Efficacy and Safety of Dihydroartemisinin-Piperaquine *Versus* Artemether-Lumefantrine for Treatment of Uncomplicated *Plasmodium Falciparum* Malaria In African Children: A Systematic Review And Meta-Analysis of Randomized Control Trials

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Research

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Abstract

Background: Emergence of *Plasmodium falciparum* resistance to artemisinin and its derivatives poses a threat to global effort in controlling malaria. Resistance has already emerged to most antimalarial drugs in common use. On the other hand, significant number of the developing world in genral and African population in particular is sufferring from malaria of whom many are children.The aim of this review was, therefore, to compare the efficacy and safety of dihydroartemisinin-piperaquine and artemether-lumefantrine for treatment of uncomplicated *P.falciparum* malaria in African children.

Method: A computerized systematic search method was used to search for articles from online databases PubMed/ MEDLINE, Embase, and Cochrane Center for Clinical Trial database (CENTRAL) for retrieving randomized control trials comparing efficacy and safety of DHA-PQ and AL for treatment of uncomplicated *P.falciparum* malaria in African children. The search was performed from August 2020 to 30 April 2021. Using Rev-Man software (V5.4), R-studio, and Comprehensive Meta-analysis software, the extracted data from eligible studies were pooled as risk ratio (RR) with 95% confidence interval (CI).

Result: In this review, 25 studies which involved a total of 13,198 participants were included. PCR unadjusted treatment failure in children aged between 6 months and 15 years was significantly lower in DHA-PQ treatment arm on day 28 than that of AL (RR 0.14, 95% CI 0.08 to 0.26; participants = 1302; studies = 4; I^2 = 0%, high quality of evidence). Consistently, the PCR adjusted treatment failure was significantly lower with DHA-PQ treatment group on day 28 (RR 0.45, 95% CI 0.29 to 0.68; participants = 8508; studies = 16; I^2 = 51%, high quality of evidence) and on day 42 (RR 0.60, 95% CI 0.47 to 0.78; participants = 5959; studies = 17; I^2 = 0%, high quality of evidence). However, the efficacy was ≥95% in both treatment groups on day 28. On days 28 and 42, a significant increase in serum hemoglobin level from the baseline was also observed in DHA-PQ treatment arm (SMD 0.15, 95% CI 0.05 to 0.26; participants = 2715; studies = 4; I^2 = 32%, high quality of evidence) and (MD 0.35, 95% CI 0.12 to 0.59; participants = 1434; studies = 3; I^2 = 35%, high quality of evidence), respectively. 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), vomiting (RR 1.02, 95% CI 0.87 to 1.19; participants = 8789; studies = 13; I^2 = 20%, 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 DHA-PQ reduces new infection and recrudescence with significant impact on hemoglobin recovery more than AL, and both drugs are well tolerated. DHA-PQ may, therefore be recommended as a first line treatment for uncomplicated *P.falciparum* malaria in Africa, while use of AL continues.

Background

Malaria is the major cause for two third of deaths among children under the age of five though it is a preventable and treatable disease [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 and covers two asexual cycles, and also rapidly decreases the number of the parasite by a factor of approximately 10,000 in each 48-hrs asexual cycle. The partner drug with a longer half-life eliminates the residual parasite over several weeks post treatment, reducing repeated episodes, and onward transmission, especially in high and seasonal transmission areas [4]. Artemisinin and partner drugs protect each other to prevent resistance development [5–8].

The efficacies of artemisinin based combinations has been excellent in Africa [9, 10], Numerous trials have reported that dihydroartemisinin/piperaquine is highly effective in treatment of uncomplicated *P.falciparum* malaria [11–15]. A previous review reported that prolongation of the QTc interval; pyrexia, early vomiting, and diarrhea were common in patients treated with DHA-PQ [16]. Meanwhile the emergence of antimalarial resistance has become a great public health challenge and continues to be a leading threat to ongoing malaria control efforts [17]. Resistance to ACT in Southeast Asia is becoming the highest concern [18]. There are a few reports on artemisinin resistance mediated by mutations *kelch13 (K13)* gene in Greater Mekong Sub-region [19], Sudan [20], higher prevalence (42%) in Myanmar [21], and low frequency of *kelch13 (K13)* gene mutation in 18 Sub-Saharan African countries [22, 23]. In addition, over the past ten years a decline in parasitological response in Nigeria [24], decrease in PCR corrected therapeutic efficacy of ACT below 80% in Burkina Faso[25] have been noticed, Moreover, increase in copy number of *plasmepsin* genes associated with decrease in effectiveness of piperaquine has been arisen in South East Asia [26–28].

With the concern on resistance in South East Asia [26, 28–30], but with potential benefits of DHA-PQ over other ACTs [7, 31], it is necessary to assess if the antimalarial treatment efficacy of this regimen in Africa has changed. Although several studies were conducted to assess the efficacy of ACT in adults yielding different success rates in Africa [32–34], there has been no systematic review and/or meta-analysis conducted to obtain strong evidence about the outcome of malaria treatment and artemisinin resistance in African Children. This systematic review and meta-analysis was, therefore, conducted to evaluate the efficacy and safety of DHA-PQ versus AL for treatment of uncomplicated *p. falciparum* malaria in African children in order to assist policymakers to design appropriate national treatment policies and treatment protocols.

Methods

This protocol has been registered at the International Prospective Register of Systematic Reviews (PROSPERO) database, ID: CRD42020200337 [35]. The Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA 2020) guideline was followed to select studies to be included [36].

Eligibility Criteria

Studies

Randomized controlled trials conducted in Africa which compared the efficacy and safety of DHA-PQ versus AL for treatment of uncomplicated *falciparum* malaria in children, written in English, and published between 2004 to April 2021 were included. The PICOS format was used to identify eligible studies **[37].**

Participants

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

Interventions

- A three days course of dihydroartemisinin-piperaquine (20mg dihydroartemisinin and 160 mg piperaquine) given as a multiple dose.
- The body weight adjusted target doses and ranges for children weighting <25kg are 4(2-10) mg/kg per day dihydroartemisinin and 24(20-32) mg/kg per day piperaquine, once a day for three 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

The WHO Methods and techniques for clinical trials on antimalarial drug efficacy classification of genotyping to identify parasite populations were used to determine treatment outcome [38]. It is classified as;

Early treatment failure *(ETF):* Dangerous signs or severe malaria on days 1, 2, or 3 in the presence of parasitemia; or parasitaemia on day 2 higher than on day 0; or parasitaemia and axillary temperature > 37.5 °C on day three; or parasitaemia on day 3 > 20% of count on day 0 or development of danger signs, or severe malaria after day three with parasitemia; or presence of *P. falciparum* parasitemia and axillary temperature > 37.5 °C on or after day 4; or presence of *P. falciparum* parasitemia after day 7.

Late clinical failure (LCF): Dangerous signs or severe malaria in the presence of parasitemia between days 4 and 28 (days 4- 42) in patients who did not previously meet any of the criteria for early treatment failure; or presence of parasitemia between days 4 and 28 (days 4- 42) with axillary temperature ≥ 37.5 °C in patients who did not previously meet any of the criteria for early treatment failure.

Late parasitological failure (LPF):Presence of parasitemia between days 7 and 28 (day 7-42) with axillary temperature < 37.5 °C in patients who did not previously meet any of the criteria for early treatment or late clinical failure.

Adequate clinical and parasitological response (ACPR):Before and after PCR correction was used to show the treatment success and was defined as absence of parasitemia by the end of treatment (day 28) regardless of axillary temperature without previously meeting any of the benchmarks of early treatment failure or late clinical failure or late parasite logical failure.

PCR genotyping to define treatment success corresponding to current World Health Organization (WHO) recommendation was used [38]. Adverse events including serious adverse events were also assessed.

PCR-unadjusted total failure: PCR-unadjusted total failure (*P. falciparum*) was calculated as the sum of late and early treatment failures (without PCR adjustment). The denominator was excluding participants who did not satisfy the inclusion criteria after randomization and those outcomes not available (for example, those who were lost to follow-up, withdrew consent, other species infection, took another antimalarial, or failed to complete treatment).

PCR-adjusted total failure: calculated PCR-adjusted total failure (P. falciparum) as the sum of early treatment failures plus late treatment failures due to PCR-confirmed recrudescence. Participants with indeterminate PCR results, missing PCR results or PCR-confirmed new infections were measured to be involuntary withdrawals and excluded them from the calculation. The denominator excludes participants who did not satisfy the inclusion criteria after randomization, participants with (falciparum reinfection, other species mixed with falciparum reinfection, and undetermined or missing PCR) and those participants for whom an outcome was not available (for example, those who were lost to follow-up, withdrew consent, other species infection, took another antimalarial, or failed to complete treatment).

Secondary outcomes

- Fever clearance: the proportion of patients a febrile on each day within 3 days,
- Parasite clearance: the proportion of patients clear of parasites on each day within three days,
- Gametocyte carriage at baseline and between day 1 to day 42 post- treatment
- Change in serum hemoglobin level from baseline (zero to minimum 28 days and 42 days follow-up) was also evaluated.

Electronic searches

A computerized systematic search method was used to search for 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 **[37]**. 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 S1.

Study selection, data collection, and data analysis

The Cochrane Handbook for Systematic Reviews of Interventions [39] was followed. Furthermore, the software package provided by Cochrane (RevMan 5.4) and additionally, R-Studio and Comprehensive Meta-analysis version 3 software's were also 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 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, treatment failure, fever clearance, parasite clearance, gametocyte carriage, serum hemoglobin recovery, and adverse events 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. Missing data were requested from the authors whenever necessary.

For dichotomous outcomes, the number of participants experiencing the event and the number of participants in each treatment group were documented. For continuous outcomes, the arithmetic means and standard deviations for each treatment group collectively with the numbers of participants in each group were extracted.

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' [37]. The risks were classified as high risk, unclear risk, and low risk.

Measures of treatment effect

The main outcomes in this review were total treatment failure on days 28, 42, and 63; PCR-adjusted and PCR unadjusted. Dichotomous data were combined and presented using risk ratios. Continuous data were summarized by arithmetic means and standard deviations, and then data were combined using mean differences. Risk ratios, mean differences, and standardized mean difference were 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 (to detect overlapping CI) 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 [40].

- 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.

Outlier and influence case analysis

To assess the distortion in the pooled effect estimate caused by one or more studies with**extreme effect sizes, the pooled effect checked again by removing outliers from the analysis [41]. In addition, to assess if the effect doesn't depend on one single study and whether there are studies which heavily push the effect of our analysis into one direction, influence case analysis was done [41].** To further investigate the contribution of each study to the overall heterogeneity of our meta-analysis, Baujat Plot was used [42].

GOSH Plot Analysis

To further investigate the pattern of effect sizes and heterogeneity in our data, GOSH Plot Analysis (Graphic Display of Heterogeneity (GOSH) plots) was used. Using this plot, different sub-clusters with different effect size which were candidate for subgroup analysis were identified. When substantial heterogeneity (I^2> 50%) was identified, it was reported, and possible causes by subgroup analyses were explored.

Assessment of reporting bias

To assess the possibility of publication bias, funnel plots for asymmetry (Egger's test P<0.05) were used. When the Egger's test showed publication bias, the P-curve was used to estimates the presence of a "true" effect size behind our findings, and that the results were not the product of publication bias and P-hacking alone [43, 44].

