RESEARCH

Open Access



Safety of dihydroartemisinin-piperaquine versus artemether-lumefantrine for the treatment of uncomplicated Plasmodium falciparum malaria among children in Africa: a systematic review and meta-analysis of randomized control trials

Dawit Getachew Assefa^{1,2*}^(b), Eden Dagnachew Zeleke^{1,3}, Wondwosen Molla⁴, Nebiyu Mengistu⁵, Ahmedin Sefa⁶, Andualem Mebratu⁴, Asresu Feleke Bate⁶, Etaferaw Bekele⁶, Gizachew Yesmaw¹ and Eyasu Makonnen^{1,7}

Abstract

Background: The efficacies of artemisinin based combinations have been excellent in Africa, but also comprehensive evidence regarding their safety would be important. The aim of this review was to synthesize available evidence on the safety of dihydroartemisinin-piperaquine (DHA-PQ) compared to artemether-lumefantrine (AL) for the treatment of uncomplicated *Plasmodium falciparum* malaria among children in Africa.

Methods: A systematic literature search was done to identify relevant articles from online databases PubMed/ MEDLINE, Embase, and Cochrane Center for Clinical Trial database (CENTRAL) for retrieving randomized control trials comparing safety of DHA-PQ and AL for treatment of uncomplicated *P. falciparum* malaria among children in Africa. The search was performed from August 2020 to 30 April 2021. Using Rev-Man software (V5.4.1), the extracted data from eligible studies were pooled as risk ratio (RR) with 95% confidence interval (CI).

Results: In this review, 18 studies were included, which involved 10,498 participants were included. Compared to AL, DHA-PQ was associated with a slightly higher frequency of early vomiting (RR 2.26, 95% Cl 1.46 to 3.50; participants = 7796; studies = 10; $I^2 = 0\%$, high quality of evidence), cough (RR 1.06, 95% CI 1.01 to 1.11; participants = 8013; studies = 13; l² = 0%, high quality of evidence), and diarrhoea (RR 1.16, 95% CI 1.03 to 1.31; participants = 6841; studies = 11; I^2 = 8%, high quality of evidence) were more frequent in DHA-PQ treatment arm.

Conclusion: From this review, it can be concluded that early vomiting, diarrhoea, and cough were common were significantly more frequent in patients who were treated with the DHA-PQ than that of AL, and both drugs are well tolerated. More studies comparing AL with DHA-PQ are needed to determine the comparative safety of these drugs.

¹ Center for Innovative Drug Development and Therapeutic Trials

Addis Ababa, Ethiopia

Full list of author information is available at the end of the article



© The Author(s) 2021. Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/. The Creative Commons Public Domain Dedication waiver (http://creativeco mmons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

^{*}Correspondence: dawit.getachew@aau.edu.et

for Africa (CDT-Africa), College of Health Sciences, Addis Ababa University,

Keywords: Uncomplicated *Plasmodium falciparum*, Adverse event, Pediatrics, Children, Safety, Randomized control trial, Artemisinin-based combination therapy, Dihydroartemisinin-piperaquine, Artemether-lumefantrine, Systematic review, Meta-analysis, Africa

Background

Malaria is the major cause for vast majority of deaths among children under the age of five [1-3]. In 2019, an estimated 229 million cases were reported globally from 87 malaria endemic countries [3], of which 215 million cases were reported in the World Health Organization (WHO) African Region [3]. The risk of malaria infections among children aged under five years was higher in 2018, and *Plasmodium falciparum* parasite were responsible for an estimated 24 million malaria cases in African children [1].

All African counties, where *P. falciparum* malaria is endemic, have introduced the recommended artemisinin-based combination therapy (ACT) in the confirmed cases of *P. falciparum* malaria since 2004 [1]. The artemisinin component is active against the asexual stage of the parasite responsible for the disease, but also the sexual stages of the parasite involved in the transmission to mosquitoes. The partner drug with a longer half-life eliminates the residual parasite over several weeks post treatment [4]. Artemisinin and partner drugs protect each other to prevent resistance development [5–8].

The efficacies of artemisinin-based combinations have been excellent in Africa [9, 10]. Artemether-lumefantrine (AL) is one of the most commonly used combinations in sub-Saharan Africa. It is the first-line treatment for uncomplicated malaria in several countries [11, 12]. AL showed good safety and tolerability profile [10, 13, 14]. Hence, previous reviews reported mild or moderate severity adverse event of gastrointestinal and nervous systems in patients who were treated with AL [15] and prolongation of the QTc interval; pyrexia, early vomiting, and diarrhoea were common in patients treated with DHA-PQ [16].

In the majority of African countries, the first-line treatment for uncomplicated malaria is generally AL or AS/ AQ, with DHA-PQ as a second-line treatment in many countries [11, 12]. Most of the previous studies have compared the efficacies of AL and other artemisininbased combinations [17, 18], but also comprehensive evidence regarding their safety would be important. Given the wide range of ACT available for treatment the malaria and their potential adverse events (AEs), it is vital to compare their safety profiles. This systematic review and meta-analysis was, therefore, to synthesize available evidence on the safety of dihydroartemisinin-piperaquine compared to artemether-lumefantrine for the treatment of uncomplicated *P. falciparum* malaria among children in Africa.

Methods

This protocol has been registered at the International Prospective Register of Systematic Reviews (PROSPERO) database, ID: CRD42020200337 [19]. The methods and findings of the review have been reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA 2020) [20].

Eligibility criteria

The PICOS format was used to identify eligible studies [21].

Participants

Children having uncomplicated falciparum malaria residing in Africa, regardless of gender, were included.

Interventions

A target dose (range) of 4 (2–10) mg/kg bw per day dihydroartemisinin and 18 (16–27) mg/kg bw per day piperaquine given once a day for 3 days for children weighing \geq 25 kg. The target doses and ranges for children weighing <25 kg are 4 (2.5–10) mg/kg bw per day dihydroartemisinin and 24 (20–32) mg/kg bw per day piperaquine once a day for 3 days.

Comparator

The 1:6 fixed dose combination tablet consisting artemether (20 mg) and lumefantrine (120 mg).

The body weight-adjusted dosages used have been: 25–35 kg, 3 tablets per dose: 15 to 25 kg, 2 tablets per dose; and < 15 kg, 1 tablet.

The medication administered twice a day for three days (total six doses). The first two doses taken eight hours apart; the third dose is taken after 24 h the first and then every 12 h on days 2 and 3.

Outcome measures

Adverse events including serious adverse events were also assessed. An adverse event (AE) was defined as any unfavourable, unintended sign, symptom, syndrome, or disease that develops or worsens with the use of a medicinal product, regardless of whether it is related to the actual medicinal product. A serious AE was defined as any untoward medical occurrence that at any dose; resulted in death; was life threatening; requiring hospitalization or prolongation of hospitalization; resulted in a persistent or significant disability or incapacity; or caused a congenital anomaly or birth defect [22].

Studies

Randomized controlled trials conducted in Africa which compared the safety of DHA-PQ versus AL for the treatment of uncomplicated falciparum malaria in children, written in English, and published between 2004 to April 2021 were included.

Electronic searches

A systematic literature search was done to identify relevant articles from online databases PubMed/ MEDLINE, Embase, and Cochrane Center for Clinical Trial database (CENTRAL). The search was limited to human trials, randomized control trials, and published between 2004 and April 2021. The search was done according to guidance provided in the Cochrane Handbook for Systematic Reviews of Interventions [21]. Additionally, to search and assess ongoing or unpublished trials, ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform, and the US Food and Drug Administration (FDA) were searched.

The search strategies in PubMed for the MeSH terms and text words was "Child"[Mesh]) AND "Plasmodium falciparum"[Mesh]) OR "Acute malaria" [Supplementary Concept]) OR "Artemether, Lumefantrine Drug Combination/therapeutic use"[Mesh]) OR "Lumefantrine"[Mesh]) OR "dihydroartemisinin" [Supplementary Concept]) OR "piperaquine" [Supplementary Concept]) OR ("Randomized Controlled Trial" [Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh] OR "Controlled Clinical Trial" [Publication Type])) AND ("Drug Therapy"[Mesh] OR "Drug Therapy, Combination" [Mesh] OR "drug therapy" [Subheading])) AND ("Africa"[Mesh] OR "Africa South of the Sahara"[Mesh] OR "Africa, Western"[Mesh] OR "Africa, Southern" [Mesh] OR "Africa, Northern" [Mesh] OR "Africa, Eastern" [Mesh] OR "Africa, Central" [Mesh]. The searching strategies for Cochrane Center for Clinical Trial database (CENTRAL) and Embase are found in Additional file 1.

Study selection, data collection, and data analysis

The Cochrane Handbook for Systematic Reviews of Interventions [23] was followed. Furthermore, the software package provided by Cochrane (RevMan 5.4.1) was used. To import the research articles from the electronic databases and remove duplicates, ENDNOTE software version X7 was used. Two authors independently review the results of the literature search and obtained full-text copies of all potentially relevant trials. Disagreements were resolved through discussion. When clarification was necessary, the trial authors were contacted for further information. The screening and selection process was reported in a PRISMA flow chart (Fig. 1).

Data extraction and management

The title and abstract was produced from the electronic search, and was independently screened by two authors based on RCTs that were assessed human *P. falciparum* malaria. The information collected were trial characteristics including methods, participants, interventions, and outcomes as well as data on dose and drug ratios of the combinations. Also, relevant information such as title, journal, year of publication, publication status, study design, study setting, malaria transmission intensity, follow-up period, sample size, funding of the trial or sources of support, baseline characteristics of study subjects and adverse events including serious AEs were extracted from each article using the well-prepared extraction format in the form of a table adapted from Cochrane and modified to make suitable for this study.

Furthermore, the number of participants randomized, and the number analysed in each treatment group for each outcome were also collected. One author independently extracted data and information collected was cross-checked by another investigator. The number of participants experiencing the event and the number of participants in each treatment group were documented.

Assessment of risk of bias in included studies

The risk of bias for each trial was evaluated by two review authors independently using the Cochrane Collaboration's tool for assessing the 'Risk of bias' [21]. To decrease the risk of bias amongst six domains: sequence generation; allocation concealment; blinding (of participants, personnel, and outcome assessors); incomplete outcome data; selective outcome reporting; and other sources of bias, this guidance were used. The risks were classified as high risk, unclear risk, and low risk.

Measures of treatment effect

The main outcomes in this review were total of patients who experienced one or more adverse events. A number of patients with AEs from the studies were combined and presented using risk rations accompanied by 95% CIs.

Assessment of heterogeneity

Heterogeneity among the included trials was assessed by inspecting the forest plots and the Cochrane Q and I^2 statistic used to measure heterogeneity among the trials in



each analysis, the Chi² test with a P < 0.10 to indicate statistical significance was used, and the results were interpreted following Cochrane Handbook for Systematic Reviews of Interventions Version 6.0, Chapter 10: Analyzing data and undertaking meta-analyses [24].

Assessment of reporting bias

To assess the possibility of publication bias, funnel plots for asymmetry (Egger's test P < 0.05) were used [25].

Data synthesis

The meta-analyses was done consistent with the recommendations of Cochrane [23]. To aid interpretation, identity codes were given to included trials together with the first author, year of publication, and three first letter of the country where the trial being conducted. Trials were shown in forest plots in chronological order of the year the trials were published. A random-effects model was used, as trials were done by different researchers, operating independently, and it could be implausible that all the trials had functionally equivalence, with a common effect estimate.

Sensitivity analysis

To investigate the strength of the methodology used in the primary analysis and to restore the integrity of the randomization process, a series of sensitivity analyses were conducted using following steps were used: adding and excluding trials which were classified as high risk for bias back into the analysis in a stepwise fashion, and to assess the influence of small-study effects on the results of our meta-analysis, fixed-effect and random-effects estimates of the intervention effect were compared.

Quality of evidence

Quality of evidence was assessed using GRADE criteria and the GRADE pro software [26]. The results were presented in a 'Summary of Findings' table. Randomized trials are initially categorized as high quality but downgraded after assessment of five criteria [27]. The levels of evidence were defined as 'high', 'moderate', 'low', or 'very low'. The recommendations of Section 8.5 and Chapter 13 of the Cochrane Handbook for Systematic Reviews of Interventions was followed [28]. The imprecision was judged based on the optimal information size criteria and CI [29].

Results

A total of 3211 studies through the databases were searched, of which 49 full-text trials for eligibility were assessed and 18 of them fulfilled the inclusion criteria for meta-analysis and for qualitative analysis (see Fig. 1).

Characteristics of included studies

In this review, 18 studies were included, which enrolled 10,498 participants with uncomplicated *P. falciparum* malaria were included Table 1.

Characteristics of excluded studies

Thirty one studies were excluded with reason, Additional file 2.

Methodological quality and risk of bias

The 'Risk of bias' assessments were summarized in Fig. 2.

Adverse events

Gastrointestinal adverse events

Early vomiting The relative risk of early vomiting in patients treated with the DHA-PQ was higher than AL (RR 2.26, 95% CI 1.46 to 3.50; participants = 7796; studies = 10; $I^2 = 0\%$, *high quality of evidence*, Fig. 3).

Publication bias The funnel plot showed that all studies lay symmetrically around the pooled effect estimate implying that there was no publication bias (P = 0.5, Additional file 3).

Diarrhoea Similarly, the relative risk of early vomiting in patients treated with the DHA-PQ was higher than AL (RR 1.16, 95% CI 1.03 to 1.31; participants = 6841; studies = 11; $I^2 = 8\%$, *high quality of evidence*, Fig. 3).

Publication bias The funnel plot showed that all studies lay symmetrically around the pooled effect estimate implying that there was no publication bias (P = 0.9, Additional file 4).

Other gastrointestinal adverse events

The risk of vomiting did not have significant difference between the two treatment groups (RR 1.02, 95% CI 0.87

to 1.19; participants=8789; studies=13; I^2 =20%, *high quality of evidence*, Fig. 4). Similarly, there was no significant difference between the two treatment groups on the relative risk of anorexia (RR 0.95, 95% CI 0.84 to 1.07; participants=6841; studies=11; I^2 =0%, *high quality of evidence*), abdominal pain (RR 0.80, 95% CI 0.57 to 1.11; participants=2732; studies=8; I^2 =53%, *high quality of evidence*, Fig. 4), gastroenteritis (RR 0.57, 95% CI 0.19 to 1.68; participants=469, and loss of appetite (RR 2.06, 95% CI 0.52 to 8.14; participants=469; studies=1, [40]).

Cardio-respiratory adverse events

Cough Cough was the most common cardio-respiratory adverse event, and significantly higher number of participants from DHA-PQ treatment group experienced cough (RR 1.06, 95% CI 1.01 to 1.11; participants = 8013; studies = 13; $I^2 = 0\%$, *high quality of evidence*, Fig. 5).

Publication bias The funnel plot shows that all studies lie symmetrically around the pooled effect estimate implying that there was no publication bias (P=0.84, Additional file 5).

Other cardiorespiratory and hematological adverse events

The relative risk of developing coryza did not have significant difference between the two treatment groups (RR 1.00, 95% CI 0.92 to 1.10; participants = 832; studies = 2; $I^2 = 0\%$, Fig. 5). In addition, the relative risk of respiratory adverse events such as rhinorrhea, respiratory tract infection, rhinitis, and pallor was not significantly different between the two treatment groups (RR 1.59, 95% CI 0.89 to 2.83; participants = 442; studies = 1, [45]), (RR 1.23, 95% CI 0.59 to 2.57; participants = 299; studies = 1, [37]), (RR 3.35, 95% CI 1.11 to 10.12; participants = 469; studies = 1, [40]), 95% CI 0.91 to 1.92; participants = 1548; studies = 1, [34]). Similarly, the relative risk of cardiac adverse events like QTc interval prolongation (Fridericia's correction and Bazett's correction) was not significantly different between the two treatment groups (RR 0.98, 95% CI 0.51 to 1.90; participants = 1548; studies = 1, [34] and (RR 0.98, 95% CI 0.09 to 10.81 and RR 1.32, 95% CI 0.91 to 1.92, participants = 1548, studies = 1, [34]).

