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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

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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% CI 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; $I^2 = 0\%$, 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.

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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 artemisinin-based 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 ≥ 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

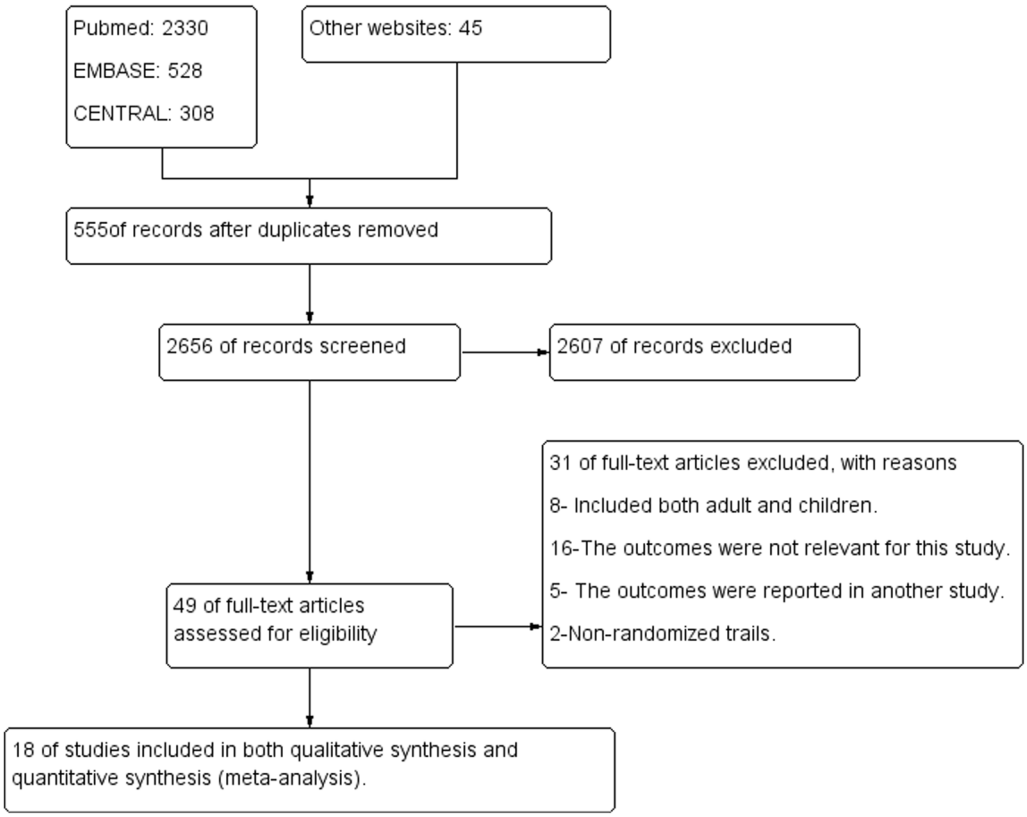

Fig. 1 PRISMA study flow diagram of the study

each analysis, the Chi^2 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

Table 1 Characteristics of included studies

S. No	Study ID	Study design	Study setting and period	Transmission	Follow up	Subjects			Patient important outcome	DHA-PQ	AL
						Number of participants		Inclusion age			
						DHA-PQ	AL				
1	Kamya-2007-UGA [30]	Single-blind, RCT	Rural health center, March,2006-July, 2006	High transmission	42 days	253	256	6 months–10 years	Vomiting	65	65
									Diarrhoea	25	19
									Anorexia	90	91
									Abdominal pain	19	20
									weakness/ malaise	85	103
									Cough	136	133
									Coryza	127	121
									Pruritus	14	22
									SAE	4	2
2	Zongo-2007-BNF [31]	Single blind RCT	Government health dispensaries, August 2006-January 2007	High transmission	42 days	196	197	6 months–10 years	Early vomiting	7	3
									Vomiting	20	27
									Diarrhoea	14	13
									Anorexia	8	6
									Abdominal pain	10	21
									Cough	49	52
									Weakness/ Malaise	5	3
									Pruritus	5	11
									Headache	11	22
3	Mens-2008-KEN [32]	Open label RCT	Health center, Apr 2007 to Jul 2007	High transmission	28 days	73	73	6 months–12 years	Headache	43	39

Table 1 (continued)

S. No	Study ID	Study design	Study setting and period	Transmission	Follow up	Subjects			Patient important outcome	DHA-PQ	AL
						Number of participants		Inclusion age			
						DHA-PQ	AL				
									Abdominal pain	25	26
									Weakness	19	30
									Anorexia	8	10
									Diarrhoea	9	7
									Cough	16	17
									Vomiting	11	9
									Pruritus	4	3
									SAE	1	0
4	Yeka-2008-UGA [33]	Single-blind, RCT	Health center, August 2006-April 2007	N/A	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	3
									SAE	5	2
5	Bassat-2009-AFR [34]	Open-label, RCT	Four rural sites and one peri-urban site, August 2005 and July 2006.		Mesoendemic	1038	510	6–59 months	Early vomiting	22	4

Table 1 (continued)

