Paediatric formulations of artemisinin-based combination therapies for treating uncomplicated malaria in children (Review)

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**ABSTRACT**

**Background**

In endemic malarial areas, young children have high levels of malaria morbidity and mortality. The World Health Organization recommends oral artemisinin-based combination therapy (ACT) for treating uncomplicated malaria. Paediatric formulations of ACT have been developed to make it easier to treat children.

**Objectives**

To evaluate evidence from trials on the efficacy, safety, tolerability, and acceptability of paediatric ACT formulations compared to tablet ACT formulations for uncomplicated *P falciparum* malaria in children up to 14 years old.

**Search methods**

We searched the Cochrane Infectious Diseases Group Specialized Register; Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE; Embase; the Latin American and Caribbean Health Science Information database (LILACS); ISI Web of Science; Google Scholar; Scopus; and the metaRegister of Controlled Trials (mRCT) to 11 December 2019.

**Selection criteria**

We included randomised controlled clinical trials (RCTs) of paediatric versus non-paediatric formulated ACT in children aged 14 years or younger with acute uncomplicated malaria.

**Data collection and analysis**

Two authors independently assessed eligibility and risk of bias, and carried out data extraction. We analyzed the primary outcomes of efficacy, safety and tolerability of paediatric versus non-paediatric ACT using risk ratios (RR) and 95% confidence intervals (CI). Secondary outcomes were: treatment failure on the last day of observation (day 42), fever clearance time, parasite clearance time, pharmacokinetics, and acceptability.
Main results

Three trials met the inclusion criteria. Two compared a paediatric dispersible tablet formulation against crushed tablets of artemether-lumefantrine (AL) and dihydroartemisinin-piperaquine (DHA-PQ), and one trial assessed artemether-lumefantrine formulated as powder for suspension compared with crushed tablets. The trials were carried out between 2006 and 2015 in sub-Saharan Africa (Benin, Mali, Mozambique, Tanzania, Kenya, Democratic Republic of the Congo, Burkina Faso, and The Gambia).

In all three trials, the paediatric and control ACT achieved polymerase chain reaction (PCR)-adjusted treatment failure rates of < 10% on day 28 in the per-protocol (PP) population.

For the comparison of dispersible versus crushed tablets, the two trials did not detect a difference for treatment failure by day 28 (PCR-adjusted PP population: RR 1.35, 95% CI 0.49 to 3.72; 1061 participants, 2 studies, low-certainty evidence). Similarly, for the comparison of suspension versus crushed tablet ACT, we did not detect any difference in treatment failure at day 28 (PCR-adjusted PP population: RR 1.64, 95% CI 0.55 to 4.87; 245 participants, 1 study).

We did not detect any difference in serious adverse events for the comparison of dispersible versus crushed tablets (RR 1.05, 95% CI 0.38 to 2.88; 1197 participants, 2 studies, low-certainty evidence), or for the comparison of suspension versus crushed tablet ACT (RR 0.74, 95% CI 0.17 to 3.26; 267 participants, 1 study).

In the dispersible ACT arms, drug-related adverse events occurred in 9% of children in the AL study and 34% of children in the DHA-PQ study. In the control arms, drug-related adverse events occurred in 12% of children in the AL study and in 42% of children in the DHA-PQ study. Drug-related adverse events were lower in the dispersible ACT arms (RR 0.78, 95% CI 0.62 to 0.99; 1197 participants, 2 studies, moderate-certainty evidence).

There was no detected difference in the rate of drug-related adverse events for suspension ACT versus crushed tablet ACT (RR 0.66, 95% CI 0.33 to 1.32; 267 participants, 1 study).

Drug-related vomiting appeared to be less common in the dispersible ACT arms (RR 0.75, 95% CI 0.56 to 1.01; 1197 participants, 2 studies, low-certainty evidence) and in the suspension ACT arm (RR 0.66, 95% CI 0.33 to 1.32; 267 participants, 1 study), but both analyses were underpowered.

No study assessed acceptability.

Authors' conclusions

Trials did not demonstrate a difference in efficacy between paediatric dispersible or suspension ACT when compared with the respective crushed tablet ACT for treating uncomplicated Plasmodium falciparum malaria in children. However, the evidence is of low to moderate certainty due to limited power. There appeared to be fewer drug-related adverse events with dispersible ACT compared to crushed tablet ACT. None of the included studies assessed acceptability of paediatric ACT formulation.

Plain Language Summary

Treating uncomplicated malaria in children: do child-friendly formulations of medicines work better than usual tablet formulations?

What is the aim of this review?

We wanted to find out about the potential benefits and harms of child-friendly formulations of artemisinin-based combination therapy (ACT) to treat uncomplicated malaria in children. We searched for studies that investigated the use of child-friendly formulations of ACTs, compared with the usual ACT tablet formulations, to treat uncomplicated malaria in children aged under 14 years. We looked for randomized controlled studies, in which the treatments the children received were decided at random. This type of study usually gives the most reliable evidence about the effects of a treatment. We found three relevant studies of two child-friendly formulations.

Key messages

Child-friendly formulations of ACT probably work as well as crushed tablets to treat uncomplicated malaria in children, and probably cause fewer unwanted effects.

What was studied in this review?

Malaria is a tropical disease spread by mosquitoes infected with Plasmodium parasites. The most common, and most serious, type of malaria is caused by Plasmodium falciparum. This parasite causes high levels of illness and death, particularly in young children in regions where malaria is widespread.

Malaria can be a mild illness, but is sometimes severe and life-threatening if not treated soon enough or with the right medicines.
Medicines based on artemisinin, a compound derived from a plant (*Artemisia annua*), are commonly taken by mouth (orally) to treat malaria in combination with other drugs. The World Health Organization recommends treating uncomplicated malaria with oral artemisinin-based combination therapy (called ACT).

Oral ACT tablets are often crushed to help make them easier for children to swallow. New formulations of oral ACTs have been developed especially for children, such as syrups, and granules, powders or tablets that can be dissolved in water, and which may be flavoured.

**What are the main results of this review?**

We found three relevant studies in 1306 children (aged 6 months to 11 years) with uncomplicated malaria. The studies were conducted in sub-Saharan Africa between 2006 and 2015. All studies were funded by pharmaceutical companies that made child-friendly formulations of the ACTs.

The studies compared crushed ACT tablets to child-friendly formulations of ACTs: these were dissolvable tablets of artemether-lumefantrine or dihydroartemisinin-piperaquine, or artemether-lumefantrine syrup.

We were interested in:

· whether children remained cured of malaria after 28 days (measured by absence of *Plasmodium* parasites in the blood); and

· whether the medicines caused any unwanted effects.

None of the studies looked at how any of the medicine formulations were accepted by children.

There may be little or no difference between the child-friendly formulations of ACTs (dissolvable tablets or syrup) and the usual crushed tablets for how many children:

· were successfully treated after 28 days; or

· experienced serious unwanted effects.

The crushed ACT tablets and the child-friendly formulations successfully treated most cases of uncomplicated malaria. After 28 days the rates of treatment failure were similar in both groups. On average, 59 of every 1000 children taking crushed ACT tablets and 62 of every 1000 children taking dissolvable tablets would still have *Plasmodium* infection (2 studies; 1139 children).

Similar numbers of serious unwanted effects were reported for the usual crushed tablets and the dissolvable tablets (2 studies; 1197 children) or syrup (1 study; 267 children), therefore differences as a result of the formulation are unlikely.

A dissolvable tablet probably reduces unwanted effects of the medicine, including vomiting (throwing up), compared with the usual crushed tablets. Children taking dissolvable tablets had fewer unwanted effects associated with the medicine (139 of every 1000 children) than those taking crushed tablets (178 of every 1000 children).

There was no difference in the number of unwanted effects found in the study with the syrup formulation compared with the usual crushed tablets.

Our confidence in our results is low to moderate. The results come from a small number of studies. All studies were supported by manufacturers of the child-friendly formulations, which could have affected how the studies were designed, conducted, and reported.

**How up-to-date is this review?**

We searched for studies that had been published up to 11 December 2019.
### Summary of findings 1. Summary of findings table 1

Dispersible tablets (paediatric formulation) of ACT compared with crushed tablets (non-paediatric formulation) of ACT for uncomplicated malaria

**Patient population:** children aged 14 years or younger with uncomplicated *P. falciparum* malaria

**Settings:** malaria-endemic areas worldwide

**Intervention:** dispersible tablet of ACT

**Comparison:** crushed tablet of ACT

| Outcomes                        | Illustrative comparative risks* (95% CI) | Relative effect (95% CI) | No of participants (studies) | Certainty of the evidence (GRADE) | Comments                                                                 |
|---------------------------------|----------------------------------------|--------------------------|------------------------------|----------------------------------|--------------------------------------------------------------------------|
| **Assumed risk**                | Corresponding risk                      |                          |                              |                                  |                                                                          |
| Crushed tablet (non-paediatric formulation) | Dispersible tablet (paediatric formulation) | RR 1.35 (0.49, 3.72) | 1061 (2 RCTs)                | Low<sup>a</sup>                    | There may be little or no difference in day-28 PCR adjusted treatment failure in PP population. |
| **Treatment failure**           |                                        |                          |                              |                                  |                                                                          |
| day-28 PCR-adjusted (PP population) | 12 per 1000 | 16 per 1000 (6 to 45) | RR 1.35 (0.49, 3.72) | 1061 (2 RCTs)                | Low<sup>a</sup>                    | There may be little or no difference in day-28 PCR adjusted treatment failure in PP population. |
| **Serious adverse events**     |                                        |                          |                              |                                  |                                                                          |
| 13 per 1000 (5 to 37)           | RR 1.05 (0.68, 1.62)                   | 1197 (2 RCTs)            | Low<sup>a</sup>                    | There may be little or no difference in serious adverse events.          |
| **Drug-related adverse events**|                                        |                          |                              |                                  |                                                                          |
| 178 per 1000 (110 to 176)       | RR 0.78 (0.62, 0.99)                   | 1197 (2 RCTs)            | Moderate<sup>c</sup>            | Paediatric formulation probably reduces drug-related adverse events.     |
| **Drug-related vomiting**       |                                        |                          |                              |                                  |                                                                          |
| 132 per 1000 (74 to 133)        | RR 0.75 (0.56, 1.01)                   | 1197 (2 RCTs)            | Low<sup>b</sup>                    | Paediatric formulation may reduce drug-related vomiting.                 |
| **Acceptability**              |                                        |                          |                              | 0 studies                        | None of the studies looked at acceptability (e.g. swallowability).         |
The basis for the **assumed risk** is the mean risk from the studies included in this review, calculated as the number of participants in the control groups with the event divided by the total number of participants in control groups. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**ACT**: artemisinin-based combination therapy; **CI**: confidence interval; **ITT**: intention-to-treat; **PP**: per protocol; **RR**: risk ratio

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**GRADE Working Group grades of evidence**

**High certainty**: further research is very unlikely to change our confidence in the estimate of effect.

**Moderate certainty**: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low certainty**: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low certainty**: we are very uncertain about the estimate.

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*a* Downgraded by 2 levels for very serious imprecision: 95% CI encompasses substantive differences in relative cure or occurrence of Serious Adverse Events.

*b* Downgraded by 2 levels for serious imprecision: 95% CI encompasses no difference to a large difference.

*c* Downgraded by 1 level for serious imprecision. Events lower with dispersible tablet, but CI excludes higher number of events.
**BACKGROUND**

**Description of the condition**

Malaria is a debilitating infectious disease with an estimated 228 million clinical cases per year. Over three billion people live at risk of malaria infection, and up to 405,000 deaths from malaria are estimated every year. Young children aged under five years suffer disproportionately from *P. falciparum* malaria, and accounted for 67% (272,000) of all global malaria deaths in 2018 (WHO 2019).

