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Efficacy and safety of re-treatment with the same artemisinin-based combination treatment (ACT) compared with an alternative ACT and quinine plus clindAMYcin after failure of first-line recommended ACT (QUINACT): a bicentre, open-label, phase 3, randomised controlled trial

Hypolite Muhindo Mavoko, Carolyn Nabasumba, Raquel Inocêncio da Luz, Halidou Tinto, Umberto D’Alessandro, Andrew Kambugu, Vito Baraka, Anna Rosanas-Urgell, Pascal Lutumba, Jean-Pierre Van geertroyden

Summary
Background Quinine or alternative artemisinin-based combination treatment (ACT) is the recommended rescue treatment for uncomplicated malaria. However, patients are often re-treated with the same ACT though it is unclear whether this is the most suitable approach. We assessed the efficacy and safety of re-treating malaria patients with uncomplicated failures with the same ACT used for the primary episode, compared with other rescue treatments.

Methods This was a bicentre, open-label, randomised, three-arm phase 3 trial done in Lisungi health centre in DR Congo, and Kozo health centre in Uganda in 2012–14. Children aged 12–60 months with recurrent malaria infection after treatment with the first-line ACT were randomly assigned to either re-treatment with the same first-line ACT, an alternative ACT, which were given for 3 days, or quinine-clindAMYcin (QnC), which was given for 5–7 days, following a 2:2:1 ratio. Randomisation was done by computer-generated randomisation list in a block design by country. The three treatment groups were assumed to have equivalent efficacy above 90%. Both the research team and parents or guardians were aware of treatment allocation. The primary outcome was the proportion of patients with an adequate clinical and parasitological response (ACPR) at day 28, in the per-protocol population. This trial was registered under the numbers NCT01374581 in ClinicalTrials.gov and PACTR20120300351114 in the Pan African Clinical Trials Registry.

Findings From May 22, 2012, to Jan 31, 2014, 571 children were included in the trial. 240 children were randomly assigned to the re-treatment ACT group, 233 to the alternative ACT group, and 98 to the QnC group. 500 children were assessed for the primary outcome. 71 others were not included because they did not complete the follow-up or PCR genotyping result was not conclusive. The ACPR response was similar in the three groups: 91·4% (95% CI 89·5–93·3) for the re-treatment ACT, 91·3% (95% CI 87·4–95·1) for the alternative ACT, and 89·5% (95% CI 83·0–96·0) for QnC. The estimates for rates of malaria recrudescence in the three treatment groups were similar (log-rank test: χ²=0·22, p=0·894). Artemether-lumefANtrine was better tolerated than QnC (p=0·005) and artesunate-amanoidiAque (p=0·001) in the modified intention-to-treat analysis. No serious adverse events were observed. The most common adverse events reported in the re-treatment ACT group were anorexia (31 [13%] of 240 patients), asthenia (20 [8%]), coughing (16 [7%]), abnormal behaviour (13 [5%]), and diarrhoea (12 [5%]). Anorexia (13 [6%] of 233 patients) was the most frequently reported adverse event in the alternative ACT group. The most commonly reported adverse events in the QnC group were anorexia (12 [12%] of 98 patients), abnormal behaviour (6 [6%]), asthenia (6 [6%]), and pruritus (5 [5%]).

Interpretation Re-treatment with the same ACT shows similar efficacy as recommended rescue treatments and could be considered for rescue treatment for Plasmodium falciparum malaria. However, the effect of this approach on the selection of resistant strains should be monitored to ensure that re-treatment with the same ACT does not contribute to P falciparum resistance.


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Introduction
Since the early 2000s, a downward trend in the malaria burden has been observed, resulting in reductions of 37% in malaria incidence and 60% in malaria mortality worldwide. Nevertheless, the malaria burden remains substantial, with an estimated 214 million cases in 2015.
Evidence before this study

Artemisinin-based combination therapies (ACTs) are recommended for first-line treatment of uncomplicated *Plasmodium falciparum* malaria. If recurrent malaria occurs before day 28, WHO recommends an alternative ACT in addition to quinine accompanied by an antibiotic having antiplasmodial properties (such as clindamycin, tetracycline, or doxycycline). This recommendation is based on expert opinion. In real-life situations, the prescriber is not always aware of former treatments and patients might be re-treated with the first-line ACT. We searched in PubMed for randomised trials without date or language restrictions, using the MeSH terms “uncomplicated malaria”, “retreatment”, “rescue therapy”, or “second-line treatment”. We did not identify any trial that had investigated the efficacy and safety of re-treatment with the first-line ACT nor with an alternative ACT. Therefore, we undertook this trial to provide evidence. Two malaria-endemic countries using different first-line ACTs were selected to host the trial (artesunate-amodiaquine in the DR Congo and artemether-lumefantrine in Uganda).