Data synthesis

The meta-analyses was done consistent with the recommendations of Cochrane [39]. 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.

Subgroup analysis and investigation of heterogeneity

The potential sources of heterogeneity were investigated through the following subgroup analyses: participants age less than five years compared with participants age between 6 months to 15 years.

Meta regression

Meta-regression was used to investigate the association of study characteristics which causes heterogeneity with treatment effect. The covariates were age, HIV status, malaria transmission intensity, risk of bias, region, and way of drug administration (night dose). The results were presented with figures and tables.

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. Furthermore, we explored the robustness of our meta-analysis results using influence analyses and the leave-one-out method.

Quality of evidence

Quality of evidence was assessed using GRADE criteria and the GRADE pro software [45]. 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 [46]. 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 [47]. The imprecision was judged based on the optimal information size criteria and CI [48].

Result

A total of 3211 studies through the databases were searched, of which 49 full-text trials for eligibility were assessed and 25 of them fulfilled the inclusion criteria for meta-analysis and for qualitative analysis **Fig 1.**

Fig. 1: PRISMA study flow diagram of the study.

Study characteristics

In this review, 25 studies were included, which enrolled 13,198 participants with uncomplicated *P. falciparum* malaria were included Additional file S2.

Methodological quality and risk of bias

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

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

Effect of interventions

Treatment failure

PCR-unadjusted total failure on day 28

The PCR adjusted treatment failure in patients between the age of 6 months and 15 years was (RR 0.14, 95% CI 0.08 to 0.26; participants = 1302; studies = 4; I^2 = 0%, *high quality of evidence*, Fig. 3). However, the PCR adjusted treatment failure in under five children was heterogonous (Tau² = 0.25; Chi² = 120.71, df = 12 (P < 0.00001); I² = 90%, *moderate quality of evidence*). So we couldn't pool the result. As there was high heterogeneity, it was more useful to consider the individual trial results. In 12/13 studies, the risk of treatment failure unadjusted by genotyping in under five children was significantly lower in DHA-PQ treatment group than that of AL. Hence, statistically significant difference was found between the two subgroups (Tau² = 0.25; Chi² = 120.71, df = 12 (P < 0.00001); I² = 90%, Fig. 3).

Meta regression of day 28 PCR-unadjusted treatment failure

Both age of the participants and malaria transmission intensity within the countries had a direct relationship with the relative risk of developing treatment failure unadjusted by genotyping (p= 0.034 and p=0.024, and Additional file S3 and Additional file S4). The relative risk of developing treatment failure unadjusted by genotyping in under five children was higher by 8.5% compared to children under age category of 6 months to 15 years, keeping malaria transmission intensity constant. Also, the relative risk of developing treatment failure unadjusted by genotyping in children living in the area where malaria transmission intensity was moderate was higher by 42.2% compared to children living in high malaria transmission setting, keeping age of children constant Table 1.

Furthermore, either the age of children or malaria transmission of the countries was associated to treatment failure (Q=8.61, df=2, P=0.0135). The risk of treatment failure varied across the studies meaning some studies had high treatment failure and others low treatment failure. Of the total variance in treatment failure, only 32% were explained by participants' age and malaria transmission intensity within the countries.

Fig.3: Forest plot of comparison between dihydroartemisinin-piperaquine and artemether-lumefantrine for treatment of uncomplicated *plasmodium falciparum* malaria in African children on PCR unadjusted

treatment failure on day 28

Table 1: Meta- regression of PCR-unadjusted treatment failure at day 28

Covariate	Coefficient	SE	95% Lower	95% Upper	Z-value	2-sided P-value
Intercept	-2.3013	0.4315	-3.1469	-1.4556	-5.33	0.0000
Age: Under five	0.9137	0.4305	0.0699	1.7575	2.12	0.0338
Transmission: Moderate	0.5776	0.2563	0.0752	1.0800	2.25	0.0242

Publication bias

The funnel plot showed that all studies lied symmetrically around the pooled effect estimate (egger's test: intercept 0.98 (95% CI -1.17,3.13), P= 0.39, Additional file S5)

PCR-adjusted total failure at day 28

On day 28, the PCR adjusted treatment failure was significantly lower in DHA-PQ group than that of AL (RR 0.45, 95% CI 0.29 to 0.68; participants = 8508; studies = 16; I^2 = 51%, *high quality of evidence,* Fig. 7).

Publication bias

The funnel plot showed that all studies lied symmetrically around the pooled effect estimate implying that there was no publication bias (egger's test: -0.19007 (95% CI -1.77,1.39), P=0.799, Additional file S6).

Fig.7: Forest plot of comparison between dihydroartemisinin-piperaquine and artemether-lumefantrine for treatment of uncomplicated *plasmodium falciparum* malaria in African children on PCR adjusted treatment failure on day 28.

PCR-unadjusted total failure at day 42

The result had an unexplained considerable heterogeneity between the included studies (Tau^2 = 0.08; Chi^2 = 62.24, df = 16 (P < 0.00001); I^2 = 74, *moderate quality of evidence,* Fig. 9). Considering individual study result, the PCR unadjusted risk of recurrent *falciparum* parasitemia in thirteen studies was significantly lower in DHA-PQ group than AL. In four studies, however, the PCR unadjusted risk of recurrent *falciparum* parasitemia did have significant difference between the two treatment groups.

Fig. 9: Forest plot of comparison between dihydroartemisinin-piperaquine and artemether-lumefantrine for treatment of uncomplicated *plasmodium falciparum* malaria in African children on PCR unadjusted treatment failure on day 42.

Publication bias

The funnel plot showed that all studies did not lie symmetrically around the pooled effect estimate implying that there was a publication bias (egger's test: -2.48 (95% CI -4.55, -0.42), P= 0.021). The P-curve evaluation showed that 13 studies were included into the analysis, of which 12 had a P-value lower than 0.025. The power of the analysis was 95% (95% CI: 87%, 98%). The result showed that the evidential value was present, and there was a true effect size behind our findings, and that the results were not the product of publication bias and P-hacking alone Fig. 10.

Fig.10: P-curve of comparison between dihydroartemisinin-piperaquine and artemether-lumefantrine for treatment of uncomplicated *plasmodium falciparum* malaria in African children on PCR unadjusted treatment failure on day 42.

PCR-adjusted total failure at day 42

The PCR adjusted treatment failure on day 42 was lower for participants treated with DHA-PQ than those treated with AL (RR 0.60, 95% CI 0.47 to 0.78; participants = 5959; studies = 17; I^2 = 0%, *high quality of evidence*, Fig.11).

Publication bias

The funnel plot showed that all studies lied symmetrically around the pooled effect estimate implying that there was no publication bias (egger's test: -1.06(95% CI -2.38, 0.25), p=0.10, Additional file S7).

Fig.11: Forest plot of comparison between dihydroartemisinin-piperaquine and artemether-lumefantrine for treatment of uncomplicated *plasmodium falciparum* malaria in African children on PCR adjusted treatment failure on day 42.

PCR-unadjusted total failure at day 63

Three studies with 3365 participants were included in this analysis. The result had considerable heterogeneity (Tau² = 0.21; Chi² = 18.62, df = 2 (P < 0.0001); I² = 89%, *moderate quality of evidence*) and we couldn't pool the result. It is more useful to consider individual trial results. On day 63, the PCR unadjusted treatment failure in participants who was treated with DHA-PQ was significantly lower than those treated with AL in the two studies. However, the relative risk of PCR unadjusted treatment failure was not significantly different between the two treatment groups, Fig.13.

Fig.13: Forest plot of comparison between dihydroartemisinin-piperaquine and artemether-lumefantrine for treatment of uncomplicated *plasmodium falciparum* malaria in African children on PCR unadjusted treatment failure on day 63.

PCR-adjusted total failure at day 63

The PCR adjusted treatment failure at day 63 was significantly lower in both treatment groups without statistically significant difference (RR 0.87, 95% CI 0.57 to 1.34; participants = 3384; studies = 4; I^2 = 28%, *high quality of evidence*, Fig.14).

Fig.14: Forest plot of comparison between dihydroartemisinin-piperaquine and artemether-lumefantrine for treatment of uncomplicated *plasmodium falciparum* malaria in African children on PCR adjusted treatment failure on day 63.

PCR unadjusted and adjusted treatment failure at day 84

Two studies had followed the patients up to 84 days. The PCR adjusted treatment failure on day 84 was more than 10% in AL treatment group [49] . On day 84, the number of re-infection was the same in both treatment groups [49, 50].

Fever clearance

Fever clearance on day 1

Fever clearance on day one was higher in patients who were treated with the DHA-PQ than AL (RR 0.93, 95% CI 0.89 to 0.98; participants = 2291; studies = 12; I^2 = 0%,).

Fever clearance at day 2

On day 2, fever had resolved in the majority of the patients regardless of the treatment group (RR 0.86, 95% CI 0.71 to 1.04; participants = 4971; studies = 11; I^2 = 31%, Additional file S8).

Fever clearance at day 3

On day 3, fever had resolved in the majority of the patients regardless of the treatment group (RR 1.07, 95% CI 0.85 to 1.34; participants = 4664; studies = 11; I^2 = 0%, Additional file S8).

Fig.15: Forest plot of comparisonbetween dihydroartemisinin-piperaquine and artemether-lumefantrine for treatment of uncomplicated *plasmodium falciparum* malaria in African children on Fever clearance on day 1.

Parasite clearance

Parasite clearance at day 1

The pooled result had a considerable heterogeneity between studies (Tau^2 = 0.01; Chi^2 = 15.69, df = 4 (P = 0.003); I^2 = 75%, Fig.16). We couldn't pool the result. On day one, the percentage of patients with

parasitaemia was significantly lower in the DHA-PQ treatment group than AL in under five children (RR 0.82, 95% CI 0.75 to 0.90; participants = 2450; studies = 4; I^2 = 65%, Fig.16). Similarly, the prevalence of parasitemia in children between the age of six months to 15 years was significantly lower in DHA-PQ treatment group than AL (RR 0.93, 95% CI 0.86 to 1.00; participants = 507; studies = 1; I^2 = 0%, Fig.16).

Fig.16: Forest plot of comparison between dihydroartemisinin-piperaquine and artemether-lumefantrine for treatment of uncomplicated *plasmodium falciparum* malaria in African children on Parasite clearance on day 1.

Parasite clearance on day 2

The pooled result showed that the percentage of patients with parasitemeia on day two was significantly lower in patients who were treated with DHA-PQ than AL (RR 0.74, 95% CI 0.61 to 0.90; participants = 6065; studies = 13; I^2 = 12%, Additional file S9).

Parasite clearance at day 3

In majority of the studies the percentage of patients with detected parasitemia was lower in both treatment groups on day 3 without significant difference (RR 0.99, 95% CI 0.50 to 1.98; participants = 6635; studies = 13; I^2 = 0%, Additional file S9).