**Description of the intervention**

Former first-line antimalarials, including chloroquine and sulfadoxine-pyrimethamine, became ineffective due to the emergence and spread of resistant parasites in virtually all malaria-endemic regions. Since the early 2000s, the novel concept of artemisinin-based combination therapy (ACT) has been established for the treatment of uncomplicated malaria and different ACTs have been clinically developed. These ACTs are characterized by high efficacy, rapid onset of action, and, at least in theory, a reduced risk for the emergence and selection of drug resistance due to the mutual protection of the combination partner drugs. ACTs are today recommended as first line therapy for uncomplicated malaria in practically all endemic regions (WHO 2019).

**How the intervention might work**

ACT is the therapeutic standard of care for uncomplicated *P. falciparum* malaria in nearly all endemic regions (WHO 2019). However, these fixed-dose ACTs were primarily developed in the form of tablet drug formulations and are therefore suitable for the treatment of adults. The oral treatment of young children, arguably the most important patient population, was not addressed adequately until recently. The lack of paediatric drug formulations (see definition below under Types of interventions) is a major impediment for the adequate treatment of young children as it necessitates the splitting of adult tablets, leading to inaccurate dosing (WHO 2015). In addition, palatability of crushed tablets poses a problem due to the pronounced bitter taste of most antimalarial drugs.

**Why it is important to do this review**

In recent years, several ACTs with paediatric drug formulations have been developed and non-inferior efficacy has been demonstrated in individual clinical trials. Paediatric ACT formulations are hypothesized to improve outpatient treatment, leading to higher treatment adherence, and may therefore result in sustained high cure rates. However, the initial rationale for the development of paediatric ACTs (i.e. improvement of drug administration, acceptability and tolerability of antimalarial treatment in young children) has not been directly addressed in most of these studies.

**OBJECTIVES**

To evaluate evidence from trials on the efficacy, safety, tolerability, and acceptability of paediatric ACT formulations compared to tablet ACT formulations for uncomplicated *P. falciparum* malaria in children up to 14 years old.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

We included randomized controlled trials (RCTs) that fulfilled the inclusion criteria, irrespective of geographical area or ethnicity.

**Types of participants**

We included children who were aged 14 years or younger and weighed up to 40 kg, and who were suffering from acute uncomplicated *P. falciparum* malaria.

**Types of interventions**

**Experimental**

Paediatric formulation of an ACT: any oral fixed-dose ACT in the form of granules, syrup, powder, or dispersible tablet, whether taste-masked, flavoured, or neither, and whether registered or under clinical development.

**Comparator**

Non-paediatric formulation of the same ACT, formulated as a tablet which may require splitting or crushing for use in children, whether registered or under clinical development.

**Types of outcome measures**

**Primary outcomes**

- Efficacy: polymerase chain reaction (PCR)-adjusted and unadjusted treatment failure on day 28 (WHO 2009).
- Safety: serious adverse events and drug-related serious adverse events (ICH 2016).
- Tolerability: adverse events and drug-related adverse events (ICH 2016).
- Tolerability of drug administration: drug-related gastrointestinal adverse events (drug-related vomiting, drug-related gastrointestinal disorders, and a composite endpoint of these two) (ICH 2016).

**Secondary outcomes**

- PCR-adjusted and unadjusted treatment failure on the last day of observation.
- Fever clearance time (FCT): calculated as the time until sustained clearance of fever.
- Parasite clearance time (PCT): given as time to negative thick blood smears.
- Pharmacokinetic parameters: $C_{max}$ (maximum serum concentration), AUC (area under the curve), $T_{1/2}$ (half-life), and $T_{max}$ (time to $C_{max}$).
- Acceptability: information on administration and dosing practice (crushing or splitting of tablet formulations, dosing of paediatric formulations, mixture with types of liquid or food, appreciation of drug formulation by caregivers and children). We planned to gather this information where available, and report it in a separate table.
Search methods for identification of studies
We attempted to identify all relevant trials, regardless of language or publication status (published, unpublished, in press, and in progress).

Electronic searches
We searched the following databases using the search terms detailed in Appendix 1:

- the Cochrane Infectious Diseases Group Specialized Register (searched 11 December 2019);
- Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 12 of 12, December 2019);
- MEDLINE (Pubmed; 1966 to 11 December 2019);
- Embase (OVID; 1946 to 11 December 2019);
- LILACS (Latin American and Caribbean Health Science Information database; 1962 to 11 December 2019);
- Science Citation Index-Expanded, Conference Proceedings Citation Index- Science (Web of Science, 1900 to11 December 2019);
- Google Scholar (accessed 11 December 2019);
- Scopus (1996 to 11 December 2019);
- Clinicaltrials.gov (accessed 11 December 2019);
- WHO International Clinical Trials Registry Platform (ICTRP) (accessed 11 December 2019).

Searching other resources
In addition to the electronic searches, we searched for relevant studies in conference abstract books, and presentations. We also asked experts in the field for unpublished or ongoing clinical trials.

Data collection and analysis
Selection of studies
Two review authors independently reviewed the results of the literature search for potentially relevant studies (RCT, paediatric formulation, acute uncomplicated *P. falciparum* malaria, and children aged up to 14 years), for which they then obtained full-text copies. The two review authors then independently assessed the identified studies for inclusion in this review, using the inclusion criteria specified in the protocol (Bélar 2012). The two review authors discussed any discrepancies between themselves, and resolved them with a third review author. They took particular care to ensure that they only included trials with multiple publications once. The 'Characteristics of excluded studies' table lists the excluded studies with paediatric ACT formulations, with reasons for their exclusion. Review authors did not consider the results of a study when deciding on its eligibility for inclusion.

Data extraction and management
Two review authors independently extracted the following data from included studies onto a data collection form:

- primary and secondary endpoints:
  - PCR-adjusted and unadjusted treatment failure in per-protocol (PP) and intention-to-treat (ITT) populations;
  - parasite clearance times;
  - fever clearance times;
  - serious adverse events, adverse events, drug-related adverse events, drug-induced vomiting, drug-induced gastrointestinal disorders;
  - acceptability;
  - pharmacokinetic characteristics of study drugs;
  - administration practice, as well as ethical clearance and obtainment of informed consent.

For dichotomous outcomes, we extracted the number of children with the event and the total number of children allocated to each treatment group. For continuous outcomes, we extracted means and standard deviations. We resolved any discrepancies in data extraction by consulting a third review author. In cases where the study did not report outcome data, we contacted the authors to obtain missing data.

Assessment of risk of bias in included studies
Two review authors independently assessed the risk of bias of every included trial following recommendations in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2017), and used the Cochrane criteria to judge results to be at low, high, or unclear risk of bias. A third review author resolved discrepancies.

Measures of treatment effect
We carried out data analysis using Review Manager 5 (RevMan 5) (Review Manager 2020). We calculated risk ratios (RR) for dichotomous data and mean differences (MD) for continuous data. We used the individual trials' definitions of ITT and PP populations, to carry out separate analyses of all efficacy outcomes.

Unit of analysis issues
We did not include any studies with non-standard designs; all included studies had one intervention and one comparator arm.

Dealing with missing data
To account for loss to follow-up, we performed analyses in the ITT population in addition to the PP population. We counted participants with missing outcome data in the ITT analysis as treatment failures, and did not impute any data.

Assessment of heterogeneity
We assessed heterogeneity by visual assessment of forest plots, and by inspecting $I^2$ and $Chi^2$ statistics.

Assessment of reporting biases
As we only included three studies, we did not construct funnel plots to obtain information about potential for publication bias.

Data synthesis
We created a 'Summary of findings' table including the following outcomes:

- treatment failure (day-28 PCR-adjusted (PP population));
- treatment failure (day-28 PCR-adjusted (ITT population));
- serious adverse events;
- drug-related adverse events;
- drug-related vomiting;
- acceptability.

No 'Summary of findings' table was created for the comparison including one study only.

This review accumulates data from a series of studies that had been performed independently and that are unlikely to be functionally identical. We therefore did not assume a common effect size. Additionally, we intended to allow the analysis to be generalized to various scenarios rather than a narrow population. Due to these reasons we chose a random-effects model.

**Certainty of the evidence**

We assessed the certainty of the evidence using GRADEpro GDT and guidance from the Cochrane Infectious Diseases Group (available from cidg.cochrane.org). We justified all decisions to downgrade the certainty of the evidence. We noted within the comments column of this table any outcome information that we considered relevant but could not incorporate into the meta-analyses.

**Subgroup analysis and investigation of heterogeneity**

We planned to perform a subgroup analysis for age (< 59 months versus > 59 months), but did not perform it due to the limited number of studies available.

**Sensitivity analysis**

Due to the limited number of studies available, we did not perform a sensitivity analysis to test the robustness of the methodology.

**RESULTS**

**Description of studies**

For details, see the 'Characteristics of included studies' and 'Characteristics of excluded studies' tables.

**Results of the search**

Searches identified 328 references. We obtained full-text copies of all 18 references that potentially met the inclusion criteria. Finally, we included three individual studies that met the full inclusion criteria; these three trials comprised 1306 children (Figure 1).

**Figure 1. Study flow diagram.**
Included studies

We included three RCTs conducted between 2006 and 2015, with sample sizes ranging from 300 to 899 children. All three RCTs were conducted in sub-Saharan Africa. Two were multicentre studies (Abdulla 2008; Gargano 2018), so the included studies took place in a total of eight different African countries (Benin, Burkina Faso, Democratic Republic of the Congo, Kenya, Mali, Mozambique, Tanzania, and The Gambia), most of them having perennial intense malaria transmission. One study was investigator-blinded (Abdulla 2008), and two studies were open-label (Gargano 2018; Juma 2008).

Study participants were male and female children with a minimum age of six months or minimum body weight of 5 kg. Maximum age differed across studies: 12 months in the study by Gargano 2018, 12 years in the Abdulla 2008 study, and 59 months in the study by Juma 2008.

Two trials investigated different oral paediatric formulations of artemether-lumefantrine (AL), either as dispersible tablet (Abdulla 2008), or powder for suspension (Juma 2008). One study investigated an oral paediatric formulation of dihydroartemisinin-piperaquine (DHA-PQ) as a dispersible tablet (Gargano 2018). Comparators were crushed tablets of the same ACT. Intervention and comparator drugs were administered under supervision over three consecutive days. Frequency of administration was the same for both comparator and intervention in two studies (Abdulla 2008; Gargano 2018). However, it is of note that the Juma 2008 study gave the intervention once daily but the comparator twice daily. In all studies, dosage of intervention and comparator were body weight adapted.

The primary efficacy endpoint of the included studies was day-28 PCR-adjusted treatment failure rate. Secondary efficacy endpoints varied across studies, and included PCR-adjusted and PCR-unadjusted treatment failure rates on days 7, 14 and 42, fever and parasite clearance times, and gametocyte clearance. Two RCTs studied pharmacokinetics (Abdulla 2008; Gargano 2018), but only one of them (Abdulla 2008) reported this. None of the studies assessed acceptability of the paediatric formulation compared to the comparator. All studies reported the number of children lost to follow-up in each arm.

Further details of included studies are presented in the 'Characteristics of included studies' table.

Excluded studies

Randomized studies investigating paediatric formulations of ACT that did not meet all inclusion criteria are presented in the 'Characteristics of excluded studies' table. In most of these excluded studies, the investigated paediatric ACT was not the same ACT as the comparator.

