efficacy of quinine plus clindamycin compared with other anti-malarials (alone or in combination) in the treatment of uncomplicated falciparum malaria [16]. Another systematic review of 14 randomized trials found no difference in efficacy between quinine plus antibiotics compared with artemisinin-based and non-artemisinin-based combinations in the treatment of uncomplicated falciparum malaria [17]. There is no published study comparing the efficacy of quinine plus clindamycin with the recommended artemisinin-based combinations in the primary treatment of uncomplicated falciparum malaria.

In Kenya, the first-line anti-malarial for treatment of children and adults with uncomplicated falciparum is artemether-lumefantrine, which is generally well-tolerated and considered a highly effective fixed-dose anti-malarial drug combination. The efficacy and safety of quinine plus clindamycin was compared to that of artemether-lumefantrine in the treatment of uncomplicated falciparum malaria in children younger than 5 years of age in western Kenya.

Methods
Study design
This was an open-label, phase 3, randomized efficacy study to compare the rates of adequate clinical and parasitological response (ACPR) and safety between quinine plus clindamycin and artemether-lumefantrine in the treatment of uncomplicated falciparum malaria in Kenyan children aged below 5 years. This study was conducted at the outpatient clinics of Ahero sub-County Referral hospital (Kisumu County) and Homabay County Referral hospital (Homabay County), in western Kenya. The trial was conducted per the Declaration of Helsinki and Good Clinical Practice guidelines.

Participants
Children were eligible for inclusion if they were aged six to 59 months, had an axillary temperature of 37.5°C or more or a history of fever in the past 24 h, microscopically-confirmed P. falciparum mono-infection and asexual parasite density of 2000 to 200,000 parasites/
also received 10 mg/kg of quinine (Universal Corpora-
oral suspension containing 75 mg/5 mL of clindamycin
administered twice daily (12 hourly) for three days as an
Kenyan National Quality Control Laboratory, Nairobi.
tration, while the quality of quinine was certified by the
US Federal Drug Adminis-
tion Ltd), rounded to the nearest half tablet, adminis-
ted twice daily (12 hourly) for three days as oral
dosage of 20 mg/kg of quinine. The quality of the clin-
damycin was certified by the US Federal Drug Admin-
istration, while the quality of quinine was certified by the
Kenyan National Quality Control Laboratory, Nairobi.

Randomization and masking
Children were randomly assigned to receive either qui-
nine plus clindamycin or artemether-lumefantrine, in a
ratio of 1:1. Treatment allocation was made in blocks of
eight according to a computer-generated randomization
list by a statistician not associated with patient manage-
ment. Sequentially numbered, sealed envelopes contain-
ing the treatment assignment were prepared according
to the randomization list. Soon after inclusion, the study
nurse allocated treatment by sequentially opening the
envelope corresponding to the treatment number. The
study was open-label, therefore, investigators and partici-
ants (or their parents or guardians) were aware of treat-
ment allocation but laboratory technicians reading blood
films were not aware of the study arm on which partici-
ants were allocated.

Procedures
Children with suspected malaria during an outpatient
visit were offered a screening blood smear test for malaria
parasitaemia. Children who tested positive for malaria
and met other study inclusion criteria were enrolled. At
enrolment, a standardized medical history was taken and
the children were clinically examined. Soon after rand-
omization, children received the first directly observed
dose of the study treatment. Children were admitted to
the paediatric ward for three days to receive observed
study treatment and for close monitoring.

Children assigned to the quinine plus clindamycin
arm received 10 mg/kg of clindamycin (Cleocin paed-
iatric® flavoured granules for oral suspension, Pfizer)
administered twice daily (12 hourly) for three days as an
oral suspension containing 75 mg/5 mL of clindamycin
for a total daily dosage of 20 mg/kg of clindamycin. They
also received 10 mg/kg of quinine (Universal Corpora-
tion Ltd), rounded to the nearest half tablet, adminis-
tered twice daily (12 hourly) for three days as oral
tables containing 300 mg of quinine for a total daily
dosage of 20 mg/kg of quinine. The quality of the clin-
damycin was certified by the US Federal Drug Adminis-
tration, while the quality of quinine was certified by the
Kenyan National Quality Control Laboratory, Nairobi.

