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 little or no attention has been given to their safety. 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 *P.falciparum* malaria among children in Africa.

Method: 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).

Result: 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 diarrhea (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, diarrhea, and cough 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.

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 by the World Health Organization (WHO) African Region [3]. The risk of malaria infections among children aged under five years was higher in 2018, and *P. 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 currently recommended Artemisinin-Based Combination Therapy (ACT) in the confirmed cases of *P. falciparum* malaria since 2004 [1]. The artemisinin component is active against the sexual stages of the parasite that facilitates transmission to mosquitos. 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 diarrhea were common in patients treated with DHA-PQ [16].

In the majority of African countries the first-line treatments for uncomplicated malaria are generally AL or AS/AQ, with DHA-PQ as a second line in many countries **[11, 12].** Most of the previous studies have compared the efficacies of AL and other artemisinin-based combinations, but little or no attention has been given to their safety. Given the wide range of ACT available for treatment the malaria and their potential AEs, it is vital to compare their safety profiles. 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 *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 [17]. The methods and findings of the review have been reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA 2020) [18].

Eligibility Criteria

The PICOS format was used to identify eligible studies **[19].**

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 to 35kg, 3 tablets per dose: 15 to 25kg, 2 tablets per dose; and <15kg, 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 hours the first and then every 12 hours on days 2 and 3.

Outcome measures

Primary outcomes

Adverse events including serious adverse events were also assessed. An adverse event (AE) was defined as any unfavorable, 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 [20].

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 **[19]**. Additionally, we searched ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform, and the US Food and Drug Administration (FDA) to search and assess ongoing or unpublished trials.

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 S 1.

Study selection, data collection, and data analysis

The Cochrane Handbook for Systematic Reviews of Interventions [21] 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 analyzed 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' [19]. 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. We used Risk ratios accompanied by 95% CIs.

Unit of analysis issues

Participants were included according to the treatment group of the randomized clinical trials.

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 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 [22].

- 0% to 40%: might not be important;
- 30% to 60%: may show moderate heterogeneity;
- 50% to 90%: may show substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Assessment of reporting bias

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

Data synthesis

The meta-analyses was done consistent with the recommendations of Cochrane [21]. 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, a series of sensitivity analyses were conducted. To restore the integrity of the randomization process, the 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 [23]. 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 [24]. 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 [25]. The imprecision was judged based on the optimal information size criteria and CI [26].

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 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, Additional file S 2.

Characteristics of exculded studies

Thirty one studies were excluded with reason, Additional file S 3.

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 lied symmetrically around the pooled effect estimate implying that there was no publication bias (P= 0.5, Additional file S 4).

Diarrhea

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 lied symmetrically around the pooled effect estimate implying that there was no publication bias (P= 0.9, Additional file S 5).

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, [27]).

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 S 6).

Other cardiorespiratory and hematological adverse events

The relative risk of developing coryza didn't 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 didn't have significant difference between the two treatment groups (RR 1.59, 95% CI 0.89 to 2.83; participants = 442; studies = 1, [28]), (RR 1.23, 95% CI 0.59 to 2.57; participants = 299; studies = 1, [29]), (RR 3.35, 95% CI 1.11 to 10.12; participants = 469; studies = 1, [27]), 95% CI 0.91 to 1.92; participants = 1548; studies = 1,[30]). Similarly, the relative risk of cardiac adverse events like QTc interval prolongation (Fridericia's correction and Bazett's correction) didn't also have significant difference between the two treatment groups (RR 0.98, 95% CI 0.51 to 1.90; participants = 1548; studies = 1, [30] 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, [30]).

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 (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, [30]), (RR 0.25, 95% CI 0.02 to 2.70; participants = 1548; studies = 1, [30]), (RR 0.98, 95% CI 0.09 to 10.81; participants = 1548; studies = 1, [30]), (RR 1.00, 95% CI 0.33 to 3.05; participants = 442; studies = 1, [28]), (RR 0.47, 95% CI 0.19 to 1.12; participants = 442; studies = 1, [28]),

(RR 0.49, 95% CI 0.07 to 3.46; participants = 418; studies = 1, [31]), (RR 1.24, 95% CI 0.54 to 2.81; participants = 469; studies = 1, [27]), (RR 0.34, 95% CI 0.01 to 8.22; participants = 703; studies = 1,[32]) and (RR 3.03, 95% CI 0.12 to 74.02; participants = 703; studies = 1, [32]), 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 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 multi-center trials, and the cause of death for seven of them was sepsis, severe malaria, and severe diarrhea. 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 lied symmetrically around the pooled effect estimate implying that there was no publication bias (P= 0.50, Additional file S 7).

