

Cochrane Database of Systematic Reviews

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

Bélard S, Ramharter M, Kurth F

Bélard S, Ramharter M, Kurth F. Paediatric formulations of artemisinin-based combination therapies for treating uncomplicated malaria in children. *Cochrane Database of Systematic Reviews* 2020, Issue 12. Art. No.: CD009568. DOI: 10.1002/14651858.CD009568.pub2.

www.cochranelibrary.com

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

 $\label{eq:copyright} @ 2020 \ The \ Authors. \ Cochrane \ Database \ of \ Systematic \ Reviews \ published \ by \ John \ Wiley \ \& \ Sons, \ Ltd. \ on \ behalf \ of \ The \ Cochrane \ Collaboration.$

WILEY



TABLE OF CONTENTS

BSTRACT	
LAIN LANGUAGE SUMM	ARY
JMMARY OF FINDINGS	
ACKGROUND	
BJECTIVES	
ETHODS	
ESULTS	
Figure 1	
Figure 2	
ISCUSSION	
JTHORS' CONCLUSION	S
CKNOWLEDGEMENTS .	
EFERENCES	
HARACTERISTICS OF ST	UDIES
ATA AND ANALYSES	
	son 1: ACT dispersible tablet versus ACT crushed tablet, Outcome 1: Day 28 PCR-adjusted treatment failure
Analysis 1.2. Compari	son 1: ACT dispersible tablet versus ACT crushed tablet, Outcome 2: Day 28 PCR-adjusted treatment failure
	ison 1: ACT dispersible tablet versus ACT crushed tablet, Outcome 3: Day 28 PCR-unadjusted treatment
	ison 1: ACT dispersible tablet versus ACT crushed tablet, Outcome 4: Day 28 PCR-unadjusted treatment
	ison 1: ACT dispersible tablet versus ACT crushed tablet, Outcome 5: PCR-adjusted treatment failure last D42) PP
	ison 1: ACT dispersible tablet versus ACT crushed tablet, Outcome 6: PCR-adjusted treatment failure last D42) ITT
	ison 1: ACT dispersible tablet versus ACT crushed tablet, Outcome 7: PCR-unadjusted treatment failure on (D42) PP
	ison 1: ACT dispersible tablet versus ACT crushed tablet, Outcome 8: PCR-unadjusted treatment failure on (D42) ITT
Analysis 1.9. Compari	ison 1: ACT dispersible tablet versus ACT crushed tablet, Outcome 9: Serious adverse events
Analysis 1.10. Compa	rison 1: ACT dispersible tablet versus ACT crushed tablet, Outcome 10: Drug-related adverse events
Analysis 1.12. Compa	rison 1: ACT dispersible tablet versus ACT crushed tablet, Outcome 11: Drug-related vomitingarison 1: ACT dispersible tablet versus ACT crushed tablet, Outcome 12: Drug-related gastrointestinal
Analysis 1.13. Comp	arison 1: ACT dispersible tablet versus ACT crushed tablet, Outcome 13: Drug-related vomiting and
-	rders
	rison 1: ACT dispersible tablet versus ACT crushed tablet, Outcome 14: Adverse events
	arison 1: ACT dispersible tablet versus ACT crushed tablet, Outcome 15: Drug-related serious adverse
	son 2: ACT suspension versus ACT crushed tablet, Outcome 1: Day 28 PCR-adjusted treatment failure PP .
	son 2: ACT suspension versus ACT crushed tablet, Outcome 2: Day 28 PCR-adjusted treatment failure ITT
PP	ison 2: ACT suspension versus ACT crushed tablet, Outcome 3: Day 28 PCR-unadjusted treatment failure
	ison 2: ACT suspension versus ACT crushed tablet, Outcome 4: Day 28 PCR-unadjusted treatment failure
Analysis 2.5. Compar	ison 2: ACT suspension versus ACT crushed tablet, Outcome 5: Serious adverse events
-	ison 2: ACT suspension versus ACT crushed tablet, Outcome 6: Drug-related adverse events
	ison 2: ACT suspension versus ACT crushed tablet, Outcome 7: Drug-related vomiting
Analysis 2.8. Compari	son 2: ACT suspension versus ACT crushed tablet, Outcome 8: Drug-related gastrointestinal disorders son 2: ACT suspension versus ACT crushed tablet, Outcome 9: Drug-related vomiting and gastrointestinal



Analysis 2.10. Comparison 2: ACT suspension versus ACT crushed tablet, Outcome 10: Fever clearance time	32
Analysis 2.11. Comparison 2: ACT suspension versus ACT crushed tablet, Outcome 11: Parasite clearance time	32
Analysis 2.12. Comparison 2: ACT suspension versus ACT crushed tablet, Outcome 12: Adverse events	32
Analysis 2.13. Comparison 2: ACT suspension versus ACT crushed tablet, Outcome 13: Drug-related serious adverse events	33
APPENDICES	33
HISTORY	35
CONTRIBUTIONS OF AUTHORS	35
DECLARATIONS OF INTEREST	35
SOURCES OF SUPPORT	35
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	36
INDEX TERMS	36



[Intervention Review]

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

Sabine Bélard^{1,2}, Michael Ramharter³, Florian Kurth^{3,4}

¹Department of Paediatric Pulmonology, Immunology and Intensive Care Medicine, Charité-Universitätsmedizin Berlin, Berlin, Germany. ²Berlin Institute of Health, Berlin, Germany. ³Department of Tropical Medicine, Bernhard Nocht Institute for Tropical Medicine & I. Department of Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany. ⁴Department of Infectious Diseases and Pulmonary Medicine, Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany

Contact: Michael Ramharter, ramharter@bnitm.de.

Editorial group: Cochrane Infectious Diseases Group. **Publication status and date:** New, published in Issue 12, 2020.

Citation: Bélard S, Ramharter M, Kurth F. Paediatric formulations of artemisinin-based combination therapies for treating uncomplicated malaria in children. *Cochrane Database of Systematic Reviews* 2020, Issue 12. Art. No.: CD009568. DOI: 10.1002/14651858.CD009568.pub2.

Copyright © 2020 The Authors. Cochrane Database of Systematic Reviews published by John Wiley & Sons, Ltd. on behalf of The Cochrane Collaboration. This is an open access article under the terms of the Creative Commons Attribution-Non-Commercial Licence, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

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 artemetherlumefantrine (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 (PCRadjusted 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 *P 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 artemetherlumefantrine 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

 \cdot 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

 \cdot 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

Summary of findings 1. Summary of findings table 1

Dispersible tablets (p	aediatric formulat	ion) of ACT compared	with crushed tabl	ets (non-paediatr	ic formulation) of	ACT for uncomplicated malaria
Patient population: c	hildren aged 14 yea	rs or younger with unco	omplicated <i>P falcip</i>	<i>arum</i> malaria		
Settings: malaria-end	emic areas worldwi	de				
Intervention: dispersi	ble tablet of ACT					
Comparison: crushed	tablet of ACT					
Outcomes	Illustrative com CI)	parative risks* (95%	Relative effect (95% CI)	No of partici- pants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk		(studies)	(010102)	
	Crushed tablet (non-paedi- atric formula- tion)	Dispersible tablet (paediatric formu- lation)				
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 ^a	There may be little or no difference in day-28 PCR adjusted treatment failure in PP popula tion.
Treatment failure day-28 PCR-adjusted (ITT population)	59 per 1000	62 per 1000 (40 to 96)	RR 1.05 (0.68, 1.62)	1139 (2 RCTs)	Low ^b	There may be little or no difference in day-28 PCR adjusted treatment failure in ITT popula tion.
Serious adverse events	13 per 1000	14 per 1000 (5 to 37)	RR 1.05 (0.38, 2.88)	1197 (2 RCTs)	Low ^a	There may be little or no difference in seriou adverse events.
Drug-related ad- verse events	178 per 1000	139 (110 to 176)	RR 0.78 (0.62, 0.99)	1197 (2 RCTs)	Moderate ^c	Paediatric formulation probably reduces dru related adverse events.
Drug-related vomit- ing	132 per 1000	99 (74 to 133)	RR 0.75 (0.56, 1.01)	1197 (2 RCTs)	Low ^b	Paediatric formulation may reduce drug rela ed vomiting.
Acceptability	-	-	-	0 studies	-	None of the studies looked at acceptability (swallowability).