Children in the artemether-lumefantrine arm received
the WHO-recommended weight-specific artemether-
lumefantrine blister packs (Coartem; Novartis Pharma,
Basel, Switzerland); The first artemether-lumefantrine
dose was given at time 0 followed by a second dose
8 h later; on days 2 and 3, the child was treated twice
per day. The dose of artemether-lumefantrine treat-
ment was based on the child’s weight: 5–15 kg, 20 mg
artemether + 120 mg lumefantrine; 15 to < 25 kg, 40 mg
artemether + 240 mg lumefantrine. Administration of
all the study drugs was directly observed by the study
nurses. All the study drugs were dispensed in a small
volume of water and dispensed by the study nurses. All
children received milk 30 min before drug administra-
tion. Children were observed for 1 h after taking the
drug to ensure retention; those who vomited within the
first 30 min received a full repeat dose; those vomiting
between 30–60 min received half the dose. Children
with repeated vomiting were withdrawn from the study.

Paracetamol syrup was administered to all children
with temperatures ≥ 38.0°C.

Children were evaluated daily in the ward and
12-hourly blood slides were taken until two consecutive
negative blood slides were obtained. Children were dis-
charged home after they were clinically stable and had
a negative slide. After discharge, the children were fol-
lowed up for 28 days. Clinical reassessments were made
on days 7, 14, 21, 28 and on any other day if the child
was perceived to be unwell. During the follow-up visits,
a standard medical history was taken, the axillary tem-
perature recorded, physical examination performed,
blood smears and filter paper for parasite genotyping
taken. On days 0 and 28, a blood sample was taken for
complete blood count and biochemistry. Post-treat-
ment, children who developed signs of severe malaria
were treated using parenteral artesunate or quinine;
children with persistent parasitaemia or who developed
recurrent parasitaemia without signs of severe malaria
were treated using dihydroartemisinin-piperazine
(Duo-cotexcin; Beijing Holley-Cotec, Beijing, China)
once daily for three days, according to the national
malaria treatment guidelines. Children who could not
continue with the study for any reason, including, ina-
bility to retain study medication due to repeated vom-
itting, progression to severe malaria, development of
concomitant illness that could interfere with outcome
classification, development of serious adverse events,
ingestion of drugs with anti-malarial activities, with-
drawal of consent or those who could not be traced,
were withdrawn from the study. Adverse events and
serious adverse events were assessed throughout the
study and if found, were monitored until they resolved.
**Laboratory assessments**

Capillary blood samples were obtained by finger prick at enrolment and follow up and were used to test for the presence of malaria parasites, determine haemoglobin (Hb) and for haematological and biochemical assessments. Thick and thin blood smears were prepared, stained with Giemsa and examined for malaria parasites. Parasite density was determined by counting the number of asexual parasites against 200 WBC in a thick smear. If *P. falciparum* gametocytes were detected, a gametocyte count was done per 500 leucocytes. Two microscopists independently read each smear, and parasite densities were computed by averaging the two counts. A third microscopist re-examined the smears if there were discordant readings with discordant results (difference in species or difference in parasite density > 50%).

The Hb level was measured using a portable HemoCue haemoglobinometer (HemoCue, Angelholm, Sweden). The haematology assessment was performed using Coulter Act Diff 2 Hematology Analyzer (Beckman Coulter, Brea, CA, USA) while the biochemical tests (alanine aminotransferase and creatinine) were done using a Reflotron Plus Chemistry Analyzer (Roche Diagnostics, Basel, Switzerland).

A dry filter paper blood spot was collected on day 0 and during follow up and used for parasite genotyping by polymerase chain reaction (PCR) analysis. To differentiate infections classified as recrudescence (same parasite strain) from a newly acquired infection (different parasite strain), a genotypic analysis based on merozoite surface protein-1 (*msp1*), merozoite surface protein-2 (*msp2*) and glutamate-rich protein (*glurp*) was performed on paired filter paper blood samples (day 0 and day of recurrent parasitaemia) [18].