Quality of the evidence

We assessed the quality of the evidence in this review 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 S 8). The quality of evidence on comparative adverse effects and serious adverse events; early vomiting, diarrhea, 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, diarrhea, 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 [33]. However, Cough was more frequent in patients who were treated with AL, but headache and runny nose were common in DHA-PQ treatment group [33]. A recent review on the efficacy and safety of the two ACT's also reported that cough, anorexia, diarrhea, and vomiting were the most common adverse events. In this review more patients from DHA-PQ treatment arm had cough than that of AL [34] 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 [35-38]. Studies from the Thailand-Myanmar border [39, 40] and elsewhere in Africa [41-44] have reported that DHA-PQ cause drug induced electrocardiographic QT prolongation. Regardless of the treatment groups, most of these adverse events are associated with age (≤18 years) [37], efavirenz-based ART [37], efavirenz-based ART [45], and administration of DHA-PQ with food could increase piperaquine exposure and it needs to be administered in fasting state [40-42].

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.

Conclusions

From this review, it can be concluded that early vomiting, diarrhea, and cough 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.

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**,** and **WHO=**World Health Organization.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing of interest

We declare that they have no competing interests.

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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 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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Figures

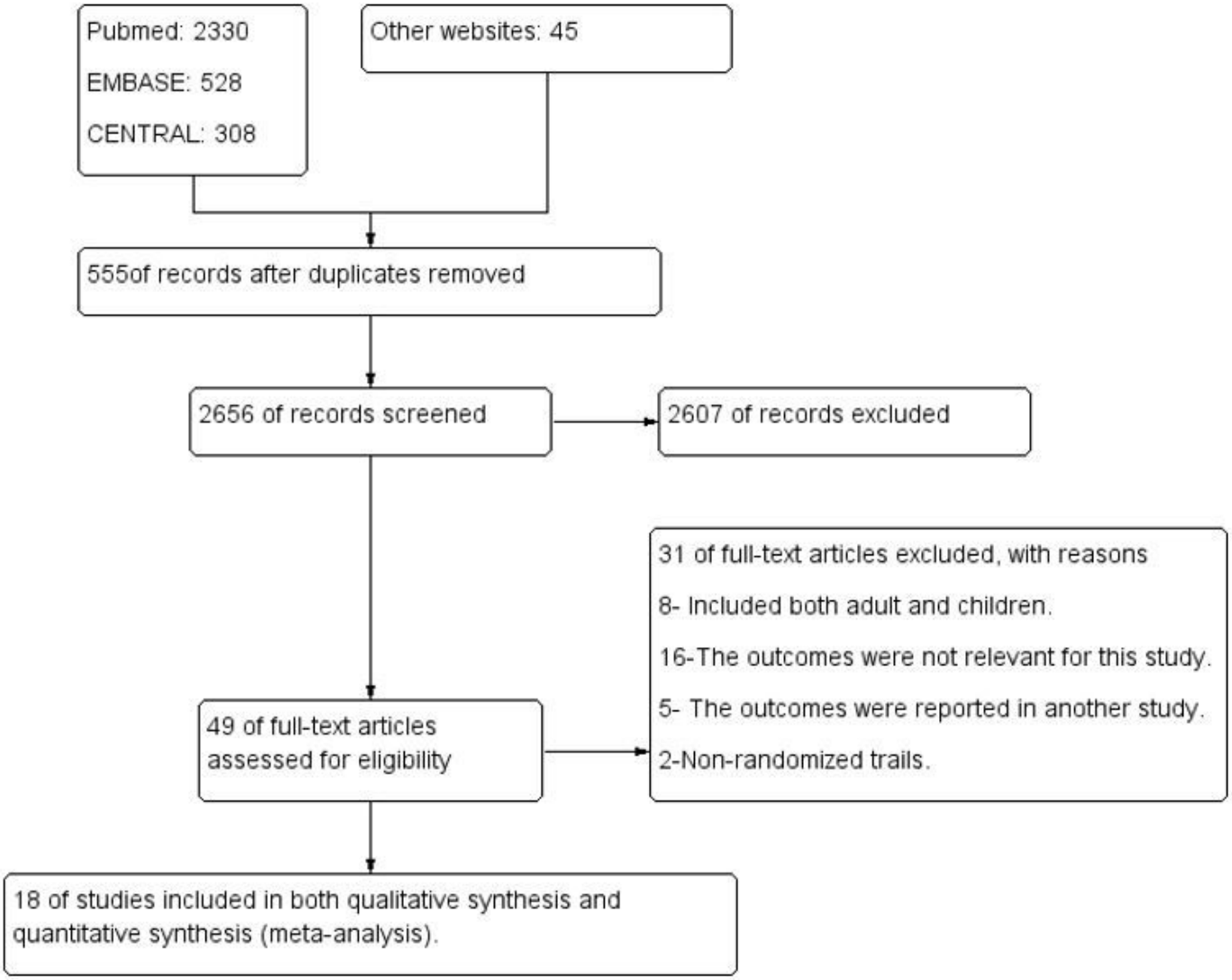

Figure 1

PRISMA study flow diagram of the study.