Added value of this study

Most ACT treatment failures are reinfections. Our findings show that the treatment of recurrent malaria episode with first-line recommended ACT has a similar efficacy as during the initial first-line treatment and as the recommended rescue treatments. Furthermore, we provide evidence to confirm WHO experts’ opinion recommending an alternative ACT as rescue treatment in addition to quinine.

Implications of all the available evidence

Most primary and community health centres in Africa have only one ACT available. The use of the same ACT as a rescue treatment might be considered. However, correct dosing strategies should be implemented and the effect of re-treatment on the population genetics of circulating *P falciparum* strains needs to be monitored.

Methods

Study design

This study was a bi-centre, phase 3b, randomised, open-label, three-arm trial done at Lisungi Health Center in Kinshasa, DR Congo, and Kazo Health Center in Mbarara, Uganda. Ethical approval was obtained from the Ethics Committee of the School of Public Health at the University of Kinshasa (DR Congo), the Uganda National Council for Science and Technology (Uganda), and the Ethics Committee of the University of Antwerp (Belgium). This trial was done in accordance with the Good Clinical and Laboratory Practices, applicable regulatory requirements, and the Declaration of Helsinki. The trial protocol is available online.

Participants

Children aged 12–59 months, weighing at least 9 kg, and attending study sites for fever or history of fever were given first-line ACT (ASAQ in DR Congo and AL in Uganda) and passively followed up (malaria was screened only in presence of symptoms) for 42 days (the pre-trial phase). The treatment was directly observed by a study nurse. The 42-day PCR-adjusted efficacy was 93·5% (data not shown) for AL in Uganda and 92·8% for ASAQ in DR Congo. Microscopy was used to diagnose malaria in children, who were then assessed for eligibility in the randomised trial. To be included in the trial, children had to fulfil all the following criteria: recurrent *Plasmodium falciparum* infection with fever or history of fever, willingness and ability of the parents or guardians to comply with the study protocol for the duration of the study, and written informed consent from parents or
guidians. Exclusion criteria were: known hypersensitivity
to or previous serious drug-related adverse events with
the study drugs, severe malaria or danger signs, treatment
failure within 14 days after treatment of the primary
episode; and bodyweight of less than 9 kg. Two written
informed consents were obtained, the first before
treatment with the first-line ACT (pre-trial phase) and the
second before recruitment in the randomised trial.

Randomisation and masking
Patients were randomly assigned to receive either the
same ACT treatment as the first-line treatment (re-
treatment ACT group), an alternative ACT to the first-
line treatment (alternative ACT group), or QnC (QnC
group), in a ratio of 2:2:1. In DR Congo, the re-treatment
ACT group were treated with ASAQ and the alternative
ACT group were treated with AL, and in Uganda the re-
treatment ACT group were treated with AL and the
alternative ACT group received ASAQ. Patients assigned
to the QnC group received the same QnC treatment in
both countries. Treatment was randomly allocated in
blocks by country according to a randomisation list that
was automatically generated by the statistical team at
the University of Antwerp before starting the study. The
treatment allocations were sealed in envelopes that were
opened by the study clinician immediately after obtaining
the written informed consent. This was an open-label
study, therefore, investigators and participants (or their
parents or guardians) were aware of study treatment

Procedures
Children received ASAQ, AL, or QnC and were followed
up for 28 days. Parents or guardians were asked to return
to the clinic for follow-up at scheduled visits on days 1, 2,
3, 7, 14, 21, and 28. They were also encouraged to attend
the clinic any time the child was unwell.

Study medications were quality assured. AL (Novartis,
Basel, Switzerland) was administered twice a day, orally
for three days. Tablets containing 20 mg of artemether
and 120 mg of lumefantrine were administered with a
cup of milk (to improve lumefantrine absorption). Dosage
was according to manufacturer’s instructions: one tablet
for children weighing 5–11·9 kg, two tablets for children
weighing 12–19·9 kg, three tablets for children weighing
20–27·9 kg, and two tablets to those weighing 28–35·5 kg. Clindamycin
(Pfizer SA/NV Brussels, Belgium) granules were
suspended in a 75 mg/5 mL solution (in sucrose, ethyl
parahydroxybenzoate, poloxamer, and artificial cherry
oil), which was administered orally twice a day for at least
5 days at a dosage of 10 mg/kg.