Neuropsychiatry adverse event

Weakness/malaise The relative risk of developing weakness or malaise was not significantly different between the two treatment groups (RR 0.88, 95% CI 0.74 to 1.03; participants = 3407; studies = 8; $I^2 = 0\%$, *high quality of evidence*, Fig. 6). Also, the relative risk of headache was not significantly different between the two treatment groups

tics of included studies
Characte
Table 1

No No	Study ID	Study	Study setting and	Transmission	Eollow un	Subjects			Patient	DHA-PO	AI
		design	period		<u>-</u> 5 5	Number of pa	irticipants	Inclusion age	important outcome	/ 	ļ
						DHA-PQ	AL				
-	Kamya-2007- UGA [30]	Single- blind, RCT	Rural health center March,2006-July, 2006	, High transmis- sion	42 days	253	256	6 months–10 years	Vomiting	65	65
									Diarrhoea	25	19
									Anorexia	06	91
									Abdominal pain	19	20
									weakness/ malaise	85	103
									Cough	136	133
									Coryza	127	121
									Pruritus	14	22
									SAE	4	2
5	Zongo-2007- BNF [31]	Single blind RCT	Government H health dispen- saries, August 2006-January	ligh transmission	42 days	196	197	6 months–10 years	Early vomiting	~	m
			7007						Vomitina	00	77
									Diarrhoea	14	13
									Anorexia	00	9
									Abdominal pain	10	21
									Cough	49	52
									Weakness/ Malaise	Ŋ	ſ
									Pruritus	5	11
									Headache	11	22
m	Mens-2008- KEN [32]	Open label RCT	Health center, H Apr 2007 to Jul 2007	ligh transmission	28 days	73	73	6 months–12 years	Headache	43	39

0
Φ
\Box
. <u> </u>
0
\cup
\sim
-
Ð
P

S. No	Study ID	Study	Study setting and	Transmission	Follow up	Subjects			Patient	DHA-PQ	AL	
		design	period			Number of pa	articipants	Inclusion age	important outcome			
						DHA-PQ	AL	1				
									Abdominal pain	25	26	
									Weakness	19	30	
									Anorexia	œ	10	
									Diarrhoea	6	7	
									Cough	16	17	
									Vomiting	11	6	
									Pruritus	4	m	
									SAE	-	0	
4	Yeka-2008- UGA [33]	Single- blind, RCT	Health center, N/A August 2006- April 2007		42 days	234	227	6 months–10 years	Vomiting	35	35	
									Diarrhoea	26	23	
									Anorexia	47	49	
									Abdominal pain	17	24	
									Weakness/ malaise	28	27	
									Cough	164	150	
									Coryza	159	150	
									Pruritus	8	ŝ	
									SAE	5	2	
Ŋ	Bassat- 2009-AFR [34]	Open- label, RCT	Four rural sites and on site, August 2005 and July	e peri-urban 2006.	Mesoen- demic	1038	510	6–59 months	Early vomiting	22	4	

(continue
-
<u>e</u>
9
Ъ

Table	1 (continued	(
S. No	Study ID	Study	Study setting and	Transmission	Follow up	Subjects			Patient	DHA-PQ	٩٢	
		design	period			Number of pa	Inticipants	Inclusion age	important outcome			
						DHA-PQ	AL					
									Vomiting	71	35	
									Splenomegaly	41	19	
									Hepatomegaly	9	ŝ	
									5 Prolonged QTc interval (Fridericia's correction)	7	-	
									Electrocar- diogram QT prolonged	26	13	
									Urticarial	-	2	
									Hypersensi- tivity	7	. 	
									Neutropenia	18	12	
									Alanine ami- notransferase increased	20	19	
									Electrocar- diogram QT prolonged	26	13	
									SAE	18	Ś	
Q	Arinaitwe- 2009-UGA [35]	Open- label RCT	Local antenatal Higl clinics in Tororo, August 2007- July 2008	h transmission	63 days	119	111	6 weeks–12 months	Vomiting	23	20	
									Diarrhoea	79	86	
									Anorexia	£	0	
									Weakness	-	0	
									Cough	177	153	
									Pruritus	0	0	
									SAE	m	,	

(continued)
-
Ð
Q
Ta

5. No	Study ID	Study	Study setting a	nd Transmission	Follow up	Subjects			Patient	DHA-PQ	AL
		aesign	period			Number of pa	Irticipants	Inclusion age	outcome		
						DHA-PQ	AL				
	Bor- rmann-2011– KEN [36]	Not described, RCT	Pingilikani study site, September 2005 to April 2008	Perennial transmis- sion	84 days	233	241	6–59 months	Early vomiting	~	4
œ	Nambozi- 2011-ZAM [37]	Open- label, RCT	Peri-urban health centers, September 2005 and May 2006	Mesoendemic	42 days	203	101	6–59 months	Anorexia	1 4	ω
									Cough	42	15
									Diarrhoea	14	4
									Fever	24	14
									Respiratory tract Infection	22	6
									Vomiting	5	4
									SAE	4	3
6	4ABC-2011- AFR [38]	Open label, RCT	Rural, urban or health facilities, 9 July 2007 and 19 June 2009	Mesoendemic, perennial and high transmission	63 days	1475	1226	6–59 months	Death up to day 63	-	ε

(continued)
-
Ð
q
Ta

	<u>-</u>	-	-	. . 	=							
S. No	Study ID	Study	Study setting and	Transmission	Follow up	Subjects			Patient	DHA-PQ	AL	
		nesign				Number of partic	ipants	Inclusion age	outcome			
						DHA-PQ	AL					
									Hepatomegaly	5	00	
									Splenomegaly	88	80	
									Anemia	141	38	
									Diarrhoea	166	142	
									Vomiting	123	102	
									Pyrexia	371	339	
									Hgb decrease	103	83	
									Anorexia	130	121	
									Cough	470	387	
									ALAT above normal range at day 0	10	16	
									ALAT above normal range at day 7	Ś	4	
									ALAT above normal range at day 28	4	-	
									Creatinine above normal range at day 0	2	0	
									Creatinine above normal range at day 7	0	0	
									Creatinine above normal range at day 28	0	2	
									SAE	10	9	
10	Agarwal -2013-KEN [39]	An open label RCT	District hospital, High October 2010 to August 2011	n transmission	42 days	137	137	6–59 months	Early vomiting	~	Ŋ	

$\overline{\mathbf{O}}$
d)
\supset
_
·=
Ę
5
0
U
\sim
_
-
d)
<u> </u>
_

Table	e 1 (continued _,	<u> </u>										
S. No	Study ID	Study	Study setting ar	nd Transmission	Follow up	Subjects			Patient	DHA-PQ	AL	
		design	period			Number of pa	articipants	Inclusion age	important outcome			
						DHA-PQ	AL	1				
									SAE	-	2	
1	Ogutu-2014- KEN [40]	Open- label, RCT	Nyando District hospital, March, 2010-30 November, 2011	Not described	42 days	227	227	6-59 months	Cough	40	37	
									Anemia	œ	10	
									Fever	14	7	
									Tinea capitis	12	10	
									Rhinitis	13	4	
									Gastroenteritis	5	6	
									Loss of appe- tite	Q	m	
									Otitis media	5	7	
12	Onyamboko- 2014-DRC [41]	Open label, RCT	Urban district of Kinshasa (DRC) (Hospi- tals), Septem- ber 2011 and November	Intense and peren- nial	42 days	228	228	3–59 months	Early vomiting	21	Ŋ	
			7012						Vomiting	17	2	
173	Kakuru- 2014-UGA [42]	Not described, RCT	District Hospi- tal, August 2007 and April 2008	High transmission	28 days	21	22	6 weeks -12 months	Vomiting	Ø	18	
									Diarrhoea	27	23	
									Anorexia	9	4	
									Weakness/ malaise	2	2	
									Cough	64	74	
4	Nji-2015-CAM [43]	Open- label, RCT	Two distinct ecological regions, 2009 to April 2013	Low to moderate transmission	42 days	288	144	6 months-10 years	Abdominal pain	13	S	

Tabl	le 1 (continued	(}										
S. No	Study ID	Study	Study setting an	d Transmission	Follow up	Subjects			Patient	DHA-PQ	AL	
		aesign	perioa			Number of p	articipants	Inclusion age	important outcome			
						DHA-PQ	AL	I				
									Anorexia	12	-	
									Diarrhoea	6	4	
									Vomiting	27	8	
									Fatigue	4	Э	
									Fever	e	2	
									Cough	18	6	
									Joint pain	2	2	
									Rash	16	4	
									SAE	0	—	
15	Ursing-2016- GUB [44]	Open- label, RCT	Bandimand Belem Health Centers, November 2012 and July 2015	Low to high trans- mission	42 days	157	155	6 months-15 years	Early vomiting	7	4	
16	Grandesso- 2018-NIG [45]	Open label, RCT	Health center, 7 June 2013 and 22 Septem- ber 2014	Not reported	42 days	221	221	6–59 months	Early vomiting	-	0	

ntinuec
l (cor
Table `

Table	e 1 (continued)												
S. No	Study ID	Study	Study setting ar	nd Tran	smission	Follow up	Subjects			Patient	DHA-PQ	AL	
	-	design	period				Number of p	barticipants	Inclusion age	important outcome			
							DHA-PQ	AL					
										Fever	94	94	
										Cough	36	22	
										Rhinorrhea	27	17	
										Diarrhoea	14	15	
										Conjunctivitis	7	15	
										Pyoderma	9	9	
										Vomiting	9	Ŋ	
										Anorexia	4	, -	
										Abdominal pain	0	-	
										Hepatomegaly	-	0	
										Splenomegaly	2	, -	
										Another AE	40	45	
										SAE	2	-	
										Early vomiting	-	2	
17	Yeka-2019-UGA	Single-	Health center H	High trans-	42 days		299	300	6–59 months	Vomiting	56	61	
	[46]	blind PCT	and Hospital, n	nission						Diarrhoea	155	114	
			2015-Decem- ber, 2016							Anorexia	12	Ś	

	Patient	DHA-PQ	AL				
Inclusion age	important outcome						
	Abdominal pain	41	45	Cough	233	203	
	Headaches	18	24	Pallor	22	13	
	weakness/ malaise	42	33	Skin rash	56	42	
	Cough	233	203	Pruritus	24	16	
	Pallor	22	13	SAE	9	9	
	Skin rash	56	42				
	c	Č	, ,				

Number of participants

Subjects

Study setting and Transmission Follow up period

Study design AL

DHA-PQ

(continued)	udy ID
-	Š
Table	S. No

0	13	42	16	9							54					
)	22	56	24	9							33	0				
5 5 5	Pallor	Skin rash	Pruritus	SAE							Vomit- ing	SAE				
2	24	33	203	13	42	16	9	-	-	21	4	2	0	54	-	
	18	42	233	22	56	24	9	0	0	17	13	ŝ	-	33	0	
pain	Headaches	weakness/ malaise	Cough	Pallor	Skin rash	Pruritus	SAE	Itchiness	Otitis media	Cough	Abdominal pain	Skin rash	Furunculosis	Vomiting	SAE	
								6-59	months							
								360								
								360								
								42 days								
								Moderate to high transmis-	sion							
								Primary health	facility and	district hospi- tal, November 2017 to Sep- tember 2018						
								Open	label, DCT							
								Gansane-	2021-BNF	[74]						
								18								



Fig. 2 A summary of review authors' judgments about each risk of bias item for each included study



(RR 0.81, 95% CI 0.47 to 1.38; participants = 598; studies = 3; $I^2 = 72\%$, Fig. 6).

Musculoskeletal/dermatological adverse events

Pruritus was the most common dermatological adverse event, and the relative risk of developing pruritus was not significantly different between the two treatment groups (RR 1.00, 95% CI 0.56 to 1.78; participants = 1952; studies = 5; $I^2 = 49\%$, moderate quality of evidence, Fig. 7). Also, the relative risk of developing skin rash was not significantly different between the two treatment groups (RR 1.40, 95% CI 0.99 to 1.96; participants = 1720; studies = 3; $I^2 = 0\%$, Fig. 7).

Other musculoskeletal/dermatological adverse events

The relative risk of musculoskeletal or dermatological adverse events such as: skin and subcutaneous disorder, urticarial, hypersensitivity, pyoderma, conjunctivitis, joint pain, tinea-capitis, itchiness, frunculosis was not significantly different between the two treatment groups (RR 1.19, 95% CI 0.78 to 1.80; participants=1548; studies=1, [34]), (RR 0.25, 95% CI 0.02 to 2.70;

participants = 1548; studies = 1, [34]), (RR 0.98, 95% CI 0.09 to 10.81; participants = 1548; studies = 1, [33]), (RR 1.00, 95% CI 0.33 to 3.05; participants = 442; studies = 1, [45]), (RR 0.47, 95% CI 0.19 to 1.12; participants = 442; studies = 1, [45]), (RR 0.49, 95% CI 0.07 to 3.46; participants = 418; studies = 1, [43]), (RR 1.24, 95% CI 0.54 to 2.81; participants = 469; studies = 1, [40]), (RR 0.34, 95% CI 0.01 to 8.22; participants = 703; studies = 1 [47]), and (RR 3.03, 95% CI 0.12 to 74.02; participants = 703; studies = 1, [47]), respectively.

Other adverse events

Pyrexia The relative risk of pyrexia was the same in both treatment groups (RR 0.94, 95% CI 0.85 to 1.04; participants = 4620; studies = 6; $I^2 = 0\%$, Fig. 8). Similarly, the relative risk of otitis media was the same in both treatment groups (RR 0.66, 95% CI 0.23 to 1.91; participants = 1157; studies = 2; $I^2 = 0\%$, Fig. 8).

Serious adverse event Fourteen studies reported 59 serious adverse events in the DHA-PQ and 35 in the AL