Risk of bias in included studies

Risk of bias is presented in tables for each included study within the 'Characteristics of included studies' table. For a summary of the 'Risk of bias' assessments see Figure 2. One study had a low risk of bias (Abdulla 2008), and two studies had a high risk of bias (Gargano 2018; Juma 2008).
Figure 2. Risk of bias summary: review authors’ judgements about each risk of bias item for each included study. Red = high risk; green = low risk; and yellow = unclear risk.

Allocation

All three studies reported using a computer-generated randomization sequence, so we judged this domain to be at low risk of bias for all of them.

We judged allocation concealment to be at low risk of bias in two studies (randomization list kept centrally and not communicated to sites (Abdulla 2008); opaque sealed envelopes (Gargano 2018)) and unclear in one study that did not report on allocation concealment (Juma 2008).
Blinding

We only judged one study to have adequate blinding and therefore to be at low risk of bias for this domain (Abdulla 2008). The other two studies reported no blinding (Juma 2008), or blinding of staff performing PCR for parasitology only (Gargano 2018). We therefore judged these to be at high risk of bias for efficacy outcomes, particularly for adverse event reporting.

Incomplete outcome data

All three studies reported the number of dropouts per treatment arm and presented analyses for the ITT and PP populations. Dropout rates were between 3% and 6%, and did not differ between intervention and treatment arms. We therefore judged the risk of bias due to incomplete outcome data to be low in all studies.

Selective reporting

All studies reported on the prespecified outcome criteria, which are also in line with standard reports. All studies reported data for drug-related adverse events. Therefore, we judged the risk of bias due to selective reporting to be low for all studies.

Other potential sources of bias

Pharmaceutical companies were involved in all three studies. Abdulla 2008 was jointly funded and sponsored by a pharmaceutical company and a non-governmental organization, and sponsors were also represented among the authors. In the Gargano 2018 study, a pharmaceutical company was the funder and sponsor, and was also responsible for study design, analyses and reporting. We judged the risk of bias due to involvement of pharmaceutical companies to be unclear for those two studies. The sponsor of the third study did not take part in trial design or analysis, but the study was funded by a pharmaceutical company which also donated intervention and comparator drugs (Juma 2008). We judged the risk of bias due to involvement of a pharmaceutical company to be low for this study.

Effects of interventions

See: Summary of findings 1 Summary of findings table 1

Due to the limited number of studies, we only assessed heterogeneity for Comparison 1 (paediatric ACT dispersible tablet versus non-paediatric ACT crushed tablet). Heterogeneity was generally low, apart from the analysis of PCR-adjusted efficacy at day 42 in the ITT population (Analysis 1.6) and the analysis of drug-related gastrointestinal disorders (Analysis 1.12).

Certainty of evidence for treatment failure on day 28 (PCR-adjusted, PP and ITT populations), serious adverse events, and drug-related vomiting was low; certainty of evidence for drug-related adverse events was moderate.

Question 1. How efficacious is the paediatric ACT formulation compared to the non-paediatric ACT formulation?

Comparison 1. Paediatric ACT dispersible tablet versus non-paediatric ACT crushed tablet

PCR-adjusted and -unadjusted treatment failures on day 28

PCR-adjusted treatment failures up to day 28 were < 2% in the intervention and control groups in PP analyses of both studies. In the ITT populations, the PCR-adjusted treatment failures up to day 28 were < 3% in the intervention and control group of the study using AL formulations (Abdulla 2008). The corresponding rates in the study using DHA-PQ formulations were 13% in the intervention group and 15% in the control group (Gargano 2018).

PCR-unadjusted treatment failures to day 28 were < 10% in the intervention and control groups in PP analyses of both studies. In the ITT populations, the PCR-unadjusted treatment failure rates to day 28 were < 10% in the intervention and control group of the study using AL formulations (Abdulla 2008) and < 20% in the intervention and control groups of the study using DHA-PQ formulations (Gargano 2018).

We found no difference in the 28-day occurrence of PCR-adjusted treatment failure between dispersible and crushed tablet ACT formulations for either the PP population (RR 1.33, 95% CI 0.49 to 3.72; 1061 participants, 2 studies; Analysis 1.1) or the ITT population (RR 1.05, 95% CI 0.68 to 1.62; 1139 participants, 2 studies; Analysis 1.2). Similarly, we found no difference in day-28 PCR-unadjusted treatment failure rates for either the PP population (RR 1.03, 95% CI 0.48 to 2.23; 1061 participants, 2 studies; Analysis 1.3) or the ITT population (RR 0.90, 95% CI 0.65 to 1.25; 1139 participants, 2 studies; Analysis 1.4).

PCR-adjusted and -unadjusted treatment failures on last day of observation (day 42)

Both studies assessed PCR-adjusted and -unadjusted treatment failures up to day 42. PCR-adjusted treatment failure rates were < 4% in the intervention and control groups in PP analyses of both studies. In the ITT populations, the PCR-adjusted treatment failures to day 42 were < 10% in the intervention and control group of the study using AL formulations (Abdulla 2008). Corresponding rates in the study using DHA-PQ formulations were 14% in the intervention group and 17% in the control group (Gargano 2018).

Data on PCR-unadjusted treatment failures to day 42 in PP analysis were only available for the study using DHA-PQ formulations (Gargano 2018). These were 24% in the intervention group and 27% in the control group. In the ITT populations, the PCR-unadjusted treatment failures to day 42 were 22% in the intervention group and 26% in the control group in the study using AL formulations (Abdulla 2008), and 32% in the intervention group and 38% in the control group of the study using DHA-PQ formulations (Gargano 2018).

There was no difference in efficacy to day 42 between intervention and control groups for any of the analyses (PCR-adjusted PP population: RR 1.07, 95% CI 0.53 to 2.13; 958 participants, 2 studies; Analysis 1.5; PCR-adjusted ITT population: RR 1.06, 95% CI 0.66 to 1.73; 1047 participants, 2 studies; Analysis 1.6; PCR-unadjusted PP population: RR 0.87, 95% CI 0.56 to 1.34; 257 participants, 1 study; Analysis 1.7; PCR-unadjusted ITT population: RR 0.86, 95% CI 0.70 to 1.05; 1047 participants, 2 studies; Analysis 1.8).

Comparison 2. Paediatric ACT suspension versus non-paediatric ACT crushed tablets

PCR-adjusted and -unadjusted treatment failures on day 28

PCR-adjusted treatment failures to day 28 were 7% in the intervention and 4% in the control groups in the PP analysis. In the ITT population, the PCR-adjusted treatment failures to day 28 were 16% in the intervention group and 11% in the control group.
PCR-unadjusted treatment failures to day 28 were 12% in the intervention group and 12% in the control group in the PP analysis. In the ITT population, the PCR-unadjusted treatment failures to day 28 were 21% in the intervention group and 18% in the control group.

There was no difference in efficacy to day 28 between suspension and crushed tablet ACT formulation (PCR-adjusted PP population: RR 1.64, 95% CI 0.55 to 4.87; 245 participants, 1 study; Analysis 2.1; PCR-adjusted ITT population: RR 1.49, 95% CI 0.79 to 2.80; 267 participants, 1 study; Analysis 2.2; PCR-unadjusted PP population: RR 1.02, 95% CI 0.52 to 2.00; 245 participants, 1 study; Analysis 2.3; PCR-unadjusted ITT population: RR 1.16, 95% CI 0.71 to 1.89; 267 participants, 1 study; Analysis 2.4).

Drug-related adverse events

Drug-related gastrointestinal adverse events (drug-related vomiting, drug-related gastrointestinal disorders, and a composite endpoint of these two)

Intervention and control arms did not differ statistically significantly in the rate of drug-related vomiting (RR 0.75, 95% CI 0.56 to 1.01; 1197 participants, 2 studies; Analysis 1.11), drug-related gastrointestinal disorders (RR 1.19, 95% CI 0.19 to 7.45; 1197 participants, 2 studies; Analysis 1.12), or drug-related vomiting and gastrointestinal disorders (RR 0.76, 95% CI 0.57 to 1.00; 1197 participants, 2 studies; Analysis 1.13).

Comparison 2. Paediatric ACT suspension versus non-paediatric ACT crushed tablet

Drug-related adverse events

In the intervention arm, 9% of children reported drug-related adverse events, compared with 14% of children in the control arm; this was not statistically significant (RR 0.66, 95% CI 0.33 to 1.32; 267 participants, 1 study; Analysis 2.6).

Drug-related gastrointestinal adverse events (drug-related vomiting, drug-related gastrointestinal disorders, and a composite endpoint of these two)

Intervention and control arms did not differ in the rate of drug-related vomiting (RR 0.66, 95% CI 0.33 to 1.32; 267 participants, 1 study; Analysis 2.7), drug-related gastrointestinal disorders (RR 0.99, 95% CI 0.06 to 15.70; 267 participants, 1 study; Analysis 2.8), or drug-related vomiting and gastrointestinal disorders (RR 0.66, 95% CI 0.33 to 1.32; 267 participants, 1 study; Analysis 2.9).

Question 4. How is the acceptability of the paediatric ACT formulation compared to the non-paediatric ACT formulation?

None of the studies reported acceptability.

Question 5. How efficacious is the paediatric ACT formulation compared to the non-paediatric ACT formulation in clearing fever and parasitaemia?

Comparison 1. Paediatric ACT dispersible tablet versus non-paediatric ACT crushed tablet

Fever Clearance Time

Only the study using AL formulations reported FCT (Abdulla 2008). Median FCT was 7.9 hours in the intervention arm and 7.8 hours in the control arm. The study using DHA-PQ formulations did not report FCT (Gargano 2018).

Parasite Clearance Time

Only the study using AL formulations reported PCT (Abdulla 2008). Median PCT was 34.3 hours in the intervention arm and 34.9 hours in the control arm. The study using DHA-PQ formulations did not report PCT (Gargano 2018).

Comparison 2. Paediatric ACT suspension versus non-paediatric ACT crushed tablet

Fever Clearance Time

Mean FCT was 41.6 (standard deviation (SD) 13.9) hours in the intervention arm and 44.4 (SD 20.1) hours in the control arm (mean difference -2.80 hours, 95% CI 6.95 to 1.35; Analysis 2.10).
Parasite Clearance Time
Mean PCT was mean 54.7 (SD 14.6) hours in the intervention arm and 53.8 (SD 15.7) hours in the control arm (mean difference 0.90 hours, 95% CI -2.74 to 4.54; Analysis 2.11).

**Question 6. Do pharmacokinetic parameters differ between the paediatric ACT formulation and the non-paediatric ACT formulation?**

Only the study using AL formulations reported pharmacokinetic parameters (Abdulla 2008).

$C_{\text{max}}$ of artemether was 175 ng/mL in the intervention group and 211 ng/mL in the control group. $C_{\text{max}}$ of DHA was 64.7 ng/mL in the intervention group and 63.7 ng/mL in the control group.

$C_{\text{max}}$ of lumefantrine was 6.3 μg/mL in the intervention group and 7.7 μg/mL in the control group. The AUC (area under the curve) for lumefantrine was 584 μg*h/mL in the intervention group and 636 μg*h/mL in the control group.

$T_{\text{max}}$ of lumefantrine was 66.31 hours in the intervention group and 66.30 hours in the control group.

**DISCUSSION**

This review summarizes the evidence on possible benefits of paediatric versus non-paediatric ACTs. Inclusion criteria applied in this review were very strict, only allowing inclusion of randomized controlled trials that compared paediatric versus non-paediatric ACTs of the same substances; hence only three studies (1306 participants) were suitable for inclusion.