Gametocyte Carriage

The pooled result showed that there was no significant difference in the appearance of gametocyte between the two treatment groups (RR 1.00, 95% CI 0.82 to 1.22; participants = 9283; studies = 14; I^2 = 40%, Additional file S10). Consistentlly, it was significantly lower in both treatment groups without significant difference on day 1-14 (RR 1.78, 95% CI 0.65 to 4.90; participants = 2294; studies = 5; I^2 = 39%), 15-28 difference (RR 0.50, 95% CI 0.09 to 2.89; participants = 2042; studies = 4; I^2 = 54%), and 29-42 (RR 0.40, 95% CI 0.13 to 1.24; participants = 1218; studies = 3; I^2 = 43%, Additional file S11)

Anemia

Mean Hemoglobin at baseline

No significant difference was found in the mean hemoglobin level at baseline in both treatment groups (SMD 0.00, 95% CI -0.06 to 0.06; participants = 10080; studies = 18; I^2 = 45%, Additional file S12). A similar result was obtained in a study conducted in Kenya [11].

Mean Hemoglobin change on day 28 from the baseline

The mean change in hemoglobin on day 28 from baseline was significantly higher in patients treated with the DHA-PQ than AL (SMD 0.15, 95% CI 0.05 to 0.26; participants = 2715; studies = 4; I^2 = 32%, *high quality of evidence,* Fig.17*)*. A study from Zambia also reported the same result [14].

Fig.17: Forest plot of comparison between dihydroartemisinin-piperaquine and artemether-lumefantrine for treatment of uncomplicated plasmodium falciparum malaria in African children on Anemia.

M*ean Hemoglobin change on day 42 from baseline*

The mean change in Hemoglobin on day 42 fom baseline was significantly higher in patients treated with DHA-PQ than AL (MD 0.35, 95% CI 0.12 to 0.59; participants = 1434; studies = 3; I^2 = 35%, *high quality of evidence,* Fig.18).

Fig.18: Forest plot of comparison between dihydroartemisinin-piperaquine and artemether-lumefantrine for treatment of uncomplicated *plasmodium falciparum* malaria in African children on Anemia.

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.20).

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 S13).

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.20).

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 S14).

Fig.20: Forest plot of comparison with dihydroartemisinin-piperaquine and artemether-lumefantrine for treatment of uncomplicated *plasmodium falciparum* malaria in African children on Gastrointestinal adverse events.

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*, Additional file S15). Simillarly, 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,* Additional file S15), 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, [51]).

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.23).

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 S16).

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.23). 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, [52]), (RR 1.23, 95% CI 0.59 to 2.57; participants = 299; studies = 1, [14]), (RR 3.35, 95% CI 1.11 to 10.12; participants = 469; studies = 1, [51]), 95% CI 0.91 to 1.92; participants = 1548; studies = 1,[53]). 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, [53] 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, [53]).

Fig.23: Forest plot of comparison between dihydroartemisinin-piperaquine and artemether-lumefantrine for treatment of uncomplicated *plasmodium falciparum* malaria in African children on Cardio-respiratory adverse events.

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*, Additional file S9). 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%, Additional file S17).

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*, Additional file S10). 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%, Additional file S18).

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, [53]), (RR 0.25, 95% CI 0.02 to 2.70; participants = 1548; studies = 1, [53]), (RR 0.98, 95% CI 0.09 to 10.81; participants = 1548; studies = 1, [53]), (RR 1.00, 95% CI 0.33 to 3.05; participants = 442; studies = 1, [52]), (RR 0.47, 95% CI 0.19 to 1.12; participants = 442; studies = 1, [52]), (RR 0.49, 95% CI 0.07 to 3.46; participants = 418; studies = 1, [54]), (RR 1.24, 95% CI 0.54 to 2.81; participants = 469; studies = 1, [51]), (RR 0.34, 95% CI 0.01 to 8.22; participants = 703; studies = 1,[25]) and (RR 3.03, 95% CI 0.12 to 74.02; participants = 703; studies = 1, [25]), 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%, Additional file S19). 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%, Additional file S19).

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. 24). 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.

Fig. 24: Forest plot of comparison between dihydroartemisinin-piperaquine and artemether-lumefantrine for treatment of uncomplicated *plasmodium falciparum* malaria in African children on Serious adverse event (including death).

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 S20).

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 efficacy and safety (Summary of findings for the main comparison; Additional file S21).

The evidence that DHA-PQ is more effective than that of AL on days 28 and 42 unadjusted by genotyping was of *high and moderate quality of evidence*. There was considerable heterogeneity between studies at day 28 and 42. In addition, DHA-PQ consistently superiority over AL on days 28 and 42 adjusted by genotyping was *of high quality of evidence* and both DHA-PQ and AL performed better than the WHO standard of 5% PCR-adjusted treatment failure on day 28 in all trials *(high quality of evidence)*. Nevertheless, the hemoglobin recovery from the baseline was significantly higher in patients who were treated with the DHA-PQ than that of AL (*high quality of evidence*). We also assessed the quality of evidence on comparative adverse effects and serious adverse events; early vomiting, diarrhea, vomiting, 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

Summary of findings

This systematic review and meta-analysis was designed to assess the therapeutic efficacy and safety of the DHA-PQ and AL for treatment of uncomplicated *P.falciparum* malaria in African children. In this study, the 28 and 42 days PCR uncorrected treatment failure of the DHA-PQ was significantly lower than that of AL (*high* and *moderate quality of evidence*). There were 19 early treatment failures in the DHA-PQ group arm versus 30 in the AL arm. The 28 and 42-days PCR corrected treatment failure in patients receiving DHA-PQ were significantly lower than those patients receiving AL (*high quality of evidence*). On day 28, the PCR corrected treatment failure was below 5% in both treatment arms and similar result was seen in the DHA-PQ treatment arm on day 42.On the contrary, a study from Burkina Faso [25] reported that the PCR corrected treatment failure in AL treatment arm was 28%. This result showed the need for national malaria treatment policy change because it was higher than the WHO cut-off (≥ 10%) [2]. However, the 63-day PCR uncorrected and corrected treatment failure in patients receiving DHA-PQ were not significantly different to those seen in patients receiving AL (*moderate* and *high quality of evidence*).

Furthermore, many under five children who were treated with DHA-PQ had parasite clearance on day 1. Consistently, on day two, participants from the DHA-PQ treatment group had parasite clearance than that of patients who were treated with AL. On day 3, the majority of the children in both treatment arms had parasite clearance.

there was no significant difference in the serum hemoglobin level between the two treatment groups at baseline. However, a significant increase in hemoglobin level was observed in patients who were treated with the DHA-PQ than those treated with AL (*high quality of evidence*) on 28 and 42 days. Both treatments were well tolerated by children. There were comparable occurrences of adverse events in both treatment arms. But, early vomiting, diarrhea, vomiting, 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 occured in all studies. But, all serious adverse events were consistent with malaria symptoms and judged to be unrelated to study medication.

Public health implications

The therapeutic efficacy of antimalarial drugs should be monitored regularly using the standard WHO protocol. It involves assessing clinical and parasitological outcomes of treatment for at least 28 days post-treatment and the appearance of the parasite in the blood also monitored. To distinguish true treatment failure from new infection, PCR genotyping should be used. If the PCR corrected treatment failure is greater than the cut-off (≥ 10%), the WHO recommends a change in the national malaria treatment policy [2].

In the majority of African countries, the first-line drugs for uncomplicated malaria is generally AL or AS/AQ, with DHA-PQ as a second line one in many countries [55, 56]. The observed lower PCR unadjusted treatment failure on days 28 and 42 in the DHA-PQ treatment arm was similar with that of former reviews from Africa [5, 7]. As seen in Myanmar, Papua New Guinea, Angola, and elsewhere in Africa, recurrent parasitemia due to recrudescence occurs significantly more frequently in those patients treated with AL in the first 28 days [21, 57–61]. In addition, DHA-PQ has shown extended post-treatment prophylactic effect in Africa, which decreased the risk of new infections after treatment compared to AL [7]. This difference might be attributed to the evening doses of AL given at home unsupervised; to administration of AL without fatty food for less than 10% of lumefantrine is absorbed in empty stomach [62] and to the longer elimination half-life of piperaquine (23–28 days) compared with that for lumefantrine (3.2 days), which provides long- lasting post treatment prophylactic effect [63, 64]. For patients who live in areas where malaria transmission is higher and reinfection is likely, longer post treatment prophylactic period might have a great advantage [65], but due to the sub-therapeutic drug levels, selection for resistant parasite may occur [66]. For a patient who lives in the area where malaria transmission intensity is low, the benefit of the drug's longer post-treatment prophylactic period is low and the probability of developing drug resistance is higher[67]. Using these drugs with longer post treatment elimination half-life in these settings might be disadvantageous.

However, no significant difference was seen on PCR adjusted treatment failure between the two treatment groups on days 28 and 42 [68, 69]. Similarly, a former review reported that in Papua New Guinea and Asia no significant difference between the two treatment groups seen on day 28 and day 63 [7]. During malaria endemics, a drug with a longer prophylactic effect might limit presumptuous transmission of malaria. On the contrary, AL has shown a significant reduction in PCR adjusted treatment failure in Asia and Senegal on days 28 and 42, respectively [5, 21, 70].

According to WHO [2, 22], suspected artemisinin resistance is defined as a delayed parasite clearance (slope half-life > 5 hr or day 3 positivity rate > 10%). Although the predominant function of artemisinin is early parasite clearance, artemisinin component and partner drugs used in various ACT may also influence early parasite clearance. The absence of artemisinin resistance and the lower percentage of patients with detected parasitaemia regardless of the treatment group on day 3 observed in this study may suggest that *P. falciparum* remains sensitive to artemisinin derivatives. Other studies conducted in Papua New Guinea [57] and elsewhere in Africa [71–73] reported that artemisinin resistance has not emerged in Africa and Ocean. Furthermore, some molecular studies in Africa showed absence of the known *klecher-13(K-13) gene* mutations associated with artemisinin resistance in South East Asia [19, 74, 75], implying that artemisinins are still effective and their capacity of parasite clearance has not been changed. However, artemisinin resistance has been spreading in South East Asia [26, 76], African countries have to be cautious about its potential emergence through continuous monitoring of the parasite clearance and efficacy of ACT, and surveillance of polymorphism in the *K-13 gene* mutation.

In Africa settings, several risk factors were associated with persistent parasitaemia on days 1 and 2 after commencement of therapy were identified [77]. Considering persistent parasitaemia on day an elevated

pre-treatment temperature and higher pretreatment parasite density with AL were independently associated with a significantly increased risk of persistent parasitaemia. Considering persistent parasitaemia on day 2, an elevated pre-treatment temperature, higher pre-treatment parasite density and being HIV infected were independently associated with a significantly increased risk of persistent parasitaemia [77].

Young children presented with acute malaria and high parasitaemia have the highest risk of anemia [78]. Especially, *p.falciparum* has a strong association with anemia in a place where malaria transmission intensity is moderate [79]. In the first two days after treatment majority of the patient's experience decrease in hemoglobin level, followed by a linear increase afterward [78]. Similarly, patients from both treatment groups experienced significant drip in hemoglobin level within the first seven days after treatment [57, 71], and hemoglobin level significantly improved in both treatment arms on days 28 and 42 [69]. On the other hand, in one study from Papua New Guinea, patients with AL treatment arm had significantly higher hemoglobin recovery from the baseline than those with DHA-PQ [57]. One Per-treatment parasitaemia, age difference, baseline hemoglobin level, helminthic infection, concurrent infection, parasite clearance rate, nutritional status, and other conditions associated with anemia determines the degree of hemoglobin drip [32, 78, 80–82].