Study or Subgroup Events Total Weight M.H. Random. 95% CI Year M.H. Random. 95% CI 120.1 Vorniting 2007-90.0 65 211 65 200 7.1% 1.000 176.132 2007 Kamya 2007-UGA 65 211 65 210 7.1% 1.000 106.71.32 2007 Vela-2008-UGA 35 198 9.93 0.930 106.11.42 2008 4 Mens-2008-UGA 23 351 20 320 6.0% 1.050 10.07.1.47 2009 4 Adabc-2011-ARM 5 199 4 100 1.4% 0.83 10.07.2.299 101 4 Adabc-2011-ARM 5 199 4 100 1.4% 0.83 10.07.2.299 101 4 100 1.4% 0.83 10.07.2.299 101 4 4 1.09.07.1.63 107 107 107.3.297 101 7 107.3.297 101 100 1.4% 1.04.02.0.87 101 100 1.090 1.090 1.090 <t< th=""><th></th><th>DHA-</th><th>PQ</th><th>ΔΙ</th><th></th><th></th><th>Risk Ratio</th><th></th><th>Risk Batio</th></t<>		DHA-	PQ	ΔΙ			Risk Ratio		Risk Batio
120.1 Venuting 20107 1000	Study or Subaroup	Events	Total	Events	Total	Weight	M-H. Random, 95% Cl	Year	M-H. Random, 95% Cl
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	1.20.1 Vomiting			210110					
$ \begin{array}{c} \mbox{Figures} 2007-UGA & 66 & 211 & 66 & 210 & 17.15 & 1.00 [0.75, 1.32 & 2007 \\ \mbox{Yebs} 2008-UGA & 35 & 213 & 35 & 198 & 9.98 & 0.39 [0.61, 1.42 & 2006 \\ \mbox{Hen} - 2008-KEN & 11 & 73 & 9 & 73 & 326 & 1.22 [0.64, 2.77] 2008 \\ \mbox{Hen} - 2008-KEN & 11 & 73 & 9 & 73 & 326 & 1.22 [0.64, 2.77] 2008 \\ \mbox{Hen} - 2008-KEN & 11 & 123 & 1468 & 102 225 & 19.8% & 1.01 [0.78, 1.29 & 2011 \\ \mbox{Hambox} 2014-UGA & 8 & 195 & 18 & 201 & 338 & 0.54 [0.24, 1.21] & 2014 \\ \mbox{Hambox} 2014-UGA & 8 & 195 & 18 & 201 & 338 & 0.54 [0.24, 1.21] & 2014 \\ \mbox{Hambox} 2014-UGA & 6 & 195 & 12 & 228 & 115 & 8.50 [1.99, 56.37] & 2014 \\ \mbox{Hambox} 2014-UGA & 6 & 195 & 12 & 228 & 115 & 8.50 [1.99, 56.37] & 2014 \\ \mbox{Hambox} 2014-UGA & 6 & 195 & 12 & 221 & 1.68 & 1.20 [0.37, 3.87] & 2018 \\ \mbox{Helexopenely}. Tau^2 = 0.01; \mbox{Ch}^{\mu} = 4.39; \mbox{df} = 12 (P = 0.24); \mbox{P} = 205 \\ \mbox{Testor overall effect } Z = 0.24 (P = 0.81) \\ \mbox{L200-VGA } & 47 & 213 & 49 & 198 & 12.4% & 0.89 [0.33, 1.21] & 2006 \\ \mbox{Helexopenely}. Tau^2 = 0.01; \mbox{Ch}^{\mu} = 4.39; \mbox{df} = 12 (P = 0.24); \mbox{P} = 205 \\ \mbox{Testor overall effect } Z = 0.24 (P = 0.81) \\ \mbox{L200-VGA } & 47 & 213 & 49 & 198 & 12.4% & 0.89 [0.33, 1.27] & 2008 \\ \mbox{Helexopenely}. Tau^2 = 0.01; \mbox{Ch}^{\mu} = 4.39; \mbox{df} = 12 (225 & 235 & 0.89 [0.33, 1.27] & 2008 \\ \mbox{Helexopenely}. Tau^2 = 0.01; \mbox{Ch}^{\mu} = 6.33; \mbox{df} = 10 & 12 & 226 & 1.38 & 0.33 (2.23) & 2011 \\ \mbox{Helexopenely}. Tau^2 = 0.01; \mbox{He} & 73; \mbox{df} = 10 & 12 & 22 & 0.25 & 0.88 [0.33, 2.23] & 2007 \\ \mbox{Helexopenely}. Tau^2 = 0.00; \mbox{He} = 6.73; \mbox{df} = 10 & 12 & 22 & 1 & 138 & 0.48 & 0.53 [0.31, 0.39] & 2007 \\ \mbox{Helexopenely}. Tau^2 = 0.00; \mbox{He} = 73; \mbox{df} = 10 & 12 & 22 & 1 & 128 & 0.48 & 0.53 [0.31, 0.89] & 2007 \\ \mbox{Helexopenely}. Tau^2 = 0.00; \mbox{He} = 73; \mbox{df} = 10 & 12 & 22 & 1 & 128 & 0.48 & 0.53 [0.31, 0.89] & 2007 \\ \mbox{Helexopenely}. Tau^2 = 0.00; \mbox{He} = 73; \mbox{df} = 10 & 12 & 22 & 1$	70000-2007-BNF	20	187	27	188	67%	0 74 10 43 1 281	2007	
Yele-2008-UGA 35 213 35 198 938 038 061 142 2008 Mem-2008-UGA 11 73 3 73 32% 122 054 277 2008 Mem-2009-UGA 23 381 20 320 60% 1.09 0.06 71, 477 2009 Annatwe-2009-UGA 23 381 20 320 60% 1.09 0.06 71, 477 2009 Annatwe-2009-UGA 123 381 20 320 60% 1.09 0.06 71, 477 2009 Annatwe-2009-UGA 123 20 51 98% 1.01 0.78, 129 2011 Nambol-2017-ZAM 5 199 4 100 1.4% 0.63 0.07, 229 2011 Kalaru-2014-UGA 815 18 20 11 33% 0.54 0.02 4, 121 2014 Organobol-2014-DRC 17 228 2 228 1.1% 6.05 0.83, 337 2014 Mi-2015-CAM 27 208 8138 37% 1.66 1078, 356 2015 Total events 467 3 912 Heterogenetic, Tau ²⁺ 0.01, Ch ²⁺ 1489, df = 12 (P = 0.24), P = 20% Testfor overall effect Z = 0.24 (P = 0.24), P = 20% Testfor overall effect Z = 0.24 (P = 0.24), P = 20% Testfor overall effect Z = 0.24 (P = 0.24), P = 20% Testfor overall effect Z = 0.24 (P = 0.24), P = 20% Testfor overall effect Z = 0.24 (P = 0.24), P = 20% Testfor overall effect Z = 0.24 (P = 0.24), P = 20% Testfor overall effect Z = 0.24 (P = 0.24), P = 20% Testfor overall effect Z = 0.24 (P = 0.24), P = 20% Testfor overall effect Z = 0.24 (P = 0.24), P = 20% Testfor overall effect Z = 0.24 (P = 0.24), P = 20% Testfor overall effect Z = 0.24 (P = 0.24), P = 20% Testfor overall effect Z = 0.24 (P = 0.24), P = 20% Testfor overall effect Z = 0.24 (P = 0.24), P = 20% Testfor overall effect Z = 0.24 (P = 0.24), P = 20% Testfor overall effect Z = 0.24 (P = 0.24), P = 0.26), P = 0.65 Total events 398 376 Heterogenety, Tau ² = 0.00, Ch ² = 3.73, df = 10 (P = 0.56), P = 0.% Testfor overall effect Z = 0.80 (P = 0.30) 1.20.3 Addominal pain Zongo-2007-BNF 10 112 21 104 12.3% 0.44 (0.22, 0.89] 2007 Heterogenety, Tau ² = 0.00, Ch ² = 3.73, df = 10 (P = 0.56), P = 0.% Testfor overall effect Z = 0.80 (P = 0.30) 1.20.3 Addominal pain Zongo-2007-BNF 13 360 4 333 6.7% Testfor overall effect Z = 0.80 (P = 0.30) 1.20.4 4.4 5 1.22 7 10.00% 0.30 [0.57, 1.11] 0.44 (20, 20, 0.55, 1.21 200 0.44 (0.22, 0.89] 2007 Heterogenety, Tau ² = 0.10; D ² = 0.00; P = 53% Testfor overal	Kamva-2007-UGA	65	211	65	210	171%		2007	+
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	Yeka-2008-UGA	35	213	35	198	9.9%	0.93 [0.61, 1.42]	2008	
Bassal-2009-47R 71 1038 35 510 11.3% 1.00 [0.67, 1.47] 2009 Armatuv-2009-UGA 23 351 20 320 6.0% 1.88 [0.59, 1.87] 2009 Armatuv-2009-UGA 23 351 20 320 6.0% 1.08 [0.59, 1.87] 2009 Armatuv-2009-UGA 18469 102 1225 198% 1.00 [0.78, 1.29] 2011 Nambol-2011-ZAM 5 199 4 100 1.4% 0.63 [0.17, 2.29] 2011 Nil-2015-CAM 27 280 8 138 3.7% 1.68 [0.78, 3.65] 2015 Grandesso-2018-WIR 6 221 5 221 1.6% 1.13 [0.20, 3.67] 2018 Yeta-2018-UGA 56 243 61 300 14.8% 1.13 [0.22, 1.56] 2019 Total events Helerogeneity Tat/= 0.01; Ch ⁺⁻ 14.86, df =12 (<i>P</i> = 0.24); <i>P</i> = 20% Test for overall effect Z = 0.24 (<i>P</i> = 0.81) 1.20.2 Anorexia Zongo-2007-BNF 8 187 6 188 1.4% 1.34 [0.47, 3.79] 2007 Kaimy-2007-UGA 90 211 91 124 (2.9 = 0.24); <i>P</i> = 20% Test for overall effect Z = 0.24 (<i>P</i> = 0.81) 1.20.2 Anorexia Zongo-2007-BNF 8 187 6 188 1.4% 1.34 [0.47, 3.79] 2007 Kaimy-2009-UGA 3 351 0 320 0.2% 6.38 [0.33, 123.11] 2008 Armatwo-2009-UGA 3 351 0 2200 25% 6.38 [0.33, 123.11] 2008 Armatwo-2009-UGA 3 351 0 2200 25% 6.38 [0.33, 123.11] 2008 Armatwo-2009-UGA 3 351 0 2200 25% 6.38 [0.33, 123.11] 2001 Helerogeneity: Tat/= 0.00; Ch ⁺⁼ 8.73, df = 10 (<i>P</i> = 0.56); <i>P</i> = 0% Test or overall effect Z = 0.88 (<i>P</i> = 0.39) 1.20.3 Abdominal pain Zongo-2007-BNF 10 1122 21 104 12.3% 0.44 [0.22, 0.89] 2007 Total events 398 67 3174 100.0% 0.95 [0.84, 1.07] Total events 398 67 3174 100.0% 0.95 [0.84, 1.07] Total events 398 (<i>P</i> = 0.39) 1.20.3 Abdominal pain Zongo-2007-BNF 10 1122 21 104 12.3% 0.53 [0.31, 0.88] 2007 Mens-2008-UEA 25 73 26 73 184 % 0.98 [0.82, 1.50] 2008 Mens-2008-UEA 25 73 26 73 187 400.0% 0.95 [0.84, 1.07] Total events 398 (<i>P</i> = 0.39) 1.20.3 Abdominal pain Zongo-2007-BNF 13 350 4 353 6.7% 3.28 [1.08, 9.55] 2019 Grandesso-2018-WIR 12 4.94, df = 7 (<i>P</i> = 0.04); <i>P</i> = 53% Test for overall effect Z = 1.33 (<i>P</i> = 0.18) Facust [DLH-QD] Facust PLU Facust [DLH-QD] Facust PLU	Mens-2008-KEN	11	73	g	73	3.2%	1 22 [0 54 2 77]	2008	_
Arinative-2009-UGA 23 351 20 320 6.0% 1.05 0.50 1.05 0.50 1.05 0.50 1.05 0.50 1.05 0.50 1.05 0.50 1.05 0.50 1.05 0.50 0.50 1.05 0.50 <td>Bassat-2009-AFR</td> <td>71</td> <td>1038</td> <td>35</td> <td>510</td> <td>11.3%</td> <td></td> <td>2000</td> <td>-</td>	Bassat-2009-AFR	71	1038	35	510	11.3%		2000	-
4ABC-2011-APR 123 1468 102 1225 19.8% 1.01 10.78, 12.9 2011 Nambod-2011-ZAM 5 193 4 100 1.4% 0.83 0.71, 229 2011 Abscur-2011-ZAM 5 193 4 100 1.4% 0.83 0.74, 129 2011 Organobox 2011-DCA 17 228 1.3% 8.50 (19.9, 9.63.7) 2014 Organobox 2011-AUR 6 221 1.5 221 1.6% 1.20 (0.37, 3.87) 2018 Vela-2013-UAA 56 243 61 300 14.8% 1.13 (0.82, 1.58) 2019 Subtoal (6% Ct) 4477 391 1.406 1.20 (0.87, 1.19) 1.406 1.20 (0.87, 1.19) Total events 467 31 1.99 1.43 0.94 (7.3, 7.9) 2007 Karmya-2007-UAA 90 211 91 20.4% 0.89 (0.3, 1.23, 112 2009 Vela-2008-UCA 3 351 0.320 0.2% 6.38 (0.3, 1.23, 112 2009 4.400-2.01 1.33 201 4.400-2.01 1.33 <td< td=""><td>Arinaitwe-2009-UGA</td><td>23</td><td>351</td><td>20</td><td>320</td><td>6.0%</td><td>1.05 [0.59, 1.87]</td><td>2000</td><td></td></td<>	Arinaitwe-2009-UGA	23	351	20	320	6.0%	1.05 [0.59, 1.87]	2000	
Nambozi 2011-ZAM 5 199 4 100 1.4% 0.83 [0.17, 229 2011 Kakur-2014-UGA 8 165 18 201 3.3% 0.54 [0.24, 121] 2014 Organobas 2014 DRC 17 228 2 228 1.1% 5.50 [1.99, 357] 2014 NII-2015-CAM 27 280 8 138 3.7% 1.66 [0.78, 356] 2015 Subtolal (95% CI) 4877 3912 100.0% 1.02 [0.87, 1.19] Yeka-2019-UGA 56 243 61 300 1.48% 1.13 [0.82, 1.56] 2019 Subtolal (95% CI) 4877 3912 100.0% 1.02 [0.87, 1.19] 1.20 Zanorexia Zongo-2007-BNF 8 1 167 6 188 1.4% 1.34 [0.47, 379] 2007 Yeka-2008-UGA 47 213 49 198 12.4% 0.89 [0.63, 1.27] 2008 Arinative-2008-UGA 47 213 49 198 112.2% 2.7% 0.89 [0.33, 1.23] 2009 Yeka-2008-UGA 47 213 49 198 110 2.2% 0.88 [0.3, 2.33] 2011 Katura-2014-UGA 6 165 4 201 1.0% 1.83 [0.56, 6.37] 2014 Arinative-2008-UGA 7 213 10 1468 121 1225 2.7% 0.89 [0.3, 1.23] 12009 Yeka-2008-UGA 47 213 12 120 2.2% 0.88 [0.3, 2.33] 2011 Katura-2014-UGA 6 165 4 201 1.0% 1.83 [0.56, 6.37] 2014 Niekatur-2014-UGA 6 165 4 201 1.0% 1.83 [0.56, 6.37] 2014 Niekatur-2014-UGA 7 228 0.5 300 2.1.6% 0.90 [0.3, 1.17] 2019 AdbC-011-XM 14 199 8 100 2.2% 0.89 [0.3, 1.23] 12009 Yeka-2019-UGA 76 229 0.5 300 2.1.6% 0.90 [0.64, 1.07] Total events 398 376 Heterogeneity: Tau ⁺ = 0.00; ChP ⁻ = 8.73, df = 10 (P = 0.56); P = 0% Test for overall effect Z = 0.38 (P = 0.38) 1.20.3 Abdominal pain Zongo-2007-UGA 19 211 32 21 0.16 3% 0.59 [0.30, 3.09] 2007 Yeka-2019-UGA 77 4 24 63 16.3% 0.59 [0.36, 1.02] 2008 Yeka-2019-UGA 77 4 24 63 16.3% 0.59 [0.36, 1.02] 2008 Yeka-2019-UGA 77 74 24 63 16.3% 0.50 [0.36, 1.02] 2008 Yeka-2019-UGA 77 74 24 63 16.3% 0.50 [0.36, 1.02] 2008 Yeka-2019-UGA 77 74 24 63 16.3% 0.50 [0.36, 1.02] 2008 Yeka-2019-UGA 77 74 24 63 16.3% 0.59 [0.30, 1.08] 2007 Yeka-2019-UGA 77 74 24 63 16.3% 0.50 [0.36, 1.02] 2008 Yeka-2019-UGA 77 74 24 63 16.3% 0.50 [0.36, 1.02] 2008 Yeka-2019-UGA 77 74 24 63 16.3% 0.50 [0.36, 1.02] 2008 Yeka-2019-UGA 77 74 24 63 16.3% 0.50 [0.36, 1.02] 2008 Yeka-2019-UGA 77 74 24 63 16.3% 0.50 [0.36, 1.02] 2008 Yeka-2019-UGA 77 74 24 63 16.3% 0.20 [0.65, 7, 1.11] Total events 138 162 Heterogene	4ABC-2011-AFR	123	1468	102	1225	19.8%	1 01 0 78 1 29	2011	+
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Namhozi-2011-7AM	5	199	4	100	1 4 %	0.63 [0.17, 2.29]	2011	
Onyamboko 2014 DRC 17 228 2 228 1.1% 8.50 (1.99, 36.37) 2014 NIJ-2015-CAM 27 280 8 138 3.7% 1.66 (0.76, 3.56) 2015 Grandesso-2018-NIR 6 221 1.6% 1.20 (0.37, 3.56) 2015 Grandesso-2018-NIR 6 221 1.6% 1.20 (0.37, 3.79) 2019 Total events 467 391 1.00 (0.87, 1.19) 1.02 (0.87, 1.19) 1.02 (0.87, 1.19) Total events 467 391 120 31, 3% 0.89 (0.79, 1.23) 2007 Mems-2008-VGA 49 211 91 210 31, 3% 0.89 (0.71, 1.3) 2008 Mens-2008-VGA 47 213 49 198 12.4% 0.89 (0.8, 1.27) 2008 Annahwe-2008-VGA 351 0.32 0.2% 0.88 (0.38, 2.03) 2011 Manabue-2006-VGA 351 0.32 (0.2% 0.89 (0.8, 7, 1.13) 2014 Manabue-2006-VGA 1.0% 1.01 (1.2, 1.03) 0.01 (1.8, 1.07) 1.01 (1.2, 1.04) <t< td=""><td>Kakuru-2014-UGA</td><td>8</td><td>165</td><td>18</td><td>201</td><td>3.3%</td><td>0.54 [0.24, 1.21]</td><td>2014</td><td></td></t<>	Kakuru-2014-UGA	8	165	18	201	3.3%	0.54 [0.24, 1.21]	2014	
$\begin{aligned} \begin{array}{c} N ^{2}2015\text{-}CAM & 27 & 280 & 8 & 138 & 3.7\% & 1.66 [0.78, 3.56] & 2015 \\ Grandesso-2018\text{-NR & 6 & 221 & 6 & 221 & 1.6\% & 1.20 [0.37, 3.87] & 2018 \\ Subtotal(95\% \text{C}) & 4877 & 3912 & 100.0\% & 1.02 [0.87, 1.19] \\ Total events & 467 & 391 \\ Heterogenelly(Tau^{\texttt{H}}=0.01; Ch^{\texttt{H}}=1.4.86, df=1.2(P=0.24), P=20\% \\ Testfor overall effect Z=0.24 (P=0.81) \\ \texttt{1.20} 2. A norexia \\ Zongo-2007\text{-ENF} & 8 & 187 & 6 & 188 & 1.4\% & 1.34 [0.47, 3.79] & 2007 \\ Karmy-2007\text{-IOA} & 8 & 73 & 10 & 73 & 2.0\% & 0.80 [0.3, 1.91] & 2008 \\ Arinative-2009\text{-UGA} & 9 & 2.11 & 91 & 210 & 31.3\% & 0.98 [0.79, 1.22] & 2007 \\ Karmy-2007\text{-IOA} & 8 & 73 & 10 & 73 & 2.0\% & 0.80 [0.3, 1.91] & 2008 \\ Arinative-2009\text{-UGA} & 3 & 351 & 0 & 320 & 0.2\% & 6.38 [0.33, 123.11] & 2009 \\ AlacC-2011\text{-AFR} & 130 & 14.68 & 121 & 1225 & 27.3\% & 0.99 [0.71, 1.13] & 2011 \\ Narmotoz & 2011\text{-}ZM & 14 & 199 & 81 & 100 & 2.2\% & 6.38 [0.33, 123.11] & 2009 \\ AlacC-2011\text{-AFR} & 130 & 14.68 & 121 & 1225 & 27.3\% & 0.99 [0.71, 1.13] & 2011 \\ Narmotoz & 3011\text{-}ZM & 14 & 199 & 81 & 100 & 2.5\% & 537 & 1014 \\ M _{2}2015\text{-}CAM & 12 & 280 & 1 & 138 & 0.4\% & 5.99 [0.74, 1.07] \\ Total events & 398 & 376 \\ Heterogeneily Tau^{*}= 0.00; Ch^{*}= 8.73, df=1 & 0(P=0.56); P=0\% \\ Test for verall effect Z=0.88 (P=0.38) \\ 1.203 Abdominal pain \\ Zongo-2007\text{-ENF & 0 & 112 & 21 & 104 & 12.3\% & 0.44 (0.22, 0.89] & 2007 \\ Yeka-2019\text{-UGA & 17 & 74 & 24 & 63 16.3\% & 0.53 [0.31, 0.89] & 2007 \\ Yeka-2019\text{-UGA & 11 & 224 & 1221 & 10.5\% & 0.33 [0.01, 8.14] & 2018 \\ Yeka-2019\text{-UGA & 11 & 124 & 45 & 125 & 12.7\% & 0.99 [0.85, 1.27] & 2019 \\ Garanae-32018\text{-KEN & 25 & 73 & 268 (P=3.3\% & 12.80 (A^{*}, 5.22) & 2018 \\ Garanae-32018-UCA & 11 & 124 & 45 & 125 & 12.7\% & 0.32 [0.65, 1.29] & 2019 \\ Garanae-32018\text{-UCA & 11 & 124 & 45 & 125 & 12.7\% & 0.32 [0.65, 1.29] & 2019 \\ Garanae-32018\text{-UA & 13 & 6 & 162 \\ Heterogeneill; \mathsf{$	Onvamboko 2014 DRC	17	228	2	228	11%	8 50 [1 99 36 37]	2014	
Orandesso-2018-NIR 6 221 5 221 1.8% 1.20 [0.37, 3.87] 2018 Yela-2019-UGA 66 243 61 300 14.9% 1.13 [0.82, 1.68] 2019 Total events 467 391 Hetrogeneity, Tau*= 0.01; Chi*= 14.96, dir=12 (P = 0.24); P = 20% Testfor overall metct Z = 0.24 (P = 0.81) 12.0.2 Anorexia Zongo-2007-BNF 8 187 6 188 1.44% 1.34 [0.47, 3.79] 2007 Yela-2008-UGA 490 211 91 210 31.3% 0.98 [0.73, 1.23] 2007 Yela-2008-UGA 47 213 49 198 12.4% 0.89 [0.63, 1.27] 2008 Yela-2008-UGA 47 213 49 198 12.25 27.3% 0.98 [0.63, 1.27] 2008 Yela-2014-UGA 6 165 4 201 10% 1.83 [0.52, 6.37] 2011 Katuru-2014-UGA 6 165 4 201 10% 0.90 [0.63, 1.07] 2019 4 Subtotal (95% C) 3667 3174 100 (P = 0.56); P = 0% 128 [0.47, 5.2] 2018 <t< td=""><td>Nii-2015-CAM</td><td>27</td><td>280</td><td>8</td><td>138</td><td>3.7%</td><td>1.66.10.78.3.561</td><td>2015</td><td></td></t<>	Nii-2015-CAM	27	280	8	138	3.7%	1.66.10.78.3.561	2015	