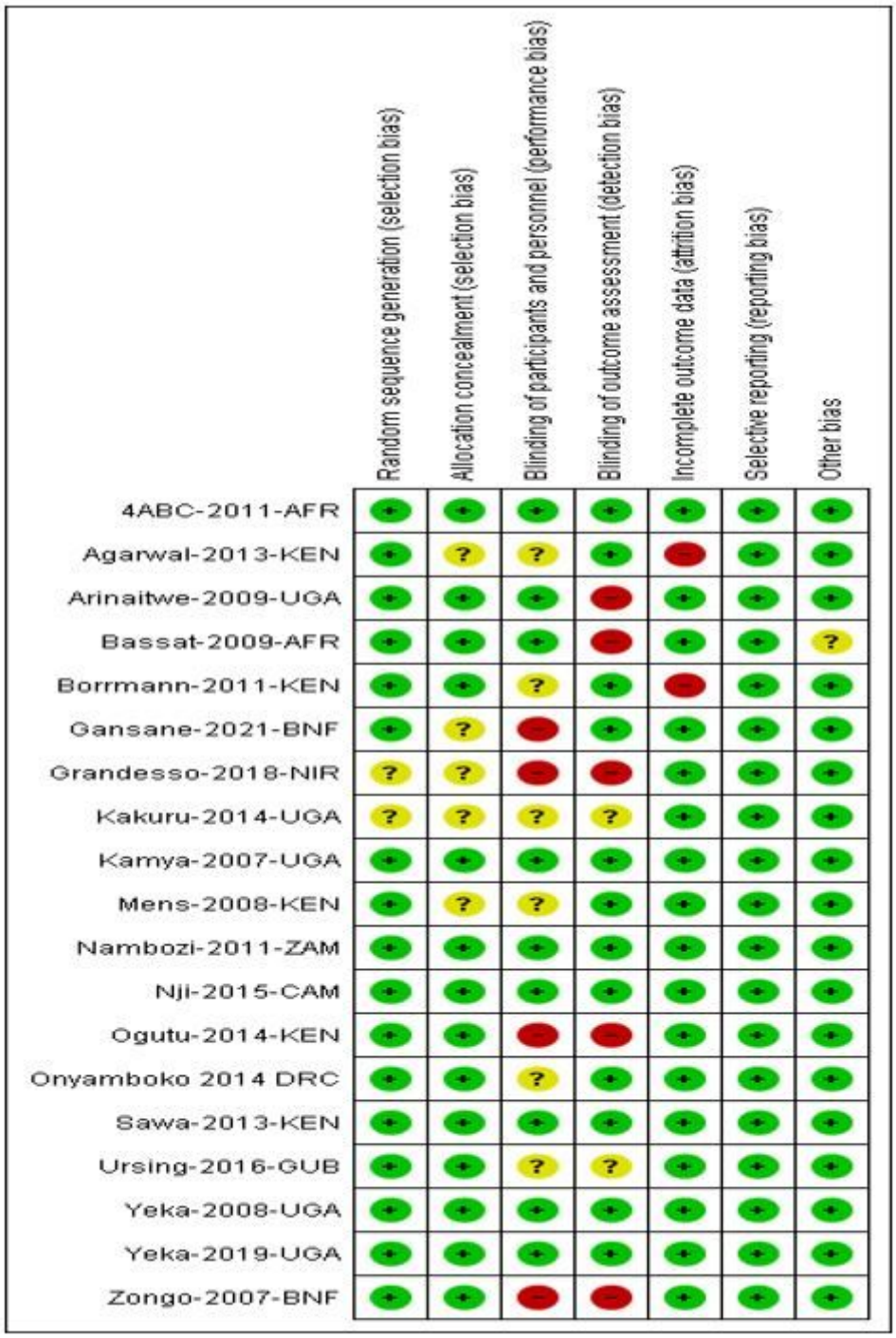

Figure 2

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

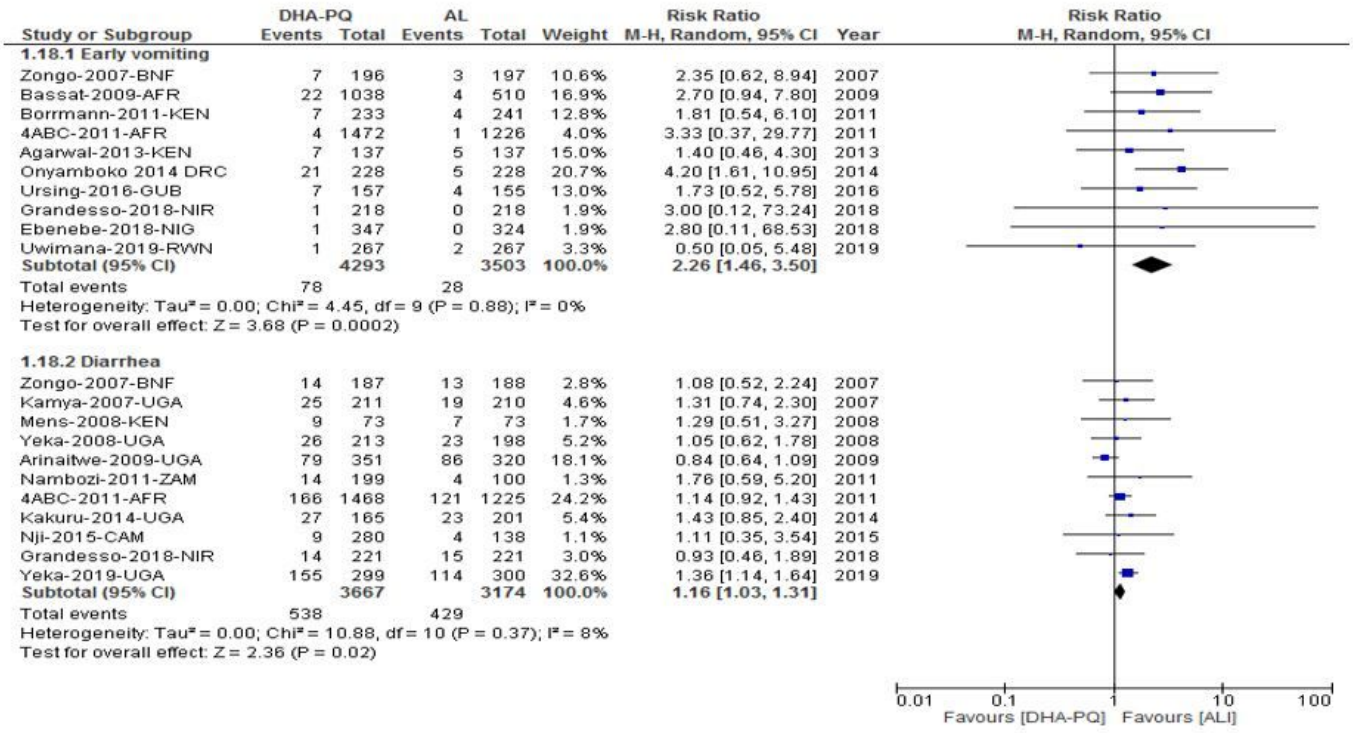

Figure 3

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.