**Summary of main results**

All three included studies showed similar efficacy for the paediatric formulation of the ACT and the non-paediatric ACT (administered as crushed tablet) in the treatment of uncomplicated *P falciparum* malaria in children. All three studies showed similar efficacy for PCR-adjusted and PCR-unadjusted day-28 PP and ITT analyses, and for PCR-adjusted day-42 PP and ITT analyses of studies comparing dispersible formulations with crushed tablet ACT.

All three included studies showed that the safety of the paediatric formulation of the ACT was similar to that of the non-paediatric ACT (administered as crushed tablet) in the treatment of uncomplicated *P falciparum* malaria in children. None of the studies reported any drug-related serious adverse events, and the rate of serious adverse events was low (2% to 3%) in intervention and control arms.

Tolerability by means of drug-related adverse events differed between paediatric ACT formulated as dispersible tablet and conventional tablet-based ACT administered as crushed tablet, with dispersible ACT showing superior tolerability. Children receiving dispersible tablet ACT had a statistically significantly lower rate of drug-related adverse events. This effect had not been shown by the individual studies, but could be demonstrated in the meta-analysis of this review, with moderate-certainty evidence (Summary of findings 1).

Drug-related vomiting occurred less commonly in children receiving dispersible ACT compared to children receiving crushed conventional tablet-based ACT; although not reaching statistical significance this may indicate a better tolerability of drug-administration for dispersible ACT, with low-certainty evidence. The only study that compared ACT suspension with ACT crushed tablet did not show any difference in tolerability, but the sample size was very small.

As malarial morbidity and mortality primarily affects young children, optimization of outpatient treatment in this patient population is most important. Effective oral antimalarial medication that is safe, well tolerated, and easy to administer in young children can therefore potentially make a difference to the large-scale reduction of malarial morbidity and mortality. Tolerability of a drug represents the degree to which overt adverse effects can be tolerated by the person taking it. Poor tolerability of a treatment may consequently lead to refusal of treatment, leading to a situation where a drug may have limited clinical therapeutic value in real-world conditions, even though it may be efficacious. The superior tolerability of dispersible tablet ACT formulation over conventional tablet-based formulation could suggest that dispersible tablet ACT formulation may indeed improve paediatric outpatient treatment; effectiveness studies are needed to confirm this.

**Overall completeness and applicability of evidence**

Several types of paediatric ACT formulations have been developed, but only two of them have been evaluated in studies that allowed us to compare paediatric versus non-paediatric ACT with the same compounds. Surprisingly, no RCT evaluated the potential benefits of paediatric formulations in terms of better acceptability or palatability, leading to improved adherence, sustained outpatient treatment, and better outcomes. This is especially noteworthy as these potential benefits are commonly cited to advocate the necessity of child-friendly medicines to improve clinical management of young children. Of note, a study by Banek 2018 found higher adherence to antimalarial treatment in African children when a paediatric formulation of AL dispersible tablets was used, compared to treatment with crushed artesunate-amodiaquine tablets. The conclusion of the Banek 2018 study was limited by the fact that different ACTs were compared.

A number of RCTs investigating paediatric ACTs did not use the same ACT in both the intervention and comparator arms, which impedes the evaluation of benefits or drawbacks relating exclusively to the formulation and not the drug (see Characteristics of excluded studies). Taste-masked granules are another common paediatric formulation, and two ACTs (artesunate-mefloquine and pyronaridine-artesunate) have been developed and are currently on the market in this form. However, the studies evaluating granule formulation ACT did not meet the inclusion criteria for this review.

As not all types of paediatric formulations of ACTs have been evaluated adequately (e.g. granule formulations), the completeness of evidence for the benefits of paediatric ACTs is limited. Moreover, the use of paediatric ACTs under real-world conditions outside of clinical trials has not been studied so far. Under such conditions, the benefits of paediatric formulations with respect to acceptability and adherence could possibly translate to higher effectiveness.

So far, evidence for the better tolerability of paediatric ACT is limited to the dispersible tablet formulation. Further studies are needed to consolidate the evidence for the benefits of paediatric ACTs, and expand it to other paediatric formulations. Moreover, solid
data on the palatability, acceptability and effectiveness are needed, to promote the further development and availability of paediatric formulations.

**Certainty of the evidence**

We assessed the certainty of the evidence using the GRADE process and summarized results in Summary of findings 1. There is low-certainty evidence that efficacy of ACTs is similar for paediatric and non-paediatric drug formulations, and also low to moderate-certainty evidence that tolerability is better for paediatric dispersible tablet ACTs than for crushed tablet ACTs (Summary of findings 1).

**Potential biases in the review process**

All trials included in this review are published, and we were unable to obtain further unpublished data.

**Agreements and disagreements with other studies or reviews**

The current review is in line with a systematic review and meta-analysis that the authors published in 2010 (Kurth 2010). The Kurth 2010 review used a protocol that was less strict with regard to inclusion criteria, and meta-analysis included non-randomized studies as well as studies that compared paediatric versus non-paediatric ACT using different drug combinations. Both reviews conclude that tolerability of paediatric ACTs is superior to non-paediatric ACTs, with equal efficacy and safety.

**AUTHORS’ CONCLUSIONS**

**Implications for practice**

Artémisinn-based combination therapies (ACTs) are the recommended first-line treatment for uncomplicated malaria in all malaria-endemic regions. Young children suffer disproportionately from malaria, and their clinical management is complex. Problems during drug administration, such as refusal to swallow tablets and drug-induced vomiting, are common in the care of young children with malaria. Paediatric formulations of ACTs appear to improve the tolerability of ACTs and reduce drug-related adverse events, such as drug-induced vomiting, without impairing efficacy or safety. Although high quality evidence for the superior tolerability of paediatric formulations only exists for dispersible tablets of ACTs, current evidence clearly supports use of paediatric ACTs in young children with malaria.

**Implications for research**

Superior tolerability has so far not been shown for other available paediatric formulations of ACTs, such as granules or suspension. Efforts should be made to develop further types of paediatric ACT formulations. For example, mini-tablets and orodispersible films have been approved for other drugs, and constitute solid dosage forms that enable easy administration (Thab et 2018).

Randomized controlled trials (RCTs) with identical compounds of the paediatric ACT formulation and the conventional tablet-based comparator ACT should be conducted, to evaluate efficacy (by cure rates or treatment failure rates), safety (by serious adverse events) and tolerability (by adverse events and drug-related adverse events), as well as tolerability of drug administration (gastrointestinal drug-related adverse events). Ideally, these RCTs would be blinded both for investigators and participants; however, blinding of participants will likely be challenging due to the differences in drug preparations.

The acceptability of drug administration in paediatric ACT formulations has not been studied systematically so far, although patient acceptability of a drug is crucial for pharmaceutical products (Ramnal 2018). Published methods for assessment of drug acceptability in children lack standardization, and different designs of reliable instruments to assess drug acceptability have been published (Ramnal 2018).

It is reasonable to hypothesize that the reduction in drug-related adverse events and drug-related vomiting shown in the context of clinical trials translates to higher treatment adherence, and therefore potentially greater effectiveness of ACTs under real-world conditions. However, this has not been assessed in clinical studies. RCTs designed to evaluate effectiveness will be able to close these knowledge gaps.

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Characteristics of included studies

**Abdulla 2008**

**Study characteristics**

| Methods | Trial design: randomized, investigator-masked, multicentre, parallel-group study. |
|---------|----------------------------------------------------------------------------------|
|         | Follow-up: 3 days of hospitalisation during treatment period; after discharge follow-up on days 7, 14, 28, and 42. |
Clinical evaluation twice daily during hospitalization. Haematological and biochemical measurements were done at baseline and on days 3, 7, 28, and 42. Thick and thin blood films were examined before every dose of study medication during the hospital stay and at every follow-up visit. 12-lead electrocardiogram was recorded at baseline and on day 3.

Participants

Number of participants: 899.

Inclusion criteria: age 12 years or younger, body weight between 5 kg and < 35 kg, fever (temperature ≥ 37.5 °C axillary or ≥ 38 °C rectally) or history of fever in the preceding 24 h, *P. falciparum* malaria (single or mixed infection) with a density between 2000/μL and 200,000/μL blood, negative pregnancy test for participants of childbearing potential, ability to take drugs by mouth and to attend the study centre on stipulated days for follow-up, provision of written informed consent by parent or guardian, and no severe and complicated malaria. Exclusion criteria were haemoglobin < 50 g/L, history of serious side-effects related to artemether-lumefantrine or similar drugs, use of antimalarial drugs or agents with antimalarial activity other than chloroquine within previous 2 weeks, use of any drug known to affect cardiac function in the preceding 4 weeks, presence of QTc prolongation or any condition known to prolong QTc, serious underlying disease, and artemether-lumefantrine treatment within the previous 30 days.

Interventions

1. Artemether-lumefantrine dispersible tablet, a sweetened cherry-flavoured formulation of 20 mg artemether and 120 mg lumefantrine, administered under supervised conditions with a cup, beaker, or syringe in suspension in 10 mL water.
2. Artemether-lumefantrine crushed tablet of 20 mg artemether and 120 mg lumefantrine, administered under supervised conditions with a cup, beaker, or syringe in suspension in 10 mL water.

Treatment was given according to bodyweight: one tablet per dose for children weighing 5 kg to 14 kg, two per dose for those weighing 15 kg to 24 kg, and three per dose for those weighing 25 kg to 34 kg. Immediately after drug administration, another 10 mL water was given with the same device. The consumption of some food or drink (e.g. breast milk, broth, or sweetened condensed milk) was recommended after the intake of medication to increase absorption.

Outcomes

Primary efficacy outcome measure:

1. PCR-adjusted cure rate on day 28.

Secondary efficacy measures:

1. Day 7 parasitological cure rate.
2. Day 14 PCR-adjusted cure rate.
3. Time to fever, parasite and gametocyte clearance.
4. Exploratory: Day 42 PCR-adjusted cure rate, ETF, LCF, LPF, ACPR, development of danger signs of malaria or severe malaria.

Safety endpoints:

1. Adverse event rates
2. Laboratory assessments, ECG data.

Notes

Eight study sites in five African countries: one centre each in Benin, Mali, Mozambique, Tanzania mainland, and Zanzibar, and three in Kenya.

Malaria transmission: at study locations, malaria transmission is intense and perennial, with the exception of the two study sites in Mozambique and Zanzibar, where malaria is mesoendemic with transmission peaks during the rainy season.

Dates: August 2006 to March 2007.

Funding: Novartis Pharma, Basel, Switzerland, and Medicines for Malaria Venture (MMV), Geneva, Switzerland.
Abdulla 2008 (Continued)

| Bias                                                                 | Authors' judgement | Support for judgement                                      |
|----------------------------------------------------------------------|--------------------|------------------------------------------------------------|
| Random sequence generation (selection bias)                         | Low risk           | Computer-generated.                                        |
| Allocation concealment (selection bias)                             | Low risk           | Randomization lists were kept centrally and were not communicated to the sites. |
| Blinding of participants and personnel (performance bias)           | Low risk           | Investigators were blinded. Treatment was prepared by staff not involved in clinical assessment, identical package was used for intervention and comparator. No blinding of participants. |
| Blinding of outcome assessment (detection bias)                     | Low risk           | Assessors of clinical outcome were blinded. Blinding of microscopists not explicitly stated. |
| Incomplete outcome data (attrition bias)                            | Low risk           | Reporting of outcome data was judged to be complete.       |
| Selective reporting (reporting bias)                                | Low risk           | All essential outcomes and measurements were reported.     |
| Other bias                                                          | Unclear risk       | Sponsors (a pharmaceutical company and an NGO) were responsible for collection and analysis of data. Authors and the sponsors were involved in study design, interpretation of data, and writing of the report. |

Gargano 2018

Study characteristics

Methods

Trial design: randomized, controlled, open-label trial.