S. No	Study ID	Study design	Study setting and period	Transmission	Follow up	Subjects			Patient important outcome	DHA-PQ	AL
						Number of participants		Inclusion age			
						DHA-PQ	AL				
									Vomiting	71	35
									Splenomegaly	41	19
									Hepatomegaly	6	3
									5 Prolonged QTc interval (Fridericia's correction)	2	1
									Electrocardiogram QT prolonged	26	13
									Urticarial	1	2
									Hypersensitivity	2	1
									Neutropenia	18	12
									Alanine aminotransferase increased	20	19
									Electrocardiogram QT prolonged	26	13
									SAE	18	5
6	Arinaitwe-2009-UGA [35]	Open-label RCT	Local antenatal clinics in Tororo, August 2007-July 2008	High transmission	63 days	119	111	6 weeks–12 months	Vomiting	23	20
									Diarrhoea	79	86
									Anorexia	3	0
									Weakness	1	0
									Cough	177	153
									Pruritus	0	0
									SAE	3	1

Table 1 (continued)

S. No	Study ID	Study design	Study setting and period	Transmission	Follow up	Subjects			Patient important outcome	DHA-PQ	AL
						Number of participants		Inclusion age			
						DHA-PQ	AL				
7	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	7	4
8	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	14	8
									Cough	42	15
									Diarrhoea	14	4
									Fever	24	14
									Respiratory tract Infection	22	9
									Vomiting	5	4
									SAE	4	3
9	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	1	3

Table 1 (continued)

S. No	Study ID	Study design	Study setting and period	Transmission	Follow up	Subjects			Patient important outcome	DHA-PQ	AL
						Number of participants		Inclusion age			
						DHA-PQ	AL				
									Hepatomegaly	5	8
									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	3	4
									ALAT above normal range at day 28	4	1
									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	6
10	Agarwal -2013-KEN [39]	An open label RCT	District hospital, October 2010 to August 2011	High transmission	42 days	137	137	6–59 months	Early vomiting	7	5

Table 1 (continued)

S. No	Study ID	Study design	Study setting and period	Transmission	Follow up	Subjects			Patient important outcome	DHA-PQ	AL
						Number of participants		Inclusion age			
						DHA-PQ	AL				
									SAE	1	2
11	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	8	10
									Fever	14	7
									Tinea capitis	12	10
									Rhinitis	13	4
									Gastroenteritis	5	9
									Loss of appetite	6	3
									Otitis media	5	7
12	Onyamboko-2014-DRC [41]	Open label, RCT	Urban district of Kinshasa (DRC) (Hospitals), September 2011 and November 2012	Intense and perennial	42 days	228	228	3–59 months	Early vomiting	21	5
									Vomiting	17	2
173	Kakuru-2014-UGA [42]	Not described, RCT	District Hospital, August 2007 and April 2008	High transmission	28 days	21	22	6 weeks -12 months	Vomiting	8	18
									Diarrhoea	27	23
									Anorexia	6	4
									Weakness/malaise	2	2
									Cough	64	74
14	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	5

Table 1 (continued)

S. No	Study ID	Study design	Study setting and period	Transmission	Follow up	Subjects			Patient important outcome	DHA-PQ	AL
						Number of participants		Inclusion age			
						DHA-PQ	AL				
									Anorexia	12	1
									Diarrhoea	9	4
									Vomiting	27	8
									Fatigue	4	3
									Fever	3	2
									Cough	18	9
									Joint pain	2	2
									Rash	16	4
									SAE	0	1
15	Ursing-2016-GUB [44]	Open-label, RCT	Bandimand Belem Health Centers, November 2012 and July 2015	Low to high transmission	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 September 2014	Not reported	42 days	221	221	6–59 months	Early vomiting	1	0

Table 1 (continued)

S. No	Study ID	Study design	Study setting and period	Transmission	Follow up	Subjects			Patient important outcome	DHA-PQ	AL
						Number of participants		Inclusion age			
						DHA-PQ	AL				
									Fever	94	94
									Cough	36	22
									Rhinorrhea	27	17
									Diarrhoea	14	15
									Conjunctivitis	7	15
									Pyoderma	6	6
									Vomiting	6	5
									Anorexia	4	1
									Abdominal pain	0	1
									Hepatomegaly	1	0
									Splenomegaly	2	1
									Another AE	40	45
									SAE	2	1
									Early vomiting	1	2
17	Yeka-2019-UGA [46]	Single-blind RCT	Health center and Hospital, October 2015-December, 2016	High transmission	42 days	299	300	6–59 months	Vomiting	56	61
									Diarrhoea	155	114
									Anorexia	12	3

Table 1 (continued)

S. No	Study ID	Study design	Study setting and period	Transmission	Follow up	Subjects			Patient important outcome	DHA-PQ	AL			
						Number of participants		Inclusion age						
						DHA-PQ	AL							
									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	6	6
									Skin rash	56	42			
									Pruritus	24	16			
									SAE	6	6			
18	Gansane-2021-BNF [47]	Open label, RCT	Primary health facility and district hospital, November 2017 to September 2018	Moderate to high transmission	42 days	360		360	6–59 months	Itchiness	0	1		
										Otitis media	0	1		
										Cough	17	21		
										Abdominal pain	13	4	Vomiting	33	54
										Skin rash	3	2	SAE	0	1
										Furunculosis	1	0			
										Vomiting	33	54			
										SAE	0	1			