Yeka-2019-UGA 56 243 61 300 14.8% 1.13 [0.02, 1.56] 2019 Subtotal (95% C) 4877 391 100.0% 1.02 [0.87, 1.19] 100.0% 1.02 [0.87, 1.19] 1.20.2 Anorexia Zongo-2007-ENF 8 187 6 188 1.4% 1.34 [0.47, 3.79] 2007 Kamya-2007-UGA 90 211 91 210 31.3% 0.98 [0.79, 1.23] 2007 Kamya-2007-UGA 90 211 91 210 31.3% 0.98 [0.79, 1.23] 2007 Veha-2008-UGA 3 351 0 30 0.2% 6.38 (0.33, 12.11] 2008 Veha-2008-UGA 3 351 0 30 1.26 2.7% 0.80 [0.36, 2.03] 2011 Mamboz-2001-UGA 6 165 4 201 1.0% 5.91 [0.78, 45.02] 2016 Veha-2008-UGA 76 299 85 3000 2.1% 0.90 [0.82, 1.107] 101 100 100 0.95 [0.84, 1.07] 101 101 100 100 100 100 100 100 100	Grandesso-2018-NIR	6	221	5	221	1.6%		2018	
Subtotal (95% CI) 4877 0.3912 100.0% 1.02 [0.87, 1.19] Total events 467 391 Heterogeneity, Tau ² = 0.17. Pat = 0.4, Gr = 1.2 (P = 0.24); P = 20% Test for overall effect Z = 0.24 (P = 0.81) 1.20.2 Anorexia Zongo-2007-BNF 8 187 6 188 1.4% 1.34 (0.47, 3.79] 2007 Karrya-2008-UGA 90 211 91 210 31.3% 0.98 (0.79, 1.23] 2007 Wens-2008-KEN 8 73 10 73 2.0% 0.89 (0.33, 1.91] 2008 Yeka-2008-UGA 47 213 49 198 12.4% 0.89 (0.63, 1.27] 2008 ARack-2011-AFR 130 1468 121 1225 27.3% 0.90 (0.71, 1.13] 2011 Namboz-2011-ZAM 14 199 8 100 2.2% 0.88 (0.38, 2.03] 2011 Kakury-2014-UGA 6 165 4 201 1.0% 1.83 (0.26, 6.37] 2019 ABC-2011-AFR 130 1468 121 1225 27.3% 0.90 (0.71, 1.13] 2011 Namboz-2011-ZAM 14 199 8 100 2.2% 0.88 (0.38, 2.03] 2011 Kakury-2014-UGA 6 165 4 201 1.0% 1.83 (0.52, 6.37] 2014 Nji-2015-CAM 12 280 1 138 0.4% 5.91 (0.78, 45.02] 2015 Grandesso-2019-NIR 4 221 1 221 0.3% 0.44 (0.22, 0.89] 2007 Total events 338 376 Heterogeneity, Tau ² = 0.00; Ch ² = 8.73, df = 10 (P = 0.56); P = 0% Test for overall effect Z = 0.38 (P = 0.38) 1.20.3 Abdominal pain Zongo-2007-BNF 10 112 21 104 12.3% 0.44 (0.22, 0.89] 2007 Mens-2008-UGA 17 74 24 63 16.3% 0.66 (0.61, 1.02] 2008 Yeka-2019-UGA 13 280 5 138 7.8% 1.28 (0.47, 3.52] 2015 Grandesso-2018-NIR 0 221 1 221 1.0% 0.33 (0.01, 8.14) 2018 UKbatal (95% CI) 1445 125 21.2% 0.92 (0.65, 1.29) 2017 Mens-2008-UGA 17 74 24 63 16.3% 0.66 (0.61, 0.2] 2008 Yeka-2019-UGA 41 124 45 125 21.2% 0.92 (0.65, 1.29) 2017 Mens-2008-UGA 17 74 24 63 16.3% 0.66 (0.61, 0.2] 2008 Yeka-2019-UGA 41 124 45 125 21.2% 0.92 (0.65, 1.29) 2017 Jotal events 138 162 Heterogeneity, Tau ² = 0.11; Ch ² = 1.49, df = 7 (P = 0.04); P = 53% Test for overall effect Z = 1.33 (P = 0.18) Fie.4 Forest plot of comparison: dibutpratemisticip-eperaousing settemethered methered methered methered method for metanolise to metanolise	Yeka-2019-UGA	56	243	61	300	14.8%	1 13 [0 82 1 56]	2019	_
Total events 467 391 Heterogeneity, Tau ² = 0.01; Ch ² = 1.4.96, df = 12 (P = 0.24); P = 20% Test for overall effect Z = 0.24 (P = 0.81) 1.20.2 Anorexia Zongo-2007-DNF 8 8 187 6 188 1.4% 1.34 (0.47, 3.79] 2007 Karrya-2007-UGA 90 211 91 210 31.3% 0.98 (0.79, 1.23) 2007 Karrya-2008-UGA 17 213 49 198 12.4% 0.93 (0.63, 1.27) 2008 Arinaltwe-2009-UGA 3 351 0 320 0.2% 6.38 (0.33, 123.11) 2009 Arinaltwe-2009-UGA 3 351 0 320 0.2% 6.38 (0.33, 123.11) 2009 Arinaltwe-2009-UGA 3 351 0 320 0.2% 0.83 (0.33, 123.11) 2009 Arinaltwe-2014-UGA 6 165 4 201 1.0% 1.83 (0.52, 6.37) 2014 Niji-2015-CAM 12 280 1 138 0.4% 5.91 (0.78, 45.02) 2015 Grandesso 2018-NIR 4 221 1 221 0.3% 4.00 (0.68, 1.17) 2019 Subtotal (95% CI) 3667 3174 100.0% 0.95 (0.84, 1.07) Total events 398 376 Heterogeneity, Tau ² = 0.00; Ch ² = 8.73, df = 10 (P = 0.56); P = 0% Test for overall effect Z = 0.88 (P = 0.38) 1.20.3 Abdominal pain 2009-UGA 19 211 36 210 16.3% 0.53 (0.31, 0.89) 2007 Karrya-2007-UGA 19 211 0.21 1.221 1.0% 0.44 (0.22, 0.89) 2007 Karrya-2007-UGA 19 211 36 210 16.3% 0.53 (0.31, 0.89) 2007 Karrya-2008-UGA 17 7 74 24 6 31 6.3% 0.53 (0.31, 0.89) 2007 Karrya-2008-UGA 17 77 42 46 31 6.3% 0.53 (0.31, 0.89) 2007 Karrya-2019-UGA 19 221 1 221 1.0% 0.33 (0.01, 6.1, 12) 2019 Nij-2015-CAM 13 280 5 138 7.8% 1.28 (0.47, 3.52) 2015 Grandesso 2018-NIR 0 221 1 221 1.0% 0.33 (0.01, 6.1, 12) 2019 Nij-2015-CAM 13 280 5 138 7.8% 1.28 (0.47, 3.52) 2015 Grandesso 2018-NIR 0 221 1 221 1.0% 0.33 (0.01, 6.1, 12) 2019 Jubtotal (95% CI) 1445 125 71.2% 0.92 (0.65, 1.29) 2019 Jubtotal (95% CI) 1445 1267 100.0% 0.80 (0.57, 1.11] Total events 138 162 Heterogeneity, Tau ² = 0.11; Ch ² = 1.4.94, df = 7 (P = 0.04); P = 53% Test for overall effect Z = 1.33 (P = 0.18) Fe.4. For exception and bit decordorum to the set meterometer for treatment for the correlation of decordorum to the set meterometer for the set meterometer and the decordorum to the set meterometer for the set meterometer to the set meterometer for the set meterometer to the set	Subtotal (95% CI)		4877		3912	100.0%	1.02 [0.87, 1.19]	2010	•
Heterogeneity: Tau ² = 0.01; Ch ² = 1.4.96, df = 12 (P = 0.24); P = 20% Test for verail effect: $Z = 0.24$ (P = 0.81) 1.20.2 Anorexia Zongo-2007-BNF 8 187 6 188 1.4% 1.34 (0.47, 3.79) 2007 Mens-2008-UGA 47 213 49 198 12.4% 0.89 (0.33, 1.21) 2008 Yeka-2008-UGA 47 213 49 198 12.4% 0.89 (0.33, 1.21) 2008 Atmaitive 2009-UGA 3 351 0 220 0.2% 6.38 (0.33, 1.22, 11) 2009 Atmaitive 2009-UGA 3 351 0 20 0.2% 6.38 (0.33, 1.22, 11) 2009 Atmaitive 2009-UGA 3 351 0 220 0.2% 6.38 (0.33, 1.22, 11) 2009 Atmaitive 2009-UGA 14 199 8 10.2 .2% 0.88 (0.38, 2.03) 2011 Namboz-2011-ZAM 14 199 8 100 2.2% 0.88 (0.38, 2.03) 2011 Nik-2015-CAM 12 280 1 138 0.4% 5.351 (0.78, 45.02) 2015 Yeka-2019-UGA 76 299 85 300 21.6% 0.90 (0.69, 1.17) 2019 Subtotal (95% Ch) 3667 3174 100.0% 0.45 (0.53, 2.00) 2018 Yeka-2019-UGA 76 299 85 300 21.6% 0.90 (0.69, 1.17) 2019 Subtotal (95% Ch) 3667 3174 100.0% 0.55 (0.31, 0.89) 2007 Heterogeneity: Tau ² = 0.00; Ch ² = 8.73, df = 10 (P = 0.56); P = 0% Test for verail effect Z = 0.38 (P = 0.38) 1.20.3 Abdominal pain Zongo-2007-UGA 19 211 36 210 16.3% 0.54 (0.51, 02) 2008 Yeka-2019-UGA 77 42 46 33 16.3% 0.66 (0.56, 1.02) 2008 Yeka-2018-UGA 17 74 24 63 16.3% 0.66 (0.56, 1.02) 2018 Yeka-2019-UGA 17 74 24 63 16.3% 0.66 (0.56, 1.02) 2018 Yeka-2019-UGA 17 74 24 63 16.3% 0.66 (0.56, 1.02) 2018 Yeka-2019-UGA 17 74 24 63 16.3% 0.66 (0.56, 1.02) 2018 Yeka-2019-UGA 17 74 24 63 16.3% 0.66 (0.56, 1.02) 2018 Yeka-2019-UGA 17 74 24 63 16.3% 0.66 (0.56, 1.20) 2008 Yeka-2019-UGA 11 24 152 71 221 1.0% 0.33 (0.01, 8.14) 2018 Jubital (95% Ch) 1445 122 71 221 1.0% 0.33 (0.61, 0.21) 2008 Yeka-2019-UGA 11 24 45 125 27.1% 0.92 (0.65, 1.21) 2019 Jubital (95% Ch) 1445 122 77 10.0% 0.08 (0.57, 1.11] Total events 138 162 Heterogeneity: Tau ² = 0.11; Ch ² = 1.494, df = 7 (P = 0.04); P = 53% Test for overall effect Z = 1.33 (P = 0.18) Fe.4. Forest plot of compartison: dibuterotrantisoin: propertisoin de transmoterotrantisoin: propertisoin de transmoterot unecoroliterum de transmoterotranting transm	Total events	467		391					
Test for overall effect Z = 0.24 (P = 0.81) 1.20.2 Anorexia Zongo-2007-BNF 8 187 6 188 1.4% 1.34 (0.47, 3.79) 2007 Kamya-2007-UGA 90 211 91 210 31.3% 0.98 (0.78, 1.23) 2007 Yeka-2008-UGA 47 213 49 198 12.4% 0.89 (0.63, 1.21) 2008 Arinaltwe-2009-UGA 3 351 0 320 0.2% 6.38 (0.33, 1.21) 2008 Arinaltwe-2009-UGA 3 351 0 320 0.2% 6.38 (0.33, 1.21) 2008 Arinaltwe-2009-UGA 47 213 49 198 12.4% 0.89 (0.63, 1.27) 2008 Arinaltwe-2009-UGA 47 213 49 198 12.4% 0.89 (0.63, 1.27) 2008 Arinaltwe-2009-UGA 47 213 49 198 100 2.2% 0.88 (0.38, 2.03) 2011 Nambozi-2011-ZAM 14 199 8 100 2.2% 0.88 (0.38, 2.03) 2011 Kakuru-2014-UGA 6 165 4 2011 1.0% 1.83 (0.52, 0.37) 2014 Nij:2015-CAM 12 280 1 138 0.4% 5.91 (0.78, 45.02) 2015 Grandesso-2018-NIR 4 221 1 221 0.3% 4.00 (0.45, 35.50) 2018 Yeka-2019-UGA 76 299 85 300 21.6% 0.90 (0.68, 1.17) 2019 Zongo-2007-NDF 10 112 21 104 12.3% 0.44 (0.22, 0.89) 2007 Heterogeneity: Tau ² = 0.00; Chi ² = 8.73, df = 10 (P = 0.56); P = 0% Test for overall effect Z = 0.88 (P = 0.38) 1.20.3 Abdominal pain Zongo-2007-NDF 10 112 21 104 12.3% 0.44 (0.22, 0.89) 2007 Mens-2008-KEN 25 73 26 73 18.4% 0.96 (0.62, 1.50) 2008 Veka-2008-UGA 17 74 4 63 16.3% 0.66 (0.63, 61, 0.2] 2008 Nij-2015-CAM 13 280 5 138 7.8% 1.28 (0.47, 3.52) 2015 Grandesso-2018-NIR 0 221 1 221 1.0% 0.33 (0.01, 8.14) 2018 Jubtotal (95K CI) 1445 125 71.0% 0.30 (0.05, 1.12] 2008 Jubtotal (95K CI) 1445 1287 100.0% 0.80 [0.57, 1.11] Garanas-2021-BNF 13 360 4 363 6.7% 3.28 (1.08, 9.55) 2021 Jubtotal (95K CI) 1445 1287 100.0% 0.80 [0.57, 1.11] Total events 138 162 Heterogeneity: Tau ² = 0.11; Chi ² = 1.43.4f, df = 7 (P = 0.04); P = 53% Test for overall effect Z = 1.33 (P = 0.18) Fe. 4. Ensure plot of comparison dibudgratemision-piperpanilor were attempthetel medianting for treatment de more medianted for encomplex attemption. Fe. 4. Ensure plot of comparison dibudgratemision-piperpanilor were attemptioned medianted for encomplex attemption. Fe. 5. Toronalt were the different disconced attemption.	Heterogeneity: Tau ² = 0.01	Chi ² = 1	14.96 r	if = 12 (P	$= 0.24^{\circ}$	n: I≧ = 20%	5		
1.20.2 Anorexia Zongo-2007-BNF 8 187 6 188 1.4% 1.34 [0.47, 3.79] 2007 Mens-2008-VEN 8 73 10 73 2.0% 0.89 [0.63, 1.27] 2008 Mens-2008-VEN 8 73 10 73 2.0% 0.89 [0.63, 1.27] 2008 Arnalive-2008-VEA 8 73 10 73 2.0% 0.89 [0.63, 1.27] 2008 Arnalive-2009-VGA 3 351 0 320 2.2% 0.88 [0.38, 2.03] 2011 Nambozi-2011-ZAM 14 199 8 100 2.2% 0.88 [0.52, 0.37] 2014 Nik-2015-CAM 12 280 1 138 0.4% 5.91 [0.78, 45.02] 2015 Grandesso-2018-NIR 4 221 1 210 0.3% 4.00 [0.68, 1.17] 2019 Subtotal (95% CI) 3667 3174 100.0% 0.95 [0.84, 1.07] 2019 4 Cango-2007-BNF 10 112 21 10.4 12.3% 0.60 [0.69, 1.17] 2019 4 Veka-2	Test for overall effect: Z = I	124 (P =	0.81)		0.21		·		
1.20.2 Anorexia Zongo-2007-RNF 8 187 6 188 1.4% 1.34 (0.47, 3.79) 2007 Kamya-2007-UGA 90 211 91 210 31.3% 0.98 (0.79, 1.23) 2007 Wens-2008-KEN 8 73 10 73 2.0% 0.89 (0.63, 1.27) 2008 Arinative-2009-UGA 47 213 49 198 12.4% 0.89 (0.63, 1.27) 2008 Arinative-2009-UGA 3 351 0 320 0.2% 6.38 (0.33, 1.21) 2008 Arinative-2009-UGA 6 10 11 125 7.3% 0.90 (0.71, 1.13) 2011 Nambozi-2011-ZAM 14 199 8 100 2.2% 0.88 (0.38, 2.03) 2011 Kakur-2014-UGA 6 165 4 201 1.0% 4.00 (0.78, 4.50.2) 2015 Grandesso-2018-NIR 4 221 1 21 0.3% 0.40 (0.22, 0.89) 2007 Kamya-2007-UGA 19 211 10 10.3% 0.45 (0.3, 10.81) 2019 0.44 (0.22, 0.89) 20			0.017						
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	1.20.2 Anorexia								
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Zongo-2007-BNF	8	187	6	188	1.4%	1.34 [0.47, 3.79]	2007	
Mens-2008-KEN 8 73 10 73 2.0% 0.80 [0.33, 1.91] 2008 Yeka-2008-UGA 47 213 49 198 12.4% 0.89 [0.33, 1.21] 2009 Arinaltwe-2009-UGA 3 351 0 320 0.2% 6.38 [0.33, 123.1] 2009 Arinaltwe-2009-UGA 3 351 0 320 0.2% 6.38 [0.33, 123.1] 2009 Arinaltwe-2019-UGA 6 165 4 201 1.0% 1.83 [0.52, 6.37] 2011 Nambozi-2011-ZAM 14 199 8 100 2.4% 0.88 [0.38, 2.03] 2011 Kakuru-2014-UGA 6 165 4 201 1.0% 1.83 [0.52, 6.37] 2014 Miceoscold 76 299 85 300 21.6% 0.90 [0.68, 1.17] 2019 Total events 398 376 10 112 21 10.4% 0.53 [0.31, 0.89] 2007 Karrya-2007-UGA 19 211 36 210 16.3% 0.53 [0.31, 0.89] 2007 Karrya-2007-UGA 17<	Kamva-2007-UGA	90	211	91	210	31.3%	0.98 [0.79, 1.23]	2007	+
Yeka-2008-UGA 47 213 49 198 12.4% 0.89 0.63, 1.27 2008 Arinaltwe-2009-UGA 3 351 0 320 0.2% 6.38 0.33, 123, 112 2009 AABC-2011-AFR 130 1468 121 122.5 0.90 0.71, 1.13 2011 Nambozi-2011-ZAM 14 199 8 100 2.2% 0.98 0.38, 2.03 2011 Kakuru-2014-UGA 6 165 4 201 1.0% 1.83 0.52, 6.37 2014 Nij-2015-CAM 12 220 1 138 0.4% 531 1078, 45.02 2015 Grandesso-2018-NIR 4 221 1 221 0.3% 0.09 0.69, 1.171 2019 Subtotal (95% CI) 3667 3174 100.0% 0.95 [0.84, 1.07] 101 10 12 11 0.44 0.22, 0.99] 2007 Kamya-2007-UGA 19 211 36 16.3% 0.53 [0.31, 0.89] 2007 Veka-2018-UGA 17 74 24 63	Mens-2008-KEN	8	73	10	73	2.0%	0.80 (0.33, 1.91)	2008	
Arinaliwe 2009-UGA 3 351 0 320 0.2% 6.38 [0.33, 123.11] 2009 ABC-2011-AFR 130 1468 121 1225 27.3% 0.90 [0.71, 1.13] 2011 Nambozi-2011-ZAM 14 199 8 100 2.2% 0.88 [0.38, 2.03] 2011 Kakuru-2014-UGA 6 165 4 201 1.0% 1.83 [0.52, 6.37] 2014 Mij-2015-CAM 12 280 1 138 0.4% 5.91 [0.78, 45.02] 2015 Grandesso-2019-NIR 4 221 1 221 0.3% 4.00 [0.45, 35.50] 2018 Veka-2019-UGA 76 299 85 300 21.6% 0.90 [0.69, 1.17] 2019 Subtotal (95% C1) 3667 3174 100.0% 0.95 [0.84, 1.07] Total events 398 376 Heterogeneity: Tau ² = 0.08 (P = 0.38) 1.20.3 Abdominal pain Zongo-2007-ENF 10 112 21 104 12.3% 0.44 [0.22, 0.89] 2007 Karrya-2007-UGA 19 211 36 210 16.3% 0.53 [0.31, 0.89] 2007 Yeka-2008-KEN 25 73 26 73 18.4% 0.96 [0.62, 1.50] 2008 Yeka-2008-KEN 13 280 5 138 7.8% 1.28 [0.47, 3.52] 2015 Grandesso-2018-NIR 0 221 1 221 1.0% 0.33 [0.01, 8.14] 2018 Veka-2018-UGA 11 24 45 125 21.2% 0.92 [0.65, 1.29] 2019 Gansane-2021-BINF 13 350 4 353 6.7% 3.28 [1.08, 9.95] 2021 Jotal events 138 162 Heterogeneity: Tau ² = 0.11; Ch ² = 1.49, df = 7 (P = 0.04); P = 53% Test for overall effect: Z = 1.33 (P = 0.18) Fig. 4. Exprest plot of comparison: dihydroartemision-piperaguine versus attemethed-interpediation for treatment of uncompletated <i>Basendum</i> m	Yeka-2008-UGA	47	213	49	198	12.4%	0.89 [0.63, 1.27]	2008	
ABC-2011-AFR 130 1468 121 1225 27.3% 0.90 [0.71, 1.13 2011 Nambozi-2011-ZAM 14 199 8 100 2.2% 0.88 [0.38, 2.03] 2011 Kakuru-2014-UGA 6 165 4 201 1.0% 1.83 [0.52, 6.37] 2014 Mil-2015-CAM 12 280 1 138 0.4% 5.91 [0.78, 45.02] 2015 Grandesso-2018-NIR 4 221 1 221 0.3% 4.00 [0.45, 35.50] 2018 Yeka-2019-UGA 76 299 85 300 21.6% 0.90 [0.69, 1.17] 2019 Subtotal (95% CI) 3667 3174 100.0% 0.95 [0.84, 1.07] Total events 398 376 Heterogeneity: Tau ² = 0.00; Chi ² = 8.73, df = 10 (P = 0.56); P = 0% Test for overall effect Z = 0.88 (P = 0.38) 1.20.3 Abdominal pain Zongo-2007-UGA 19 211 36 210 16.3% 0.53 [0.31, 0.89] 2007 Mens-2008-KEN 25 73 26 73 18.4% 0.96 [0.62, 1.50] 2008 Nji-2015-CAM 13 280 5 138 7.8% 1.28 [0.47, 3.52] 2015 Grandesso-2018-NIR 0 221 1 221 1.0% 0.33 [0.01, 8.14] 2018 Yeka-2019-UGA 41 124 45 125 21.2% 0.92 [0.65, 1.29] 2007 Mens-2028-UGA 41 124 45 126 21.2% 0.92 [0.65, 1.29] 2019 Mij-2015-CAM 13 280 5 138 7.8% 1.28 [0.47, 3.52] 2015 Grandesso-2018-NIR 0 221 1 221 1.0% 0.33 [0.01, 8.14] 2018 Yeka-2019-UGA 41 124 45 126 21.2% 0.92 [0.65, 1.29] 2021 Subtotal (95% CI) 1445 1287 100.0% 0.80 [0.57, 1.11] Total events 138 162 Heterogeneity: Tau ² = 0.11; Chi ² = 1.494, df = 7 (P = 0.04); P = 53% Test for overall effect: Z = 1.33 (P = 0.18) Fig. 4. Exprest plot of comparison: dihydroartemision-piperanulus evenus attemethed-lumefantrine for treatment of uncomplexed <i>Beamedium</i>	Arinaitwe-2009-UGA	3	351	0	320	0.2%	6.38 (0.33, 123, 11)	2009	→