In this study both drugs were well tolerated by children. 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. However, Cough was more frequent in patients who were treated with AL, but headache and runny nose were common in DHA-PQ treatment group [57]. 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 [73] 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 [83–86]. Studies from the Thailand-Myanmar border [87, 88] and elsewhere in Africa [89–92] 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) [85], efavirenz-based ART [85], efavirenz-based ART [93], and administration of DHA-PQ with food could increase piperaquine exposure and it needs to be administered in fasting state [88–90].

The current malaria treatment guideline for *P.falciparum* is effective in Africa at present. However, insufficient drug levels, ineffectiveness of antimalarial drugs, and drug resistance could lead to treatment failure. Further studies should be conducted in different African countries with different malaria transmission intensity to identify the risk factors for treatment failure.

Study limitation

This study has two limitations. Most of the studies were not blinded and the efficacy and safety assessments were potential for bias. This review could not be a strong evidence for the long term post-treatment prophylactic effect of the two drugs up to day 63.

Author's recommendations

- DHA-PQ better be the first line treatment.
- Studies that measure the efficacy of DHA-PQ and AL with 42 and 63 days follow up better be carried out.
- To identify molecular markers which are related to ACT resistance, molecular surveillance better be conducted.

Conclusion

This systematic review and meta-analysis show higher efficacy of DHA-PQ on days 28 and 42 than that of AL and tolerability of both treatments. While AL may continue to be used, DHA-PQ may be recommended as a first line treatment for uncomplicated falciparum malaria in Africa.

Abbreviations

ACT= artemisinin-based combination therapy, **ACPR**= adequate clinical and parasitological response**, AL**= artemether-lumefantrine, **BW**= Body weight, **CENTRAL=**Cochrane Central Register of Controlled Trials, **CI=**confidence interval, **CM**= complicated malaria, **DHA-PQ**= dihydroartemisinin-piperaquine, **DHS**=demographic Health Survey, **ETF**= early treatment failure**, GADE=**Grading of Recommendations, Assessment, Development, and Evaluations, **GOSH**= Graphic Display of Heterogeneity, **Hgb**= haemoglobin, **LCT**= late clinical failure, **LPF**= late parasitological failure, **PCR=**Polymerase chain reaction, **PICO=** population, Intervention, Comparison, and outcome, **PRISMA=**Preferred Reporting Items for Systematic Reviews and Meta-Analyses, **RDT=**rapid diagnostic test, **SAE**= serious adverse event, **SD**= standard deviation 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.

Funding

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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**). 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.

Acknowledgments

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.

Figures

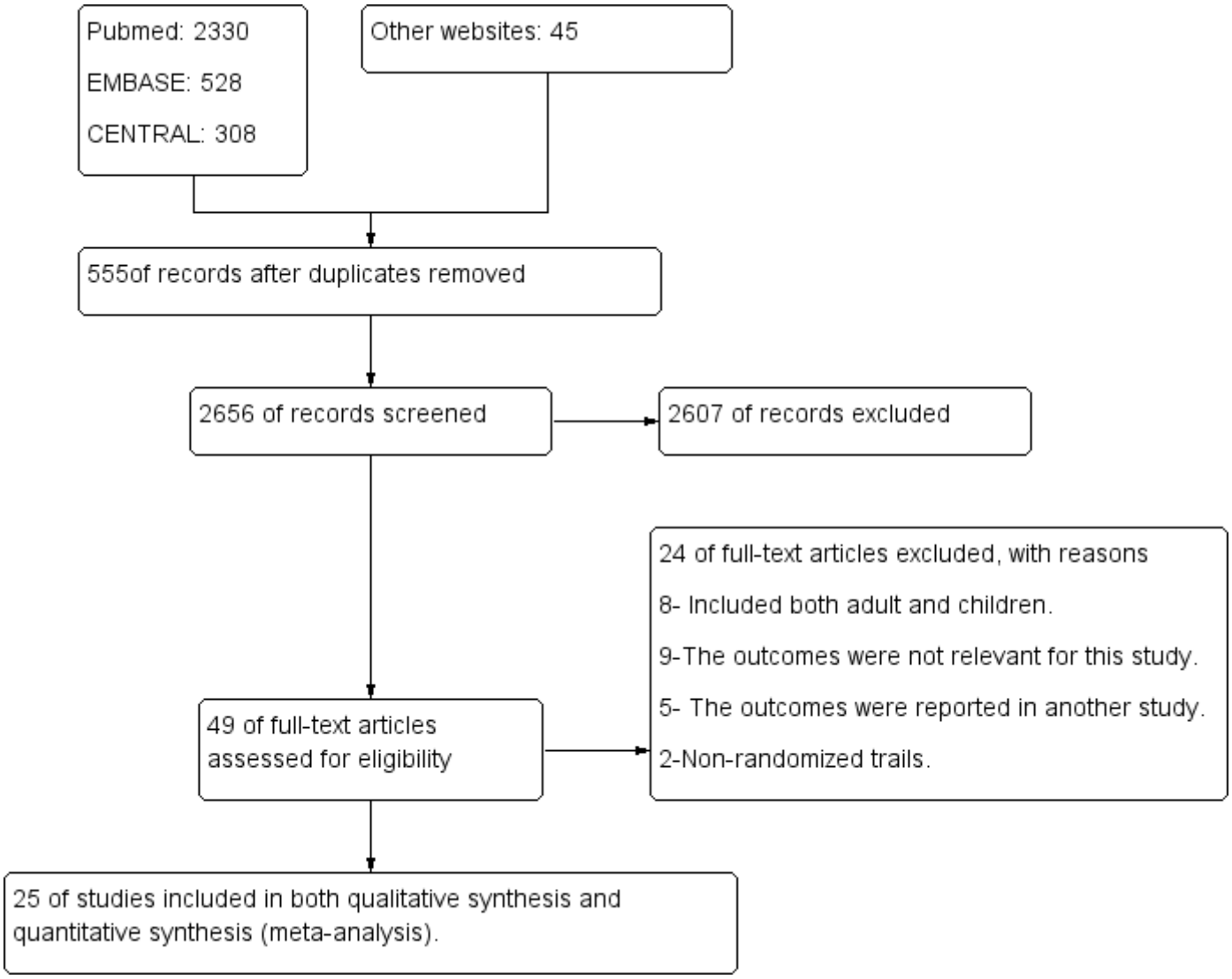

Figure 1

PRISMA study flow diagram of the study.