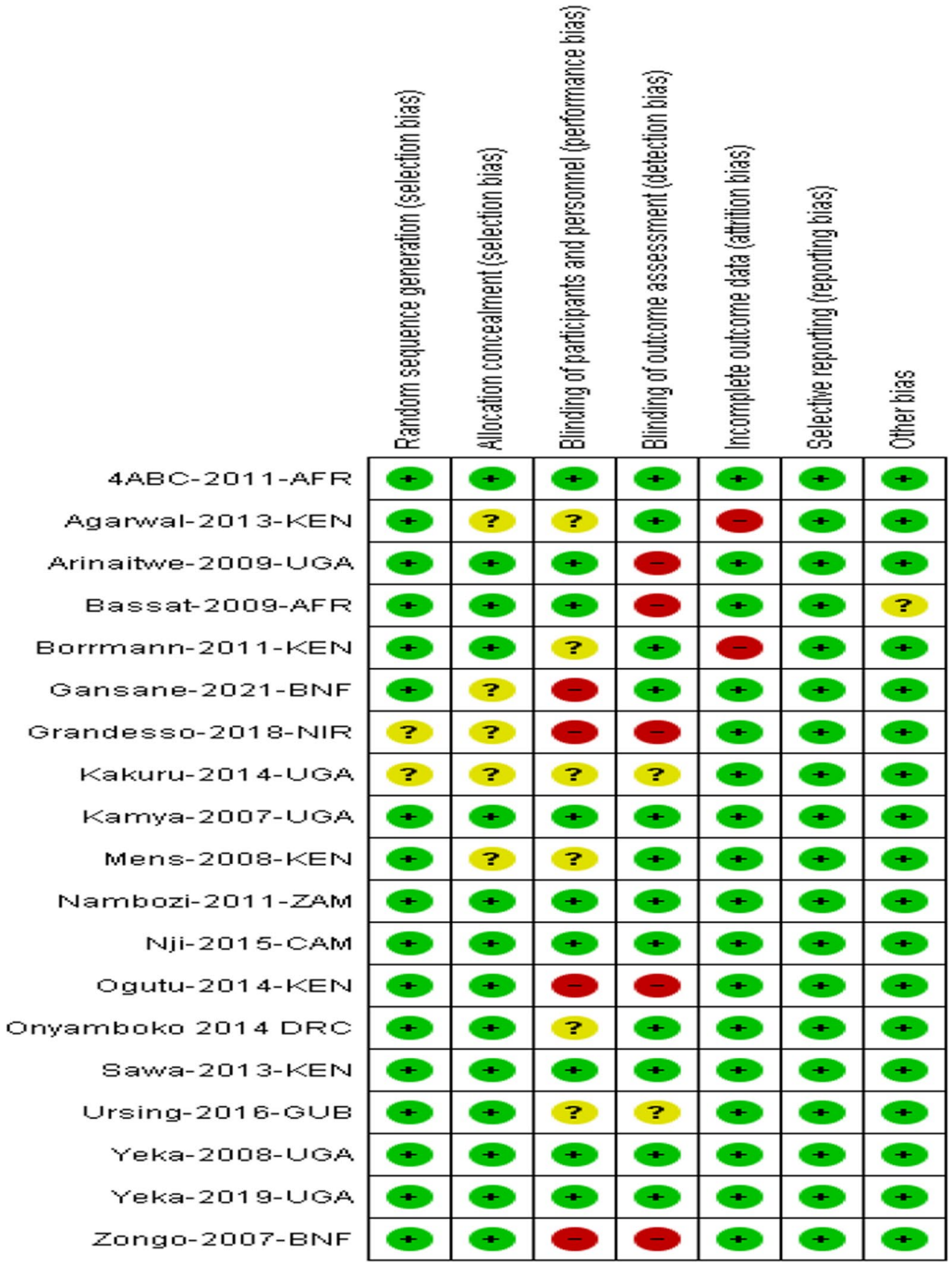

Fig. 2 A summary of review authors' judgments about each risk of bias item for each included study