Nambozi-2011-ZAM 14 199 8 100 2.2% 0.88 [0.38, 2.03, 2011 Kakuru-2014-UGA 6 165 4 201 1.0% 1.83 [0.52, 6.37] 2014 Nij-2015-CAM 12 280 1 138 0.4% 5.91 [0.78, 45.02] 2015 Grandesso-2018-NIR 4 221 1 221 0.3% 4.00 [0.45, 35.50] 2018 Yeka-2019-UGA 76 299 85 300 21.6% 0.90 [0.68, 1.17] 2019 Subtotal (95% CI) 3667 3174 100.0% 0.95 [0.84, 1.07] Total events 398 376 Heterogeneity. Tau ² = 0.00; Chi ² = 8.73, df = 10 (P = 0.56); P = 0% Test for overall effect: $Z = 0.88$ (P = 0.38) 1.20. Abdominal pain Zongo-2007-BNF 10 112 21 104 12.3% 0.44 [0.22, 0.89] 2007 Mens-2008-KEN 25 73 26 73 18.4% 0.96 [0.62, 1.50] 2008 Yeka-2019-UGA 17 74 24 63 16.3% 0.60 [0.36, 1.02] 2008 Nji-2015-CAM 13 280 5 138 7.8% 1.28 [0.47, 352] 2015 Grandesso-2018-NIR 0 221 1 221 1.0% 0.33 [10.18, 14] 2018 Yeka-2019-UGA 41 124 45 125 21.2% 0.92 [0.56, 1.29] 2019 Gansane-2021-BNF 13 350 4 353 6.7% 3.28 [1.08, 9.95] 2021 Ueka-2019-UGA 41 124 45 1267 100.0% 0.80 [0.57, 1.11] Total events 138 162 Heterogeneity. Tau ² = 0.11; Chi ² = 14.94, df = 7 (P = 0.04); P = 53% Test for overall effect: $Z = 1.33$ (P = 0.18) Fig. 4. Expect plot of comparison: dihydroartemisipin-piperanuing versus attempethel/umefacturine for treatment of uncompolicated Plotsmood um	4ABC-2011-AFR	130	1468	121	1225	27.3%	0.90 (0.71, 1.13)	2011	+
Kakuru 2014 - UGA 6 165 4 201 1.0% 1.83 [0.52, 6.37] 2014 Nji-2015-CAM 12 280 1 138 0.4% 5.91 [0.78, 45.02] 2015 Grandesso-2018-NIR 4 221 1 221 0.3% 4.00 [0.45, 35.50] 2018 Yeka-2019-UGA 76 299 85 300 21.6% 0.90 [0.69, 1.17] 2019 Subtotal (95% CI) 3667 3174 100.0% 0.95 [0.84, 1.07] 101 10.73 10.95 [0.84, 1.07] Total events 398 376 112 21 10.4 12.3% 0.44 [0.22, 0.89] 2007 Kamya-2007-UGA 18 211 36 210 16.3% 0.53 [0.31, 0.89] 2007 Mes-2008-UGA 17 74 24 63 16.3% 0.60 [0.36, 1.02] 2008 Yeka-2008-UGA 17 74 24 63 6.7% 3.28 [1.08, 9.5] 2011 Grandesso-2018-NIR 0 221 1 211 0.0% 0.38 [0.57, 1.11] 0.1 0.1 1.0	Namhozi-2011-7AM	14	199		100	2.2%	0.88 (0.38, 2.03)	2011	
NJi-2015-CAM 12 280 1 138 0.4% 5.91 [0.78, 45.02] 2015 Grandesso-2018-NIR 4 221 1 221 0.3% 4.00 [0.45, 35.50] 2018 Yeka-2019-UGA 76 299 85 300 21.6% 0.90 [0.89, 1.17] 2019 Subtotal (95% CI) 3667 3174 100.0% 0.95 [0.84, 1.07] 101 Total events 398 376	Kakuru-2014-UGA	6	165	4	201	1.0%	1.83 [0.52, 6.37]	2014	
Grandesso-2018-NIR 4 221 1 221 0.3% 4.00 [0.45, 35.50] 2018 Yeka-2019-UGA 76 299 85 300 21.6% 0.90 [0.69, 1.17] 2019 Subtotal (95% CI) 3667 3174 100.0% 0.95 [0.84, 1.07] Total events 398 376 Heterogeneity: Tau ² = 0.00; Chi ² = 8.73, df = 10 (P = 0.56); P = 0% Test for overall effect: Z = 0.88 (P = 0.38) 1.20.3 Abdominal pain Zongo-2007-UGA 19 211 36 210 16.3% 0.44 [0.22, 0.89] 2007 Kamya-2007-UGA 19 211 36 210 16.3% 0.53 [0.31, 0.89] 2007 Mens-2008-UEN 25 73 26 73 18.4% 0.96 [0.62, 1.50] 2008 Veka-2008-UGA 17 74 24 63 16.3% 0.60 [0.36, 1.02] 2008 Nji-2015-CAM 13 280 5 138 7.8% 1.28 [0.47, 3.52] 2015 Grandesso-2018-NIR 0 221 1 221 1.0% 0.33 [0.01, 8.14] 2018 Veka-2019-UGA 41 124 45 125 21.2% 0.92 [0.65, 1.29] 2019 Gansane-2021-BINF 13 350 4 353 6.7% 3.28 [1.08, 9.95] 2021 Subtotal (95% CI) 1445 1287 100.0% 0.80 [0.57, 1.11] Total events 138 162 Heterogeneity: Tau ² = 0.11; Chi ² = 14.94, df = 7 (P = 0.04); P = 53% Test for overall effect: Z = 1.33 (P = 0.18) Fig. 4. Expect plot of comparison: dihydroartemision-piperaguine versus attemether-themefantrine for treatment of uncomplicated Placemodium	Nii-2015-CAM	12	280	1	138	0.4%	5.91 (0.78, 45.02)	2015	
Yeka-2019-UGA 76 299 85 300 21.6% 0.90 0.68, 1.17 2019 Subtotal (95% CI) 3667 3174 100.0% 0.95 [0.84, 1.07] 2019 Total events 398 376 Heterogeneity: Tau ² = 0.00; Chi ² = 8.73, df = 10 (P = 0.56); I ² = 0% Test for overall effect: Z = 0.88 (P = 0.38) 1.20.3 Abdominal pain Zongo-2007-BNF 10 112 21 104 12.3% 0.44 (0.22, 0.89) 2007 Kamya-2007-UGA 19 211 36 210 16.3% 0.53 (0.31, 0.89) 2007 Mens-2008-UGA 17 74 24 63 16.3% 0.96 (0.62, 1.50) 2008 Nii-2015-CAM 13 280 5 138 7.8% 1.28 (0.47, 3.52) 2015 Grandesso-2018-NIR 0 221 1 221 0.92 (0.65, 1.29) 2019 Gasane-2021-BINF 13 350 4 355 6.7% 3.28 [1.08, 9.95] 2021 Subtotal (95% CI) 1445 1287 10.0% 0.80 [0.57, 1.11] 10	Grandesso-2018-NIR	4	221	1	221	0.3%	4.00 (0.45, 35,50)	2018	
Subtotal (95% Cl) 3667 3174 100.0% 0.95 [0.84, 1.07] Total events 398 376 Heterogeneity: Tau ² = 0.00; Chi ² = 8.73, df = 10 (P = 0.56); I ² = 0% Test for overall effect: Z = 0.88 (P = 0.38) 1.20.3 Abdominal pain Zongo-2007-BNF 10 112 21 104 12.3% 0.44 [0.22, 0.89] 2007 Karnya-2007-UGA 19 211 36 210 16.3% 0.53 [0.31, 0.89] 2007 Mens-2008-KEN 25 73 26 73 18.4% 0.96 [0.62, 1.50] 2008 Yeka-2008-UGA 17 74 24 63 16.3% 0.60 [0.36, 1.02] 2008 Nij-2015-CAM 13 280 5 138 7.8% 1.28 [0.47, 3.52] 2015 Grandesso-2018-NIR 0 221 1.22% 0.92 [0.65, 1.29] 2019	Yeka-2019-UGA	76	299	85	300	21.6%	0.90 [0.69, 1.17]	2019	
Total events 398 376 Heterogeneity: Tau ² = 0.00; Chi ² = 8.73, df = 10 (P = 0.56); I ² = 0% Test for overall effect: Z = 0.88 (P = 0.38) 1.20.3 Abdominal pain Zongo-2007-BNF 10 112 21 104 12.3% 0.44 [0.22, 0.89] 2007 Kamya-2007-UGA 19 211 36 210 16.3% 0.53 [0.31, 0.89] 2007 Mens-2008-KEN 25 73 26 73 18.4% 0.96 [0.62, 1.50] 2008 Yeka-2008-UGA 17 74 24 63 16.3% 0.60 [0.36, 1.02] 2008 Yeka-2019-UGA 13 280 5 138 7.8% 1.28 [0.47, 3.52] 2015 Grandesso-2018-NIR 0 221 1 221 1.0% 0.33 [0.01, 8.14] 2018 Yeka-2019-UGA 41 124 45 125 21.2% 0.92 [0.65, 1.29] 2019 Gansane-2021-BNF 13 350 4 353 6.7% 3.28 [1.08, 9.95] 2021 Subtotal (95% Cl) 1445 1287 100.0% 0.80 [0.57, 1.11]	Subtotal (95% CI)		3667		3174	100.0%	0.95 [0.84, 1.07]		•
Heterogeneity: Tau ² = 0.00; Ch ² = 8.73, df = 10 (P = 0.56); P = 0% Test for overall effect: $Z = 0.88$ (P = 0.38) 1.20.3 Abdominal pain Zongo-2007-BNF 10 112 21 104 12.3% 0.44 [0.22, 0.89] 2007 Karnya-2007-UGA 19 211 36 210 16.3% 0.53 [0.31, 0.89] 2007 Mens-2008-KEN 25 73 26 73 18.4% 0.96 [0.62, 1.50] 2008 Yeka-2008-UGA 17 74 24 63 16.3% 0.60 [0.36, 1.02] 2008 Yeka-2008-UGA 17 74 24 63 16.3% 0.60 [0.36, 1.02] 2008 Yeka-2019-UGA 13 280 5 138 7.8% 1.28 [0.47, 3.52] 2015 Grandesso-2018-NIR 0 221 1 221 1.0% 0.33 [0.01, 8.14] 2018 Yeka-2019-UGA 41 124 45 125 21.2% 0.92 [0.65, 1.29] 2019 Gansane-2021-BNF 13 350 4 353 6.7% 3.28 [1.08, 9.95] 2021 Subtotal (95% Cl) 1445 1287 100.0% 0.80 [0.57, 1.11] Total events 138 162 Heterogeneity: Tau ² = 0.11; Chi ² = 14.94, df = 7 (P = 0.04); I ² = 53% Test for overall effect: Z = 1.33 (P = 0.18) Fig. 4. Forest plot of comparison: dihydroartemisipin-piperaguine versus artemether-lumefantme for treatment of uncomplicated <i>Plasmachum</i>	Total events	398		376					
Test for overall effect: $Z = 0.88$ (P = 0.38) 1.20.3 Abdominal pain Zongo-2007-BNF 10 112 21 104 12.3% 0.44 [0.22, 0.89] 2007 Kamya-2007-UGA 19 211 36 210 16.3% 0.53 [0.31, 0.89] 2007 Mens-2008-KEN 25 73 26 73 18.4% 0.96 [0.62, 1.50] 2008 Yeka-2008-UGA 17 74 24 63 16.3% 0.60 [0.36, 1.02] 2008 Nji-2015-CAM 13 280 5 138 7.8% 1.28 [0.47, 3.52] 2015 Grandesso-2018-NIR 0 221 1 221 1.0% 0.33 [0.01, 8.14] 2018 Yeka-2019-UGA 41 124 45 125 21.2% 0.92 [0.65, 1.29] 2019 Gansane-2021-BNF 13 350 4 353 6.7% 3.28 [1.08, 9.95] 2021 Subtoal (95% CI) 1445 1287 100.0% 0.80 [0.57, 1.11] Total events 138 162 Heterogeneity: Tau ² = 0.11; Chi ² = 14.94, df = 7 (P = 0.04); P = 53% Test for overall effect: $Z = 1.33$ (P = 0.18) Fig. 4. Eprest plot of comparison: dihydroartemisipin-piperaguine versus artemether-lumefantrine for treatment of uncomplicated Plasmadium	Heterogeneity: Tau ² = 0.00); Chi ² = 8	3.73, df	= 10 (P =	= 0.56);	I² = 0%			
1.20.3 Abdominal pain Zongo-2007-BNF 10 112 21 104 12.3% 0.44 [0.22, 0.89] 2007 Kamya-2007-UGA 19 211 36 210 16.3% 0.53 [0.31, 0.89] 2007 Mens-2008-KEN 25 73 26 73 18.4% 0.96 [0.62, 1.50] 2008 Yeka-2008-UGA 17 74 24 63 16.3% 0.60 [0.36, 1.02] 2008 Nji-2015-CAM 13 280 5 138 7.8% 1.28 [0.47, 3.52] 2015 Grandesso-2018-NIR 0 221 1 221 1.0% 0.33 [0.01, 8.14] 2018 Yeka-2019-UGA 41 124 45 125 21.2% 0.92 [0.65, 1.29] 2019 Gansane-2021-BNF 13 350 4 353 6.7% 3.28 [1.08, 9.95] 2021 Subtotal (95% CI) 1445 1287 100.0% 0.80 [0.57, 1.11] 0.1 10 100 Fast for overall effect: Z = 1.33 (P = 0.18) 162 162 162 162 162 162 162	Test for overall effect: Z = I).88 (P =	0.38)						
1.20.3 Abdominal pain Zongo-2007-BNF 10 112 21 104 12.3% 0.44 [0.22, 0.89] 2007 Kamya-2007-UGA 19 211 36 210 16.3% 0.53 [0.31, 0.89] 2007 Mens-2008-KEN 25 73 26 73 18.4% 0.96 [0.62, 1.50] 2008 Yeka-2008-UGA 17 74 24 63 16.3% 0.60 [0.36, 1.02] 2008 Nji-2015-CAM 13 280 5 138 7.8% 1.28 [0.47, 3.52] 2015 Grandesso-2018-NIR 0 221 1 221 1.0% 0.33 [0.01, 8.14] 2018 Yeka-2019-UGA 41 124 45 125 21.2% 0.92 [0.65, 1.29] 2019 Gansane-2021-BNF 13 350 4 353 6.7% 3.28 [1.08, 9.95] 2021 Subtotal (95% CI) 1445 1287 100.0% 0.80 [0.57, 1.11] 0.1 10 100 Favours [DHA-PQ] Favours [AL] 100 100 100 100 100 Favours [AL] Favours									
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	1.20.3 Abdominal pain								
Kamya-2007-UGA 19 211 36 210 16.3% 0.53 [0.31, 0.89] 2007 Mens-2008-KEN 25 73 26 73 18.4% 0.96 [0.62, 1.50] 2008 Yeka-2008-UGA 17 74 24 63 16.3% 0.60 [0.36, 1.02] 2008 Nij-2015-CAM 13 280 5 138 7.8% 1.28 [0.47, 3.52] 2015 Grandesso-2018-NIR 0 221 1 221 1.0% 0.33 [0.01, 8.14] 2018 Yeka-2019-UGA 41 124 45 125 21.2% 0.92 [0.65, 1.29] 2019 Gansane-2021-BNF 13 350 4 353 6.7% 3.28 [1.08, 9.95] 2021 Subtotal (95% Cl) 1445 1287 100.0% 0.80 [0.57, 1.11] 0.80 [0.57, 1.11] 0.1 10 100 Fig. 4 Eorest plot of comparison: dihydroartemisipin-piperaguine versus artemether-lumefantrine for treatment of uncomplicated Plasmodium	Zongo-2007-BNF	10	112	21	104	12.3%	0.44 [0.22, 0.89]	2007	_ _
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Kamya-2007-UGA	19	211	36	210	16.3%	0.53 [0.31, 0.89]	2007	
Yeka-2008-UGA 17 74 24 63 16.3% 0.60 [0.36, 1.02] 2008 Nji-2015-CAM 13 280 5 138 7.8% 1.28 [0.47, 3.52] 2015 Grandesso-2018-NIR 0 221 1 221 1.0% 0.33 [0.01, 8.14] 2018 Yeka-2019-UGA 41 124 45 125 21.2% 0.92 [0.65, 1.29] 2019 Gansane-2021-BNF 13 350 4 353 6.7% 3.28 [1.08, 9.95] 2021 Subtotal (95% CI) 1445 1287 100.0% 0.80 [0.57, 1.11] 0 0.80 [0.57, 1.11] Total events 138 162 1445 128 53% 162 1445 10 100 Heterogeneity: Tau ² = 0.11; Chi ² = 14.94, df = 7 (P = 0.04); l ² = 53% Test for overall effect: Z = 1.33 (P = 0.18) 100 Favours [DHA-PQ] Favours [AL]	Mens-2008-KEN	25	73	26	73	18.4%	0.96 [0.62, 1.50]	2008	+
Nji-2015-CAM 13 280 5 138 7.8% 1.28 0.47 , 3.52 2015 Grandesso-2018-NIR 0 221 1 221 1.0% 0.33 0.01 , 8.14 2018 Yeka-2019-UGA 41 124 45 125 21.2% 0.92 0.65 , 1.29 2019 Gansane-2021-BNF 13 350 4 353 6.7% 3.28 10.8 , 9.95 2021 Subtotal (95% CI) 1445 1287 100.0% 0.80 $[0.57, 1.11]$ 0.80 $[0.57, 1.11]$ Total events 138 162 0.40 0.80 $[0.57, 1.11]$ 0.80 0.01 0.1 10 100 Fig. 4. Forest plot of comparison: dihydroartemisinin-piperaguine versus artemether-lumefantrine for treatment of uncomplicated Plasmodium	Yeka-2008-UGA	17	74	24	63	16.3%	0.60 [0.36, 1.02]	2008	
Grandesso-2018-NIR 0 221 1 221 1.0% 0.33 [0.01, 8.14] 2018 Yeka-2019-UGA 41 124 45 125 21.2% 0.92 [0.65, 1.29] 2019 Gansane-2021-BNF 13 350 4 353 6.7% 3.28 [1.08, 9.95] 2021 Subtotal (95% Cl) 1445 1287 100.0% 0.80 [0.57, 1.11] 0.80 [0.57, 1.11] Total events 138 162 1494, df = 7 (P = 0.04); I ² = 53% 0.80 [0.57, 1.11] 0.80 [0.57, 1.11] Test for overall effect: Z = 1.33 (P = 0.18) 100 100 100 Favours [DHA-PQ] Favours [AL]	Nji-2015-CAM	13	280	5	138	7.8%	1.28 [0.47, 3.52]	2015	
Yeka-2019-UGA 41 124 45 125 21.2% 0.92 [0.65, 1.29] 2019 Gansane-2021-BNF 13 350 4 353 6.7% 3.28 [1.08, 9.95] 2021 Subtotal (95% Cl) 1445 1287 100.0% 0.80 [0.57, 1.11] 10 100 Total events 138 162 1287 100.0% 0.80 [0.57, 1.11] 10 100 Total events 138 162 1287 100.0% 0.80 [0.57, 1.11] 10 100 Test for overall effect: Z = 1.33 (P = 0.18) 1287 100.0% 100 Favours [DHA-PQ] Favours [AL]	Grandesso-2018-NIR	0	221	1	221	1.0%	0.33 [0.01, 8.14]	2018	
Gansane-2021-BNF 13 350 4 353 6.7% 3.28 [1.08, 9.95] 2021 Subtotal (95% Cl) 1445 1287 100.0% 0.80 [0.57, 1.11] 10 100 Total events 138 162 162 162 162 162 100 100 100 100 100 100 100 100 100 100 100 100 100 Favours [DHA-PQ] Favours [AL] 100 <td>Yeka-2019-UGA</td> <td>41</td> <td>124</td> <td>45</td> <td>125</td> <td>21.2%</td> <td>0.92 [0.65, 1.29]</td> <td>2019</td> <td>-</td>	Yeka-2019-UGA	41	124	45	125	21.2%	0.92 [0.65, 1.29]	2019	-
Subtotal (95% CI) 1445 1287 100.0% 0.80 [0.57, 1.11] Total events 138 162 Heterogeneity: Tau ² = 0.11; Chi ² = 14.94, df = 7 (P = 0.04); l ² = 53% Test for overall effect: Z = 1.33 (P = 0.18) 100 Fig. 4. Forest plot of comparison: dihydroartemisinin-piperaguine versus artemether-lumefantrine for treatment of uncomplicated <i>Plasmodium</i>	Gansane-2021-BNF	13	350	4	353	6.7%	3.28 [1.08, 9.95]	2021	
Total events 138 162 Heterogeneity: Tau ² = 0.11; Chi ² = 14.94, df = 7 (P = 0.04); l ² = 53% Test for overall effect: $Z = 1.33$ (P = 0.18) 100 Fig. 4. Forest plot of comparison: dihydroartemisinin-piperaguine versus artemether-lumefantrine for treatment of uncomplicated <i>Plasmodium</i>	Subtotal (95% CI)		1445		1287	100.0%	0.80 [0.57, 1.11]		•
Heterogeneity: Tau ² = 0.11; Chi ² = 14.94, df = 7 (P = 0.04); l ² = 53% Test for overall effect: $Z = 1.33$ (P = 0.18) 0.01 0.1 1 10 $100Favours [DHA-PQ] Favours [AL]Fig. 4. Forest plot of comparison: dihydroartemisinin-piperaguine versus artemether-lumefantrine for treatment of uncomplicated Plasmodium$	Total events	138		162					
Test for overall effect: Z = 1.33 (P = 0.18) 0.01 0.1 1 10 Fig. 4. Forest plot of comparison: dihydroartemisinin-piperaguine versus artemether-lumefantrine for treatment of uncomplicated Plasmodium	Heterogeneity: Tau ² = 0.11	; Chi ² = 1	14.94, 0	if = 7 (P =	: 0.04);	l² = 53%			
Fig. 4 Forest plot of comparison: dihydroartemisinin-piperaguine versus artemether-lumefantrine for treatment of uncomplicated <i>Plasmodium</i>	Test for overall effect: Z = 1	1.33 (P =	0.18)						
Fig. 4 Forest plot of comparison: dihydroartemisinin-piperaguine versus artemether-lumefantrine for treatment of uncomplicated <i>Plasmodium</i>									
U.U.U.U.I.I.I.U.100 Favours [DHA-PQ] Favours [AL] Fig. 4 Forest plot of comparison: dihydroartemisinin-piperaguine versus artemether-lumefantrine for treatment of uncomplicated <i>Plasmodium</i>									
Fig. 4 Forest plot of comparison: dihydroartemisinin-piperaguine versus artemether-lumefantrine for treatment of uncomplicated <i>Plasmodium</i>									Eavours (DHA-PO) Eavours (AL)
	Fig. 4 Forest plot of comp	arison [,] di	hvdroa	rtemisini	in-nine	raquines	ersus artemether-lume	fantrin	e for treatment of uncomplicated Plasmodium