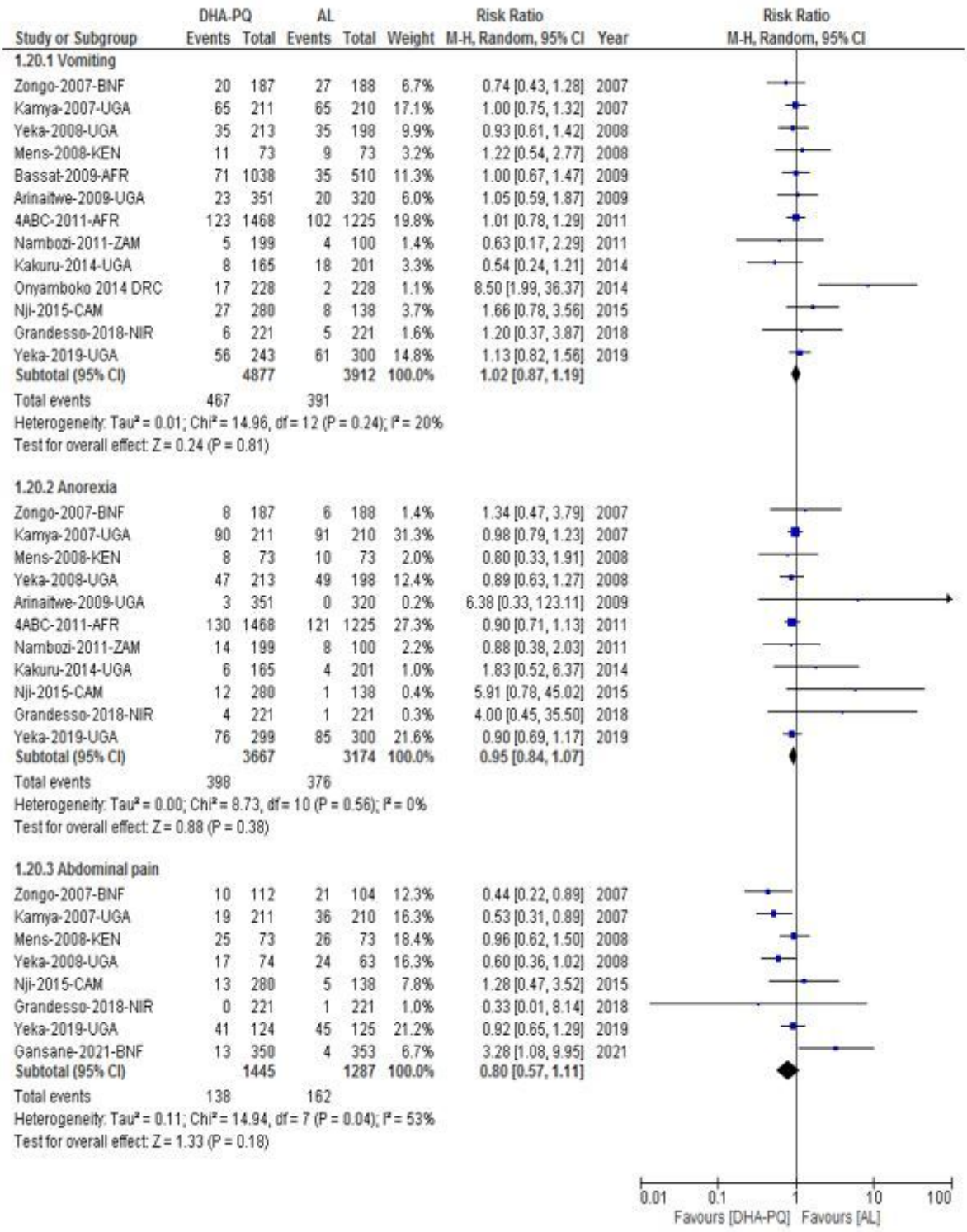

Figure 4

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