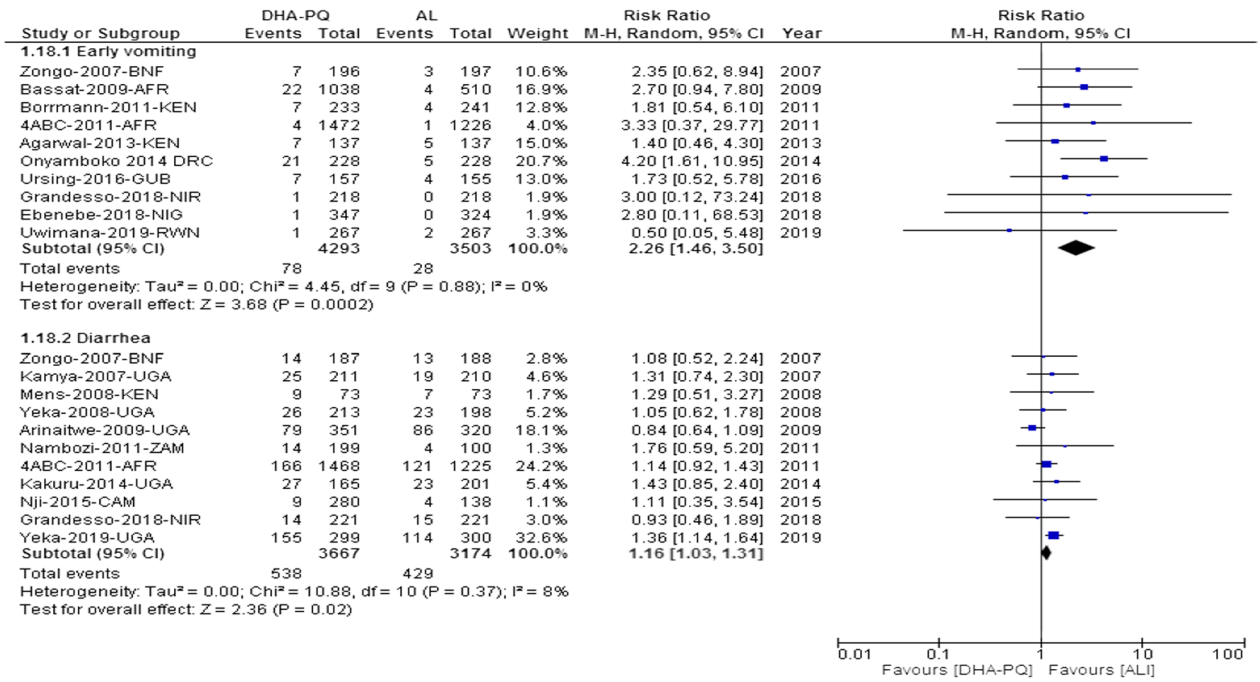

Fig. 3 Forest plot of comparison with dihydroartemisinin-piperaquine and artemether-lumefantrine for treatment of uncomplicated *plasmodium falciparum* malaria among children in Africa on gastrointestinal adverse events