falciparum malaria among children in Africa, outcome: Gastrointestinal adverse events

	DHA-	PQ	AL	2		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% Cl
1.22.1 Cough								
Zongo-2007-BNF	49	187	52	188	2.2%	0.95 [0.68, 1.32]	2007	-
Kamya-2007-UGA	136	211	133	210	12.0%	1.02 [0.88, 1.17]	2007	+
Yeka-2008-UGA	164	213	150	198	21.3%	1.02 [0.91, 1.13]	2008	+
Mens-2008-KEN	16	73	17	73	0.7%	0.94 [0.52, 1.72]	2008	
Arinaitwe-2009-UGA	177	351	153	320	10.4%	1.05 [0.90, 1.23]	2009	+
4ABC-2011-AFR	470	1468	387	1225	20.0%	1.01 [0.91, 1.13]	2011	†
Nambozi-2011-ZAM	42	199	15	100	0.9%	1.41 [0.82, 2.41]	2011	
Kakuru-2014-UGA	64	165	74	201	3.6%	1.05 [0.81, 1.37]	2014	+
Ogutu-2014-KEN	40	231	37	238	1.5%	1.11 [0.74, 1.68]	2014	
Nji-2015-CAM	18	280	9	138	0.4%	0.99 [0.45, 2.14]	2015	
Grandesso-2018-NIR	36	221	22	221	1.0%	1.64 [1.00, 2.69]	2018	
Yeka-2019-UGA	233	299	203	300	25.4%	1.15 [1.04, 1.27]	2019	•
Gansane-2021-BNF	17	350	21	353	0.6%	0.82 [0.44, 1.52]	2021	
Subtotal (95% CI)		4248		3765	100.0%	1.06 [1.01, 1.11]		
Total events	1462		1273					
Heterogeneity: Tau ² = 0.	.00; Chi² =	9.62, 0	df = 12 (P	= 0.65); I² = 0%			
Test for overall effect: Z :	= 2.28 (P	= 0.02)						
1.22.2 Anemia								
4ABC-2011-AFR	141	1468	38	1225	55.3%	3.10 [2.18, 4.39]	2011	-
Ogutu-2014-KEN	8	231	10	238	44.7%	0.82 [0.33, 2.05]	2014	B
Subtotal (95% CI)		1699		1463	100.0%	1.71 [0.47, 6.23]		
Total events	149		48					
Heterogeneity: Tau ² = 0.	75; Chi ² =	7.06, 0	df = 1 (P =	= 0.008); I ^z = 869	6		
Test for overall effect: Z	= 0.82 (P	= 0.41)						
1.22.3 Corvza								
Kamva-2007-UGA	127	211	121	210	32.6%	1.04 [0.89, 1.23]	2007	+
Yeka-2008-UGA	159	213	150	198	67.4%	0.99 [0.88, 1.10]	2008	
Subtotal (95% CI)		424		408	100.0%	1.00 [0.92, 1.10]		T
Total events	286		271					
Heterogeneity: Tau ² = 0.	00: Chi ² =	0.37.	df = 1 (P =	= 0.54);	l ² = 0%			
Test for overall effect: Z:	= 0.09 (P	= 0.93)		2.2.1/1				
		,						
							F	
							0.0	J1 U.1 1 10 100
Fin F. Frank alat (a altheory					Favours (DHA-PQ) Favours (AL)
Plasmodium falciparum m	iparison b ialaria am	etweel ong ch	ildren in	Africa d	smin-pip on cardio	-respiratory adverse eve	er-iurnetan ents	unne for treatment of uncomplicated