**Outcome classification**

The primary efficacy endpoint was PCR-corrected adequate clinical and parasitological response (ACPR) on day 28 in the per-protocol population. ACPR is defined by WHO as the absence of parasitaemia on day 28, irrespective of axillary temperature, in a participant who has not previously met the criteria for early treatment failure, late clinical failure or late parasitological failure [2]. Secondary efficacy endpoints were assessed in the per-protocol population, and included the proportion of children with early treatment failure (with a modified definition to include presence of parasitaemia with or without signs of severe malaria), late parasitological failure and late clinical failure; the proportion of children with recrudescence or re-infection; the proportion of children with parasitaemia on day 2 and 3; the rate of gametocyte carriage; change in Hb from day 0 and the proportion of children with anaemia (Hb < 11 g/dL).

The safety endpoints included adverse events in children who had received at least one dose of the study medication. Only those events which occurred after the start of treatment or which worsened after starting treatment were considered. An adverse event was defined as any undesirable medical occurrence following administration of study treatment, irrespective of its causal relationship to the study medications. Adverse events were considered as serious if they were fatal, life-threatening, resulted in prolonged hospitalization, caused persistent/ significant disability, or required specific medical or surgical intervention to prevent permanent impairment.

**Statistical analysis**

With 80% power and a two-sided type I error of 0.05, we calculated that 167 children would be needed in each treatment group to detect a significant difference in ACPR rate, assuming a PCR-corrected ACPR rate of 97.4% with artether-lumefantrine [19] and 90% with quinine plus clindamycin by day 28 after treatment [13]. An additional 25 children per treatment group were included to allow for loss to follow up and non-compliance. The total sample size was 384 (i.e., 192 per treatment group).

Data collected were recorded on paper-based case-record forms, entered into computers using Epi info (US Centers for Disease Control, Atlanta) and analyzed with SPSS for Windows (version 16.0) and Stata (version 14.0). We summarized the baseline characteristics using descriptive statistics. The efficacy was analysed using two methods: per-protocol analysis, where children who were withdrawn from the study or who were lost to follow-up were excluded from the analysis, and an intention to treat analysis, where all enrolled children are included in the analysis until the last day before drop-out.

Proportions were compared between treatment groups using the chi-squared test. For all comparisons, artether-lumefantrine served as the reference group. Results are presented as risk differences, together with their 95% confidence intervals (CI). Normally distributed continuous variables were compared using the Student’s *t*-test. A two-tailed *p*-value less than 0.05 was considered statistically significant. For analysis of drug safety, the percentage of children who had each adverse event were compared between treatment groups.

**Results**

**Participants**

Between March 2014 and November 2014, a total of 1427 children were screened for eligibility; of these, 1043 were excluded for various reasons, including negative malaria smear, low parasite density, mixed plasmodial infections, recent ingestion of anti-malarial drugs, concomitant...
illnesses or lack of consent. A total of 384 children were enrolled and randomized equally to receive quinine plus clindamycin (n = 192) or artemether-lumefantrine (n = 192). At baseline, the children in both treatment groups were comparable on all variables that were measured, except for the proportion of anaemia which was significantly higher in the artemether-lumefantrine group (see Table 1). After enrollment, 4.2% (8/192) of children in the quinine plus clindamycin arm and 5.7% (11/192) in the artemether-lumefantrine arm were lost to follow up. Similarly, 1.0% (2 children) in the quinine plus clindamycin arm and 5.2% (10 children) in the artemether-lumefantrine arm were withdrawn from the study for various reasons. Thus, the primary outcomes were available for 94.8% (182 children) in the quinine plus clindamycin and 89.1% (171 children) in the artemether-lumefantrine arms, respectively (Fig. 1).

Efficacy

The proportion of children with an adequate clinical and parasitological response (ACPR) was significantly lower in the quinine plus clindamycin group compared with the artemether-lumefantrine group, before and after adjusting the findings by genotyping. For the per-protocol population, the PCR-corrected ACPR was achieved in 44% (80/182) of the children (95% CI 36.8% to 51.2%) in the quinine plus clindamycin group and 97.1% (166/171) of the children (95% CI 94.6% to 99.6%) in the artemether-lumefantrine group (treatment difference – 53.1%, 95% CI -43.5% to – 62.7%). The PCR-corrected and PCR-uncorrected results were similar in the intention-to-treat population (see Table 2).