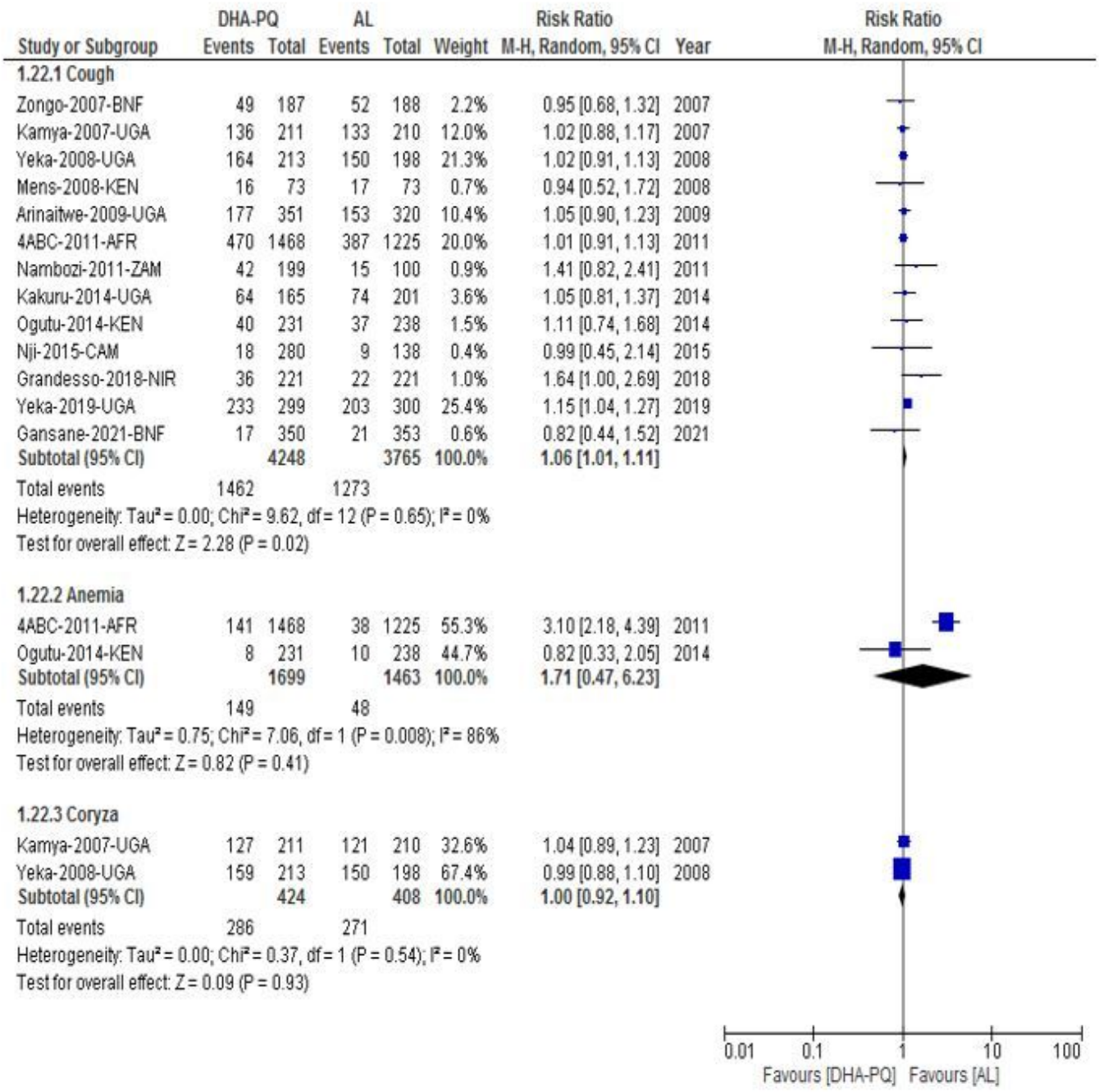

Figure 5

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.