Cochrane Library

*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

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.

^aDowngraded by 2 levels for very serious imprecision: 95% CI encompasses substantive differences in relative cure or occurrence of Serious Adverse Events. ^bDowngraded by 2 levels for serious imprecision: 95% CI encompasses no difference to a large difference.

^cDowngraded by 1 level for serious imprecision. Events lower with dispersible tablet, but CI excludes higher number of events.

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



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 disproportionally 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 malariaendemic 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; 1982 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 (Bélard 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:

- intervention drug, with drug formulation and regimen, comparator drug with regimen;
- study location, study period, study design;
- age and weight range of participants, number of participants randomized and number of participants in each treatment arm for each outcome;

- primary and secondary endpoints:
 - PCR-adjusted and unadjusted treatment failure in perprotocol (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 I² and Chi² 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.

Figure 1. Study flow diagram.

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.

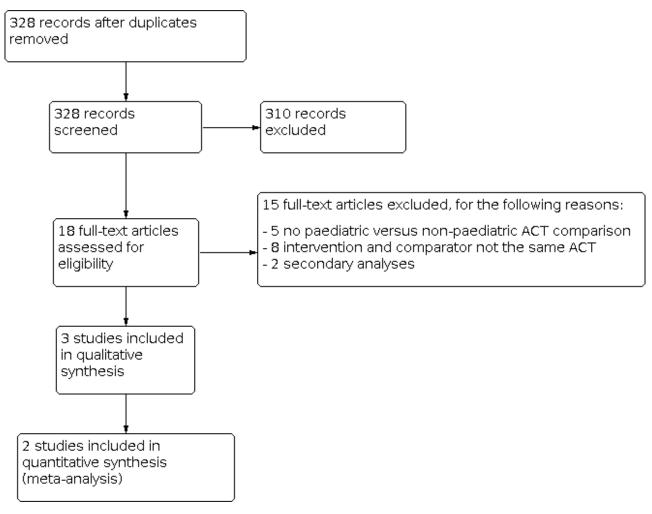
RESULTS

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).



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.



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 dihydroartemisininpiperaquine (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

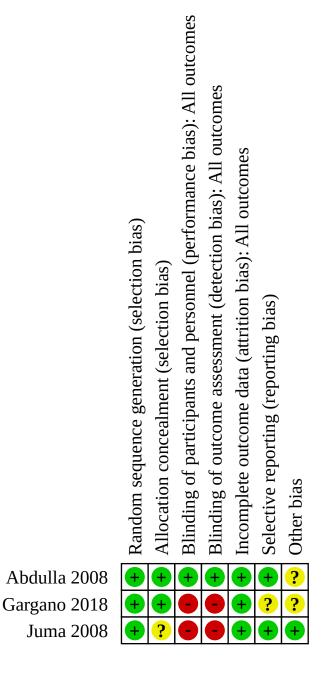
Randomized studies investigating paediatric formulations of ACT that did not meet all inclusion criteria are presented in the 'Characteristics of excluded studies' table. In most of these excluded studies, the investigated paediatric ACT was not the same ACT as the comparator.

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 drugrelated 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 nonpaediatric 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 1.35, 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 2.25; 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 failures 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).

PCR-adjusted and -unadjusted treatment failure rates on last day of observation (day 28)

The study's last day of observation was day 28; therefore efficacy on the last day of observation is the same as the data for day 28.

Question 2. How safe is the paediatric ACT formulation compared to the non-paediatric ACT formulation?

Comparison 1. Paediatric ACT dispersible tablet versus nonpaediatric ACT crushed tablet

Serious adverse events and drug-related serious adverse events

The rate of serious adverse events was < 2% in the intervention and control arms of both studies. There were no drug-related serious adverse events in either study.

Dispersible ACT and crushed tablet ACT were equally safe, with no difference in the rate of serious adverse events (RR 1.05, 95% CI 0.38 to 2.88; 1197 participants, 2 studies; Analysis 1.9).

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

Serious adverse events and drug-related serious adverse events

The rate of serious adverse events was 2% in the intervention arm and 3% in the control arm; no serious adverse event was drugrelated.

Suspension ACT and crushed tablet ACT were equally safe, with no difference in the rate of serious adverse events (RR 0.74, 95% CI 0.17 to 3.26; 267 participants, 1 study; Analysis 2.5).

Question 3. How is tolerability of the paediatric ACT formulation compared to the non-paediatric ACT formulation?

Comparison 1. Paediatric ACT dispersible tablet versus nonpaediatric ACT crushed tablet

Drug-related adverse events

In the intervention 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. The lower rate of drug-related adverse events in the intervention arms was statistically significant (RR 0.78, 95% CI 0.62 to 0.99; 1197 participants, 2 studies; $l^2 = 0\%$; Analysis 1.10).

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 drugrelated 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 nonpaediatric 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% Cl -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_{max} of artemether was 175 ng/mL in the intervention group and 211 ng/mL in the control group. C_{max} of DHA was 64.7 ng/mL in the intervention group and 63.7 ng/mL in the control group.

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

T_{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 artesunateamodiaquine 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

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.

Cochrane Database of Systematic Reviews

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 metaanalysis 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 nonpaediatric ACT using different drug combinations. Both reviews conclude that tolerability of paediatric ACTs is superior to nonpaediatric ACTs, with equal efficacy and safety.

AUTHORS' CONCLUSIONS

Implications for practice

Artemisinin-based combination therapies (ACTs) are the recommended first-line treatment for uncomplicated malaria in all malaria-endemic regions. Young children suffer disproportionally 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 (Thabet 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 (Ranmal 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 (Ranmal 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.

ACKNOWLEDGEMENTS

The Academic Editor is Dr Joseph Okebe.

The editorial base of the Cochrane Infectious Diseases Group is funded by UK aid from the UK government for the benefit of lowand middle-income countries (project number 300342-104). The views expressed do not necessarily reflect the UK government's official policies.

We thank Dr Maria Esterhuyse, Vlakkral GmbH, for editorial support.



REFERENCES

References to studies included in this review

Abdulla 2008 {published data only}

* Abdulla S, Sagara I, Borrmann S, D'Alessandro U, González R, Hamel M, et al. Efficacy and safety of artemether-lumefantrine dispersible tablets compared with crushed commercial tablets in African infants and children with uncomplicated malaria: a randomised, single-blind, multicentre trial. *Lancet* 2008;**372**(9652):1819-27. [DOI: 10.1016/S0140-6736(08)61492-0]

Bassat Q, González R, Machevo S, Nahum A, Lyimo J, Maiga H, et al. Similar efficacy and safety of artemether-lumefantrine (Coartem®) in African infants and children with uncomplicated falciparum malaria across different body weight ranges. *Malaria Journal* 2011;**10**:369. [DOI: 10.1186/1475-2875-10-369]

Djimde AA, Tekete M, Abdulla S, Lyimo J, Bassat Q, Mandomando I, et al. Pharmacokinetic and pharmacodynamic characteristics of a new pediatric formulation of artemetherlumefantrine in African children with uncomplicated Plasmodium falciparum malaria. *Antimicrobial Agents and Chemotherapy* 2011;**55**(9):3994–9. [DOI: 10.1128/AAC.01115-10]

Gargano 2018 {published data only}

Gargano N, Madrid L, Valentini G, D'Alessandro U, Halidou T, Sirima S, et al. Efficacy and tolerability outcomes of a phase II, randomized, open-label, multicenter study of a new waterdispersible pediatric formulation of dihydroartemisininpiperaquine for the treatment of uncomplicated plasmodium falciparum malaria in African infants. *Antimicrobial Agents and Chemotherapy* 2018;**62**(1):e00596-17. [DOI: 10.1128/ AAC.00596-17]

Juma 2008 {published data only}

Juma EA, Obonyo CO, Akhwale WS, Ogutu BR. A randomized, open-label, comparative efficacy trial of artemetherlumefantrine suspension versus artemether-lumefantrine tablets for treatment of uncomplicated Plasmodium falciparum malaria in children in western Kenya. *Malaria Journal* 2008;**7**:262. [DOI: 10.1186/1475-2875-7-262]

References to studies excluded from this review

Banek 2018 {published data only}

Banek K, Webb EL, Smith SJ, Chandramohan D, Staedke SG. Adherence to treatment with artemether-lumefantrine or amodiaquine-artesunate for uncomplicated malaria in children in Sierra Leone: a randomized trial. *Malaria Journal* 2018;**17**(1):222.