A significantly higher proportion of children in the quinine plus clindamycin group developed early treatment failure, 53.8% (98/182) compared with 0.6% (1/171) in the artemether-lumefantrine group (treatment difference 50.5%, 95% CI 43.3% to 57.6%) (see Table 3).

A total of 62 children developed recurrent parasitaemia between day 7 and day 28. Overall, 14.3% (26 children) of children on the quinine plus clindamycin arm compared with 21.1% (36 children) on the artemether-lumefantrine arm developed recurrent parasitaemia. 12.1% (22 children) of late treatment failure were categorized as re-infections on the quinine plus clindamycin arm compared with 18.7% (32 children) in the artemether-lumefantrine arm. Similar proportions (2%) of recrudescent infections were found between those on quinine plus clindamycin arm compared with those on the artemether-lumefantrine arm (see Table 3).

Parasite clearance was significantly slower in the quinine plus clindamycin group than in the artemether-lumefantrine group. By day 3, 50.3% (94/187) of the children in the quinine plus clindamycin group were parasitaemic compared with 0.5% (1/188) children in the artemether-lumefantrine group (difference 49.8%, 95% CI 42.6% to 57.0%). In both treatment groups, parasitaemia was cleared on day 7 (see Table 3).

In both treatment groups, the proportion of children with gametocytes decreased during follow up. However, this decrease was faster with artemether-lumefantrine compared to quinine plus clindamycin (see Table 3).

By day 28, the prevalence of anaemia had reduced by 31% (from 69.8% at enrollment to 38.8%) in the quinine plus clindamycin group and by 30.2% (from 75.5% at enrolment to 45.3%) in the artemether-lumefantrine group (p = 0.372) (Table 3). On day 28, the mean Hb concentration was 10.96 g/dl (SD 1.47) in the quinine plus clindamycin group and 10.68 g/dl (SD 1.29) in the

Table 1  Baseline characteristics of the study participants

| Variable                          | Quinine plus clindamycin | Artemether-lumefantrine |
|-----------------------------------|--------------------------|--------------------------|
| Number                            | 192                      | 192                      |
| Study Centre                      |                          |                          |
| Ahero sub-District Hospital       | 135                      | 141                      |
| Homabay District Hospital         | 57                       | 51                       |
| Mean age, months (SD)             | 31.7 (14.7)              | 33.2 (14.4)              |
| Male sex (%)                      | 98 (51.0%)               | 101 (52.6%)              |
| Mean axillary Temperature (°C) (SD) | 37.6 (1.0)              | 37.4 (1.0)              |
| Patients with fever, ≥ 38.0°C (%) | 69 (35.9%)               | 55 (28.6%)               |
| Median bodyweight (Kg) (IQR)      | 12.5 (6.0 to 20.0)       | 13.5 (6.5 to 24.0)       |
| Mean haemoglobin (g/dL) (SD)      | 9.84 (1.7)               | 9.84 (1.67)              |
| Patients with anaemia (%)         | 134 (69.8%)              | 145 (75.5%)              |
| Patients carrying gametocytes (%) | 8 (4.2%)                 | 6 (3.1%)                 |
| Geometric mean for asexual parasitaemia per µL (95%CI) | 54,173 (45,794 to 64,084) | 56,951 (48,813 to 66,447) |
artemether-lumefantrine group ($z = 1.341$, $p = 0.179$). The mean increase in Hb was significant within treatment groups but was not significantly different between the treatment groups (Table 4).

**Safety**

A total of 302 adverse event episodes were reported (Table 5). Overall, 74% (142/192) adverse events were observed in the quinine plus clindamycin group and 83% (160/192) in the artemether-lumefantrine group. The most common adverse events (> 5%) in the quinine plus clindamycin arm were anaemia, anorexia, cough, diarrhoea, runny nose, and weakness of the body, while on the artemether-lumefantrine, the most common were anaemia, anorexia, cough, diarrhoea, runny nose and skin rash.