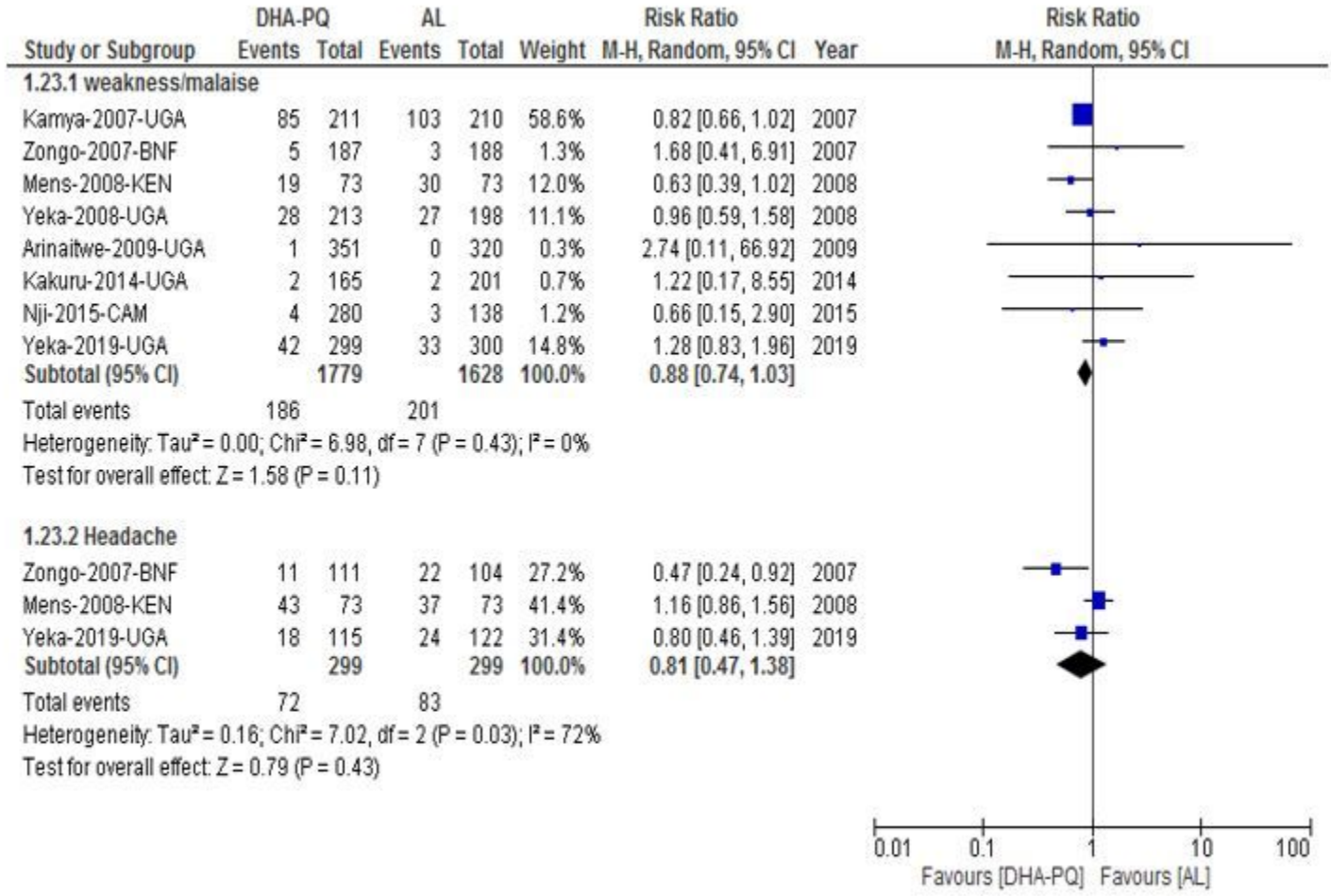

Figure 6

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

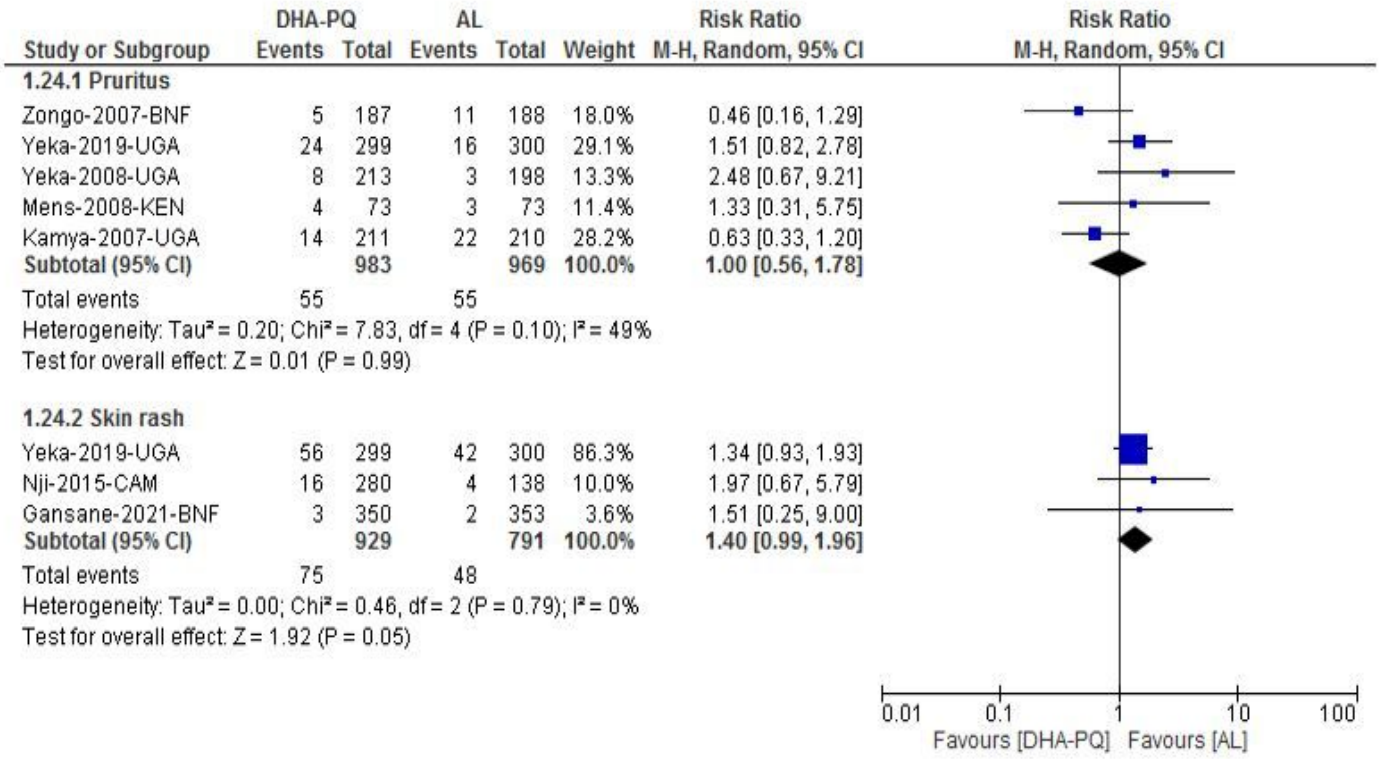

Figure 7

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.