(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

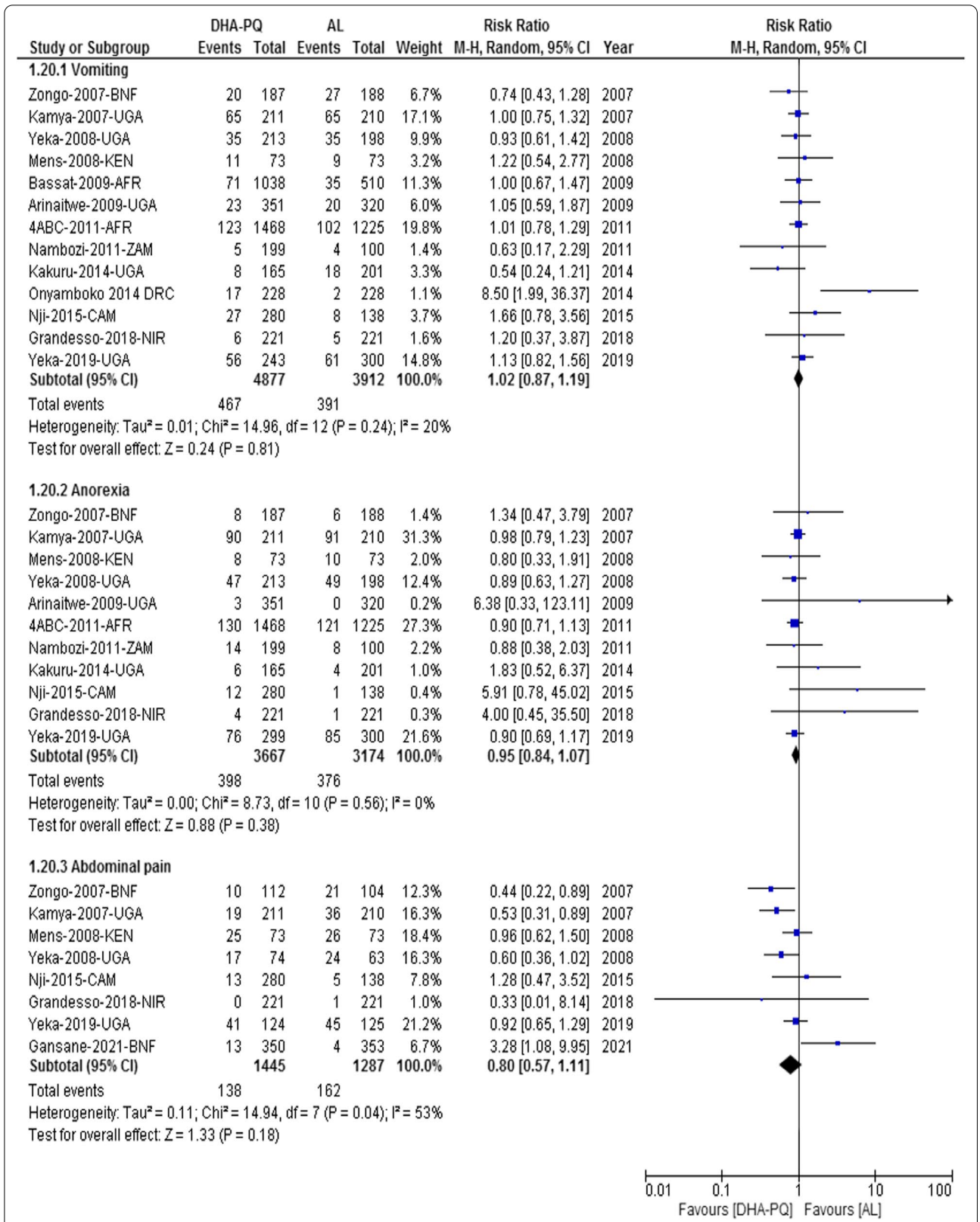

Fig. 4 Forest plot of comparison: dihydroartemisinin-piperaquine versus artemether-lumefantrine for treatment of uncomplicated *Plasmodium falciparum* malaria among children in Africa, outcome: Gastrointestinal adverse events

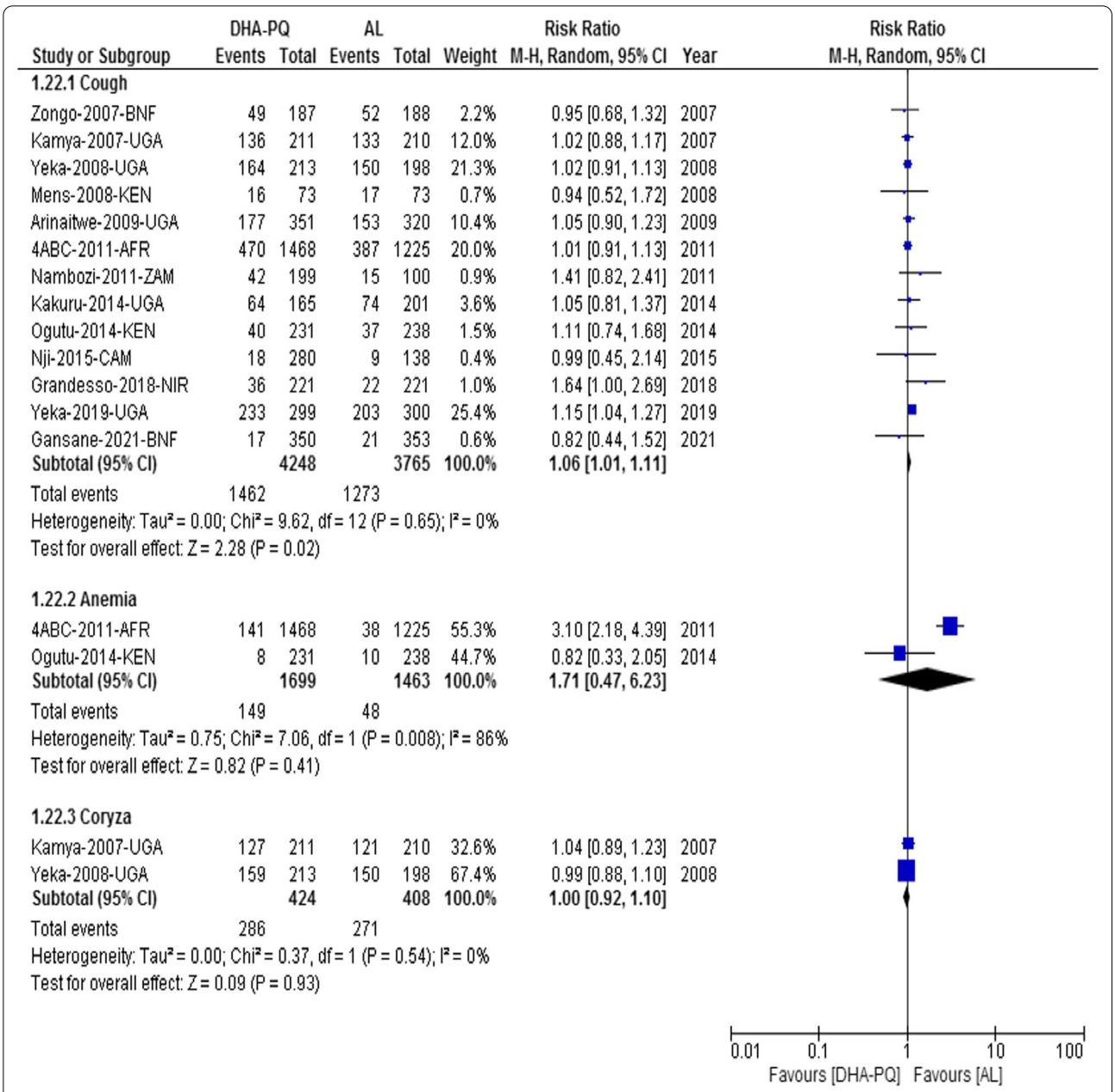

Fig. 5 Forest plot of comparison between dihydroartemisinin-piperaquine and artemether-lumefantrine for treatment of uncomplicated *Plasmodium falciparum* malaria among children in Africa on cardio-respiratory adverse events