Dama 2018 {published data only}

Dama S, Niangaly H, Djimde M, Sagara I, Guindo CO, Zeguime A, et al. A randomized trial of dihydroartemisinin-piperaquine versus artemether-lumefantrine for treatment of uncomplicated Plasmodium falciparum malaria in Mali. *Malaria Journal* 2018;**17**(1):347.

Faye 2010 {published data only}

Faye B, Ndiaye JL, Tine R, Sylla K, Gueye A, Lo AC, et al. A randomized trial of artesunate mefloquine versus artemether lumefantrine for the treatment of uncomplicated Plasmodium falciparum malaria in Senegalese children. *American Journal of Tropical Medicine and Hygiene* 2010;**82**(1):140-4.

Faye 2012 {published data only}

Faye B, Kuete T, Kiki-Barro CP, Tine RC, Nkoa T, Ndiaye JL, et al. Multicentre study evaluating the non-inferiority of the new paediatric formulation of artesunate/amodiaquine versus artemether/lumefantrine for the management of uncomplicated Plasmodium falciparum malaria in children in Cameroon, Ivory Coast and Senegal. *Malaria Journal* 2012;**11**:433.

Kayentao 2012 {published data only}

Kayentao K, Doumbo OK, Penali LK, Offianan AT, Bhatt KM, Kimani J, et al. Pyronaridine-artesunate granules versus artemether-lumefantrine crushed tablets in children with Plasmodium falciparum malaria: a randomized controlled trial. *Malaria Journal* 2012;**11**(1):364.

Ogutu 2014 {published data only}

Ogutu BR, Onyango KO, Koskei N, Omondi EK, Ongecha JM, Otieno GA, et al. Efficacy and safety of artemether-lumefantrine and dihydroartemisinin-piperaquine in the treatment of uncomplicated Plasmodium falciparum malaria in Kenyan children aged less than five years: results of an open-label, randomized, single-centre study. *Malaria Journal* 2014;**13**:33. [DOI: 10.1186/1475-2875-13-33]

Paczkowski 2016 {published data only}

Paczkowski M, Mwandama D, Marthey D, Luka M, Makuta G, Sande J, et al. In vivo efficacy of artemether-lumefantrine and artesunate-amodiaquine for uncomplicated Plasmodium falciparum malaria in Malawi. *Malaria Journal* 2016;**15**:236.

Roth 2018 {published data only}

Roth JM, Sawa P, Makio N, Omweri G, Osoti V, Okach S, et al. Pyronaridine-artesunate and artemether-lumefantrine for the treatment of uncomplicated Plasmodium falciparum malaria in Kenyan children: a randomized controlled non-inferiority trial. *Malaria Journal* 2018;**17**(1):199.

Sagara 2018 {published data only}

Sagara I, Beavogui AH, Zongo I, Soulama I, Borghini-Fuhrer I, Fofana B, et al. Pyronaridine–artesunate or dihydroartemisinin– piperaquine versus current first-line therapies for repeated treatment of uncomplicated malaria: a randomised, multicentre, open-label, longitudinal, controlled, phase 3b/4 trial. *Lancet* 2018;**391**(10128):1378-90.

Sirima 2016 {published data only}

Sirima SB, Ogutu B, Lusingu JP, Mtoro A, Mrango Z, Ouedraogo A, et al. Comparison of artesunate-mefloquine and artemether-lumefantrine fixed-dose combinations for treatment of uncomplicated Plasmodium falciparum malaria in children younger than 5 years in sub-Saharan Africa: a



randomised, multicentre, phase 4 trial. *Lancet Infectious Diseases* 2016;**16**(10):1123-33.

Tahar 2014 {published data only}

Tahar R, Almelli T, Debue C, Foumane NV, Djaman AJ, Whegang YS, et al. Randomized trial of artesunateamodiaquine, atovaquone-proguanil, and artesunateatovaquone-proguanil for the treatment of uncomplicated falciparum malaria in children. *Journal of Infectious Diseases* 2014;**210**(12):1962-71.

Toure 2011 {published data only}

Toure OA, Kouame MG, Didier YJ, Berenger AA, Djerea K, Genevieve GO, et al. Artesunate/mefloquine paediatric formulation vs. artemether/lumefantrine for the treatment of uncomplicated Plasmodium falciparum in Anonkoua koute, Cote d'Ivoire. *Tropical Medicine & International Health* 2011;**16**(3):290-7.

Additional references

GRADEpro GDT [Computer program]

McMaster University (developed by Evidence Prime) GRADEpro GDT. Hamilton (ON): McMaster University (developed by Evidence Prime), accessed November 2019. Available at gradepro.org.

Higgins 2017

Higgins JP, Altman DG, Sterne JA, editor(s). Chapter 8: Assessing risk of bias in included studies. In: Higgins JP, Churchill R, Chandler J, Cumpston MS, editor(s), Cochrane Handbook for Systematic Reviews of Interventions version 5.2.0 (updated June 2017). The Cochrane Collaboration, 2017. Available from www.training.cochrane.org/handbook.

ICH 2016

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2). Available at: https://database.ich.org/sites/ default/files/E9_Guideline.pdf 2016.

Kurth 2010

Kurth F, Bélard S, Adegnika AA, Gaye O, Kremsner PG, Ramharter M. Do paediatric drug formulations of artemisinin combination therapies improve the treatment of children

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

with malaria? A systematic review and meta-analysis. *Lancet Infectious Diseases* 2010;**10**(2):125-32.

Ranmal 2018

Ranmal SR, O'Brien F, Lopez F, Ruiz F, Orlu M, Tuleu C, et al. Methodologies for assessing the acceptability of oral formulations among children and older adults: a systematic review. *Drug Discovery Today* 2018;**23**(4):830-47.

Review Manager 2020 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration Review Manager 5 (RevMan 5). Version 5.4. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2020.

Thabet 2018

Thabet Y, Klingmann V, Breitkreutz J. Drug formulations: standards and novel strategies for drug administration in pediatrics. *Journal of Clinical Pharmacology* 2018;**58**(Suppl 10):26-35.