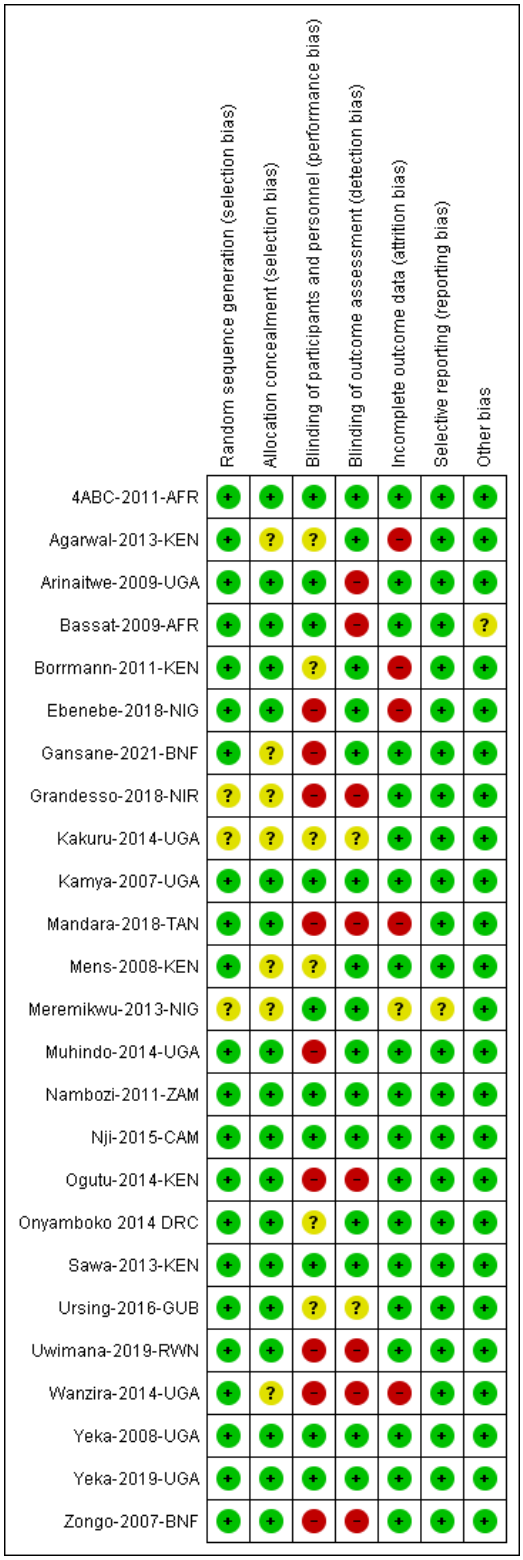

Figure 2

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

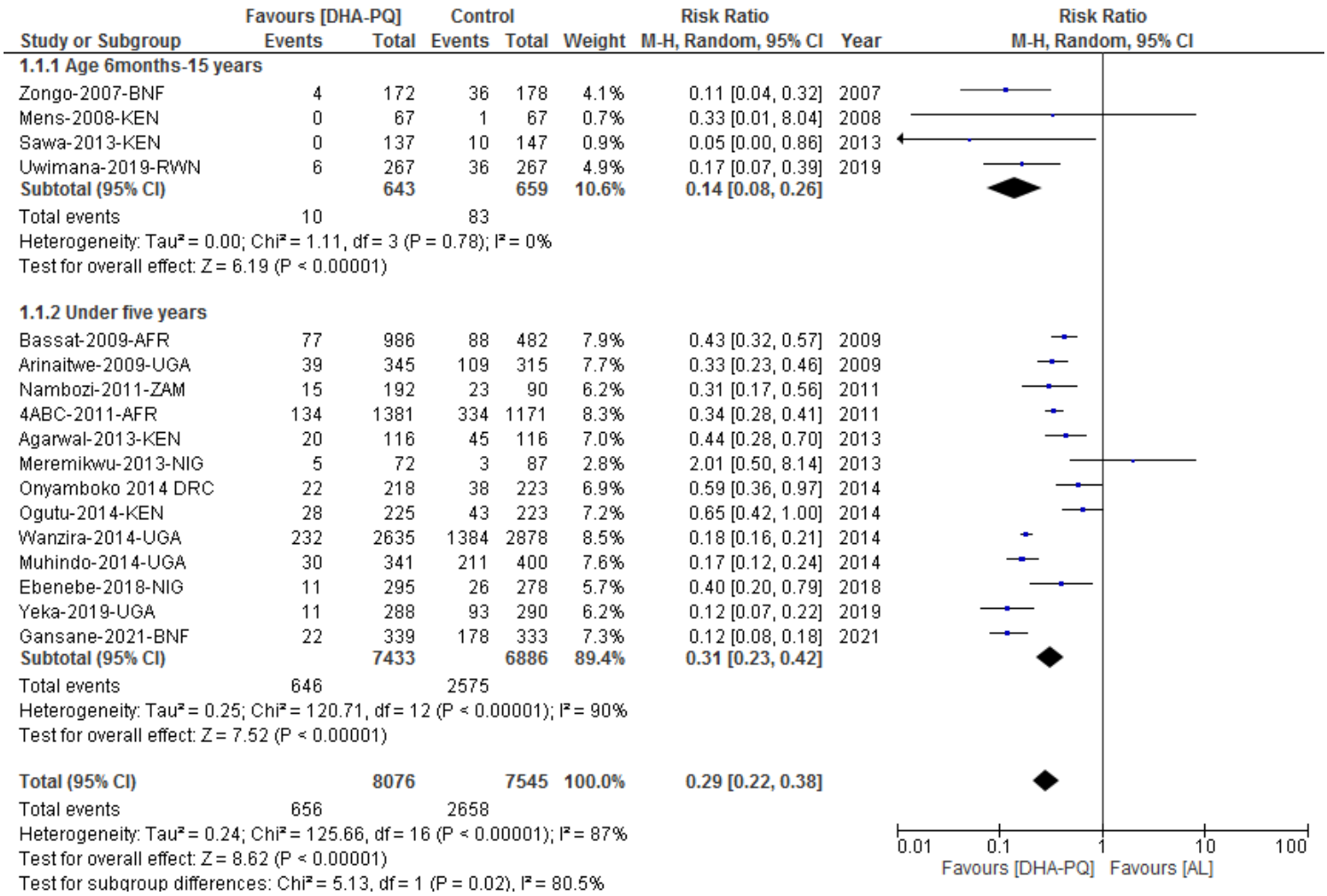

Figure 3

Forest plot of comparison between dihydroartemisinin-piperaquine and artemether-lumefantrine for treatment of uncomplicated plasmodium falciparum malaria in African children on PCR unadjusted treatment failure on day 28

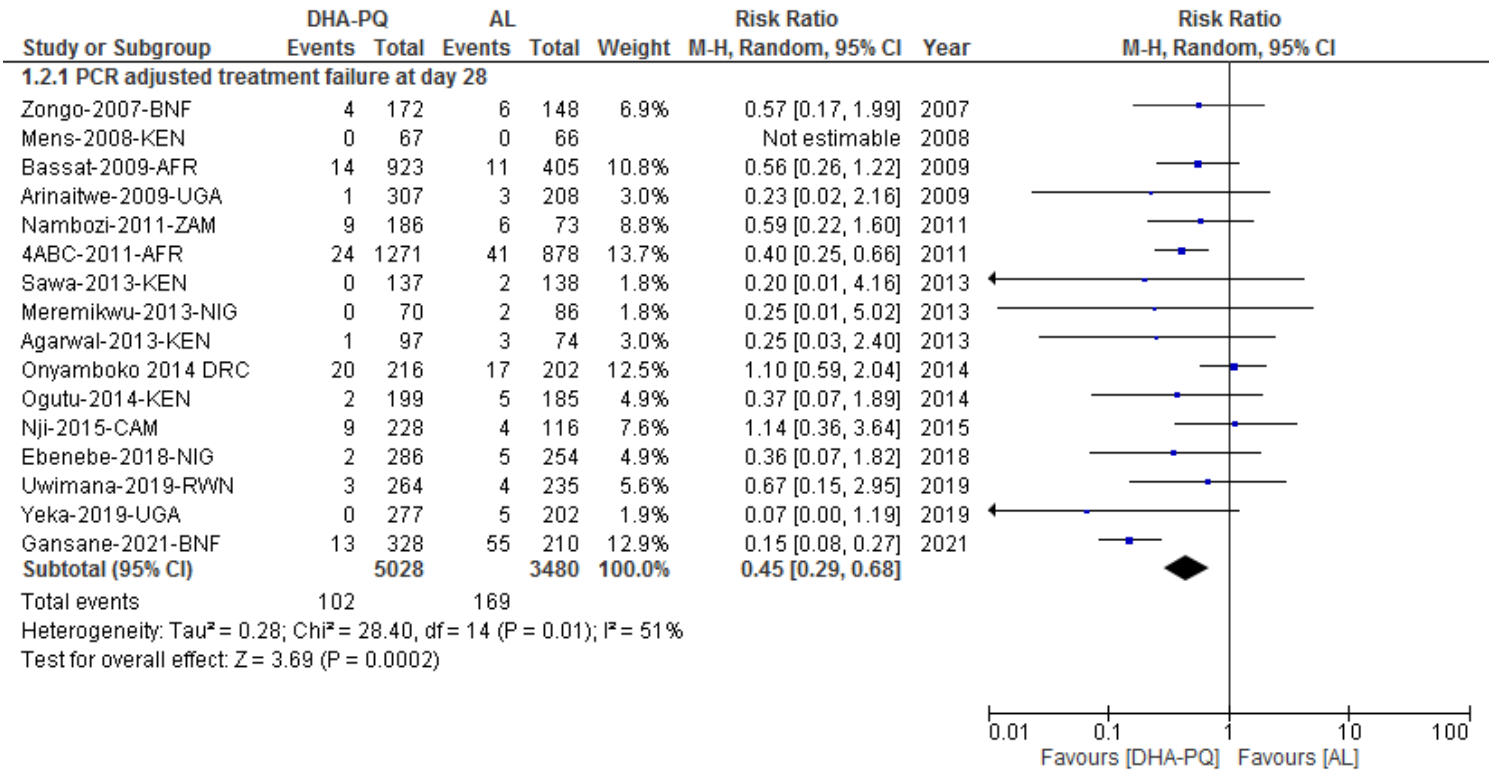

Figure 4

Forest plot of comparison between dihydroartemisinin-piperaquine and artemether-lumefantrine for treatment of uncomplicated plasmodium falciparum malaria in African children on PCR adjusted treatment failure on day 28.

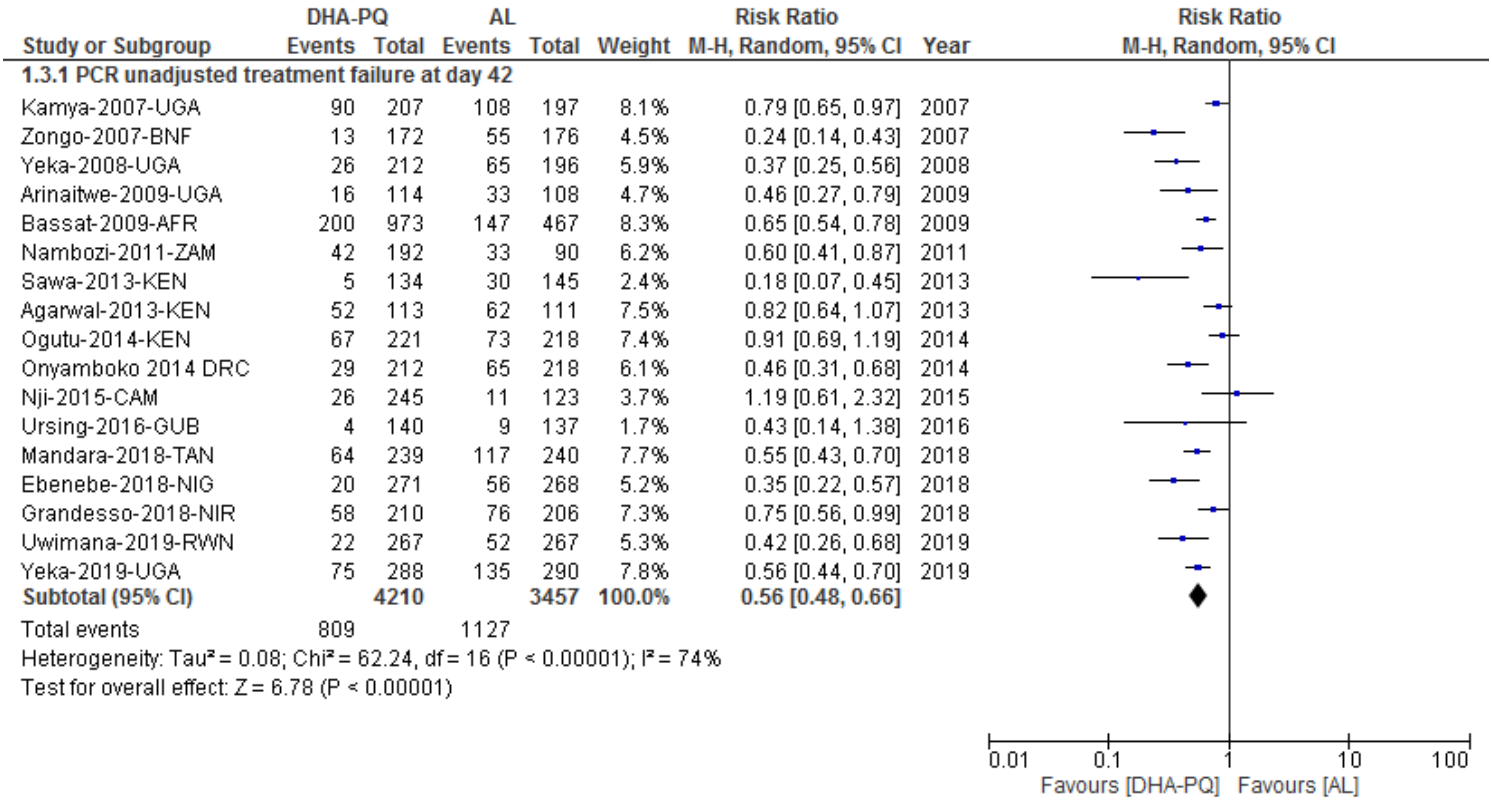

Figure 5

Forest plot of comparison between dihydroartemisinin-piperaquine and artemether-lumefantrine for treatment of uncomplicated plasmodium falciparum malaria in African children on PCR unadjusted treatment failure on day 42.