Most of the adverse events were mild or moderate intensity. None of the adverse events was related to the study drugs. Three children treated using quinine plus clindamycin experienced a serious adverse event each. They all developed signs of severe malaria. All these children recovered completely after receiving treatment with intravenous artesunate with or without a blood transfusion for severe anaemia. There were no serious adverse events in the artemether-lumefantrine group. No child died in the study. Following the study treatment,
measures of liver and kidney function did not change significantly between the treatment groups (Table 4).

**Discussion**

Quinine plus clindamycin was significantly less effective than artemether-lumefantrine in the treatment of uncomplicated malaria in Kenyan children. Three days of treatment with quinine plus clindamycin was associated with a significantly low cure rate, a slower parasite clearance rate, a higher risk of early treatment failure and a greater predisposition to developing serious adverse events. Overall, this study does not support the treatment of young children with uncomplicated falciparum malaria using a short course of quinine plus clindamycin. Most of the recurrent infections in this study were due to re-infections, indicating a high malaria transmission in the study site.

Artemisinin-based combination therapy (ACT) is the recommended first-line treatment for patients diagnosed with uncomplicated falciparum malaria in all malaria-endemic regions. In 2010, the WHO recommended second-line treatment with a combination of quinine or artesunate with an antibiotic with anti-malarial activity [12]. However, PCR-corrected ACPR rates of 44% was found with quinine plus clindamycin and 97% with artemether-lumefantrine on day 28 after treatment of children with uncomplicated falciparum malaria in western Kenya. This is inconsistent with the findings of the QUINACT trial or the review by Song et al. [17, 20]. In the QUINACT trial, quinine plus clindamycin was
administered for 5 to 7 days and had similar efficacy as artesunate plus amodiaquine and artemether-lumefantrine which were administered as rescue treatment for recurrent falciparum malaria in children [20]. A review comparing quinine-based with non-artemisinin-based and artemisinin-based anti-malarials found no significant difference in efficacy between quinine plus antibiotics compared with artemisinin-based combination treatments [17].

Some explanations for the low unexpected cure rates following treatment with quinine plus clindamycin can be posited. First, in this study, we gave quinine plus clindamycin treatment twice daily for three days based on a meta-analysis which found that a 3-day regimen of 12-hourly quinine plus clindamycin treatment was more effective than quinine alone, and on the assumption that a shorter treatment course would enhance compliance and minimize the incidence of adverse events [13]. The 2015, the WHO guidelines recommended that treatment with quinine plus clindamycin should be administered for seven days [2]. The same guidelines recommend that intravenous quinine should be given at a dose of 10 mg/kg three times a day (total daily dosage of 30 mg/kg) for 7 days. Lower doses of quinine (20 mg/kg/day, instead of 30 mg/kg/day) or shorter treatment courses have been associated with a lower treatment efficacy and lower risks of adverse events [21]. In the QUINACT study, quinine plus clindamycin was administered for 5 to 7 days and resulted in a higher efficacy compared to ACT which were given for 3 days [20]. It is unclear whether superior results would have been obtained by increasing the duration or frequency of treatment to 7 days. Secondly, the low cure rates observed in this study may have resulted from the low efficacy of quinine, suggested by reports of declining quinine efficacy in malaria-endemic areas [22–26]. Reduced sensitivity of malaria parasites to quinine therapy may result from easy accessibility and overuse. However, the efficacy of quinine in the treatment of uncomplicated falciparum malaria has not been evaluated in western Kenya. Lastly, the slow action of clindamycin may have contributed to the elevated risk of early treatment failure and reduced rate of ACPR. A total of 98 children treated with quinine plus clindamycin developed early treatment failure which was defined as parasitaemia on day 3, with or without signs of severe malaria. This may have resulted from the slow action of clindamycin with the subsequent delay in parasite and fever clearance [13].

Delayed clearance of malaria parasites by the third day after treatment is a strong predictor of treatment failure. By the third day after treatment, half of the children treated with quinine plus clindamycin in our study were still parasitaemic, consistent with the QUINACT trial that found a significantly slower rate of parasite clearance in children treated with quinine plus clindamycin compared to those who received ACT for recurrent falciparum malaria in children [20].