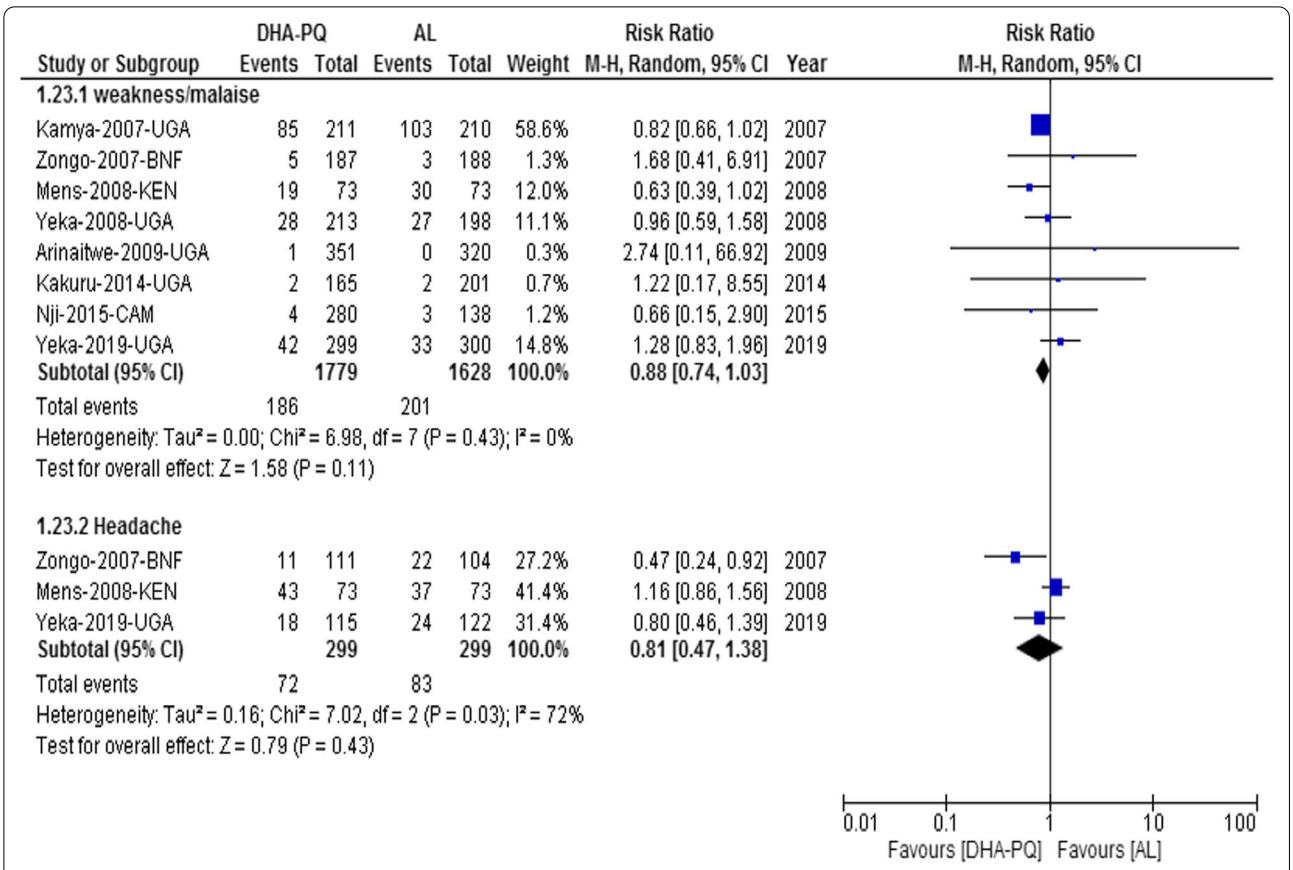

Fig. 6 Forest plot of comparison: dihydroartemisinin-piperaquine versus artemether-lumefantrine for treatment of uncomplicated *Plasmodium falciparum* malaria among children in Africa, outcome: Neuropsychiatry adverse event