Follow-up: 3 days of hospitalisation during treatment period; after discharge follow-up on days 7, 14, 21, 28 and 42.

Specific time points of clinical and parasitological evaluation not reported. Hematology and biochemistry were taken at enrolment and at day 7 and then repeated at day 28 if clinically significant abnormalities were detected at day 7.

12-lead ECG recorded at baseline and then repeated at day 2 before the last drug administration, as well as after 4 to 6 h of drug intake. An ECG was also recorded at day 7 and repeated at day 28 if clinically relevant abnormalities were detected at day 7.

Participants

Number of participants: 300

Inclusion criteria: Age 6 to 12 months, bodyweight ≥5 kg, P. falciparum monoinfection with asexual parasite densities between 1000 and 200,000 parasites/L of blood, fever (axillary temperature of ≥37.5 °C), or a history of fever in the preceding 48 h. Children with previous treatment with antimalarials, acute malnutrition, severe malaria, danger signs, moderate/severe anaemia (Hb 7 g/dL), a family history of sudden death or known congenital prolongation of the QT interval, or treatment with QT prolongation inducers or strong cytochrome-P450 inhibitors/inducers or antiretroviral drugs (or lactated by HIV-positive women under antiretroviral therapy) were excluded.
Interventions

1. The DHA-PQ dispersible formulation was a coformulated, water-dispersible flat tablet, provided in two different strength dosages: 10/80 mg and 20/160 mg of dihydroartemisinin/piperaquine tetraphosphate (as cellulose-microencapsulated piperaquine tetraphosphate) and other components (cellulose, starch, croscarmellose, black cherry flavour, saccharine, sucrose, and magnesium stearate).

2. The marketed Eurartesim formulation was a coformulated, film-coated tablet, provided in one strength of 20/160 mg of DHA-PQ (Sigma-Tau, Italy).

Both formulations were administered once a day for three consecutive days, according to body weight.

Participants weighing 5 kg to 7 kg received a daily dose of 10/80 mg of DHA-PQ, while participants weighing 7 kg to 13 kg received a daily dose of 20/160 mg of DHA-PQ. The first dose was administered as soon as randomization was done, and deliberate efforts were made to ensure that no food was administered in the following 3 h. For the other doses, children should not have been fed in the 3 h before drug intake and for the following 3 h. However, for infants needing food during the restricted periods, this was limited to breast milk or a low-fat maize porridge.

Outcomes

Primary efficacy outcome measure:

1. PCR-adjusted adequate clinical parasitological response (ACPR) at day 28.

Secondary efficacy measures:

1. Day 28, PCR-unadjusted ACPR;
2. Day 42, PCR-adjusted and -unadjusted ACPR;
3. Proportion of participants with early and late treatment failure (ETF and LTF);
4. Asexual parasite density and clearance time;
5. Fever clearance time and gametocyte carriage over time;
6. Kaplan-Maier survival analysis for new infections and recrudescences over time.

Safety endpoints:

1. Adverse event occurrence;
2. Changes in hematology, blood chemistry, vital signs, and ECG parameters.

Notes

Seven study sites in five African countries: Centro de Investigação em Saúde da Manhiça, Maputo, Mozambique; Kinshasa School of Public Health, University of Kinshasa, Democratic Republic of the Congo; Centre Muraz Bobo-Dioulasso, Nanoro, Burkina Faso; Centre National de Recherche et de Formation en Paludisme, Ouagadougou, Burkina Faso; Ifakara Health Institute, Bagamoyo, Tanzania; National Institute for Medical Research, Korogwe, Tanzania; and Medical Research Council Unit, The Gambia.

Transmission: intense perennial transmission

Dates: November 2013 to June 2015

Funding: Sigma-Tau Industrie Farmaceutiche Riunite S.p.A. (Italy) was the Sponsor and Funder of this trial as part of the clinical development program for the new paediatric formulation of Eurartesim. IS-Global is a member of the CERCA Programme, Generalitat de Catalunya (Spain).

Risk of bias

| Bias                          | Authors' judgement | Support for judgement                                      |
|-------------------------------|--------------------|------------------------------------------------------------|
| Random sequence generation (selection bias) | Low risk           | Computer-generated by external company.                    |
| Allocation concealment (selection bias) | Low risk           | Treatment allocation concealed in sealed opaque envelopes, opened by investigators only after randomization. |
### Gargano 2018 (Continued)

| Bias Type                                      | Risk Level | Description                                                                                   |
|-----------------------------------------------|------------|----------------------------------------------------------------------------------------------|
| Blinding of participants and personnel (per- | High risk  | No blinding of participants and personnel. Blinding only for PCR parasitology to distinguish  |
| formance bias) All outcomes                   |            | between new infection and recrudescence.                                                     |
| Blinding of outcome assessment (detection     | High risk  | Only staff performing the PCR for distinction between reinfection and recrudescence were     |
| bias) All outcomes                            |            | blinded.                                                                                      |
| Incomplete outcome data (attrition bias) All  | Low risk   | Reporting of outcome data was judged to be complete.                                          |
| outcomes                                       |            |                                                                                               |
| Selective reporting (reporting bias)          | Unclear risk| This study mentioned investigation of pharmacokinetics but did not report pharmacokinetic     |
|                                              |            | data ("The results presented here are part of a large study that was designed to evaluate   |
|                                              |            | also the population pharmacokinetics").                                                       |
| Other bias                                    | Unclear risk| The funder and sponsor of the study was the pharmaceutical company Sigma-Tau; study design,   |
|                                              |            | analyses and reporting were done by the funder and sponsor.                                   |

### Juma 2008

#### Study characteristics

| Methods                                                        | Trial design: randomized, controlled, open-label trial. |
|----------------------------------------------------------------|--------------------------------------------------------|
| Follow-up                                                      | 3 days of hospitalization during treatment period; after discharge follow-up on days 7, 14, 28. |
| Clinical and parasitological evaluation                       | days 0, 1, 2, 3, 7, 14, 28, comprising clinical history, physical examination, and thick and thin blood smears for malaria parasites. |
| Haemoglobin measured                                          | on days 0, 7, 14, 28.                                   |

| Participants | Number of participants: 267 |
|--------------|------------------------------|
| Inclusion criteria: age 6 to 59 months, bodyweight ≥ 5 kg, a history of fever in the previous 24 h or measured fever (axillary temperature ≥ 37.5°C), monoinfection with *P. falciparum* with parasitaemia in the range of 2000/μL - 200,000/μL asexual parasites, no other cause of fever than suspected malaria, and no general danger signs or signs of severe and complicated falciparum malaria as per WHO guidelines. |

| Interventions | 1. Artemether-lumefantrine powder for suspension 15 mg/90 mg, 5 mL after reconstitution (Co-artesiane® Dafra Pharma NV); administration once daily at hour 0, 24, 48 based on participant’s weight. |
|---------------|----------------------------------------------------------------------------------|
|               | 2. Artemether-lumefantrine crushed tablets 20 mg/120 mg fixed dose combination (Coartem®, Novartis, Switzerland) mixed with water, twice daily over 3 days. |
|               | Treatment doses were calculated based on participant’s weight and administered directly observed under inpatient care; dosage is not described in more detail. |

| Outcomes | Primary efficacy outcome measure: |
|----------|----------------------------------|
|          | 1. PCR-adjusted cure rate by day 28. |
|          | Secondary efficacy outcome measure: |
|          | 1. PCR-adjusted cure rate by day 14; |
|          | 2. Parasite clearance time; |
3. Fever clearance time.
Safety endpoints not stated.

Notes
Study centre: Chulaimbo Health Centre in Kisumu District in western Kenya.
Transmission: high perennial malaria transmission in the lowlands around Lake Victoria, transmission
peaks March to May and October to December.
Dates: May 2007 to December 2007
Funding: Research Grant from Dafra Pharma NV, Belgium.

Risk of bias

| Bias                                      | Authors' judgement | Support for judgement |
|-------------------------------------------|--------------------|-----------------------|
| Random sequence generation (selection bias) | Low risk           | Randomization code was computer-generated without stratification, from which treatment groups were assigned. |
| Allocation concealment (selection bias)   | Unclear risk       | Not stated            |
| Blinding of participants and personnel (performance bias) All outcomes | High risk          | Open-label study      |
| Blinding of outcome assessment (detection bias) All outcomes | High risk          | Open-label study      |
| Incomplete outcome data (attrition bias) All outcomes | Low risk           | Loss to follow-up reported, low dropout rate. |
| Selective reporting (reporting bias)      | Low risk           | All essential outcomes and measurement were reported. |
| Other bias                                | Low risk           | Trial design and analysis not performed by sponsor. The study was funded by a research grant from a pharmaceutical company, which also donated Co-artesiane® powder for suspension and Coartem® tablets. |

ACPR: adequate clinical parasitological response; DHA-PQ: dihydroartemisinin-piperaquine; ECG: electrocardiogram; ETF: early treatment failure; LCF: late clinical failure; LPF: late parasitological failure; LTF: late treatment failure; NGO: non-governmental organization; PCR: polymerase chain reaction; WHO: World Health Organization

Characteristics of excluded studies [ordered by study ID]

| Study   | Reason for exclusion                                                                 |
|---------|---------------------------------------------------------------------------------------|
| Banek 2018 | The paediatric ACT investigated in this prospective open, randomized clinical trial was Coartem Dispersible by Novartis Pharmaceuticals, Basel, Switzerland (same as used in the Abdulla 2008 study). This paediatric formulation is a sweet-tasting and easy-to-administer tablet of 20 mg artemether and 120 mg lumefantrine.  
  The study was excluded from the review because the comparator ACT was not the same drug combination but amodiaquine-artesunate. |
| Study       | Reason for exclusion                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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| Study          | Reason for exclusion                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sagara 2018    | The paediatric ACTs investigated in this phase 3b/4 comparative, randomised, multicentre, open-label, longitudinal clinical study were pyronaridine–artesunate granules (Shin Poong Pharmaceutical, Ansan, South Korea), artemether–lumefantrine dispersible tablets (Novartis Pharma AG, Basel, Switzerland), and dissolved artesunate–amodiaquine tablets (Sanofi, Paris, France). The study was excluded from the review because the paediatric ACTs were not directly compared to an ACT containing the same drug. |
| Sirima 2016    | The paediatric ACT investigated in this phase 4, multicentre, open-label, randomised, non-inferiority trial was Coartem Dispersible by Novartis Pharmaceuticals, Basel, Switzerland (same as in Abdul-lah 2008). This fixed-dose artemether–lumefantrine dispersible tablet (20 mg artemether and 120 mg lumefantrine,) containing flavouring was dispersed in 200 mL milk (or breast milk). The study was excluded from the review because the comparator ACT was not the same drug combination but artesunate-mefloquine. |
| Tahar 2014     | The paediatric ACT investigated in this open-label, randomized study was Camoquin syrup by Pfizer Afrique de l’Ouest, Dakar, Senegal. This paediatric formulation was a non-fixed dose combination of 10 mg amodiaquine base/mL syrup plus artesunate tablets. The study was excluded from the review because the intervention ACT was not a fixed-dose combination and only partly a paediatric formulation, and the comparator ACT was not the same drug combination but atovaquone-proguanil. |
| Toure 2011     | The paediatric ACT investigated in this randomized open-label clinical trial was Artequin Paediatric by Mephla Ltd, Aesch, Switzerland (same paediatric ACT as in the Faye 2010 study). This paediatric formulation is a preparation of granules of 50 mg of artesunate and 125 mg of mefloquine; the active ingredients are formulated as taste-masked granules (mango flavour). Granules were mixed with yoghurt before being administered directly into the mouth. The study was excluded from the review because the comparator ACT was not the same drug combination but artemether-lumefantrine. |