### Table 4 Haematological and biochemical assessments

|                      | Quinine plus clindamycin | Artemether-lumefantrine | P-value |
|----------------------|--------------------------|-------------------------|---------|
|                      | No. tested Mean (SD)     | No. tested Mean (SD)    |         |
| White blood cell count (10^9/L) |                       |                        |         |
| Day 0                | 132 9.31 (4.2)           | 134 10.10 (7.8)        | 0.311   |
| Day 28               | 51 7.92 (3.3)            | 118 7.71 (3.3)         | 0.701   |
| P value              | 0.035                    | 0.002                  |         |
| Lymphocyte count (%) |                          |                        |         |
| Day 0                | 131 30.06 (12.7)         | 133 34.5 (42.1)        | 0.252   |
| Day 28               | 50 45.2 (14.7)           | 118 47.4 (13.5)        | 0.345   |
| <0.0001              | 0.0016                   |                        |         |
| Red blood cell count (10^12/L) |                    |                        |         |
| Day 0                | 132 4.38 (4.3)           | 133 3.93 (1.00)        | 0.451   |
| Day 28               | 51 4.56 (1.05)           | 118 4.39 (0.90)        | 0.275   |
| 0.768                | 0.0002                   |                        |         |
| Haemoglobin concentration (g/dl) |                    |                        |         |
| Day 0                | 131 9.64 (1.8)           | 133 9.8 (1.6)          | 0.425   |
| Day 28               | 51 10.9 (1.5)            | 118 10.6 (1.2)         | 0.070   |
| <0.0001              | <0.0001                  |                        |         |
| Alkaline phosphatase concentration (U/L) |                |                        |         |
| Day 0                | 164 21.1 (14.7)          | 164 20.5 (18.5)        | 0.738   |
| Day 28               | 58 17.7 (8.7)            | 129 17.7 (7.7)         | 0.997   |
| 0.098                | 0.108                    |                        |         |
| Creatinine concentration (µmol/L) |                    |                        |         |
| Day 0                | 164 44.3 (16.5)          | 164 46.5 (31.9)        | 0.432   |
| Day 28               | 58 49.2 (16.6)           | 129 46.1 (15.2)        | 0.219   |
| 0.054                | 0.896                    |                        |         |

### Table 5 Adverse events

| Adverse event              | Quinine plus clindamycin N = 192 (%) | Artemether-lumefantrine N = 192 (%) |
|---------------------------|--------------------------------------|-------------------------------------|
| Anaemia                   | 32 (17)                              | 28 (14.6)                           |
| Abdominal pain            | 2 (1)                                | 2 (1)                               |
| Anorexia                  | 17 (8.9)                             | 21 (10.9)                           |
| Cough                     | 26 (13.5)                            | 39 (20.3)                           |
| Diarrhoea                 | 19 (9.9)                             | 12 (6.3)                            |
| Itchy skin                | 4 (2.1)                              | 2 (1)                               |
| Runny nose                | 12 (6.3)                             | 36 (18.8)                           |
| Skin rash                 | 6 (3.1)                              | 10 (5.2)                            |
| Weakness of the body      | 14 (7.3)                             | 7 (3.6)                             |
| Vomiting                  | 7 (3.6)                              | 3 (1.6)                             |
| Severe malaria            | 3 (2)                                | 0                                   |
|                           | 142                                  | 160                                 |
falciparum malaria [20]. On day three, 52% (95/182) of children randomized to quinine plus clindamycin who were still parasitaemic were treated with dihydroartemisinin-piperaquine, as rescue treatment and they had complete parasite clearance by day 7. It is not clear whether the parasites would have cleared on day 7 without the rescue treatment. However, the risk of reinfection and recrudescence on the quinine plus clindamycin arm was possibly reduced by the post-treatment prophylaxis arising from the long half-life of piperaquine. In the revised edition of WHO guidelines (2015) for the treatment of malaria, based on expert opinion, quinine plus clindamycin was abandoned from the list of second-line treatments for uncomplicated falciparum malaria due to poor adherence associated with the 7-day treatment [2]. This study provides the evidence to support this decision. Quinine plus clindamycin may be suitable for the treatment of uncomplicated falciparum malaria in children for whom tetracycline and doxycycline are contraindicated. However, the combination may be disadvantaged by the co-administration of the regimens, the complex dosing regime, the long duration of treatment, the cost and the limited availability of paediatric formulation of clindamycin [13]. The meta-analysis by Song et al. found that treatment with quinine plus antibiotics was associated with an increased risk of tinnitus and vomiting [17]. In our study, the combination of quinine with clindamycin was well tolerated and had a comparable safety profile to artemether-lumefantrine. These findings are similar to those of the QUINACT study [20, 27]. The relative safety and the low efficacy observed on the quinine plus clindamycin arm could be explained by the lower quinine dose that was administered over a short treatment period (three days). However, children who received quinine plus clindamycin were more likely to develop severe adverse events associated with worsening of the malaria infection.