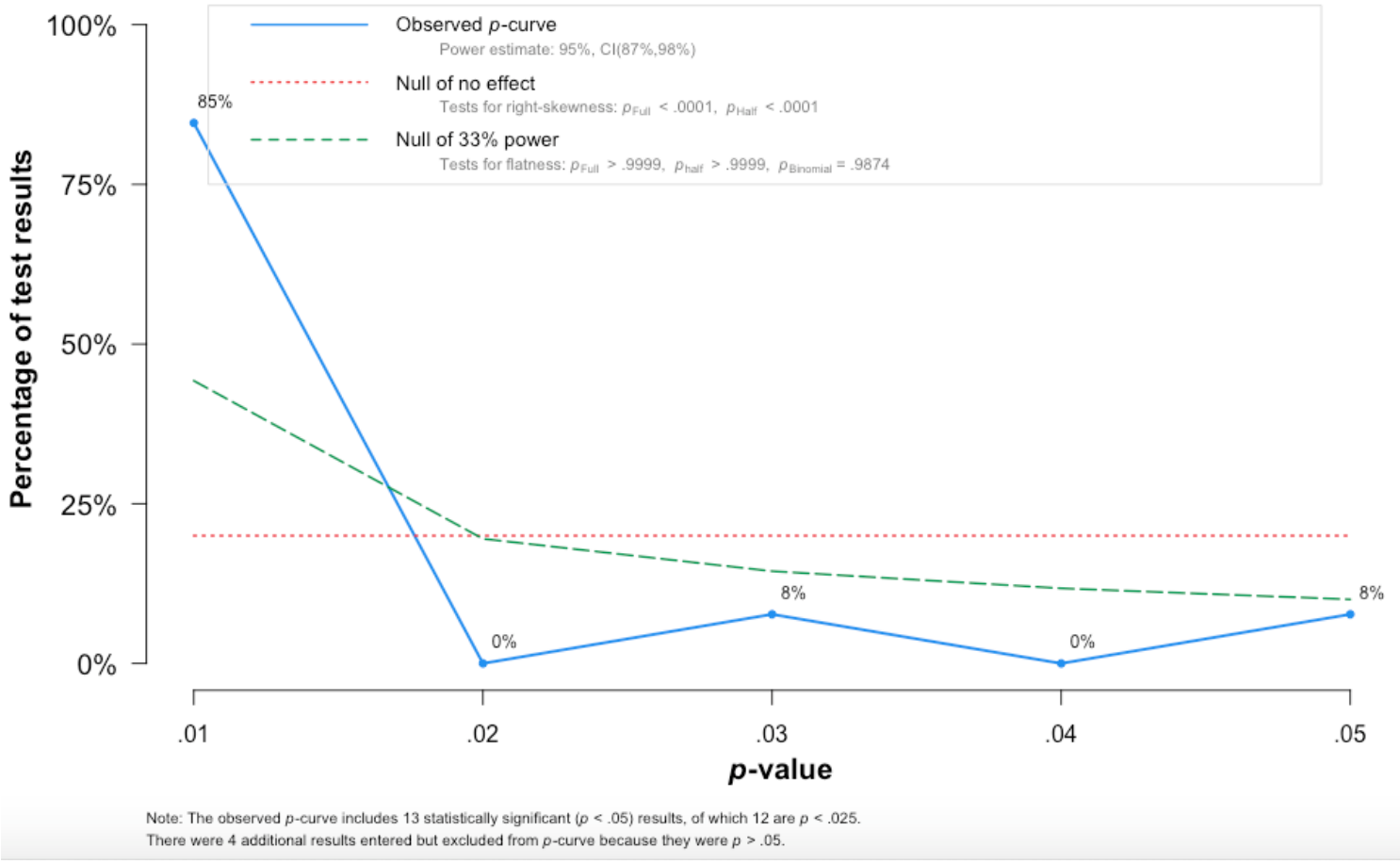

Figure 6

P-curve of comparison between dihydroartemisinin-piperaquine and artemether-lumefantrine for treatment of uncomplicated plasmodium falciparum malaria in African children on PCR unadjusted treatment failure on day 42.

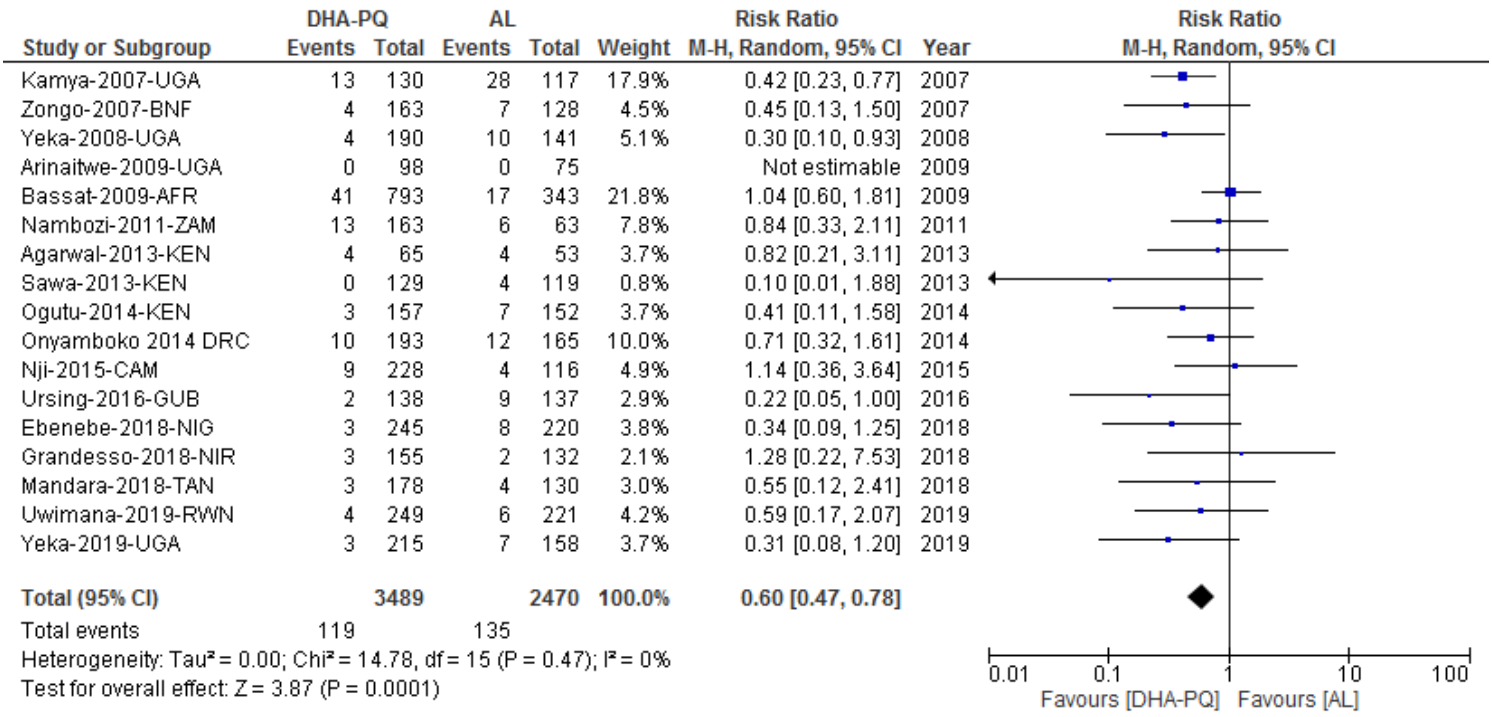

Figure 7

Forest plot of comparison between dihydroartemisinin-piperaquine and artemether-lumefantrine for treatment of uncomplicated plasmodium falciparum malaria in African children on PCR adjusted treatment failure on day 42.

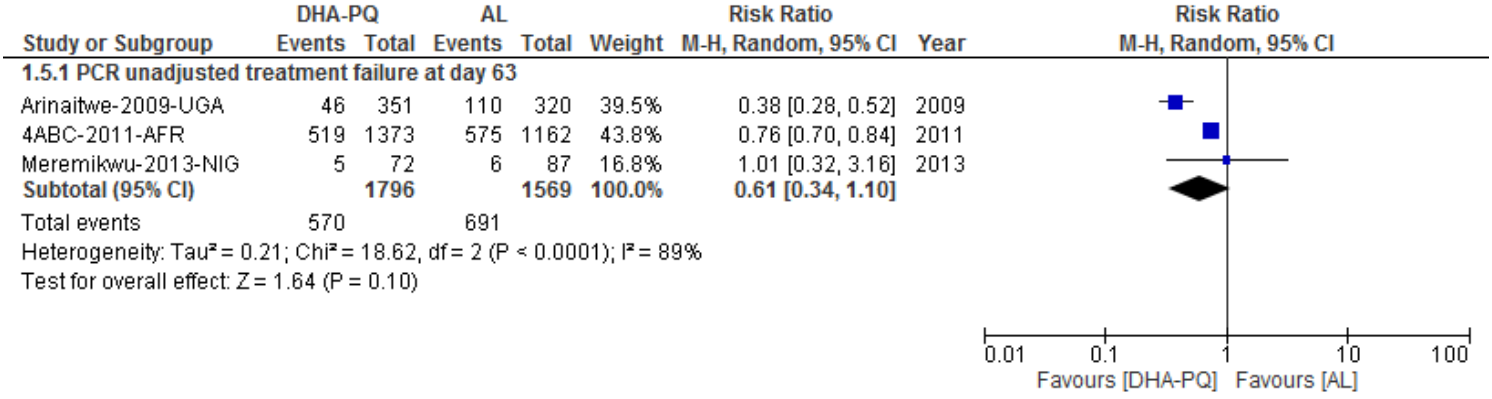

Figure 8

Forest plot of comparison between dihydroartemisinin-piperaquine and artemether-lumefantrine for treatment of uncomplicated plasmodium falciparum malaria in African children on PCR unadjusted treatment failure on day 63.

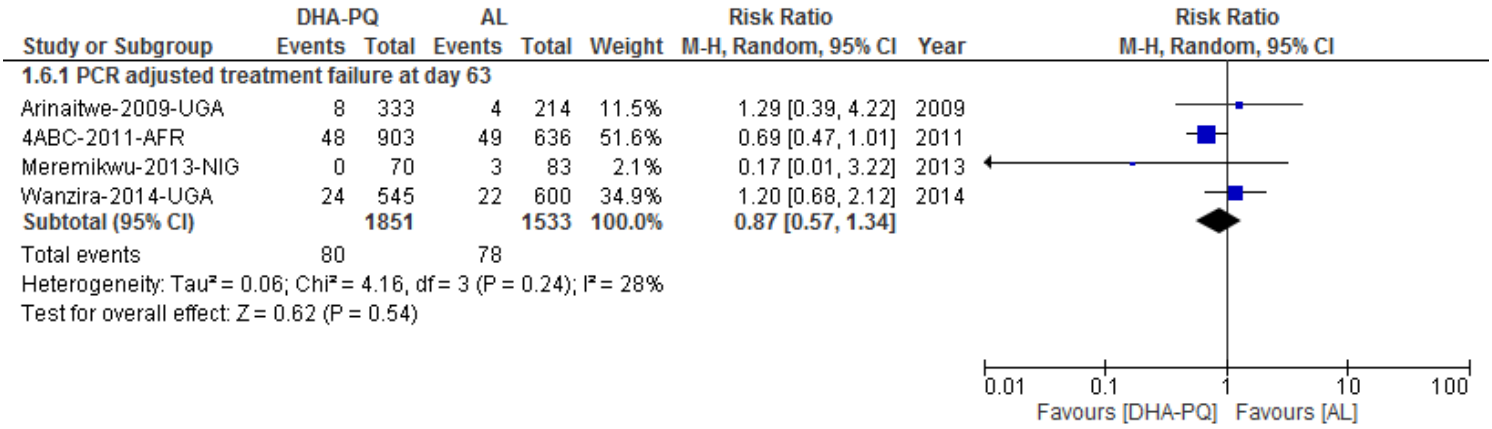

Figure 9

Forest plot of comparison between dihydroartemisinin-piperaquine and artemether-lumefantrine for treatment of uncomplicated plasmodium falciparum malaria in African children on PCR adjusted treatment failure on day 63.