All ASAQ and AL treatments were administered on
site, under the direct supervision of study nurses. For
logistical reasons, in DR Congo, children assigned to the
QnC group were admitted to hospital for the first 3 days
of the trial. On the fourth day, the first two doses were
given under supervision, and the third, evening dose was
given at home by the parent or guardian. After the drug
was administered on site, children were kept at the clinic
for 60 min. A full dose was repeated if vomiting occurred
within 30 min of administration, and a half dose was
administered if vomiting occurred between 30 and
60 min. In case of persistent vomiting, the patient was
withdrawn from the study and referred to the health
facility for parenteral treatment.

Microscopy examination involved collecting thick and
thin blood films at each visit and staining with with
10% Giemsa within 10 min. Parasites were counted over
200 white blood cells, and density per μL estimated
assuming 8000 white blood cells per μL. Each slide
was read independently by two microscopists; a third
reading was done in case of discrepancies between the
first two readings. The Institute of Tropical Medicine in
Antwerp was responsible for microscopy external quality
control and two laboratory-specific monitoring visits
were done at both sites by experts from the malaria unit.
Haemoglobin was measured at days 0, 14, and 28, by use
of a portable spectrophotometer (Hemocontrol, EKF
Diagnostics, Barleben, Germany). At each visit, dried
blood spots were obtained on filter paper (Whatman
3 MM, Maidstone, UK) and air-dried before storage.
DNA was extracted from dried blood spots according to
the manufacturer’s instructions (QIAamp DNA Mini Kit,
Hilden, Germany). To distinguish between a new
infection and a recrudescence, we did PCR genotyping of
the polymorphic regions of the gene encoding merozoite
surface protein-1 (MSPI), the gene encoding merozoite
surface protein-2 (MSP2), and glutamate-rich protein
(GLURP), as described previously.13,14 Briefly, we
compared the genetic signatures of the samples at day 0
(D0) and day X (DX, at treatment failure). If at least one
identical allele was found in these paired samples at each
of the three loci, the failure was classified as recrudescent.
When the amplification reaction for one locus proved to
be negative for either one or both of the paired samples,
the outcome was classed as indeterminate. To assess
genotyping-adjusted outcomes, recurrent parasitaemia
due to new infections was considered as adequate clinical
and parasitological response (ACPR).

Outcome
The primary outcome was the proportion of children with
ACPR after PCR adjustment at day 28 and measured
in the per-protocol population. The ACPR was defined as
the absence of parasitaemia at the end of the study follow-up period (day 28), regardless of tympanic temperature, without having previously met any of the criteria for early and late treatment failure. In the PCR-adjusted analyses, children with recurrent infection were considered ACPR if this was classified as a new infection. Primary outcome was assessed in children who completed 28 days of follow-up without having recurrent malaria and those who experienced recurrent malaria but in whom PCR genotyping revealed a new infection (ie, initial parasites had been successfully cleared before the onset of a new episode), with children who had indeterminate PCR genotyping results being excluded from the data analyses.

Secondary efficacy outcomes were assessed in the per-protocol population. This population included children who had a known efficacy endpoint, without any criteria of protocol violation. They included fever clearance time (FCT), defined as the time, in days, from randomisation to the first two consecutive measurements of tympanic temperature lower than 38.0°C on different days; haemoglobin changes between days 0, 14, and 28; asexual parasite clearance time defined as the time, in days, from randomisation to two consecutive negative blood slides (obtained on different days).

Safety endpoints were defined as adverse events in children who had received at least one dose of the study medication. An adverse event was defined as any untoward medical occurrence, regardless of its relation to the study medication, in accordance with the International Conference of Harmonisation guidelines (ICH). Investigators used clinical judgment to assess causality, and the association was defined as definitely unrelated, unlikely to be related, possibly related, probably related, and definitely related. Only adverse events that were assessed as at least possibly related to the study drug were considered. These events were grouped according to the WHO adverse-reaction terminology (WHO-ART).
### Statistical analysis

We hypothesised that all three treatment groups would have similar efficacy and would be superior to 90%. The PCR-adjusted efficacy in any treatment group was assumed to be 95%. Thus, the hypothesis was accepted if the two-sided 95% CI (Wilson’s test) fell entirely above 90%. We therefore needed a sample size of 248 children (124 per site) to show with 80% power that the efficacy of re-treatment with the same ACT was at least 90%. Treatment with QnC was intended as the benchmark with half of participants, given that its administration is more demanding, particularly in the context of directly observed treatment (administered three times a day for 7 days). Assuming 15% of children would be unable to be assessed, the required sample size was 714 (357 per site).