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

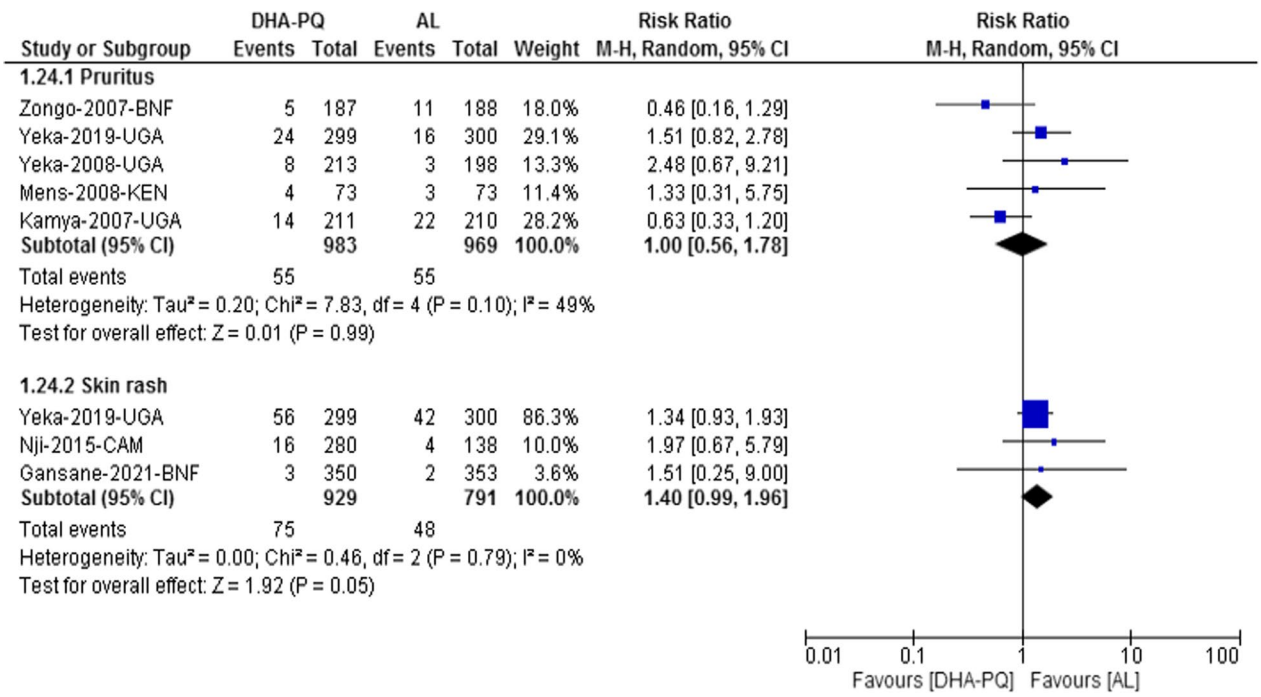

Fig. 7 Forest plot of comparison: dihydroartemisinin-piperaquine versus artemether-lumefantrine for treatment of uncomplicated *Plasmodium falciparum* malaria among children in Africa, outcome: Musculoskeletal/dermatological adverse events