WHO 2009

World Health Organization. Methods for surveillance of antimalarial drug efficacy. WHO Library 2009 2009. [ISBN 978 92 4 159753 1]

WHO 2015

World Health Organization. Guidelines for the treatment of malaria - 3rd edition. www.who.int/malaria/publications/ atoz/9789241549127/en/2015 2015. [ISBN 978 92 4 154912 7]

WHO 2019

World Health Organization. World malaria report 2019. www.who.int/publications-detail/world-malaria-report-2019 2019. [ISBN 978-92-4-156572-1]

References to other published versions of this review

Bélard 2012

Bélard S, Kurth F, Ramharter M. Paediatric formulations of artemisinin-combination therapies for treating uncomplicated malaria in children. *Cochrane Database of Systematic Reviews* 2012, Issue 1. Art. No: CD009568. [DOI: 10.1002/14651858.CD009568]

* Indicates the major publication for the study

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.



bdulla 2008 (Continued)	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 electrocar- diogram was recorded at baseline and on day 3.				
Participants	Number of participants: 899.				
	Inclusion criteria: age 12 years or younger, bodyweight 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, <i>P falciparum</i> 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	 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:				
	 Day 7 parasitological cure rate. Day 14 PCR-adjusted cure rate. Time to fever, parasite and gametocyte clearance. Exploratory: Day 42 PCR-adjusted cure rate, ETF, LCF, LPF, ACPR, development of danger signs o malaria or severe malaria. 				
	Safety endpoints:				
	 Adverse event rates Laboratory assessments, ECG data. 				
Notes	Eight study sites in five African countries: one centre each in Benin, Mali, Mozambique,Tanzania main- land, and Zanzibar, and three in Kenya.				
	Malaria transmission: at study locations, malaria transmission is intense and perennial, with the excep- tion of the two study sites in Mozambique and Zanzibar, where malaria is mesoendemic with transmis- sion 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 genera- tion (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 (perfor- mance bias) All outcomes	Low risk	Investigators were blinded. Treatment was prepared by staff not involved in clinical assessment, identical package was used for intervention and compara- tor. No blinding of participants.
Blinding of outcome as- sessment (detection bias) All outcomes	Low risk	Assessors of clinical outcome were blinded. Blinding of microscopists not explicitly stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reporting of outcome data was judged to be complete
Selective reporting (re- porting bias)	Low risk	All essential outcomes and measurements were reported.
Other bias	Unclear risk	Sponsors (a pharmaceutical company and an NGO) were responsible for col- lection and analysis of data. Authors and the sponsors were involved in study design, interpretation of data, and writing of the report.

Gargano 2018

Study characteristic	S
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 biochem- istry were taken at enrolment and at day 7 and then repeated at day 28 if clinically significant abnor- malities 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 clinica ly relevant abnormalities were detected at day 7.
Participants	Number of participants: 300
	Inclusion criteria: Age 6 to 12 months, bodyweight ≥5 kg, <i>P falciparum</i> monoinfection with asexual par- asite 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-pos itive women under antiretroviral therapy) were excluded.

(selection bias)

Trusted evidence. Informed decisions. Better health.

Gargano 2018 (Continued)				
Interventions	 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 compo- nents (cellulose, starch, croscarmellose, black cherry flavour, saccharine, sucrose, and magnesium stearate). 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 wer	e administered once a day for three consecutive days, according to body weight.		
	weighing 7 kg to 13 kg as soon as randomizat ministered in the follow drug intake and for the	5 kg to 7 kg received a daily dose of 10/80 mg of DHA-PQ, while participants received a daily dose of 20/160 mg of DHA-PQ. The first dose was administered ion was done, and deliberate efforts were made to ensure that no food was ad- wing 3 h. For the other doses, children should not have been fed in the 3 h before e following 3 h. However, for infants needing food during the restricted periods, ast 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:			
	 Day 28, PCR-unadjusted ACPR; Day 42, PCR-adjusted and -unadjusted ACPR; Proportion of participants with early and late treatment failure (ETF and LTF); Asexual parasite density and clearance time; Fever clearance time and gametocyte carriage over time; Kaplan-Maier survival analysis for new infections and recrudescences over time. 			
	Safety endpoints:			
	 Adverse event occu Changes in hemato 	rrence; logy, blood chemistry, vital signs, and ECG parameters.		
Notes	Mozambique; Kinshasa Congo; Centre Muraz B mation en Paludisme,	e African countries: Centro de Investigação em Saude da Manhiça, Maputo, a School of Public Health, University of Kinshasa, Democratic Republic of the obo-Dioulasso, Nanoro, Burkina Faso; Centre National de Recherche et de For- Ouagadougou, Burkina Faso; Ifakara Health Institute, Bagamoyo, Tanzania; Na- lical Research, Korogwe, Tanzania; and Medical Research Council Unit, The Gam		
	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 genera- tion (selection bias)	Low risk	Computer-generated by external company.		
Allocation concealment	Low risk	Treatment allocation concealed in sealed opaque envelopes, opened by inves		

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.

tigators only after randomization.

Gargano 2018 (Continued)

Blinding of participants and personnel (perfor- mance bias) All outcomes	High risk	No blinding of participants and personnel. Blinding only for PCR parasitology to distinguish between new infection and recrudescence.
Blinding of outcome as- sessment (detection bias) All outcomes	High risk	Only staff performing the PCR for distinction between reinfection and recrude- scence were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reporting of outcome data was judged to be complete.
Selective reporting (re- porting 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 Sig- ma-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 ex- amination, and thick and thin blood smears for malaria parasites.
	Haemoglobin was measured on days 0, 7, 14, 28.
Participants	Number of participants: 267
	Inclusion criteria: age 6 to 59 months, bodyweight \geq 5 kg, a history of fever in the previous 24 h or mea- sured fever (axillary temperature \geq 37.5°C), monoinfection with <i>P falciparum</i> 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	 Artemether-lumefantrine powder for suspension 15 mg/90 mg, 5 mL after reconstitution (Co-arte-siane® Dafra Pharma NV); administration once daily at hour 0, 24, 48 based on participant's weight. 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:
	 PCR-adjusted cure rate by day 14; Parasite clearance time;

Juma 2008 (Continued)	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 genera- tion (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 (perfor- mance bias) All outcomes	High risk	Open-label study
Blinding of outcome as- sessment (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 (re- porting 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-art siane® 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 com- bination but amodiaquine-artesunate.