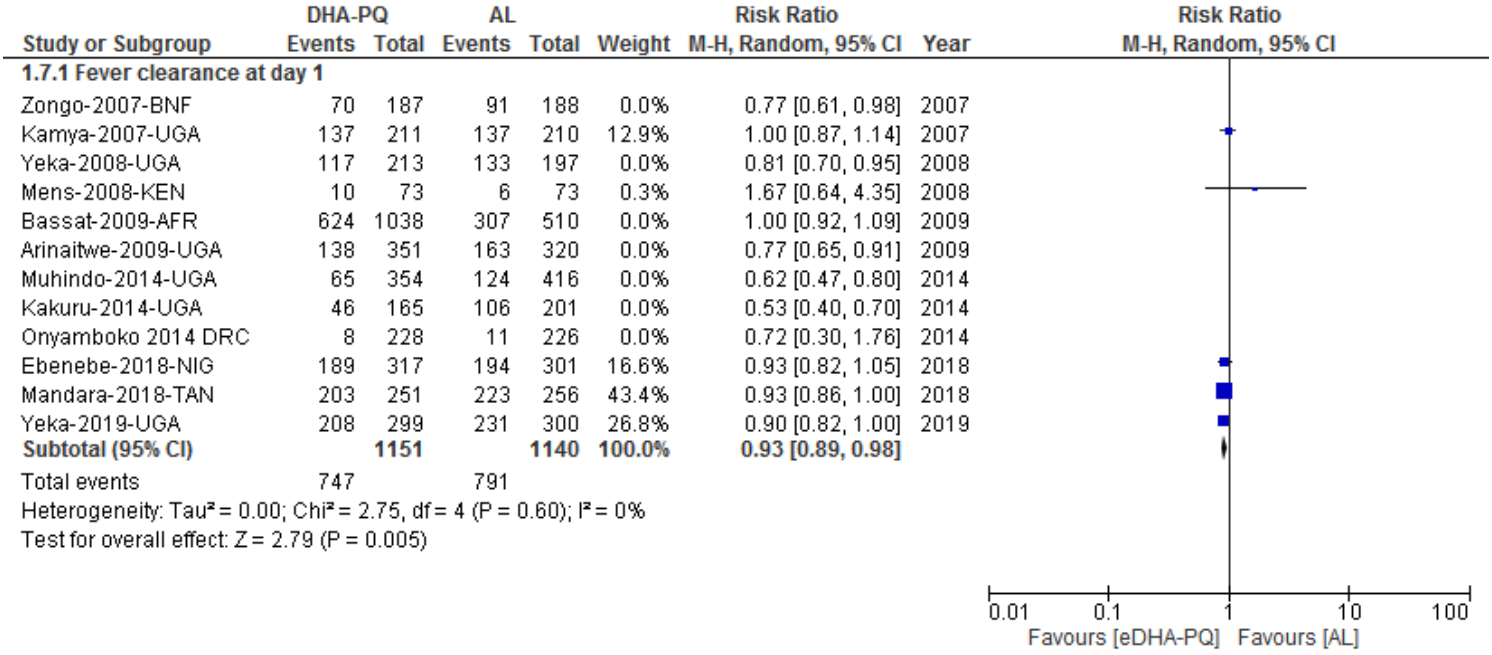

Figure 10

Forest plot of comparisonbetween dihydroartemisinin-piperaquine and artemether-lumefantrine for treatment of uncomplicated plasmodium falciparum malaria in African children on Fever clearance on day 1.

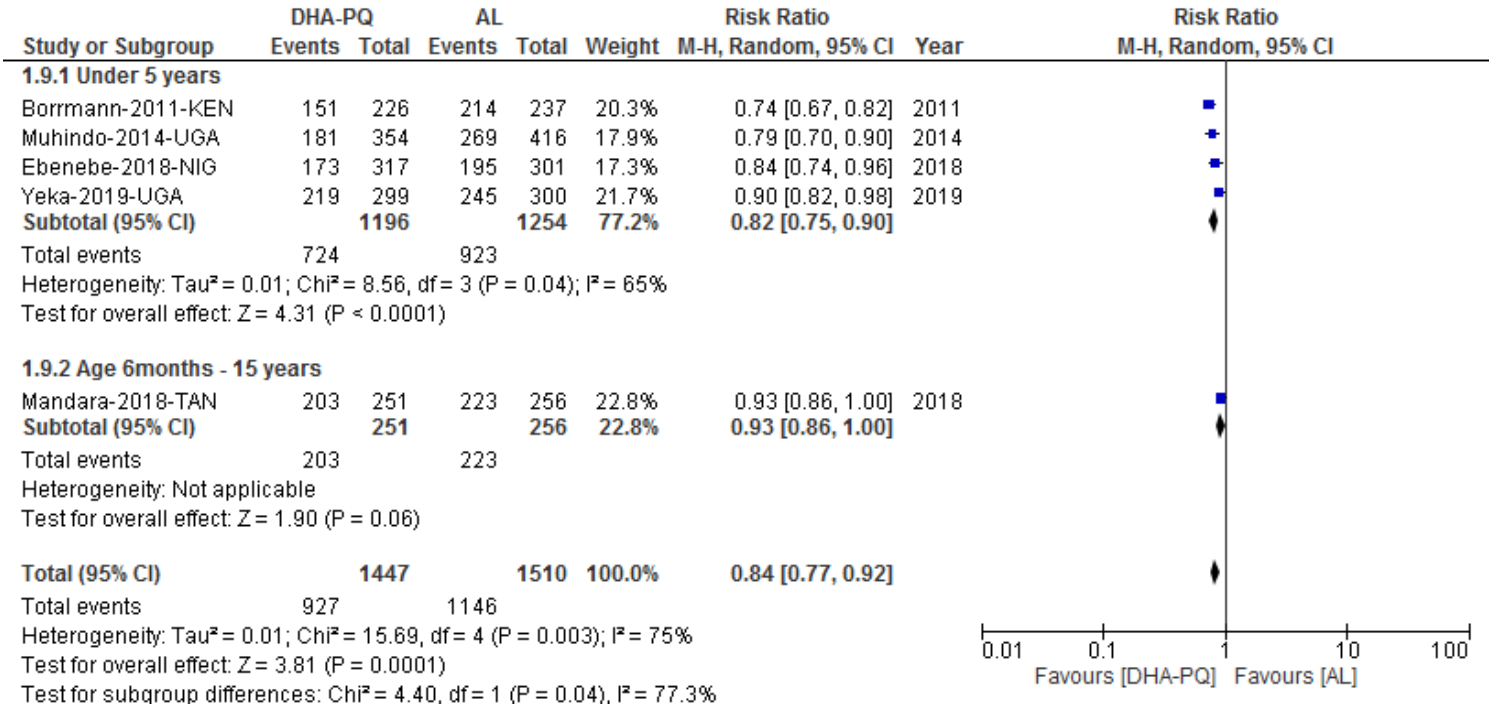

Figure 11

Forest plot of comparison between dihydroartemisinin-piperaquine and artemether-lumefantrine for treatment of uncomplicated plasmodium falciparum malaria in African children on Parasite clearance on day 1.

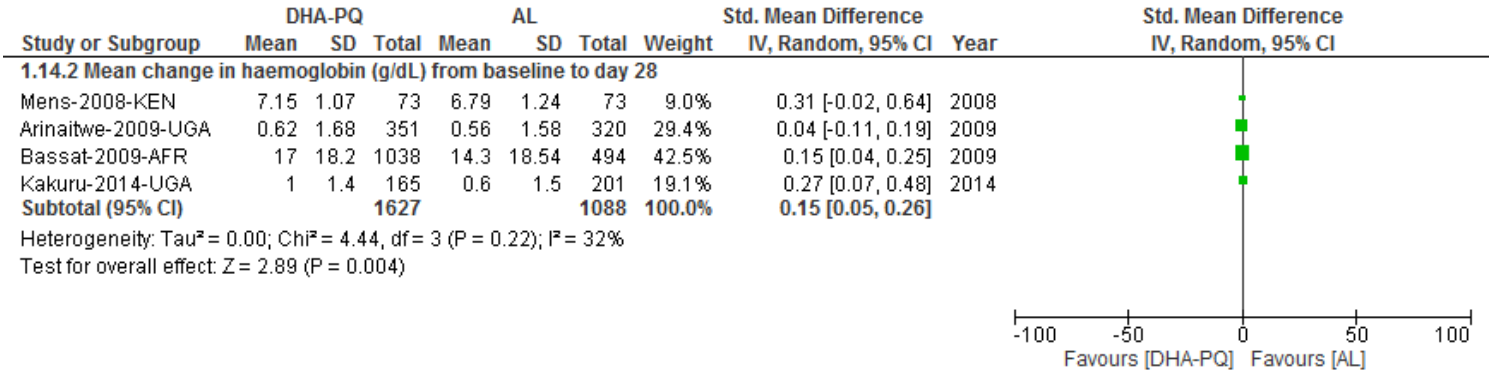

Figure 12

Forest plot of comparison between dihydroartemisinin-piperaquine and artemether-lumefantrine for treatment of uncomplicated plasmodium falciparum malaria in African children on Anemia.

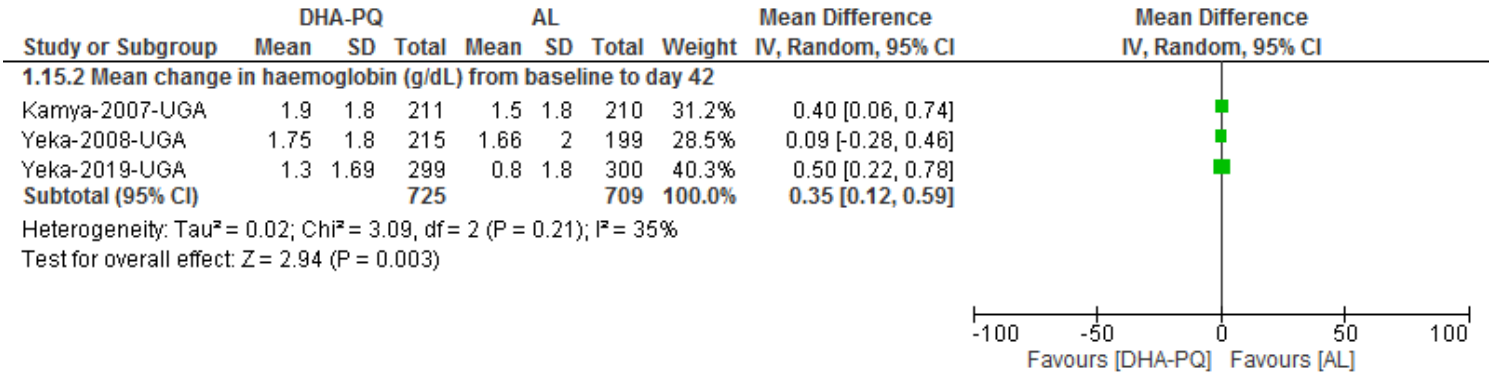

Figure 13

Forest plot of comparison between dihydroartemisinin-piperaquine and artemether-lumefantrine for treatment of uncomplicated plasmodium falciparum malaria in African children on Anemia.