Using DataFax (Clinical DataFax Systems Inc, ON, Canada), data recorded on paper case report forms (CRFs) were sent weekly from both sites to a centralised database located at the Infectious Diseases Institute, University of Makerere, Uganda. Most of the data analysis was done with Stata version 11 (Stata Corp, Lakeway, College Station, TX, USA). We used descriptive statistics to summarise the baseline characteristics. We applied haemoglobin concentration of 100 g/L as a cutoff for anaemia as in previous studies. The efficacy analysis was done according to both a per-protocol and a modified intention-to-treat approach. In the modified intention-to-treat approach, children excluded after enrolment were censored at the time of their final examination. We did some post-hoc analyses of Nelson-Aalen cumulative hazard estimates to generate the curves for risk of PCR-adjusted and PCR-unadjusted treatment failure. We compared survival curves by a log-rank test. Children who had each adverse event between treatment groups.

The study is registered in ClinTrials.gov, NCT01374581, and the Pan African Clinical Trials Registry, PACTR201203000351114. External monitoring for purposes of guaranteeing data quality and good clinical practice (GCP) compliance was done by the Amsterdam Institute for Global Health and Development.

### Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.
outcomes were available for 223 (93%) children in the re-treatment ACT, for 219 (94%) in the alternative ACT, and for 89 (91%) in the QnC groups (figure 1). The most common reasons for not completing the follow-up were persistent vomiting, inattendence at follow-up, and withdrawal of informed consent. Baseline characteristics were similar across the three treatment groups (table 1).

The proportions of children who were excluded from the per-protocol population were similar in the three treatment groups, and their baseline characteristics did not differ from those included in the study. For the assessment of the primary outcome, 15 children assigned to the same ACT, 13 children in the alternative ACT group, and three from the QnC group were excluded because of indeterminate PCR genotyping results (figure 1).

After PCR adjustment, ACPR assessed at day 28 was reached in 190 of 208 patients (91·4%; 95% CI 87·5–95·2) for the re-treatment ACT group, in 188 of 206 patients (91·3%; 87·4–95·1) for the alternative ACT group, and 77 of 86 patients (89·5%; 83·0–96·0) for the QnC group (table 2). The difference in efficacy between the re-treatment ACT and the alternative ACT groups was 0·08% (95% CI −5·2 to 5·7); 1·81% (−4·9 to 10·6) between the re-treatment ACT and the QnC groups, and 1·73% (−5·0 to 10·6) between the alternative ACT and the QnC groups. PCR-unadjusted and PCR-adjusted ACPR values were similar in both study sites after stratification (table 2, appendix). The rates of recrudescence in the three treatment groups were similar (log-rank test: χ²=0·22, p=0·894; figure 2). Within the per-protocol population, 88 children (40 re-treatment ACT, 35 alternative ACT, and 13 QnC treatment groups) still had similar strains as at the initial enrolment in the pre-trial phase. After rescue treatment, the proportion of persistent recrudescence was distributed in the three groups as follows: five (13%) of 40 children in the re-treatment ACT group, four (11%) of 35 children in the alternate ACT group, and four (31%) in the QnC treatment group.

The unadjusted ACPR in the per-protocol population was 135 of 223 patients (60·5%; 95% CI 54·1–67·0) for the re-treatment ACT, 123 of 219 patients (56·2%; 49·6–62·8) for the alternative ACT, and 63 of 89 patients (70·8%; 61·3–80·3) for the QnC group (appendix). No treatment failure occurred before day 14. The sensitivity analysis in the modified intention-to-treat population showed that the proportion of patients with PCR-unadjusted ACPR was 135 of 236 patients (57·2%; 95% CI 50·8–63·5) when the treatment given to children with an unknown efficacy endpoint was considered as a treatment failure and was 145 of 236 (61·4%; 55·2–67·7) when treatment was considered as successful in the re-treatment ACT group. In the group given an alternative ACT, the ACPR ranged from 123 of 230 patients (53·5; 47·0–59·9) to 132 of 230 (57·4%; 50·9–63·8), with ACPR values ranging from 63 of 93 patients (67·7%; 58·2–77·3) to 66 of 93 (71·0%; 61·7–80·3) in the group treated with QnC. Malaria recurrent infection tended to occur later in