Cochrane Library

Dama 2018 The paediatric ACT investigated in this prospective open, randomized clinical trial was an oral suspension of 30 mg of dihydroartemisinin and 720 mg of piperaquine in 60 mL solution Malacur ⁴ , SALVAT, S.A., Sahon, DHA-PQ suspension was administrated to body weight 3.5kg to 5 kg: 5 mL; 6kg to 9kg: 10 mL; 10kg to 12 kg: 15 mL; 13kg to 17 kg: 20 mL). The study was excluded from the review because the comparator ACT was not the same drug com- bination but artemether-lumediantrine. Fays 2010 The paediatric ACT investigated in this prospective open, randomized clinical trial was Artequin paediatric by Mepha Ltd, Aesch, Switzerland. This paediatric formulation is a preparation of gran- ules of 50 mg of attesunate and 12 mg of melloquine as a fixed-dose combination that is direct. Iy applied into the mouth of the child. This paediatric ACT is suitable for children with body weight ranging from 126 to 20 kg. Fays 2012 The paediatric ACT investigated in this multicentre open, comparative and randomized phase IV trial was Camoquin Plus Paediatric by Plizer. This paediatric formative and randomized phase IV trial was Camoquin Plus Paediatric by Plizer. This paediatric formation and the comparator ACT was not the same drug com- bination but artemethe-lumefantrine. Fays 2012 The paediatric ACT investigated in this multicentre, open, comparative and randomized phase IV trial was Camoquin Plus Paediatric by Plizer. This paediatric formatiation as a nor-fixed preparation of artsunate and amodiaquine in suspension coming with 1 bottle containing artemeter- land and the comparator ACT was not the same drug combination but artemether-lumefantrine. Kayentao 2012 The paediatric ACT investigated in this multicentre, comparative, andomized,	Study	Reason for exclusion
bination but artemether-lumefantrine. Faye 2010 The paediatric ACT investigated in this prospective open, randomized clinical trial was Artequin paediatric for Migha Ltd, Aesch, Switzerland. This paediatric for Mulation is a preparation of granules of S0 mg of artesunate and 125 mg of melloquine as a fixed-dose combination that is direct-ly applied into the mouth of the child. This paediatric ACT is suitable for children with body weight ranging from 10 kg to 20 kg. Faye 2012 The study was excluded from the review because the comparator ACT was not the same drug combination but artemether-lumefantrine. Faye 2012 The paediatric ACT investigated in this multicentre open, comparative and randomized phase IV trial was Canoquin Plus Paediatric by Pizer. This paediatric formulation is a non-fixed preparation of artesunate and amadiaquine in suspension coming with 1 bottle containing antesunate in pow. der dosed at 160 mg/80 mL to suspend, and 1 bottle containing amodiaquine in syrup dosed at 50 mg/5 mL. Kayentao 2012 The paediatric ACT investigated in this multicentre, comparative, randomized, open-label, paral-leie-group clinical trial was Sama by Shin Poong Pharmaceutical Company, Ltd, Ansan, Korea. This paediatric formulation is a preparation of granules of pyronaridine and artesunate (60/20 mg) supplied in aschets from which oral suspensions were prepared by stirring the sachet into 50 mL to water, milk, or soup. Ogutu 2014 The paediatric ACT investigated in this was an open-label, randomized, single-centre study was Coartem Dispersible by Novarits Pharmaceuticals, Basel, Switzerland Chinster tablet of 20 mg artemether and 120 mg lumefantrine. Into study ways were dispersed to a smalt volume of water or milk. <t< td=""><td>Dama 2018</td><td>pension of 90 mg of dihydroartemisinin and 720 mg of piperaquine in 60 mL solution (Malacur®, SALVAT, S.A., Spain). DHA–PQ suspension was administrated to body weight (3.5kg to 5 kg: 5 mL;</td></t<>	Dama 2018	pension of 90 mg of dihydroartemisinin and 720 mg of piperaquine in 60 mL solution (Malacur®, SALVAT, S.A., Spain). DHA–PQ suspension was administrated to body weight (3.5kg to 5 kg: 5 mL;
paediatric by Mepha Ltd, Aesch, Switzerland. This paediatric formulation is a preparation of granulates of 50 mg of artesunate and 125 mg of mefloquine as fixed-dose combination that is direct-ly applied into the mouth of the child. This paediatric ACT is suitable for children with body weight ranging from 10 kg to 20 kg. The study was excluded from the review because the comparator ACT was not the same drug combination but attemether-lumefantrine. Faye 2012 The paediatric ACT investigated in this multicentre open, comparative and randomized phase W trial was Camoquin Plus Paediatric by Pfizer. This paediatric formulation is a non-fixed preparation of artesunate and amodiaquine in suspension coming with 1 bottle containing artesunate in pow-der dosed at 160 mg/80 mL to suspend, and 1 bottle containing artesunate in pow-der dosed at 160 mg/80 mL to suspend, and 1 bottle containing annotiaquine in superator ACT was not a fixed dose combination but artemether-lumefantrine. Kayentao 2012 The paediatric formulation is a preparation of granules of pyronaridine and artesunate inpow-der dosed at 160 mg/80 mL to suspend, and 1 bottle containing anno, Korea. This paediatric formulation is a preparation of granules of pyronaridine and artesunate (6/20 mg) supplied in sachest from which oral suspensions were prepared by stirring the sachet into 50 mL of water, milk, or soup. The study was excluded from the review because the comparator ACT was not the same drug combination but artemether-lumefantrine. Ogutu 2014 The paediatric ACT investigated in this was an open-label, randomized, single-centre study was Coartem Dispersible by Novartis Pharmaceuticals, Basel, Switzerland (same as in Abdulla 2008). This paediatric formulation is a sweet-tasting and easy-to-administer tablet of 20 m		
bination but artemether-lumefantrine. Faye 2012 The paediatric ACT investigated in this multicentre open, comparative and randomized phase IV trial was Camoquin Plus Paediatric by Pfizer. This paediatric formulation is a non-fixed preparation of artesunate and anoudiaquine in suspension coming with 1 bottle containing artesunate in pow-der dosed at 160 mg/80 mL to suspend, and 1 bottle containing artesunate in pow-der dosed at 160 mg/80 mL to suspend, and 1 bottle containing artesunate in pow-der dosed at 160 mg/80 mL to suspend, and 1 bottle containing artesunate in pow-der dosed at 160 mg/80 mL to suspend, and 1 bottle containing artesunate in pow-der dose at 160 mg/80 mL to suspend, and 1 bottle containing artesunate in pow-der dose at 160 mg/80 mL to suspend, and 1 bottle containing artesunate in pow-der dose at 160 mg/80 mL to suspend, and 1 bottle containing artesunate in pow-der dose at 160 mg/80 mL to suspend, and 1 bottle containing artesunate for promative, randomized, open-label, paral-lel-group clinical trial was Pyramax by Shin Poong Pharmaceutical Company, Ltd., Ansan, Korea. This paediatric formulation is a preparation of granules of pyronaridine and artesunate (60/20 mg) supplied in sachets from which oral suspensions were prepared by stirring the sachet into 50 mL of water, milk, or soup. Ogutu 2014 The paediatric ACT investigated in this was an open-label, randomized, single-centre study was Coartem Dispersible by Novartis Pharmaceuticals, Basel, Switzerland (same as in Abdulla 2008). This paediatric formulation is a sweet-tasting and easy-to-administer tablet of 20 mg artemether and 120 mg lumefantrine. In this study drugs were dispersed in a small volume of water or milk. The study was excluded from the review because the comparator ACT was not the same drug combination but dihydroartemisinin-piperaquine. Paczkowski 2016	Faye 2010	paediatric by Mepha Ltd, Aesch, Switzerland. This paediatric formulation is a preparation of gran- ules of 50 mg of artesunate and 125 mg of mefloquine as a fixed-dose combination that is direct- ly applied into the mouth of the child. This paediatric ACT is suitable for children with body weight
rial was Camoquin Plus Paediatric by Pfizer. This paediatric formulation is a non-fixed preparation of artesunate and amodiaquine in suspension coming with 1 bottle containing artesunate in powder dosed at 160 mg/80 mL to suspend, and 1 bottle containing amodiaquine in syrup dosed at 50 mg/5 mL. The study was excluded from the review because the intervention ACT was not a fixed dose combination and the comparator ACT was not the same drug combination but artemether-lumefantrine. Kayentao 2012 The paediatric ACT investigated in this multicentre, comparative, randomized, open-label, parallel-group clinical trial was Pyramax by Shin Poong Pharmaceutical Company, Ltd, Ansan, Korea. This paediatric formulation is a preparation of granules of pyronaridine and artesunate (60/20 mg) supplied in sachets from which oral suspensions were prepared by stirring the sachet into 50 mL of water, milk, or soup. Ogutu 2014 The paediatric ACT investigated in this was an open-label, randomized, single-centre study was Coartem Dispersible by Novartis Pharmaceuticals, Basel, Switzerland (same as in Abdulla 2008). This paediatric formulation is a sweet-tasting and easy-to-administer tablet of 20 mg artemether and 120 mg lumefantrine. In this study drugs were dispersed in a small volume of water or milk. The study was excluded from the review because the comparator ACT was not the same drug combination but artemether and 120 mg lumefantrine. In this trandomized trial investigated 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; treatment was directly administered with clean water. Paczkowski 2016 The paediatric ACT investigated In this randomized c		