Co-administration of quinine with clindamycin is the recommended first-line anti-malarial treatment in the first trimester of pregnancy [2]. However, in endemic areas, treatment of pregnant women with malaria in the first trimester has largely relied on quinine monotherapy due to the unavailability or cost of clindamycin [28]. Quinine therapy is known to be associated with low adherence due to tolerability (from bitter taste and adverse effects) and the need for multiple doses (three times a day) for 7 days [29, 30]. Interestingly, quinine plus clindamycin has not been evaluated in any clinical studies involving pregnant women in the first trimester. Despite insufficient safety data, the available efficacy data suggests that ACTs may be recommended in the treatment of confirmed malaria in the first trimester of pregnancy [31, 32].

In sub-Saharan Africa, artemether-lumefantrine is generally well tolerated and effective. On day 28, we found a PCR-corrected ACPR rate of 97% in children treated with artemether-lumefantrine. This confirms that in western Kenya, artemether-lumefantrine is still effective in treating children with uncomplicated falciparum malaria, but close monitoring of the efficacy of artemether-lumefantrine should continue. For treatment with artemisinin-based combinations, the WHO has recommended a change of treatment policy when the ACPR drops below 90%. In sub-Saharan Africa, ACPR rates below 90% have been reported for artemether-lumefantrine from Angola [33, 34], Gambia [35] and Malawi [36].

This study had the following limitations. The study was in western Kenya, meaning that the results may not apply to other malaria-endemic regions with different malaria transmission and drug resistance patterns. The study was open-label, suggesting that a remote susceptibility to bias may exist due to the awareness of participants and investigators of the treatment assignment. An active control (artemether-lumefantrine) arm was used, hence, a lower difference in ACPR was expected between the two treatments. This study was of short duration (28 days) and was not powered to detect statistically significant differences in adverse events. This study was limited to children with falciparum malaria. The results may, therefore, not apply to other Plasmodium species or adults. Finally, the implications of the unexpected low cure rate observed with quinine plus clindamycin are unclear, recalling that sample size was computed on the assumption of a 90% cure rate.

**Conclusion**

This was the first randomized trial evaluating the efficacy of a low-dose, short course of quinine plus clindamycin compared with artemether-lumefantrine in the treatment of initial uncomplicated falciparum malaria infection in children below 5 years. The study found no evidence of a beneficial effect with a short treatment course of quinine plus clindamycin compared with artemether-lumefantrine for children with uncomplicated falciparum malaria. This study supports the decision by WHO to discourage the use of quinine plus clindamycin as a second-line treatment for uncomplicated falciparum malaria in children.

**Abbreviations**

ACPR: Adequate clinical and parasitological response; ACT: Artemisinin-based combination therapy; CI: Confidence interval; Glurp: Glutamte rich protein; g/dl: Grams per decilitre; Hb: Haemoglobin; IQR: Interquartile range; MSP: Merozoite surface protein; MUAC: Mid-upper arm circumference; N: Number; PCR: Polymerase chain reaction; SD: Standard deviation; SE: Standard error; WBC: White blood cells; WHO: World Health Organization.
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Authors’ contributions

CO, EJ, and BO initiated the idea. CO and EJ wrote the study protocol. CO, EJ, VW and BO supervised the data collection. CO and VW analyzed and interpreted the data. CO drafted the manuscript. All authors contributed to the writing of the paper and approved the final version.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Declarations

Ethics approval and consent to participate

The study protocol was approved by the Ethics Review Committee of the Kenya Medical Research Institute (SSC # 2357) and the study is registered with the corresponding author on reasonable request.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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