### Results

From May 22, 2012 (the DR Congo site started on Aug 23, 2012), to Jan 31, 2014, 699 children were assessed for eligibility after having a recurrent infection with the first-line ACT treatment (ASAQ in DR Congo and AL in Uganda; figure 1). Of these children, 571 fulfilled the recruitment criteria. 516 of 571 eligible patients (90%) had parasitaemia of greater than 2000 asexual parasites per μL at recruitment (table 1). 240 children were randomly assigned to receive the re-treatment ACT (95 ASAQ in DR Congo and 145 AL in Uganda), 233 to the alternative ACT (107 AL in DR Congo and 126 ASAQ in Uganda), and 98 to QnC (40 in DR Congo and 58 in Uganda). Treatment
the patients assigned to QnC, compared with the other groups (log-rank test \( \chi^2=5.73, p=0.056 \); appendix).

Fever resolution was less rapid in children assigned to QnC treatment than in children assigned to either ACT treatment group (appendix). The proportion of children with parasitaemia on days 1, 2, and 3 was higher in the QnC group than in either of the ACT treatment groups. On day 7, all children had negative blood smears. The parasite clearance trend can be seen in the appendix. Children given QnC had a longer half-life parasite clearance (mean 6·2 h; SD 2·1), than did those treated with AL (2·7 h; 1·0) or ASAQ (2·4 h; 1·3; both \( p<0.0001 \)), although this parasite clearance was similar between the ACT groups (\( p=0.40 \)). The observation was similar when stratified by site, although the QnC group was under-represented.

On day 28, the mean haemoglobin increased by 12 g/L (SD 17) in the re-treatment ACT, 11 g/L (18) in the alternative ACT, and 16 g/L (14) in the QnC groups (appendix). When pooled by regimen, the mean increase was 11 g/L (18) for AL and 12 g/L (18) for ASAQ (appendix). None of the differences between mean increases were significant.

Pooling data by regimen, 252 children were assigned to AL and 221 were assigned to ASAQ. The baselines for the two groups were similar (appendix). The PCR-unadjusted ACPR value for AL was 133 of 236 (56·4; 95% CI 50·0–62·7), and 125 of 206 (60·7%; 53·9–67·4) for ASAQ (appendix). The PCR-unadjusted ACPR was similar for both AL and ASAQ treatment groups (199 of 219; 90·9%; 87·0–94·7 vs 179 of 195; 91·8%–87·9–95·7) with a log-rank test \( \chi^2 = 0.20 \) (\( p=0.903 \); appendix). The percentage of children with fever on days 1, 2, and 3 was lower in the ASAQ group than the AL and QnC treatment groups (appendix). None of the differences between mean increases were significant.

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Overall, 235 adverse events were observed (table 3). The most common events (>5%) reported in the re-treatment ACT group were anorexia, asthenia, coughing, abnormal behaviour, and diarrhoea. Anorexia was the most frequently reported adverse event in the alternative ACT group, although anorexia, abnormal behaviour, asthenia, and pruritus were the most commonly reported after treatment with QnC. None of the adverse events were considered serious. The group assigned to alternative ACT had fewer drug-related adverse events than the re-treatment ACT group (\( p<0.0001 \)) and the QnC treatment group (\( p=0.40 \)). The observation was similar when stratified by site, although the QnC group was under-represented.

On day 28, the mean haemoglobin increased by 12 g/L (SD 17) in the re-treatment ACT, 11 g/L (18) in the alternative ACT, and 16 g/L (14) in the QnC groups (appendix). When pooled by regimen, the mean increase was 11 g/L (18) for AL and 12 g/L (18) for ASAQ (appendix). None of the differences between mean increases were significant.
small to estimate the actual efficacy of QnC by site. In previous trials in Uganda, the proportion of PCR-adjusted treatment failure after treatment with quinine was 11.4% in Tororo and 69% in Kampala. It is worth noting that the study by Achan and colleagues showed only an estimation of quinine effectiveness as the treatment was not directly observed and the study reflects poor treatment adherence. There is a paucity of data on the efficacy of quinine as a treatment for uncomplicated malaria in DR Congo.