nation and the comparator ACT was not the same drug combination but artemether-lumefantrine. Kayentao 2012 The paediatric ACT investigated in this multicentre, comparative, randomized, open-label, paral- lel-group clinical trial was Pyramax by Shin Poong Pharmaceutical Company, Ltd., Ansan, Korea. This paediatric formulation is a preparation of granules of pyronaridine and artesunate (60/20 mg) supplied in sachets from which oral suspensions were prepared by stirring the sachet into 50 mL of water, milk, or soup. The study was excluded from the review because the comparator ACT was not the same drug com- bination but artemether-lumefantrine. Ogutu 2014 The paediatric ACT investigated in this was an open-label, randomized, single-centre study was Coartem Dispersible by Novartis Pharmaceuticals, Basel, Switzerland (same as in Abdulla 2008). This paediatric formulation is a sweet-tasting and easy-to-administer tablet of 20 mg artemether and 120 mg lumefantrine. In this study drugs were dispersed in a small volume of water or milk. The study was excluded from the review because the comparator ACT was not the same drug com- bination but dihydroartemisinin-piperaquine. Paczkowski 2016 The paediatric ACT investigated in this randomized trial investigated Coartem Dispersible by No- vartis Pharmaceuticals, Basel, Switzerland (same as used in the Abdulla 2008 study). This paedi- atric formulation is a sweet-tasting and easy-to-administer tabled 020 mg artemether and 120 mg lumefantrine; treatment was directly administer tabled 020 mg artemether and 120 mg lumefantrine; treatment was directly administer tabled 02 mg artemether and 120 mg lumefantrine; treatment was directly administer date of 20 mg artemether and 120 mg lumefantrine; treatment was directly administere date of 20 mg artemether and 120 mg lumefantri	Faye 2012	trial was Camoquin Plus Paediatric by Pfizer. This paediatric formulation is a non-fixed preparation of artesunate and amodiaquine in suspension coming with 1 bottle containing artesunate in pow- der dosed at 160 mg/80 mL to suspend, and 1 bottle containing amodiaquine in syrup dosed at 50
lel-group clinical trial was Pyramax by Shin Poong Pharmaceutical Company, Ltd., Ansan, Korea. This paediatric formulation is a preparation of granules of pyronaridine and artesunate (60/20 mg) supplied in sachets from which oral suspensions were prepared by stirring the sachet into 50 mL of water, milk, or soup.The study was excluded from the review because the comparator ACT was not the same drug com- bination but artemether-lumefantrine.Ogutu 2014The paediatric ACT investigated in this was an open-label, randomized, single-centre study was Coartem Dispersible by Novartis Pharmaceuticals, Basel, Switzerland (same as in Abdulla 2008). This paediatric formulation is a sweet-tasting and easy-to-administer tablet of 20 mg artemether and 120 mg lumefantrine. In this study drugs were dispersed in a small volume of water or milk. The study was excluded from the review because the comparator ACT was not the same drug com- bination but dihydroartemisinin-piperaquine.Paczkowski 2016The paediatric ACT investigated in this randomized trial investigated Coartem Dispersible by No- vartis Pharmaceuticals, Basel, Switzerland (same as used in the Abdulla 2008 study). This paedi- atric formulation is a sweet-tasting and easy-to-administer tablet of 20 mg artemether and 120 mg lumefantrine; treatment was directly administered with clean water.Paczkowski 2016The paediatric ACT investigated in this randomized trial investigated Coartem Dispersible by No- vartis Pharmaceuticals, Basel, Switzerland (same as used in the Abdulla 2008 study). This paedi- atric formulation is a sweet-tasting and easy-to-administer tablet of 20 mg artemether and 120 mg lumefantrine; treatment was directly administered with clean water.Paczkowski 2018The paediatric ACT investigated in this randomized controlled non-inferiority trial was Pyramax by Shin		
bination but artemether-lumefantrine. Ogutu 2014 The paediatric ACT investigated in this was an open-label, randomized, single-centre study was Coartem Dispersible by Novartis Pharmaceuticals, Basel, Switzerland (same as in Abdulla 2008). This paediatric formulation is a sweet-tasting and easy-to-administer tablet of 20 mg artemether and 120 mg lumefantrine. In this study drugs were dispersed in a small volume of water or milk. The study was excluded from the review because the comparator ACT was not the same drug com- bination but dihydroartemisinin-piperaquine. Paczkowski 2016 The paediatric ACT investigated in this randomized trial investigated Coartem Dispersible by No- vartis Pharmaceuticals, Basel, Switzerland (same as used in the Abdulla 2008 study). This paedi- atric formulation is a sweet-tasting and easy-to-administer tablet of 20 mg artemether and 120 mg lumefantrine; treatment was directly administered with clean water. The study was excluded from the review because the comparator ACT was not the same drug com- bination but artesunate-amodiaquine. Roth 2018 The paediatric ACT investigated in this randomized controlled non-inferiority trial was Pyramax by Shin Poong Pharmaceutical Company, Ltd., Ansan, Korea (same as in Kayentao 2012). This paedi- atric formulation is a preparation of granules of pyronaridine and artesunate (60/20 mg) supplied in sachets; oral suspensions were prepared immediately before dosing, whereby granules were stirred into 50 mL lemonade. The study was excluded from the review because the comparator ACT was not the same drug com- stirred into 50 mL lemonade.	Kayentao 2012	lel-group clinical trial was Pyramax by Shin Poong Pharmaceutical Company, Ltd., Ansan, Korea. This paediatric formulation is a preparation of granules of pyronaridine and artesunate (60/20 mg) supplied in sachets from which oral suspensions were prepared by stirring the sachet into 50 mL of
Coartem Dispersible by Novartis Pharmaceuticals, Basel, Switzerland (same as in Abdulla 2008). This paediatric formulation is a sweet-tasting and easy-to-administer tablet of 20 mg artemether and 120 mg lumefantrine. In this study drugs were dispersed in a small volume of water or milk.The study was excluded from the review because the comparator ACT was not the same drug com- bination but dihydroartemisinin-piperaquine.Paczkowski 2016The paediatric ACT investigated in this randomized trial investigated Coartem Dispersible by No- vartis Pharmaceuticals, Basel, Switzerland (same as used in the Abdulla 2008 study). This paedi- atric formulation is a sweet-tasting and easy-to-administer tablet of 20 mg artemether and 120 mg lumefantrine; treatment was directly administered with clean water.Roth 2018The paediatric ACT investigated in this randomized controlled non-inferiority trial was Pyramax by Shin Poong Pharmaceutical Company, Ltd., Ansan, Korea (same as in Kayentao 2012). This paedi- atric formulation is a preparation of granules of pyronaridine and artesunate (60/20 mg) supplied in sachets; oral suspensions were prepared immediately before dosing, whereby granules were stirred into 50 mL lemonade. The study was excluded from the review because the comparator ACT was not the same drug com-		
bination but dihydroartemisinin-piperaquine.Paczkowski 2016The paediatric ACT investigated in this randomized trial investigated 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; treatment was directly administered with clean water.The study was excluded from the review because the comparator ACT was not the same drug combination but artesunate-amodiaquine.Roth 2018The paediatric ACT investigated in this randomized controlled non-inferiority trial was Pyramax by Shin Poong Pharmaceutical Company, Ltd., Ansan, Korea (same as in Kayentao 2012). This paediatric formulation is a preparation of granules of pyronaridine and artesunate (60/20 mg) supplied in sachets; oral suspensions were prepared immediately before dosing, whereby granules were stirred into 50 mL lemonade.The study was excluded from the review because the comparator ACT was not the same drug com-	Ogutu 2014	Coartem Dispersible by Novartis Pharmaceuticals, Basel, Switzerland (same as in Abdulla 2008). This paediatric formulation is a sweet-tasting and easy-to-administer tablet of 20 mg artemether
vartis Pharmaceuticals, Basel, Switzerland (same as used in the Abdulla 2008 study). This paedi- atric formulation is a sweet-tasting and easy-to-administer tablet of 20 mg artemether and 120 mg lumefantrine; treatment was directly administered with clean water.The study was excluded from the review because the comparator ACT was not the same drug com- bination but artesunate-amodiaquine.Roth 2018The paediatric ACT investigated in this randomized controlled non-inferiority trial was Pyramax by Shin Poong Pharmaceutical Company, Ltd., Ansan, Korea (same as in Kayentao 2012). This paedi- atric formulation is a preparation of granules of pyronaridine and artesunate (60/20 mg) supplied in sachets; oral suspensions were prepared immediately before dosing, whereby granules were stirred into 50 mL lemonade.The study was excluded from the review because the comparator ACT was not the same drug com-		
Both 2018The paediatric ACT investigated in this randomized controlled non-inferiority trial was Pyramax by Shin Poong Pharmaceutical Company, Ltd., Ansan, Korea (same as in Kayentao 2012). This paedi- atric formulation is a preparation of granules of pyronaridine and artesunate (60/20 mg) supplied in sachets; oral suspensions were prepared immediately before dosing, whereby granules were stirred into 50 mL lemonade.The study was excluded from the review because the comparator ACT was not the same drug com-	Paczkowski 2016	vartis Pharmaceuticals, Basel, Switzerland (same as used in the Abdulla 2008 study). This paedi- atric formulation is a sweet-tasting and easy-to-administer tablet of 20 mg artemether and 120 mg
Shin Poong Pharmaceutical Company, Ltd., Ansan, Korea (same as in Kayentao 2012). This paedi- atric formulation is a preparation of granules of pyronaridine and artesunate (60/20 mg) supplied in sachets; oral suspensions were prepared immediately before dosing, whereby granules were stirred into 50 mL lemonade. The study was excluded from the review because the comparator ACT was not the same drug com-		
	Roth 2018	Shin Poong Pharmaceutical Company, Ltd., Ansan, Korea (same as in Kayentao 2012). This paedi- atric formulation is a preparation of granules of pyronaridine and artesunate (60/20 mg) supplied in sachets; oral suspensions were prepared immediately before dosing, whereby granules were