ACT: artemisinin-based combination therapy; DHA-PQ: dihydroartemisinin-piperaquine;

DATA AND ANALYSES

Comparison 1. ACT dispersible tablet versus ACT crushed tablet

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method                          | Effect size       |
|---------------------------|----------------|---------------------|---------------------------------------------|-------------------|
| 1.1 Day 28 PCR-adjusted treatment failure PP | 2              | 1061                | Risk Ratio (M-H, Random, 95% CI)            | 1.35 [0.49, 3.72] |
| 1.2 Day 28 PCR-adjusted treatment failure ITT | 2              | 1139                | Risk Ratio (M-H, Random, 95% CI)            | 1.05 [0.68, 1.62] |
| 1.3 Day 28 PCR-unadjusted treatment failure PP | 2              | 1061                | Risk Ratio (M-H, Random, 95% CI)            | 1.03 [0.48, 2.25] |
| 1.4 Day 28 PCR-unadjusted treatment failure ITT | 2              | 1139                | Risk Ratio (M-H, Random, 95% CI)            | 0.90 [0.65, 1.25] |
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---------------------------|----------------|---------------------|-------------------|-------------|
| 1.5 PCR-adjusted treatment failure last day of observation (D42) PP | 2 | 958 | Risk Ratio (M-H, Random, 95% CI) | 1.07 [0.53, 2.13] |
| 1.6 PCR-adjusted treatment failure last day of observation (D42) ITT | 2 | 1047 | Risk Ratio (M-H, Random, 95% CI) | 1.06 [0.66, 1.73] |
| 1.7 PCR-unadjusted treatment failure last day of observation (D42) PP | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 1.8 PCR-unadjusted treatment failure last day of observation (D42) ITT | 2 | 1047 | Risk Ratio (M-H, Random, 95% CI) | 0.86 [0.70, 1.05] |
| 1.9 Serious adverse events | 2 | 1197 | Risk Ratio (M-H, Random, 95% CI) | 1.05 [0.38, 2.88] |
| 1.10 Drug-related adverse events | 2 | 1197 | Risk Ratio (M-H, Random, 95% CI) | 0.78 [0.62, 0.99] |
| 1.11 Drug-related vomiting | 2 | 1197 | Risk Ratio (M-H, Random, 95% CI) | 0.75 [0.56, 1.01] |
| 1.12 Drug-related gastrointestinal disorders | 2 | 1197 | Risk Ratio (M-H, Random, 95% CI) | 1.19 [0.19, 7.45] |
| 1.13 Drug-related vomiting and gastrointestinal disorders | 2 | 1197 | Risk Ratio (M-H, Random, 95% CI) | 0.76 [0.57, 1.00] |
| 1.14 Adverse events | 2 | 1197 | Risk Ratio (M-H, Random, 95% CI) | 0.96 [0.90, 1.03] |
| 1.15 Drug-related serious adverse events | 2 | 1197 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |

Analysis 1.1. Comparison 1: ACT dispersible tablet versus ACT crushed tablet, Outcome 1: Day 28 PCR-adjusted treatment failure PP

Study | Paediatric Formulation Events | Total | Crushed Tablet Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|------|-----------------------------|-------|-----------------------|-------|--------|--------------------------------|
| Abdulla 2008 | 7 | 398 | 6 | 406 | 88.2% | 1.19 [0.40, 3.51] |
| Gargano 2018 | 3 | 173 | 0 | 84 | 11.8% | 3.42 [0.18, 65.45] |
| Total (95% CI) | 10 | 571 | 6 | 490 | 100.0% | 1.35 [0.49, 3.72] |

Total events: Heterogeneity: Tau² = 0.00; Chi² = 0.44, df = 1 (P = 0.51); P = 9%
Test for overall effect: Z = 0.50 (P = 0.56)
Test for subgroup differences: Not applicable

Favours paediatric form. Favours tablet
**Analysis 1.2. Comparison 1: ACT dispersible tablet versus ACT crushed tablet, Outcome 2: Day 28 PCR-adjusted treatment failure ITT**

| Study or Subgroup | Paediatric Formulation | Crushed Tablet | Weight | Risk Ratio        | Risk Ratio        |
|-------------------|------------------------|----------------|--------|-------------------|-------------------|
|                   | Events                 | Total          | Events | Total             | M-H, Random, 95% CI | M-H, Random, 95% CI |
| Abdulla 2008      | 21                     | 418            | 423    | 46.1%             | 1.33 [0.70, 2.51]  |                  |
| Gargano 2018      | 26                     | 199            | 15     | 53.9%             | 0.86 [0.48, 1.55]  |                  |
| **Total (95% CI)**| **617**                | **522**        |        | **100.0%**        | **1.05 [0.68, 1.62]** |                  |
| Total events:     | 47                     | 31             |        |                   |                   |                  |

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.96$, df = 1 ($P = 0.33$); $I^2 = 0$

Test for overall effect: $Z = 0.23$ ($P = 0.82$)

Test for subgroup differences: Not applicable

**Analysis 1.3. Comparison 1: ACT dispersible tablet versus ACT crushed tablet, Outcome 3: Day 28 PCR-unadjusted treatment failure PP**

| Study or Subgroup | Paediatric Formulation | Crushed Tablet | Weight | Risk Ratio        | Risk Ratio        |
|-------------------|------------------------|----------------|--------|-------------------|-------------------|
|                   | Events                 | Total          | Events | Total             | M-H, Random, 95% CI | M-H, Random, 95% CI |
| Abdulla 2008      | 30                     | 398            | 39     | 406               | 0.78 [0.50, 1.24]  |                  |
| Gargano 2018      | 15                     | 173            | 4      | 84                | 1.62 [0.62, 5.32]  |                  |
| **Total (95% CI)**| **571**                | **490**        |        | **100.0%**        | **1.03 [0.48, 2.25]** |                  |
| Total events:     | 45                     | 43             |        |                   |                   |                  |

Heterogeneity: $\tau^2 = 0.18$; $\chi^2 = 2.02$, df = 1 ($P = 0.16$); $I^2 = 50$

Test for overall effect: $Z = 0.08$ ($P = 0.93$)

Test for subgroup differences: Not applicable

**Analysis 1.4. Comparison 1: ACT dispersible tablet versus ACT crushed tablet, Outcome 4: Day 28 PCR-unadjusted treatment failure ITT**

| Study or Subgroup | Paediatric Formulation | Crushed Tablet | Weight | Risk Ratio        | Risk Ratio        |
|-------------------|------------------------|----------------|--------|-------------------|-------------------|
|                   | Events                 | Total          | Events | Total             | M-H, Random, 95% CI | M-H, Random, 95% CI |
| Abdulla 2008      | 33                     | 418            | 40     | 423               | 0.83 [0.54, 1.30]  |                  |
| Gargano 2018      | 30                     | 199            | 19     | 99                | 0.99 [0.61, 1.63]  |                  |
| **Total (95% CI)**| **617**                | **522**        |        | **100.0%**        | **0.90 [0.65, 1.25]** |                  |
| Total events:     | 71                     | 59             |        |                   |                   |                  |

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.27$, df = 1 ($P = 0.60$); $I^2 = 0$

Test for overall effect: $Z = 0.61$ ($P = 0.54$)

Test for subgroup differences: Not applicable
Analysis 1.5. Comparison 1: ACT dispersible tablet versus ACT crushed tablet, Outcome 5: PCR-adjusted treatment failure last day of observation (D42) PP

| Study or Subgroup | Paediatric Formulation | Crushed Tablet | Risk Ratio | Risk Ratio |
|-------------------|------------------------|----------------|------------|------------|
| Gargano 2018      | 6                      | 173            | 3          | 84         | 25.9% | 0.97 [0.25, 3.79] |
| Abdulla 2008      | 12                     | 349            | 11         | 352        | 74.1% | 1.10 [0.49, 2.46] |
| **Total (95% CI)**| **522**                | **436**        | **100.0%** | **1.07 [0.53, 2.13]** |

Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%
Test for overall effect: Z = 0.18 (P = 0.86)
Test for subgroup differences: Not applicable

Favours paediatric form.  
Favours tablet.

Analysis 1.6. Comparison 1: ACT dispersible tablet versus ACT crushed tablet, Outcome 6: PCR-adjusted treatment failure last day of observation (D42) ITT

| Study or Subgroup | Paediatric Formulation | Crushed Tablet | Risk Ratio | Risk Ratio |
|-------------------|------------------------|----------------|------------|------------|
| Abdulla 2008      | 34                     | 377            | 25         | 372        | 53.1% | 1.34 [0.82, 2.20] |
| Gargano 2018      | 20                     | 199            | 17         | 99         | 46.9% | 0.62 [0.47, 1.42] |
| **Total (95% CI)**| **576**                | **471**        | **100.0%** | **1.06 [0.66, 1.73]** |

Heterogeneity: Tau² = 0.05; Chi² = 1.70, df = 1 (P = 0.19); I² = 41%
Test for overall effect: Z = 0.26 (P = 0.80)
Test for subgroup differences: Not applicable

Favours paediatric form.  
Favours tablet.

Analysis 1.7. Comparison 1: ACT dispersible tablet versus ACT crushed tablet, Outcome 7: PCR-unadjusted treatment failure last day of observation (D42) PP

| Study or Subgroup | Paediatric Formulation | Crushed Tablet | Risk Ratio | Risk Ratio |
|-------------------|------------------------|----------------|------------|------------|
| Gargano 2018      | 41                     | 173            | 23         | 84         | 0.87 [0.56, 1.34] |

Favours paediatric form.  
Favours tablet.
### Analysis 1.8. Comparison 1: ACT dispersible tablet versus ACT crushed tablet, Outcome 8: PCR-unadjusted treatment failure last day of observation (D42) ITT

| Study or Subgroup | Paediatric Formulation Events | Total | Crushed Tablet Events | Total | Weight | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|------------------|-------------------------------|-------|-----------------------|-------|--------|-------------------------------|-------------------------------|
| Abdulla 2008 (1) | 84                            | 377   | 95                    | 372   | 61.1%  | 0.87 [0.68 , 1.13]            |                               |
| Gargano 2018     | 64                            | 199   | 38                    | 99    | 38.9%  | 0.84 [0.61 , 1.15]            |                               |
| **Total (95% CI)** | **576**                      | **471** | **100.0%**          |      |        | **0.86 [0.70 , 1.05]**       |                               |
| Total events:    |                               |       |                       |       |        |                               |                               |

**Heterogeneity:** Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.85); I² = 0%

Test for overall effect: Z = 1.49 (P = 0.14)

Test for subgroup differences: Not applicable

Favours paediatric form.  
Favours tablet

### Footnotes

(1) No absolute numbers reported, experimental 77.7% vs. control 74.5%

### Analysis 1.9. Comparison 1: ACT dispersible tablet versus ACT crushed tablet, Outcome 9: Serious adverse events

| Study or Subgroup | Paediatric Formulation Events | Total | Crushed Tablet Events | Total | Weight | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|------------------|-------------------------------|-------|-----------------------|-------|--------|-------------------------------|-------------------------------|
| Abdulla 2008     | 7                             | 447   | 6                     | 452   | 86.7%  | 1.18 [0.40 , 3.48]            |                               |
| Gargano 2018     | 1                             | 199   | 1                     | 99    | 13.3%  | 0.50 [0.03 , 7.87]            |                               |
| **Total (95% CI)** | **646**                      | **551** | **100.0%**          |      |        | **1.05 [0.38 , 2.88]**       |                               |
| Total events:    |                               |       |                       |       |        |                               |                               |