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

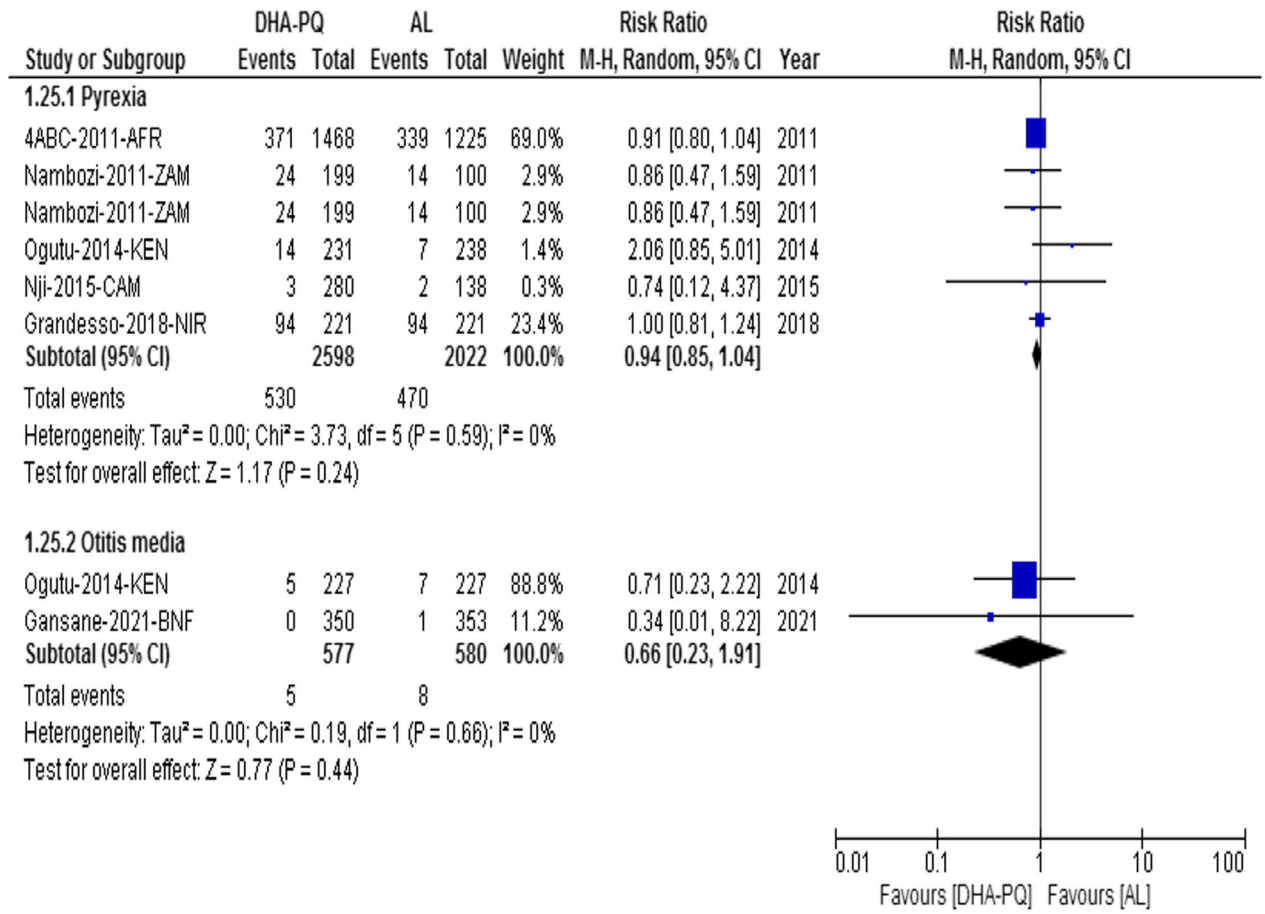

Fig. 8 Forest plot of comparison: dihydroartemisinin-piperaquine versus artemether-lumefantrine for treatment of uncomplicated *Plasmodium falciparum* malaria among children in Africa, outcome: Other Adverse events

[17]. Regardless of the treatment groups, most of these adverse events are associated with age (≤ 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.

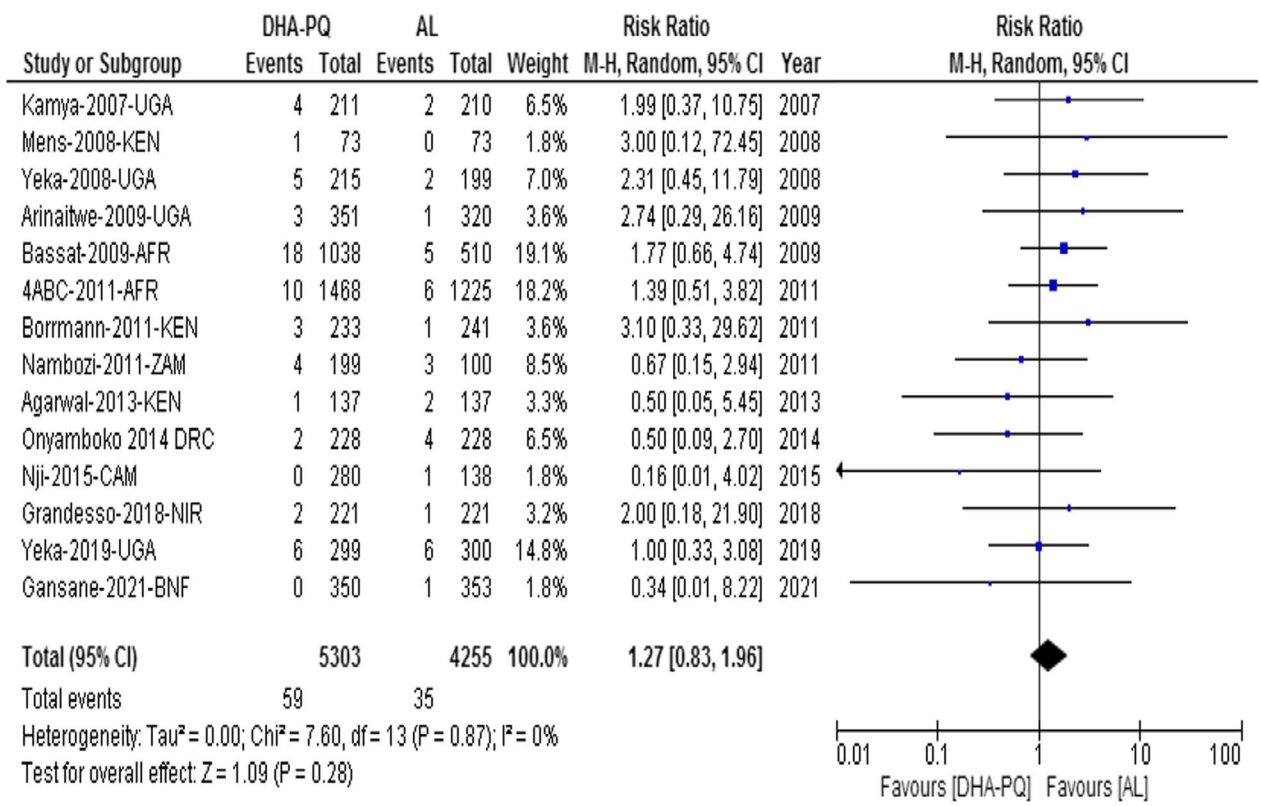

Fig. 9 Forest plot of comparison between dihydroartemisinin-piperaquine and artemether-lumefantrine for treatment of uncomplicated *Plasmodium falciparum* malaria among children in Africa on serious adverse event (including death)

Abbreviations

AE: Adverse event; ACT: Artemisinin-based combination therapy; AL: Artemether-lumefantrine; ART: Antiretroviral therapy; BW: Body weight; CENTRAL: 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.

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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.

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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.

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