Despite good PCR-adjusted efficacy and tendency for a long post-treatment prophylactic period, QnC might not be suitable for rescue treatment for several reasons, including the long duration of treatment and poor tolerance, which can affect adherence, thereby resulting in poor effectiveness. Additionally, the availability of clindamycin is restricted in most sub-Saharan settings, particularly for children. Clindamycin can also induce antibiotic-associated diarrhoea and its use on a large scale in malaria treatment (in combination with quinine) could contribute to the spread of bacterial resistance. The paediatric formulation (granules for oral suspension in sucrose, ethyl parahydroxybenzoate, poloxamer, and artificial cherry oil) is unstable and requires storage at 25°C or less, which poses a challenge in many endemic areas.

In a study done in Uganda, Yeka and colleagues reported that alternative ACT is a better rescue treatment than quinine. However, the option of re-treating with the same ACT used for the primary episode was not considered. The risk of recurrent infections was much higher in Tororo, where the study was done, than that observed in Kazo, a difference related to the much higher intensity of transmission.

The proportion of children with detectable parasitaemia on days 1, 2, and 3 was higher in the QnC group than in the ACT groups. The added value of clindamycin to the reduction in asexual parasite clearance time with quinine is uncertain. Two children (1%) of 135 in the AL group in Uganda had microscopically detectable parasitaemia on day 3 after re-treatment. This outcome is not common with ACT. In DR Congo, all children randomly assigned to the ACT groups cleared parasites by day 3. Close monitoring (every 6 h) showed a similar parasite clearance half-life for ASAQ and AL, but much longer for QnC. The number of children involved in this analysis was small as this study procedure was added as a protocol amendment during the study. It is important to provide more data on the parasite clearance estimations, since these data would provide relevant information for the surveillance of artemisinin resistance. It is worth mentioning that with almost 1000 samples obtained in the DR Congo site, we contributed to the publication by the Karma consortium, in which it is indicated that K13 resistance is most probably not present in DR Congo.

The group re-treated with the same ACT had more adverse events because of the higher proportion of adverse events in the DR Congo site. In principle, re-treatment with the same ACT does not reduce the safety profile. The adverse events observed in the group treated with QnC are likely to be caused by quinine, given that clindamycin is reported to be well tolerated. The group assigned to AL treatment had fewer adverse events than the groups given ASAQ or QnC. In general, both AL and ASAQ are well tolerated.

This study has some limitations. The sample size calculation was based on the assumption of a 95% efficacy for the three rescue treatments, which required the lower limit of the 95% CI to be above 90%. However, the point estimate of the PCR-adjusted efficacy of all treatments was lower than expected. Therefore, both ACTs had a similar 95% CI with a lower limit of 87.5% for the same ACT and 87.4% for the alternative ACT groups. The availability of resistance marker results could provide additional arguments for or against re-treatment with the same ACT although this information could be acquired in a classic randomised trial design. Because of potential residual submicroscopic parasitaemia that could persist after ACT treatment, the conventional PCR-adjustment used in this study might have some limitations in the classification of new infections and recrudescence, which might be avoided by the use of quantitative PCR.

Few trials have investigated the rescue treatment of uncomplicated malaria. This study provides evidence on the 28-day efficacy of re-treatment with the same ACT, a relatively common practice. The study also contributes to the scarce information on the efficacy of QnC. The high proportion of new infections is an indicator of the high malaria transmission in the study areas. The failure to clear recrudescence parasites seemed to be similar in both ACT groups, but higher in the QnC group. The number of patients in this subset might not allow making a conclusive statement in terms of significance. A study including a population aged more than 5 years and a longer follow-up period would provide more evidence for the generalisability of these results. The 42 days of passive follow-up in pre-trial phase and a shorter 28 days of active follow-up in the study phase was necessary to protect the quality of data and avoid the overcrowding of study sites.

Conclusion
If we consider the poor effectiveness and tolerability of quinine, the reduced availability of the paediatric formulation of clindamycin, and the availability of only one first-line ACT at the community level in many settings, we conclude that a rescue treatment with the same ACT in correct doses as recommended could be an alternative option to quinine or the not always available alternative ACT. More evidence is needed before assessing the generalisability of this statement and caution is paramount when re-treating with the first-line ACT in areas where resistance to the partner drug has been confirmed.

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Contributors
HT, JPVg, PL, UDA, and HMM initiated the idea. HMM, HT, PL, and JPVg wrote the study protocol. HMM, CN, RIdL, AK, JPVg, and PL were involved in the acquisition of data. VB and AR-U supervised and interpreted molecular analysis. HMM and JPVg analysed and interpreted the data. HMM drafted the manuscript. All authors contributed to the writing of the paper, and approved the final version.

Declaration of interest
We declare no competing interests.

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