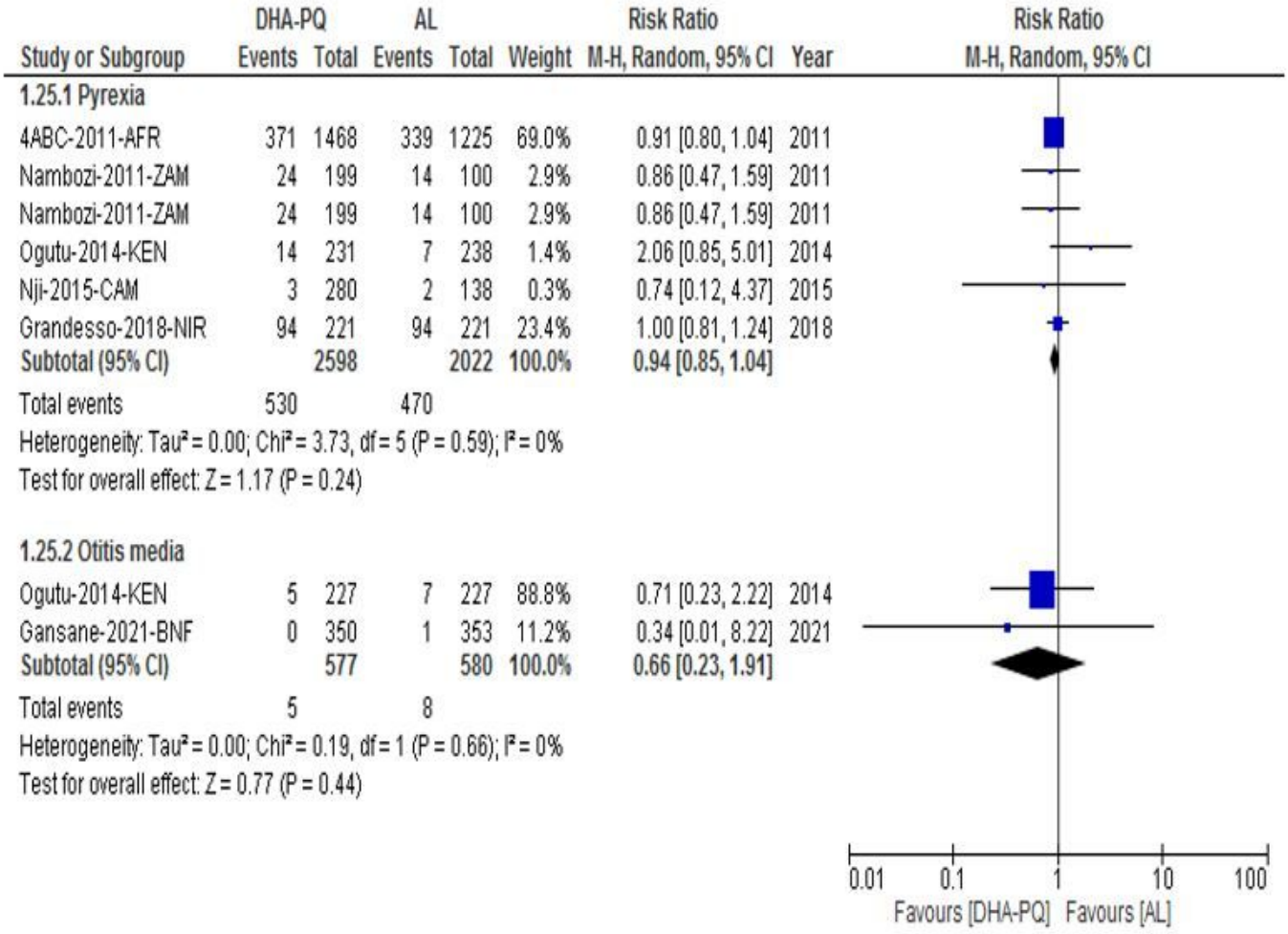

Figure 8

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

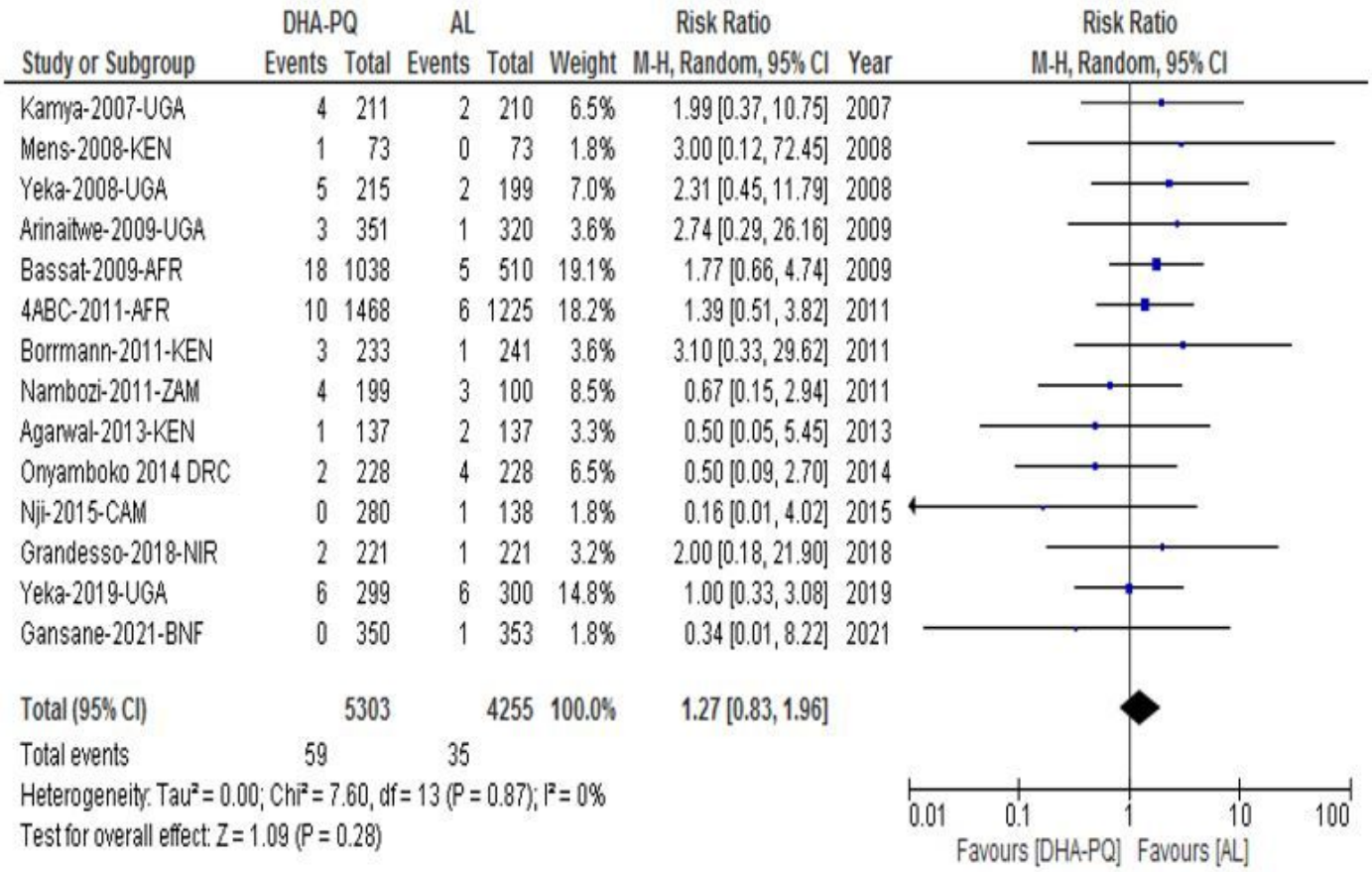

Figure 9

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).

Supplementary Files

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