treatment groups. However, the distributions of serious adverse events were not significantly different in the two treatment groups (RR 1.27, 95% CI 0.83 to 1.96; participants=9558; studies=14; $I^2=0\%$, *high quality of evidence*, Fig. 9). Eight deaths were reported from two multicenter trials, and the cause of death for seven of them was sepsis, severe malaria, and severe diarrhoea. But, the causal relationship of the study drug and death of one participant didn't rule out. All serious adverse events were likely a consequence of malaria and judged to be unrelated to study medications.

Publication bias The funnel plot showed that all studies lay symmetrically around the pooled effect estimate implying that there was no publication bias (P=0.50, Additional file 6).

Quality of the evidence

The quality of the evidence in this review assessed using the GRADE approach and presented the evidence in three summary of findings tables for safety (Summary of findings for the main comparison; Additional file 7). The quality of evidence on comparative adverse effects and serious adverse events; early vomiting, diarrhoea, and cough were slightly more frequent in the DHA-PQ arm (*high quality of evidence*). Generally, the quality of evidence of safety of the two treatments was high quality.

Discussion

In this study both drugs were well tolerated by children. There were comparable occurrences of adverse events in both treatment arms. But, early vomiting, diarrhoea, and cough were common were significantly more frequent in



patients who were treated with the DHA-PQ than that of AL (*high quality of evidence*). All serious adverse events were not related to study medications. Eight deaths have occurred in all studies. But, all serious adverse events were consistent with malaria symptoms and judged to be unrelated to study medication.

As also seen in one study from Papua New Guinea, the overall frequency of adverse events were slightly higher in DHA-PQ treatment arm than that of AL [48]. However, cough was more frequent in patients who were treated with AL, but headache and runny nose were common in DHA-PQ treatment group [48]. A recent review on the efficacy and safety of the two ACT's also reported that cough, anorexia, diarrhoea, and vomiting were the most common adverse events. In this review more patients from DHA-PQ treatment arm had cough than that of AL [49] and similarly, gastrointestinal adverse events were more frequent in patients who were treated with DHA-PQ in another study done in South East Asia and Africa [50–53]. Studies from the Thailand-Myanmar border [54, 55] and elsewhere in Africa [56–58] have reported that DHA-PQ cause drug induced electrocardiographic QT prolongation, but a recent study also reported that the QT prolongation caused by piperaquine is not associated with an increased risk of sudden death [59]. In breastfeeding infants DHA–PQ has previously been linked to an increased risk of vomiting [60]. The mechanism accountable for the increased risk of early vomiting among breastfeeding participants treated with DHA– PQ is not known.

However, the temporal relationship suggests that the susceptibility of gastric mucosa of breastfed infants could be related to the pro-emetic effect of piperaquine than that in weaned infants [60]. To determine whether the co-administered milk may also affect this interaction further assessment might be needed [60]. However, the absence of effect with AL implies that the mechanism is given to DHA–PQ, most likely piperaquine



[17]. Regardless of the treatment groups, most of these adverse events are associated with age (\leq 18 years), efavirenz-based ART [52], efavirenz-based ART [53], and administration of DHA-PQ with food could increase piperaquine exposure and it needs to be administered in fasting state [53, 54, 61].

Most of the RCTs reported AEs rather than adverse reactions of the antimalarial drugs. This made it difficult to determine the causal relationship between the antimalarial drugs and the AEs. It was, therefore, difficult to determine whether an adverse event is symptomatic of the disease or drug related. In some other studies, safety reporting was either selective or inadequate, with some authors failing to indicate the severity of AEs. Some of these limitations have been identified in studies evaluating the quality of safety reporting in RCTs.

Conclusion

From this review, it can be concluded that early vomiting, diarrhoea, and cough were common were significantly more frequent in patients who were treated with the DHA-PQ than that of AL, and both drugs are well tolerated. More studies comparing AL with DHA-PQ are needed to determine the comparative safety of these drugs.

	DHA-I	PQ	AL			Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
Kamya-2007-UGA	4	211	2	210	6.5%	1.99 [0.37, 10.75]	2007	
Mens-2008-KEN	1	73	0	73	1.8%	3.00 [0.12, 72.45]	2008	
Yeka-2008-UGA	5	215	2	199	7.0%	2.31 [0.45, 11.79]	2008	
Arinaitwe-2009-UGA	3	351	1	320	3.6%	2.74 [0.29, 26.16]	2009	
Bassat-2009-AFR	18	1038	5	510	19.1%	1.77 [0.66, 4.74]	2009	
4ABC-2011-AFR	10	1468	6	1225	18.2%	1.39 [0.51, 3.82]	2011	
Borrmann-2011-KEN	3	233	1	241	3.6%	3.10 (0.33, 29.62)	2011	
Nambozi-2011-ZAM	4	199	3	100	8.5%	0.67 [0.15, 2.94]	2011	
Agarwal-2013-KEN	1	137	2	137	3.3%	0.50 [0.05, 5.45]	2013	
Onyamboko 2014 DRC	2	228	4	228	6.5%	0.50 [0.09, 2.70]	2014	
Nji-2015-CAM	0	280	1	138	1.8%	0.16 [0.01, 4.02]	2015	<
Grandesso-2018-NIR	2	221	1	221	3.2%	2.00 [0.18, 21.90]	2018	
Yeka-2019-UGA	6	299	6	300	14.8%	1.00 [0.33, 3.08]	2019	_
Gansane-2021-BNF	0	350	1	353	1.8%	0.34 [0.01, 8.22]	2021	
Total (95% CI)		5303		4255	100.0%	1.27 [0.83, 1.96]		•
Total events	59		35					
Heterogeneity: Tau ² = 0.01	0; Chi² = 1	7.60, df	= 13 (P =	= 0.87);	l² = 0%			
Test for overall effect: Z =	1.09 (P =	0.28)	,	//				U.U1 U.1 1 1U 100 Favours [DHA-PQ] Favours [AL]

Fig. 9 Forest plot of comparison between dihydroartemisinin-piperaquine and artemether-lumefantrine for treatment of uncomplicated *Plasmodium falciparum* malaria among children in Africa on serious adverse event (including death)

Abbreviations

AE: Adverse event; ACT: Artemisinin-based combination therapy; AL: Artemether-lumefantrine; ART: Antiretroviral therapy; BW: Body weight; CEN-TRAL: Cochrane Central Register of Controlled Trials; CI: Confidence interval; DHA-PQ: Dihydroartemisinin-piperaquine; GADE: Grading of recommendations assessment development and evaluations; PICO: Population intervention comparison and outcome; PRISMA: Preferred reporting items for systematic reviews and meta-analyses; RCTs: Randomized control trials; RR: Risk ratio; WHO: World Health Organization.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12936-021-04032-2.

Additional file 1. Detailed search strategy.

Additional file 2. Characteristics of excluded studies.

Additional file 3. Funnel plot of comparison: dihydroartemisinin-piperaquine versus artemether-lumefantrine for treatment of uncomplicated *Plasmodium falciparum* malaria among African children, outcome: Gastrointestinal adverse events (early vomiting).

Additional file 4. Funnel plot of comparison: dihydroartemisinin-piperaquine versus artemether-lumefantrine for treatment of uncomplicated *Plasmodium falciparum* malaria among African children, outcome: Gastrointestinal adverse events (diarrhoea). Additional file 5. Funnel plot of comparison: dihydroartemisinin-piperaquine versus artemether-lumefantrine for treatment of uncomplicated *Plasmodium falciparum* malaria among African children, outcome: Cough.

Additional file 6. Funnel plot of comparison: dihydroartemisinin-piperaquine versus artemether-lumefantrine for treatment of uncomplicated *Plasmodium falciparum* malaria among African children, outcome: Serious adverse event (including death).

Additional file 7. GRADE summary of findings table on adverse events and serious adverse events.

Acknowledgements

We would like to express our gratitude to the Center for Innovative Drug Development and Therapeutic Trials for Africa (CDT-Africa), College of Health Sciences, Addis Ababa University, for funding the study.

Authors' contributions

DGA developed the protocol as used in [7]. For this review, DGA reviewed the reference list, extracted data, and entered it into Review Manager (Rev-Man 5.4.1). DGA, EDZ, WM, NM, AS, AM, AFB, and EB conducted the analyses, constructed summary of findings tables, and evaluated the quality of evidence using the GRADE approach. EM and GY were responsible for the quality assessment and review of the study. All authors reviewed and edited the manuscript.

Funding

This review was funded by Center for Innovative Drugs and Therapeutic Trial for Africa (CDT-Africa), Addis Ababa University.