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 Pharmaceuti- cal, 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-inferiori- ty trial was Coartem Dispersible by Novartis Pharmaceuticals, Basel, Switzerland (same as in Abdul- la 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 com- bination but artesunate-mefloquine.
Tahar 2014	The paediatric ACT investigated in this open-label, randomized study was Camoquin syrup by Pfiz- er Afrique de l'Ouest, Dakar, Senegal. This paediatric formulation was a non-fixed dose combina- tion 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 com- bination 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 Mepha 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 ac- tive 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 com- bination 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 partici- pants	Statistical method	Effect size
1.1 Day 28 PCR-adjusted treatment fail- ure PP	2	1061	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.49, 3.72]
1.2 Day 28 PCR-adjusted treatment fail- ure 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 partici- pants	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 select- ed
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 dis- orders	2	1197	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.19, 7.45]
1.13 Drug-related vomiting and gas- trointestinal 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

	Paediatric Fo	rmulation	Crushed	Tablet		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% C	I
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)		571		490	100.0%	1.35 [0.49 , 3.72]		
Total events:	10		6					
Heterogeneity: Tau ² = 0).00; Chi ² = 0.44, d	f = 1 (P = 0.5)	51); I ² = 0%				0.005 0.1 1 10	200
Test for overall effect: 2	Z = 0.58 (P = 0.56)					Favour	s paediatric form. Favour	
Test for sub group differ	Net analian	L].					-	

Test for subgroup differences: Not applicable

Cochrane Info Library Bet

Trusted evidence. Informed decisions. Better health.

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

	Paediatric Fo	mulation	Crushed	Tablet		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95	% CI
Abdulla 2008	21	418	16	423	46.1%	1.33 [0.70 , 2.51]		
Gargano 2018	26	199	15	99	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				Ĭ	
Heterogeneity: Tau ² = 0	.00; Chi ² = 0.96, d	f = 1 (P = 0.3)	33); I ² = 0%				0.005 0.1 1 1	10 200
Test for overall effect: 2	Z = 0.23 (P = 0.82)					Favour	s paediatric form. Fav	ours tablet
Test for subgroup differ	ences: Not applica	ble						

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

	Paediatric Fo	rmulation	Crushed	Tablet		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Abdulla 2008	30	398	39	406	67.2%	0.78 [0.50 , 1.24]	-
Gargano 2018	15	173	4	84	32.8%	1.82 [0.62 , 5.32]	
Total (95% CI)		571		490	100.0%	1.03 [0.48 , 2.25]	•
Total events:	45		43				Ť
Heterogeneity: Tau ² = 0.	.18; Chi ² = 2.02, d	f = 1 (P = 0.1)	.6); I ² = 50%	6			0.005 0.1 1 10 200
Test for overall effect: Z	= 0.08 (P = 0.93)					Favou	rs paediatric form. Favours tablet
Test for subgroup different	ences: Not applica	ble					

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

	Paediatric Fo	mulation	Crushed	Tablet		Risk Ratio	Risk I	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Rando	om, 95% CI	
Abdulla 2008	33	418	40	423	55.8%	0.83 [0.54 , 1.30]	-	_	
Gargano 2018	38	199	19	99	44.2%	0.99 [0.61 , 1.63]	-	F	
Total (95% CI)		617		522	100.0%	0.90 [0.65 , 1.25]		•	
Total events:	71		59				1		
Heterogeneity: Tau ² = 0	.00; Chi ² = 0.27, d	f = 1 (P = 0.6)	50); I ² = 0%	•			0.01 0.1 1	10 100	
Test for overall effect: 2	Z = 0.61 (P = 0.54)					Favou	rs paediatric form.	Favours tablet	
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

cochrane

Librarv

Trusted evidence. Informed decisions.

Better health.

	Paediatric For	mulation	Crushed	Tablet		Risk Ratio	Risk Rat	io
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random,	95% CI
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]	•	
Total events:	18		14				Ť	
Heterogeneity: Tau ² = 0	0.00; Chi ² = 0.02, d	f = 1 (P = 0.8)	8); I ² = 0%			0.	01 0.1 1	10 100
Test for overall effect: 2	Z = 0.18 (P = 0.86)					Favours j	paediatric form.	Favours tablet
Test for subgroup differences: Not applicable								

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

	Paediatric Fo	mulation	Crushed	Tablet		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Abdulla 2008	34	377	25	372	53.1%	1.34 [0.82 , 2.20]	-
Gargano 2018	28	199	17	99	46.9%	0.82 [0.47 , 1.42]	
Total (95% CI)		576		471	100.0%	1.06 [0.66 , 1.73]	•
Total events:	62		42				Ĭ
Heterogeneity: Tau ² = 0.	.05; Chi ² = 1.70, d	f = 1 (P = 0.1)	.9); I ² = 41%	6		(0.01 0.1 1 10 100
Test for overall effect: Z	= 0.26 (P = 0.80)					Favours	paediatric form. Favours tablet
Test for subgroup differe	ences: Not applica	ble					-

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 For Events	rmulation Total	Crushed Events	Tablet Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Gargano 2018	41	173	23	84	0.87 [0.56 , 1.34]	+
					••	01 0.1 1 10 100 Daediatric 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

	Paediatric Fo	mulation	Crushed	Tablet		Risk Ratio	Risk F	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Rando	m, 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:	148		133				•	
Heterogeneity: Tau ² = 0	0.00; Chi ² = 0.04, d	f = 1 (P = 0.8)	85); I ² = 0%				0.01 0.1 1	10 100
Test for overall effect: 2	Z = 1.49 (P = 0.14)					Favou	rs paediatric form.	Favours tablet
Test for subgroup differ	ences: Not applica	ble						

Footnotes

Cochrane

Librarv

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

Trusted evidence. Informed decisions.

Better health.