**Heterogeneity:** Tau² = 0.00; Chi² = 0.33, df = 1 (P = 0.57); I² = 0%

Test for overall effect: Z = 0.10 (P = 0.92)

Test for subgroup differences: Not applicable

Favours paediatric form.  
Favours tablet

### Analysis 1.10. Comparison 1: ACT dispersible tablet versus ACT crushed tablet, Outcome 10: Drug-related adverse events

| Study or Subgroup | Paediatric Formulation Events | Total | Crushed Tablet Events | Total | Weight | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|------------------|-------------------------------|-------|-----------------------|-------|--------|-------------------------------|-------------------------------|
| Abdulla 2008     | 42                            | 447   | 56                    | 452   | 38.8%  | 0.76 [0.52 , 1.11]            |                               |
| Gargano 2018     | 67                            | 199   | 42                    | 99    | 61.2%  | 0.79 [0.59 , 1.07]            |                               |
| **Total (95% CI)** | **646**                      | **551** | **100.0%**          |      |        | **0.78 [0.62 , 0.99]**       |                               |
| Total events:    |                               |       |                       |       |        |                               |                               |

**Heterogeneity:** Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.85); I² = 0%

Test for overall effect: Z = 2.07 (P = 0.04)

Test for subgroup differences: Not applicable

Favours paediatric form.  
Favours tablet
## Analysis 1.11. Comparison 1: ACT dispersible tablet versus ACT crushed tablet, Outcome 11: Drug-related vomiting

| Study or Subgroup | Paediatric Formulation | Crushed Tablet | Risk Ratio | Risk Ratio |
|-------------------|------------------------|----------------|------------|------------|
|                   | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI |
| Abdulla 2008      | 33     | 447   | 42     | 452   | 44.2% | 0.79 [0.51, 1.23] |
| Gargano 2018      | 45     | 199   | 31     | 99    | 55.8% | 0.72 [0.49, 1.07] |
| **Total (95% CI)**| **78** | **551** | **646** | **100.0%** | **0.75 [0.56, 1.01]** |

Heterogeneity: Tau² = 0.00; Chi² = 1.00, df = 1 (P = 0.31); I² = 0%
Test for overall effect: Z = 1.91 (P = 0.06)
Test for subgroup differences: Not applicable

Favours paediatric form.

## Analysis 1.12. Comparison 1: ACT dispersible tablet versus ACT crushed tablet, Outcome 12: Drug-related gastrointestinal disorders

| Study or Subgroup | Paediatric Formulation | Crushed Tablet | Risk Ratio | Risk Ratio |
|-------------------|------------------------|----------------|------------|------------|
|                   | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI |
| Abdulla 2008      | 2      | 447   | 0      | 452   | 28.7% | 5.06 [0.24, 105.01] |
| Gargano 2018      | 4      | 199   | 3      | 99    | 71.3% | 0.66 [0.15, 2.91] |
| **Total (95% CI)**| **6**  | **551** | **646** | **100.0%** | **1.19 [0.19, 7.45]** |

Heterogeneity: Tau² = 0.66; Chi² = 1.45, df = 1 (P = 0.23); I² = 31%
Test for overall effect: Z = 0.18 (P = 0.85)
Test for subgroup differences: Not applicable

Favours paediatric form.

## Analysis 1.13. Comparison 1: ACT dispersible tablet versus ACT crushed tablet, Outcome 13: Drug-related vomiting and gastrointestinal disorders

| Study or Subgroup | Paediatric Formulation | Crushed Tablet | Risk Ratio | Risk Ratio |
|-------------------|------------------------|----------------|------------|------------|
|                   | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI |
| Abdulla 2008      | 34     | 447   | 42     | 452   | 41.6% | 0.82 [0.53, 1.26] |
| Gargano 2018      | 49     | 199   | 34     | 99    | 58.4% | 0.72 [0.50, 1.03] |
| **Total (95% CI)**| **83** | **551** | **646** | **100.0%** | **0.76 [0.57, 1.00]** |

Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 1 (P = 0.64); I² = 0%
Test for overall effect: Z = 1.95 (P = 0.05)
Test for subgroup differences: Not applicable

Favours paediatric form.
### Analysis 1.14. Comparison 1: ACT dispersible tablet versus ACT crushed tablet, Outcome 14: Adverse events

| Study or Subgroup | Paediatric Formulation Events | Total | Crushed Tablet Events | Total | Weight | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|-------------------|-------------------------------|-------|-----------------------|-------|--------|--------------------------------|--------------------------------|
| Abdulla 2008      | 307                           | 447   | 318                   | 452   | 60.8%  | 0.98 [0.90, 1.06]              |                                |
| Gargano 2018      | 160                           | 199   | 84                    | 99    | 39.2%  | 0.95 [0.85, 1.06]              |                                |
| **Total (95% CI)**| **467**                       | **646**| **551**               | **100.0%**|        | **0.96 [0.90, 1.03]**         |                                |
| Heterogeneity: Tau² = 0.00; Chi² = 0.19, df = 1 (P = 0.66); I² = 0% |
| Test for overall effect: Z = 1.04 (P = 0.30) |
| Test for subgroup differences: Not applicable |

**Paediatric Formulation**
- Events: 307
- Total: 447

**Crushed Tablet**
- Events: 160
- Total: 199

**Total events:** 467

**Risk Ratio**
- M-H, Random, 95% CI: 0.98 [0.90, 1.06]

**Favours paediatric form.**

### Analysis 1.15. Comparison 1: ACT dispersible tablet versus ACT crushed tablet, Outcome 15: Drug-related serious adverse events

| Study or Subgroup | Paediatric Formulation Events | Total | Crushed Tablet Events | Total | Weight | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|-------------------|-------------------------------|-------|-----------------------|-------|--------|--------------------------------|--------------------------------|
| Abdulla 2008      | 0                             | 447   | 0                     | 452   |        | Not estimable                   |                                |
| Gargano 2018      | 0                             | 199   | 0                     | 99    |        | Not estimable                   |                                |
| **Total (95% CI)**| **646**                       | **551**|                      |       |        | **Not estimable**               |                                |
| Heterogeneity: Not applicable |
| Test for overall effect: Not applicable |
| Test for subgroup differences: Not applicable |

**Paediatric Formulation**
- Events: 0
- Total: 0

**Crushed Tablet**
- Events: 0
- Total: 0

**Total events:** 0

**Risk Ratio**
- M-H, Random, 95% CI: Not estimable

**Favours paediatric form.**

### Comparison 2. ACT suspension versus ACT crushed tablet

| Outcome or subgroup title       | No. of studies | No. of participants | Statistical method               | Effect size                  |
|---------------------------------|----------------|---------------------|---------------------------------|-----------------------------|
| 2.1 Day 28 PCR-adjusted treatment failure PP | 1              |                      | Risk Ratio (M-H, Random, 95% CI) | Totals not selected         |
| 2.2 Day 28 PCR-adjusted treatment failure ITT | 1              |                      | Risk Ratio (M-H, Random, 95% CI) | Totals not selected         |
| 2.3 Day 28 PCR-unadjusted treatment failure PP | 1              |                      | Risk Ratio (M-H, Random, 95% CI) | Totals not selected         |
| 2.4 Day 28 PCR-unadjusted treatment failure ITT | 1              |                      | Risk Ratio (M-H, Random, 95% CI) | Totals not selected         |
| 2.5 Serious adverse events      | 1              |                      | Risk Ratio (M-H, Random, 95% CI) | Totals not selected         |
| 2.6 Drug-related adverse events | 1              |                      | Risk Ratio (M-H, Random, 95% CI) | Totals not selected         |
| 2.7 Drug-related vomiting       | 1              |                      | Risk Ratio (M-H, Random, 95% CI) | Totals not selected         |
| Outcome or subgroup title                                    | No. of studies | No. of participants | Statistical method                          | Effect size          |
|--------------------------------------------------------------|----------------|---------------------|---------------------------------------------|----------------------|
| 2.8 Drug-related gastrointestinal disorders                   | 1              |                     | Risk Ratio (M-H, Random, 95% CI)            | Totals not selected  |
| 2.9 Drug-related vomiting and gastrointestinal disorders      | 1              |                     | Risk Ratio (M-H, Random, 95% CI)            | Totals not selected  |
| 2.10 Fever clearance time                                    | 1              |                     | Mean Difference (IV, Random, 95% CI)        | Totals not selected  |
| 2.11 Parasite clearance time                                 | 1              |                     | Mean Difference (IV, Random, 95% CI)        | Totals not selected  |
| 2.12 Adverse events                                         | 1              |                     | Risk Ratio (M-H, Random, 95% CI)            | Totals not selected  |
| 2.13 Drug-related serious adverse events                     | 1              |                     | Risk Ratio (M-H, Random, 95% CI)            | Totals not selected  |

**Analysis 2.1. Comparison 2: ACT suspension versus ACT crushed tablet, Outcome 1: Day 28 PCR-adjusted treatment failure PP**

| Study or Subgroup | Paediatric Formulation | Crushed Tablet | Risk Ratio M-H, Random, 95% CI |
|-------------------|------------------------|----------------|--------------------------------|
| Juma 2008         | 8                      | 5              | 1.64 [0.55, 4.87]              |

**Analysis 2.2. Comparison 2: ACT suspension versus ACT crushed tablet, Outcome 2: Day 28 PCR-adjusted treatment failure ITT**

| Study or Subgroup | Paediatric Formulation | Crushed Tablet | Risk Ratio M-H, Random, 95% CI |
|-------------------|------------------------|----------------|--------------------------------|
| Juma 2008         | 21                     | 14             | 1.49 [0.79, 2.80]              |
Analysis 2.3. Comparison 2: ACT suspension versus ACT crushed tablet, Outcome 3: Day 28 PCR-unadjusted treatment failure PP

| Study or Subgroup | Paediatric Formulation Events | Total | Crushed Tablet Events | Total | Risk Ratio M-H, Random, 95% CI |
|-------------------|-----------------------------|-------|-----------------------|-------|-------------------------------|
| Juma 2008         | 15                          | 121   | 15                    | 124   | 1.02 [0.52, 2.00]             |

Favours paediatric form.  Favours tablet

Analysis 2.4. Comparison 2: ACT suspension versus ACT crushed tablet, Outcome 4: Day 28 PCR-unadjusted treatment failure ITT

| Study or Subgroup | Paediatric Formulation Events | Total | Crushed Tablet Events | Total | Risk Ratio M-H, Random, 95% CI |
|-------------------|-----------------------------|-------|-----------------------|-------|-------------------------------|
| Juma 2008         | 28                          | 134   | 24                    | 133   | 1.16 [0.71, 1.89]             |

Favours paediatric form.  Favours tablet

Analysis 2.5. Comparison 2: ACT suspension versus ACT crushed tablet, Outcome 5: Serious adverse events

| Study or Subgroup | Paediatric Formulation Events | Total | Crushed Tablet Events | Total | Risk Ratio M-H, Random, 95% CI |
|-------------------|-----------------------------|-------|-----------------------|-------|-------------------------------|
| Juma 2008         | 3                           | 134   | 4                     | 133   | 0.74 [0.17, 3.26]             |