Availability of data and materials

All relevant data are within the manuscript and its supporting information files.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication

Not applicable.

Competing interests

We declare that they have no competing interests.

Author details

¹Center for Innovative Drug Development and Therapeutic Trials for Africa (CDT-Africa), College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia. ²School of Public Health, College of Health Science and Medicine, Dilla University, Dilla, Ethiopia. ³Department of Midwifery, College of Health Science, Bule Hora University, Bule Hora, Ethiopia. ⁴Department of Midwifery, College of Health Science and Medicine, Dilla University, Dilla, Ethiopia. ⁵Department of Psychiatry, College of Health Science and Medicine, Dilla University, Dilla, Ethiopia. ⁶Department of Nursing, College of Health Science and Medicine, Dilla University, Dilla, Ethiopia. ⁷Department of Pharmacology and Clinical Pharmacy, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia.

Received: 28 August 2021 Accepted: 18 December 2021 Published online: 04 January 2022

References

- WHO . World Malaria Report 2019. Geneva: World Health Organization; 2019.
- 2. WHO. Guidelines for treatment of malaria. 3rd ed. Geneva: World Health Organization; 2015.
- World malaria report 2020: 20 years of global progress and challenges. Geneva: World Health Organization; 2020.
- Bretscher MT, Griffin JT, Hugo P, Baker M, Ghani A, Okell L. A comparison of the duration of post-treatment protection of artemether-lumefantrine, dihydroartemisinin-piperaquine and artesunate-amodiaquine for the treatment of uncomplicated malaria. Malar J. 2014;13:19.
- Sinclair D, Zani B, Donegan S, Olliaro P, Garner P. Artemisinin-based combination therapy for treating uncomplicated malaria. Cochrane Database Syst Rev. 2009;2009:CD007483.
- WHO. World Malaria Report 2014. Geneva: World Health Organization; 2014.
- Zani B, Gathu M, Donegan S, Olliaro PL, Sinclair D. Dihydroartemisininpiperaquine for treating uncomplicated *Plasmodium falciparum* malaria. Cochrane Database Syst Rev. 2014;2014:CD010927.
- Fairhurst RM, Dondorp AM. Artemisinin-resistant *Plasmodium falcipa*rum malaria. Microbiol Spectr. 2016;4(10):1128.
- Plucinski MM, Dimbu PR, Macaia AP, Ferreira CM, Samutondo C, Quivinja J, et al. Efficacy of artemether–lumefantrine, artesunate– amodiaquine, and dihydroartemisinin–piperaquine for treatment of uncomplicated *Plasmodium falciparum* malaria in Angola, 2015. Malar J. 2017;16:62.
- Davlantes E, Dimbu PR, Ferreira CM, Florinda Joao M, Pode D, Félix J, et al. Efficacy and safety of artemether–lumefantrine, artesunate–amodiaquine, and dihydroartemisinin–piperaquine for the treatment of uncomplicated *Plasmodium falciparum* malaria in three provinces in Angola, 2017. Malar J. 2018;17:144.
- 11. World Health Organization. World Malaria Report 2017. Geneva: World Health Organization; 2017.
- Ministry of Health, Uganda. Uganda Clinical Guidelines. National Guidelines for Management of Common Conditions. Kampala: Ministry of Health; 2016. p. 195–9.

- Makanga M, Bassat Q, Falade CO, Premji ZG, Krudsood S, Hunt P, et al. Efficacy and Safety of artemether-lumefantrine in the treatment of acute, uncomplicated *Plasmodium falciparum* malaria: a pooled analysis. Am J Trop Med Hyg. 2011;85:793–804.
- Ebstie YA, Zeynudin A, Belachew T, Desalegn Z, Suleman S. Assessment of therapeutic efficacy and safety of artemether-lumefantrine (Coartem[®]) in the treatment of uncomplicated *Plasmodium falciparum* malaria patients in Bahir Dar district, Northwest Ethiopia: an observational cohort study. Malar J. 2015;14:236.
- Falade C, Manyando C. Safety profile of Coartem[®]: the evidence base. Malar J. 2009;8:S6.
- European Medicines Agency. Eurartesim (dihydroartemisinin/piperaquine) 20 mg/160 mg and 40 mg/320 mg film-coated tablets: EU summary of product characteristics [online]. 2017.
- Assefa DG, Yismaw G, Makonnen E. Efficacy of dihydroartemisininpiperaquine versus artemether-lumefantrine for the treatment of uncomplicated *Plasmodium falciparum* malaria among children in Africa: a systematic review and meta-analysis of randomized control trials. Malar J. 2021;20:340.
- Assefa DG, Yismaw G, Makonnen E. Comparative effect of dihydroartemisinin-piperaquine and artemether-lumefantrine on gametocyte clearance and haemoglobin recovery in children with uncomplicated *Plasmodium falciparum* malaria in Africa: a systematic review and metaanalysis of randomized control trials. Int J Infect Dis. 2021;113:136–47.
- Assefa DG, Zeleke ED, Molla W, Mengistu N, Sefa A, Mebratu A, et al. Systematic review and meta-analysis of the efficacy and safety of Dihydroartemisinin Piperaquine versus Artemether-Lumefantrine for the treatment of uncomplicated falciparum malaria in African children. PROSPERO. 2020. https://www.crd.york.ac.uk/prospero/display_record. php?ID=CRD42020200337.
- Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
- 21. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions, 2011. www.cochrane-handbook.org.
- 22. WHO. Methods for surveillance of antimalarial drug efficacy. Geneva: World Health Organization; 2009.
- 23. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). 2021. www.training.cochrane.org/handbook.
- 24. Deeks JJ, Higgins JPT, Altman DG. Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., Eds. Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). 2021. www.training. cochrane.org/handbook.
- Lin L, Chu H. Quantifying publication bias in meta-analysis. Biometrics. 2018;74:785–94.
- 26. McMaster University GRADEproGDT. McMasterUniversity (developed by Evidence Prime), 2020. https://gradepro.org/.
- Schünemann, Brożek, Guyatt, Oxman. Introduction to GRADE Handbook (Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach), 2013. https://gradepro.org.
- Higgins JPT, SavovicJ, PageMJ, ElbersRG, Sterne JAC. Chapter 8: Assessing risk of bias in a randomized trial. Cochrane Handbook for Systematic Reviews ofInterventions version 6.0 (updated July 2019). 2019. www.train ing.cochrane.org/handbook.
- 29 Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence–imprecision. J Clin Epidemiol. 2011;64:1283–93.
- Kamya MR, Yeka A, Bukirwa H, Lugemwa M, Rwakimari JB, Staedke SG, et al. Artemether-lumefantrine versus dihydroartemisinin-piperaquine for treatment of malaria: a randomized trial. PLoS Clin Trials. 2007;2:e20.
- 31. Zongo I, Dorsey G, Rouamba N, Dokomajilar C, Sere Y, Rosenthal PJ, et al. Randomized comparison of amodiaquine plus sulfadoxine-pyrimethamine, artemether-lumefantrine, and dihydroartemisinin-piperaquine for the treatment of uncomplicated *Plasmodium falciparum* malaria in Burkina Faso. Clin Infect Dis. 2007;45:1453–61.
- 32. Mens PF, Sawa P, van Amsterdam SM, Versteeg I, Omar SA, Schallig HD, et al. A randomized trial to monitor the efficacy and effectiveness by QT-NASBA of artemether-lumefantrine versus

dihydroartemisinin-piperaquine for treatment and transmission control of uncomplicated *Plasmodium falciparum* malaria in western Kenya. Malar J. 2008;7:237.

- Yeka A, Dorsey G, Kamya MR, Talisuna A, Lugemwa M, Rwakimari JB, et al. Artemether-lumefantrine versus dihydroartemisinin-piperaquine for treating uncomplicated malaria: a randomized trial to guide policy in Uganda. PLoS ONE. 2008;3:e2390.
- 34 Bassat Q, Mulenga M, Tinto H, Piola P, Borrmann S, Menendez C, et al. Dihydroartemisinin-piperaquine and artemether-lumefantrine for treating uncomplicated malaria in African children. A randomised, non-inferiority trial. PLoS ONE. 2009;4:e7871.
- Arinaitwe E, Sandison TG, Wanzira H, Kakuru A, Homsy J, Kalamya J, et al. Artemether-lumefantrine versus dihydroartemisinin-piperaquine for falciparum malaria: a longitudinal, randomized trial in young Ugandan children. Clin Infect Dis. 2009;49:1629–37.
- Borrmann S, Sasi P, Mwai L, Bashraheil M, Abdallah A, Muriithi S, et al. Declining responsiveness of *Plasmodium falciparum* infections to artemisinin-based combination treatments on the Kenyan coast. PLoS ONE. 2011;6:e26005.
- Nambozi M, Van Geertruyden JP, Hachizovu S, Chaponda M, Mukwamataba D, Mulenga M, et al. Safety and efficacy of dihydroartemisinin-piperaquine versus artemether-lumefantrine in the treatment of uncomplicated *Plasmodium falciparum* malaria in Zambian children. Malar J. 2011;10:50.
- Four Artemisinin-Based Combinations Study Group. A head-to-head comparison of four artemisinin-based combinations for treating uncomplicated malaria in African children: a randomized trial. PLoS Med. 2011;8:e1001119.
- Agarwal A, McMorrow M, Onyango P, Otieno K, Odero C, Williamson J, et al. A randomized trial of artemether-lumefantrine and dihydroartemisininpiperaquine in the treatment of uncomplicated malaria among children in western Kenya. Malar J. 2013;12:254.
- 40. Ogutu BR, Onyango KO, Koskei N, Omondi EK, Ongecha JM, Otieno GA, et al. Efficacy and safety of artemether-lumefantrine and dihydroartemisininpiperaquine 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. Malar J. 2014;13:33.
- 41. Onyamboko MA, Fanello CJ, Wongsaen K, Tarning J, Cheah PY, Tshefu KA, et al. Randomized comparison of the efficacies and tolerabilities of three artemisinin-based combination treatments for children with acute *Plasmodium falciparum* malaria in the Democratic Republic of the Congo. Antimicrob Agents Chemother. 2014;58:5528–36.
- Kakuru A, Achan J, Muhindo MK, Ikilezi G, Arinaitwe E, Mwangwa F, et al. Artemisinin-based combination therapies are efficacious and safe for treatment of uncomplicated malaria in HIV-infected Ugandan children. Clin Infect Dis. 2014;59:446–53.
- 43. Nji AM, Ali IM, Moyeh MN, Ngongang EO, Ekollo AM, Chedjou JP, et al. Randomized non-inferiority and safety trial of dihydroartemisin-piperaquine and artesunate-amodiaquine versus artemether-lumefantrine in the treatment of uncomplicated *Plasmodium falciparum* malaria in Cameroonian children. Malar J. 2015;14:27.
- Ursing J, Rombo L, Rodrigues A, Kofoed PE. Artemether-lumefantrine versus dihydroartemisinin-piperaquine for treatment of uncomplicated *Plasmodium falciparum* malaria in children aged less than 15 years in Guinea-Bissau - an open-label non-inferiority randomised clinical trial. PLoS ONE. 2016;11:e0161495.
- 45. Grandesso F, Guindo O, WoiMesse L, Makarimi R, Traore A, Dama S, et al. Efficacy of artesunate-amodiaquine, dihydroartemisinin-piperaquine and artemether-lumefantrine for the treatment of uncomplicated *Plasmodium falciparum* malaria in Maradi. Niger Malar J. 2018;17:52.
- Yeka A, Wallender E, Mulebeke R, Kibuuka A, Kigozi R, Bosco A, et al. Comparative efficacy of artemether-lumefantrine and dihydroartemisinin-piperaquine for the treatment of uncomplicated malaria in Ugandan children. J Infect Dis. 2019;219:1112–20.
- 47. Gansané A, Moriarty LF, Ménard D, Yerbanga I, Ouedraogo E, Sondo P, et al. Anti-malarial efficacy and resistance monitoring of artemetherlumefantrine and dihydroartemisinin-piperaquine shows inadequate efficacy in children in Burkina Faso, 2017–2018. Malar J. 2021;20:48.
- Tavul L, Hetzel MW, Teliki A, Walsh D, Kiniboro B, Rare L, et al. Efficacy of artemether–lumefantrine and dihydroartemisinin–piperaquine for the treatment of uncomplicated malaria in Papua New Guinea. Malar J. 2018;17:350.
- Assefa DG, Zeleke ED, Bekele D, Tesfahunei HA, Getachew E, Joseph M, et al. Efficacy and safety of dihydroartemisinin–piperaquine versus

artemether–lumefantrine for treatment of uncomplicated *Plasmodium falciparum* malaria in Ugandan children: a systematic review and metaanalysis of randomized control trials. Malar J. 2021;20:174.

- Myint HY, Ashley EA, Day NP, Nosten F, White NJ. Efficacy and safety of dihydroartemisinin-piperaquine. Trans R Soc Trop Med Hyg. 2007;101:858–66.
- Kakolwa MA, Mahende MK, Ishengoma DS, Mandara CI, Ngasala B, Kamugisha E, et al. Efficacy and safety of artemisinin-based combination therapy, and molecular markers for artemisinin and piperaquine resistance in Mainland Tanzania. Malar J. 2018;17:369.
- Creek D, Bigira V, Arinaitwe E, Wanzira H, Kakuru A, Tappero J, et al. Increased risk of early vomiting among infants and young children treated with dihydroartemisinin-piperaquine compared with artemether-lumefantrine for uncomplicated malaria. Am J Trop Med Hyg. 2010;83:873–5.
- 53. Yavo W, Faye B, Kuete T, Djohan V, Oga SA, Kassi RR, et al. Multicentric assessment of the efficacy and tolerability of dihydroartemisinin-piperaquine compared to artemether-lumefantrine in the treatment of uncomplicated *Plasmodium falciparum* malaria in sub-Saharan Africa. Malar J. 2011;10:198.
- 54. Saito M, Yotyingaphiram W, Cargill Z, Gilder ME, Min AM, Phyo AP, et al. Electrocardiographic effects of four antimalarials for pregnant women with uncomplicated malaria on the Thailand-Myanmar border: a randomised controlled trial. Antimicrob Agents Chemother. 2021;65:e02473-e2520.
- Manning J, Vanachayangkul P, Lon C, Spring M, So M, Sea D, et al. Randomized, double-blind, placebo-controlled clinical trial of a two-day regimen of dihydroartemisinin-piperaquine for malaria prevention halted for concern over prolonged corrected QT interval. Antimicrob Agents Chemother. 2014;58:6056–67.
- Oduro AR, Owusu-Agyei S, Gyapong M, Osei I, Adjei A, Yawson A, et al. Postlicensure safety evaluation of dihydroartemisinin piperaquine in the three major ecological zones across Ghana. PLoS ONE. 2017;12:e0174503.
- Kabanywanyi AM, Baiden R, Ali AM, Mahende MK, Ogutu BR, Oduro A, et al. Multi-country evaluation of safety of dihydroartemisinin/piperaquine post-licensure in African public hospitals with electrocardiograms. PLoS ONE. 2016;11:e0164851.
- Mhamilawa LE, Wikström S, Mmbando BP, Ngasala B, Mårtensson A. Electrocardiographic safety evaluation of extended artemether-lumefantrine treatment in patients with uncomplicated *Plasmodium falciparum* malaria in Bagamoyo District. Tanzania Malar J. 2020;19:250.
- Chan XHS, Win YN, Mawer LJ, Tan JY, Brugada J, White NJ. Risk of sudden unexplained death after use of dihydroartemisinin–piperaquine for malaria: a systematic review and Bayesian meta-analysis. Lancet Infect Dis. 2018;18:913–23.
- 60. Sevene E, Banda CG, Mukaka M, Maculuve S, Macuacua S, Vala A, et al. Efficacy and safety of dihydroartemisinin–piperaquine for treatment of *Plasmodium falciparum* uncomplicated malaria in adult patients on antiretroviral therapy in Malawi and Mozambique: an open label nonrandomized interventional trial. Malar J. 2019;8:277.
- Funck-Brentano C, Bacchieri A, Valentini G, Pace S, Tommasini S, Voiriot P, et al. Effects of dihydroartemisinin-piperaquine phosphate and artemether-lumefantrine on QTc interval prolongation. Sci Rep. 2019;9:777.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