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

	Paediatric Fo	rmulation	Crushed	l Tablet		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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:	8		7				T	
Heterogeneity: Tau ² = 0	.00; Chi ² = 0.33, d	f = 1 (P = 0.5)	57); I ² = 0%	5		0	01 0.1 1 10	100
Test for overall effect: 2	Z = 0.10 (P = 0.92)					Favours	paediatric form. Favours ta	ablet
Test for subgroup differ	ences: Not applica	ble						

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

	Paediatric Fo	rmulation	Crushed	Tablet		Risk Ratio		Risk F	latio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Rando	m, 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]		۲		
Total events:	109		98					•		
Heterogeneity: Tau ² = 0.	00; Chi ² = 0.04, d	f = 1 (P = 0.3)	85); I ² = 0%				0.01	0.1 1	10	100
Test for overall effect: Z	= 2.07 (P = 0.04)					Favou	ırs paedia	atric form.	Favours ta	ablet
Test for subgroup differe	ences: Not applica	ble								

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

	Paediatric Fo	mulation	Crushed	Tablet		Risk Ratio	Risk R	atio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Randon	n, 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)		646		551	100.0%	0.75 [0.56 , 1.01]		
Total events:	78		73				•	
Heterogeneity: Tau ² = 0	0.00; Chi ² = 0.10, d	f = 1 (P = 0.7)	75); I ² = 0%			0.0	1 0.1 1	10 100
Test for overall effect: 2	Z = 1.91 (P = 0.06)					Favours pa	ediatric form.	Favours tablet
Test for subgroup differ	rences. Not applica	bla				_		

Test for subgroup differences: Not applicable

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

	Paediatric For	mulation	Crushed	Tablet		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Rand	om, 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]	l		 	
Total (95% CI)		646		551	100.0%	1.19 [0.19 , 7.45]	I			
Total events:	6		3							
Heterogeneity: Tau ² = 0	.66; Chi ² = 1.45, d	f = 1 (P = 0.2)	23); I ² = 319	6			0.01	0.1	1 10	100
Test for overall effect: Z	= 0.18 (P = 0.85)					Favoi	ırs paedi	atric form.	Favours ta	ablet
Test for subgroup differ	ences: Not applica	ble								

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

	Paediatric Fo	rmulation	Crushed	Tablet		Risk Ratio	Risk I	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Rando	m, 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)		646		551	100.0%	0.76 [0.57 , 1.00]	•	
Total events:	83		76				•	
Heterogeneity: Tau ² = 0	.00; Chi ² = 0.22, d	f = 1 (P = 0.6)	54); I ² = 0%	•			0.01 0.1 1	10 100
Test for overall effect: Z	L = 1.95 (P = 0.05)					Favou	rs paediatric form.	Favours tablet
Test for subgroup differ	ences: Not applica	ble						

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

	Paediatric Fo	rmulation	Crushed	Tablet		Risk Ratio	Risk	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Rando	om, 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]		i i
Total (95% CI)		646		551	100.0%	0.96 [0.90 , 1.03]		
Total events:	467		402					
Heterogeneity: Tau ² = 0	0.00; Chi ² = 0.19, d	f = 1 (P = 0.6)	56); I ² = 0%			0.0	01 0.1 1	10 100
Test for overall effect: 2	Z = 1.04 (P = 0.30)					Favours p	aediatric form.	Favours tablet
Test for sub-survey differ	Not on line	h].				-		

Test for subgroup differences: Not applicable

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

	Paediatric Fo	rmulation	Crushed	Tablet		Risk Ratio	Risk Ra	tio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random	ı, 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		
Total events:	0		0					
Heterogeneity: Not applica	ible					0.001	0.1 1	10 1000
Test for overall effect: Not	applicable					Favours pae	diatric form.	Favours tablet
Test for subgroup difference	es: Not applica	ible				-		

Comparison 2. ACT suspension versus ACT crushed tablet

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
2.1 Day 28 PCR-adjusted treat- ment failure PP	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.2 Day 28 PCR-adjusted treat- ment failure ITT	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.3 Day 28 PCR-unadjusted treat- ment failure PP	1		Risk Ratio (M-H, Random, 95% Cl)	Totals not selected
2.4 Day 28 PCR-unadjusted treat- ment failure ITT	1		Risk Ratio (M-H, Random, 95% Cl)	Totals not selected
2.5 Serious adverse events	1		Risk Ratio (M-H, Random, 95% Cl)	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 partici- pants	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 For Events	rmulation Total	Crushed Events	Tablet Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% C	I
Juma 2008	8	121	5	124	1.64 [0.55 , 4.87]	-+	
					0. Favours p	01 0.1 1 10 Daediatric form. Favours	100 tablet

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

	Paediatric Fo	mulation	Crushed	Tablet	Risk Ratio	Risk	Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Rand	om, 95% CI
Juma 2008	21	134	14	133	1.49 [0.79 , 2.80]	-	
					Favour	0.01 0.1 s paediatric form.	1 10 100 Favours tablet

ochrane

Analysis 2.3. Comparison 2: ACT suspension versus ACT crushed tablet, Outcome 3: Day 28 PCR-unadjusted treatment failure PP

	Paediatric Fo		Crushed		Risk Ratio		Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Rand	om, 95% CI
Juma 2008	15	121	15	124	1.02 [0.52 , 2.00]		-
						.01 0.1 5 paediatric form.	10 100 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 For Events	rmulation Total	Crushed Events	Tablet Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Juma 2008	28	134	24	133	1.16 [0.71 , 1.89]	
						diatric form. Favours tablet

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

Study or Subgroup	Paediatric Fo Events	rmulation Total	Crushed Events	Tablet Total	Risk Ratio M-H, Random, 95% CI	Risk H M-H, Rando	
Juma 2008	3	134	4	133	0.74 [0.17 , 3.26]		
						0.01 0.1 1 s paediatric form.	10 100 Favours tablet

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

	Paediatric Fo		Crushed		Risk Ratio	Risk Ra	
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random	ь, 95% СІ
Juma 2008	12	134	18	133	0.66 [0.33 , 1.32]	-+-	
					Favour	0.01 0.1 1 rs paediatric form.	10 100 Favours tablet

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

	Paediatric Fo	mulation	Crushed	Tablet	Risk Ratio	Risk R	atio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Randor	n, 95% CI
Juma 2008	12	134	18	133	0.66 [0.33 , 1.32]	-+-	
					0.01	0.1 1	10 100
					Favours pae	diatric form.	Favours tablet



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

	Paediatric Fo	mulation	Crushed	Tablet	Risk Ratio	Risk Ra	ntio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Randon	ı, 95% CI
Juma 2008	1	134	1	133	0.99 [0.06 , 15.70]		
					⊢ 0.0: Favours pa	1 0.1 1 lediatric form.	10 100 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 For Events	rmulation Total	Crushed Events	Tablet Total	Risk Ratio M-H, Random, 95% CI	Risk Ra M-H, Randon	
Juma 2008	12	134	18	133	0.66 [0.33 , 1.32] 0.01 Fayours pag	0.1 1 ediatric form.	10 10 Favours tablet

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

Paediatr	ic Formu	lation	Cru	shed Tabl	et	Mean Difference	Mean Difference	
Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI	
41.6	13.9	134	44.4	20.1	133	-2.80 [-6.95 , 1.35]	+	
						-100		⊣ 100
	Mean	Mean SD		Mean SD Total Mean	Mean SD Total Mean SD	Mean SD Total Mean SD Total	Mean SD Total Mean SD Total IV, Random, 95% CI 41.6 13.9 134 44.4 20.1 133 -2.80 [-6.95, 1.35] -100 -100 -100 -100 -100 -100	Mean SD Total Wean SD Total IV, Random, 95% CI IV, Random, 95% CI 41.6 13.9 134 44.4 20.1 133 -2.80 [-6.95, 1.35] + -100 -50 0 50 50 50

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

	Paediati	ic Formu	lation	Cru	shed Tabl	et	Mean Difference	Mean Dif	ference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Randon	ı, 95% CI
Juma 2008	54.7	14.6	134	53.8	15.7	133	0.90 [-2.74 , 4.54]	+	
							Favou	-100 -50 0 Irs paediatric form.	50 100 Favours crushed tablet

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

Study or Subgroup	Paediatric For Events	mulation Total	Crushed Events	Tablet Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Juma 2008	70	134	62	133	1.12 [0.88 , 1.43]	#
					0.01 Favours pa	L 0.1 1 10 100 aediatric form Favours tablet

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

Study or Subgroup	Paediatric Fo Events	rmulation Total	Crushed Events	Tablet Total	Risk Ratio M-H, Random, 95% CI	Risk 1 M-H, Rando	
Juma 2008	0	134	0	133	Not estimable		
						01 0.1 1 paediatric form.	10 100 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" [Publica- tion 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)



#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.

31 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 pediatr* or paediatr* 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

SCI-EXPANDED, CPCI-S (Web of Science) # 1 TOPIC: (malaria and falciparum) AND TOPIC: (artemisin* or dihydroartemis*) 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 (artemis* 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 artemis\$ [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*

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.



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 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