Favours paediatric form.  Favours tablet

Analysis 2.6. Comparison 2: ACT suspension versus ACT crushed tablet, Outcome 6: Drug-related adverse events

| Study or Subgroup | Paediatric Formulation Events | Total | Crushed Tablet Events | Total | Risk Ratio M-H, Random, 95% CI |
|-------------------|-----------------------------|-------|-----------------------|-------|-------------------------------|
| Juma 2008         | 12                          | 134   | 18                    | 133   | 0.66 [0.33, 1.32]             |

Favours paediatric form.  Favours tablet

Analysis 2.7. Comparison 2: ACT suspension versus ACT crushed tablet, Outcome 7: Drug-related vomiting

| Study or Subgroup | Paediatric Formulation Events | Total | Crushed Tablet Events | Total | Risk Ratio M-H, Random, 95% CI |
|-------------------|-----------------------------|-------|-----------------------|-------|-------------------------------|
| Juma 2008         | 12                          | 134   | 18                    | 133   | 0.66 [0.33, 1.32]             |

Favours paediatric form.  Favours tablet
### Analysis 2.8. Comparison 2: ACT suspension versus ACT crushed tablet, Outcome 8: Drug-related gastrointestinal disorders

| Study or Subgroup | Paediatric Formulation | Crushed Tablet | Risk Ratio | Risk Ratio |
|-------------------|------------------------|----------------|------------|------------|
|                   | Events | Total | Events | Total | M-H, Random, 95% CI | M-H, Random, 95% CI |
| Juma 2008         | 1      | 134   | 1      | 133    | 0.99 [0.06, 15.70]  |

**Favours paediatric form.**

**Favours tablet.**

### Analysis 2.9. Comparison 2: ACT suspension versus ACT crushed tablet, Outcome 9: Drug-related vomiting and gastrointestinal disorders

| Study or Subgroup | Paediatric Formulation | Crushed Tablet | Risk Ratio | Risk Ratio |
|-------------------|------------------------|----------------|------------|------------|
|                   | Events | Total | Events | Total | M-H, Random, 95% CI | M-H, Random, 95% CI |
| Juma 2008         | 12     | 134   | 18     | 133    | 0.66 [0.33, 1.32]  |

**Favours paediatric form.**

**Favours tablet.**

### Analysis 2.10. Comparison 2: ACT suspension versus ACT crushed tablet, Outcome 10: Fever clearance time

| Study or Subgroup | Paediatric Formulation | Crushed Tablet | Mean Difference | Mean Difference |
|-------------------|------------------------|----------------|----------------|----------------|
|                   | Mean | SD | Total | Mean | SD | Total | IV, Random, 95% CI | IV, Random, 95% CI |
| Juma 2008         | 41.6 | 13.9 | 134   | 44.4 | 20.1 | 133   | -2.80 [-6.95, 1.35] |

**Favours paediatric form.**

**Favours crushed tablet.**

### Analysis 2.11. Comparison 2: ACT suspension versus ACT crushed tablet, Outcome 11: Parasite clearance time

| Study or Subgroup | Paediatric Formulation | Crushed Tablet | Mean Difference | Mean Difference |
|-------------------|------------------------|----------------|----------------|----------------|
|                   | Mean | SD | Total | Mean | SD | Total | IV, Random, 95% CI | IV, Random, 95% CI |
| Juma 2008         | 54.7 | 14.6 | 134   | 53.8 | 15.7 | 133   | 0.90 [-2.74, 4.54] |

**Favours paediatric form.**

**Favours crushed tablet.**

### Analysis 2.12. Comparison 2: ACT suspension versus ACT crushed tablet, Outcome 12: Adverse events

| Study or Subgroup | Paediatric Formulation | Crushed Tablet | Risk Ratio | Risk Ratio |
|-------------------|------------------------|----------------|------------|------------|
|                   | Events | Total | Events | Total | M-H, Random, 95% CI | M-H, Random, 95% CI |
| Juma 2008         | 70     | 134   | 62     | 133    | 1.12 [0.88, 1.43]  |

**Favours paediatric form.**

**Favours crushed tablet.**
Analysis 2.13. Comparison 2: ACT suspension versus ACT crushed tablet, Outcome 13: Drug-related serious adverse events

| Study or Subgroup | Paediatric Formulation Events | Crashed Tablet Events | Risk Ratio M-H, Random, 95% CI |
|-------------------|-------------------------------|-----------------------|--------------------------------|
| Juma 2008         | 0                             | 0                     | Not estimable                  |

Risk Ratio: M-H, Random, 95% CI

| 0.01 | 0.1 | 1   | 10  | 100 |

Favours paediatric form.  
Favours tablet

APPENDICES

Appendix 1. Detailed search strategy

MEDLINE (PubMed)

#1 Search falciparum malaria Field: Title/Abstract OR "Malaria, Falciparum" [Mesh]
#2 Search arte* or Dihydroarte* Field: Title/Abstract
#3 Search "Artemisinins"[Mesh] OR "artemisinine" [Supplementary Concept]
#4 Search child* or pediatr* or paediatr* or infant* Field: Title/Abstract
#5 Search ((arte* or Dihydroarte*) OR #3
#6 Search (#5) AND #4
#7 Search (#6) AND #1
#8 Search "Randomized Controlled Trial" [Publication Type] OR "Controlled Clinical Trial" [Publication Type] OR (randomized OR placebo ) Field:Title/Abstract OR "clinical trials as topic" [Mesh] OR (randomly OR trial ) Field:Title/Abstract
#9 Search (#7) AND #8

Search Name: Cochrane Central Register of Controlled Trials: Issue 12 of 12, December 2019

ID Search Hits

#1 malaria:ti,ab,kw (Word variations have been searched)
#2 arte* or Dihydroarte*
#3 MeSH descriptor: [Artemisinins] explode all trees
#4 #2 or #3
#5 #1 and #4
#6 child* or pediatr* or paediatr* or infant*:ti,ab,kw (Word variations have been searched)

Paediatric formulations of artemisinin-based combination therapies for treating uncomplicated malaria in children (Review)  
Copyright © 2020 The Authors. Cochrane Database of Systematic Reviews published by John Wiley & Sons, Ltd. on behalf of The Cochrane Collaboration.
#7 #5 and #6
#8 falciparum or uncomplicated
#9 #7 and #8

**Database: Embase**

**Search Strategy:**

```
1 malaria/ or malaria.mp.
2 Plasmodium/ or plasmodium.mp.
3 1 or 2
4 arte*.mp.
5 artemisinin derivative/ or artemisinin/ or artemisinin.mp.
6 dihydroartemisinin/ or dihydroarte*.mp.
7 4 or 5 or 6
8 3 and 7
9 (child* or pediatric or infant*).mp.
10 8 and 9
11 (randomized or randomised or placebo or double-blind* or single-blind*).ti. or (randomized or randomised or placebo or double-blind* or single-blind*).ab.
12 randomized controlled trial/ or controlled clinical trial/
13 11 or 12
14 10 and 13
```

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**SCI-EXPANDED, CPCI-S (Web of Science)**

```
# 1  TOPIC: (malaria and falciparum) AND TOPIC: (artemisin* or dihydroartem* ) AND TOPIC: (child* or pediatric or infant or paediatric) AND TOPIC: (randomized or double-blind* or single-blind* )

Indexes=SCI-EXPANDED, CPCI-S
```

**Scopus:** (TITLE-ABS-KEY (malaria) AND TITLE-ABS-KEY (artemisin* OR dihydroarte* ) AND TITLE-ABS-KEY (child* OR pediatric OR paediatric OR infant* ) ) AND TITLE-ABS-KEY ( randomized AND controlled AND trial )

**Database: LILACS**

Search on: malaria and artemisin$ [Words] and child$ or pediatric or paediatric [Words] and random$ or placebo or trial$ [Words]

**Clinicaltrials.gov**

artemisinins | Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | Interventional Studies | Malaria,Falciparum | Child

**WHO ICTRP:** malaria and arte* and child*
Appendix 2. Prespecified changes for review update

| Protocol section          | Summary of change                                                                                                                                 |
|---------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| Background and research question | References were updated to include the most recent evidence on the review topic. No change needed regarding the research question as the topic is still relevant as it is. |
| Inclusion criteria        | We updated the following inclusion criteria                                                                                                         |
|                           | • Participant inclusion criterion of body weight > 5 kg was removed.                                                                                  |
|                           | • Comparator inclusion criterion was changed to be the same ACT as the intervention ACT only (same partner drug compound), formulated as tablet possibly requiring splitting or crushing for use in children. |
| Methods                   | We updated the following.                                                                                                                             |
|                           | • Assessment of risk of bias in included studies: we listed new tools for assessing risk of bias (Cochrane Handbook Chapter 8 and 12)              |
|                           | • Data synthesis: we added that we will prepare a ‘Summary of findings’ table, specified the outcomes to be included in the table, and the tool (GRADE) to assess the quality of evidence. |

This table was approved by the CIDG editorial team on 9 May 2018.

HISTORY

Protocol first published: Issue 1, 2012
Review first published: Issue 12, 2020

CONTRIBUTIONS OF AUTHORS

SB, MR, and FK all contributed equally to the design of this review.

SB: performed the literature search, identified studies, extracted data, analysed data, and wrote the manuscript.

MR: analysed data and contributed to writing the manuscript.

FK: performed the literature search, identified studies, extracted data, analysed data, and wrote the manuscript.

DECLARATIONS OF INTEREST

SB participated as investigator in the clinical development of artesunate–mefloquine (sponsored by Mepha, Aesch, Switzerland) between 2005 and 2006, and pyronaridine–artesunate (sponsored by Medicines for Malaria Venture, Geneva, Switzerland) between 2006 and 2008.

MR has participated as investigator in the clinical development of pyronaridine-artesunate (sponsored by Medicines for Malaria Venture, Geneva, Switzerland) in 2005-2020, artesunate-mefloquine (sponsored by Mepha, Aesch, Switzerland) between 2005-2006, and artemether-lumefantrine in 2006-2008. He has received consulting fees from Medicines for Malaria Venture.

FK participated as investigator in the clinical development of artesunate–mefloquine (sponsored by Mepha, Aesch, Switzerland) between 2005 and 2006, and pyronaridine–artesunate (sponsored by Medicines for Malaria Venture, Geneva, Switzerland) between 2006 and 2008.

SOURCES OF SUPPORT

Internal sources
• Liverpool School of Tropical Medicine, UK
External sources

- Foreign, Commonwealth and Development Office (FCDO), UK

  Project number 300342-104

Differences between protocol and review

Differences between the initial protocol (Bélard 2012) and updated protocol are shown in Appendix 2. We adapted the inclusion criteria following discussion with the CIDG editorial team in 2018, and did not deem the original inclusion criterion of body weight > 5 kg to be necessary. We agreed that we should only include studies that compared different formulations of the same ACT, to attain the highest possible level of evidence. We adapted the Methods section in accordance with updates of the Cochrane Handbook for Systematic Reviews of Interventions.

Differences between the updated protocol and review are that we did not do a sensitivity analysis and did not impute missing data, due to the low number of studies.

Index terms

Medical Subject Headings (MeSH)

- Antimalarials [adverse effects] [*therapeutic use]; Artemether, Lumefantrine Drug Combination [adverse effects] [*therapeutic use]; Artemisinins [adverse effects] [*therapeutic use]; Bias; Confidence Intervals; Drug Combinations; Malaria, Falciparum [*drug therapy]; Quinolines [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic; Suspensions; Tablets; Treatment Failure; Vomiting [chemically induced] [epidemiology]

MeSH check words

- Adolescent; Child; Child, Preschool; Humans; Infant