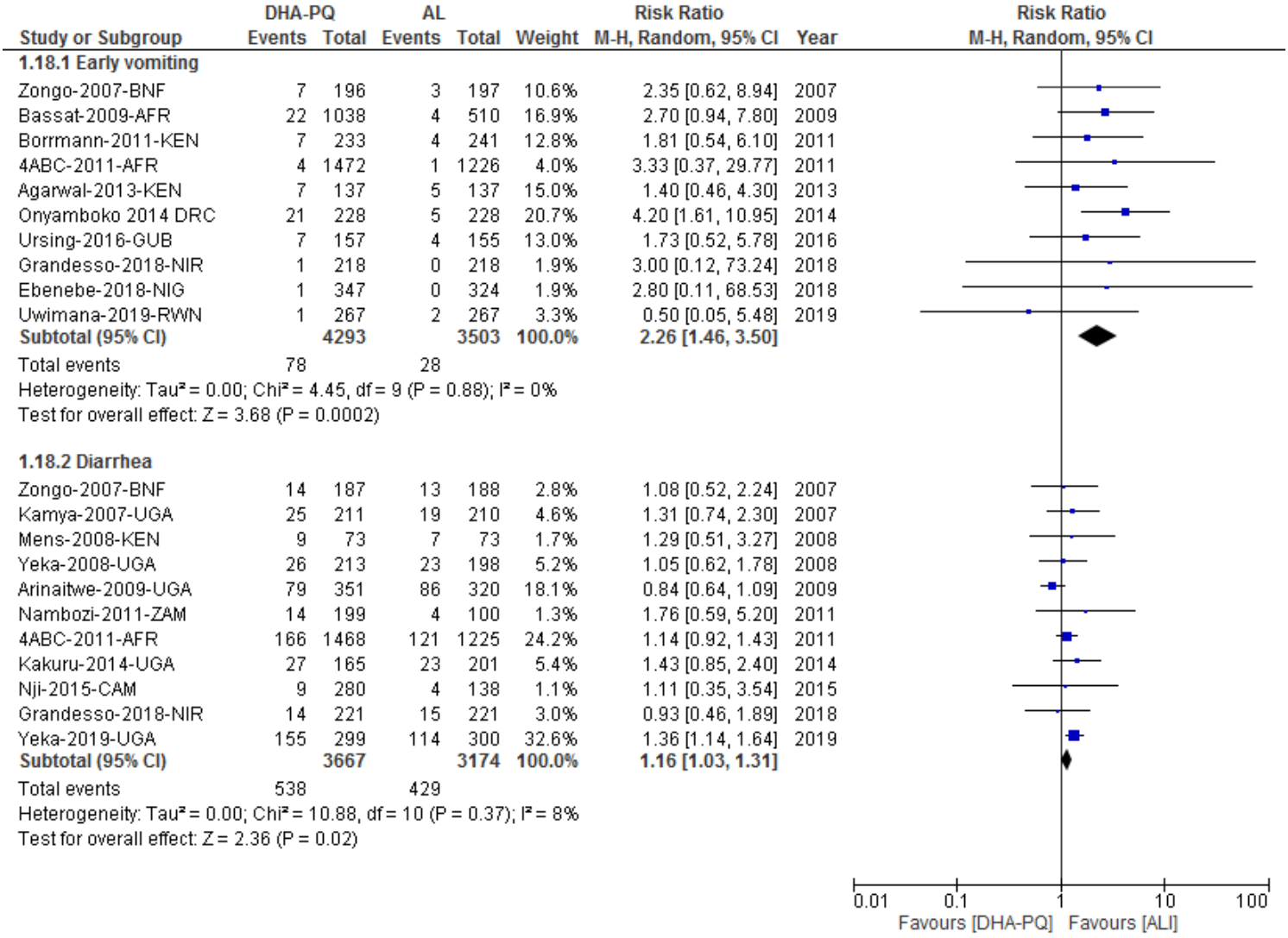

Figure 14

Forest plot of comparison with dihydroartemisinin-piperaquine and artemether-lumefantrine for treatment of uncomplicated plasmodium falciparum malaria in African children on Gastrointestinal adverse events.

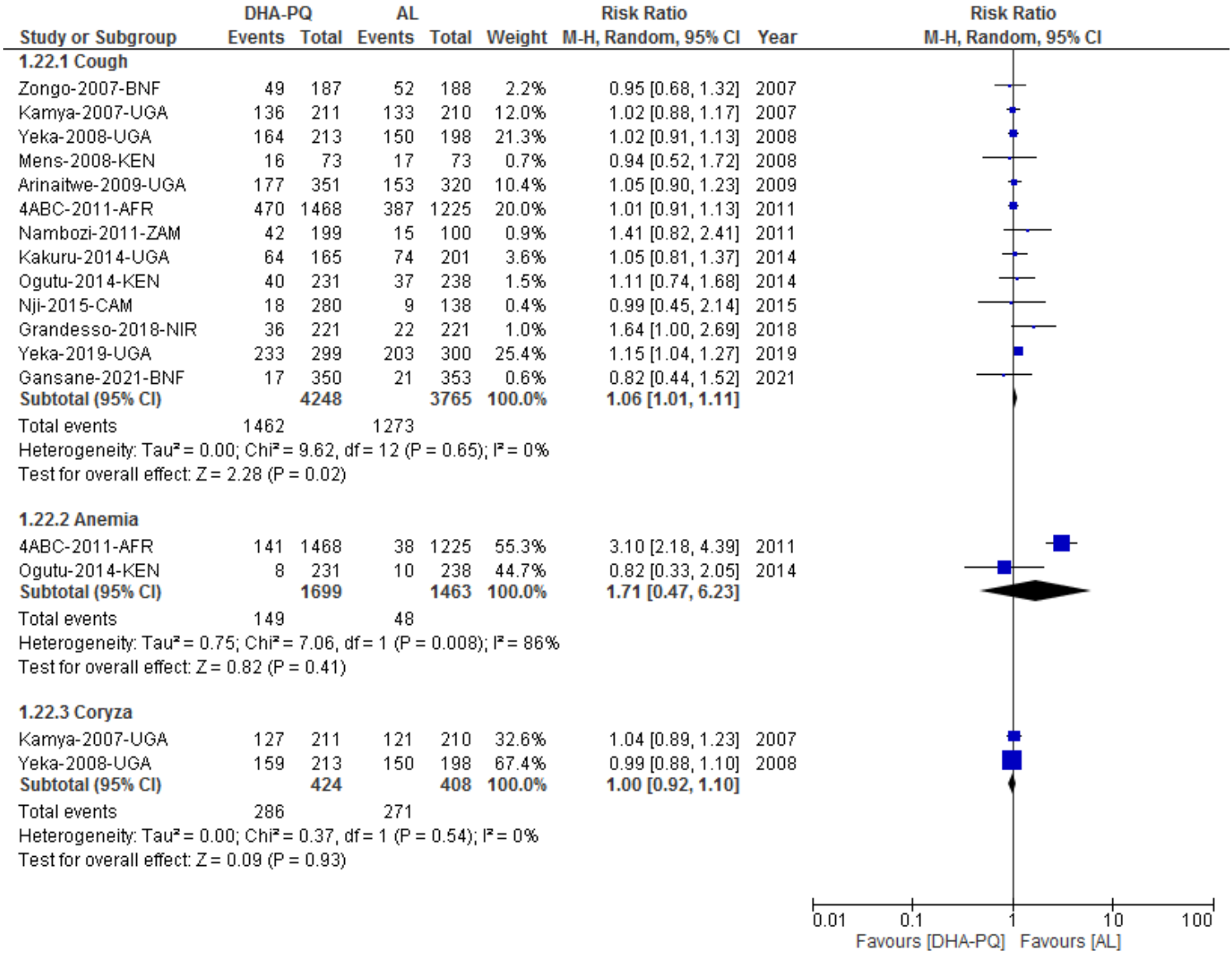

Figure 15

Forest plot of comparison between dihydroartemisinin-piperaquine and artemether-lumefantrine for treatment of uncomplicated plasmodium falciparum malaria in African children on Cardio-respiratory adverse events.

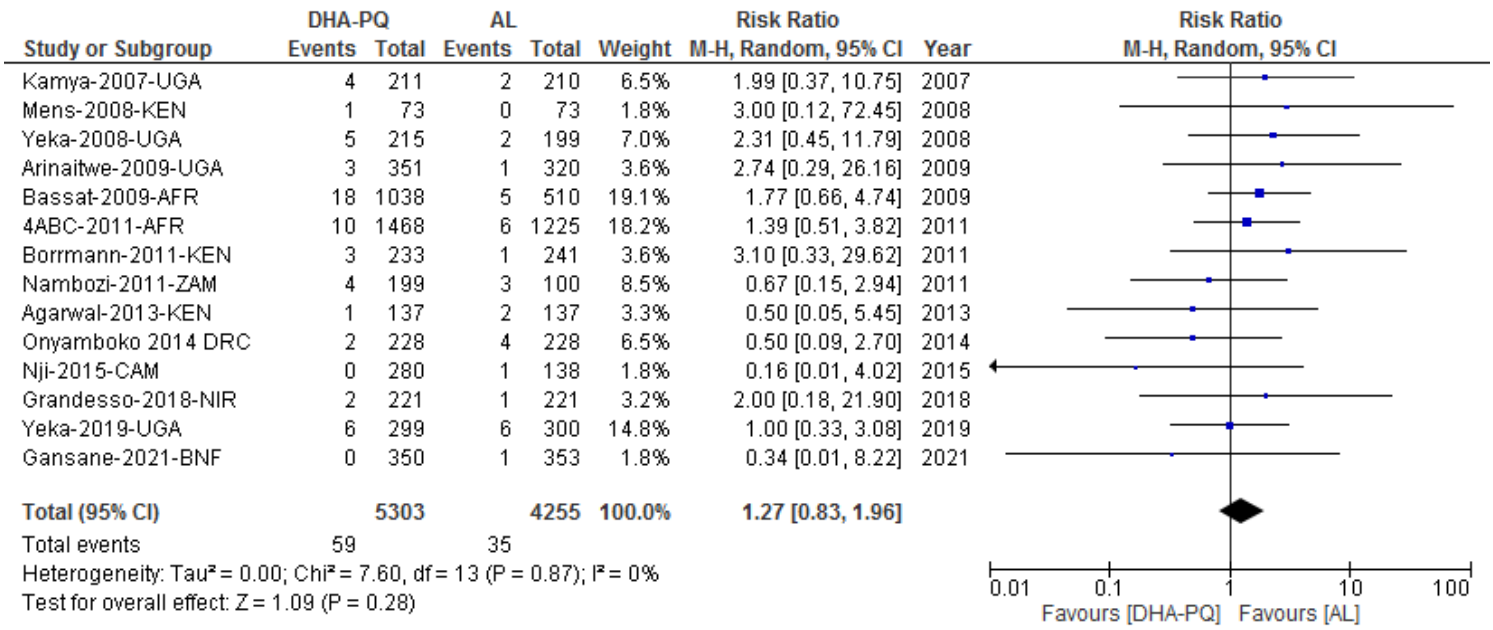

Figure 16

Forest plot of comparison between dihydroartemisinin-piperaquine and artemether-lumefantrine for treatment of uncomplicated plasmodium falciparum malaria in African children on Serious adverse event (including death).

Supplementary Files

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- AdditionalfileS15.docx
- AdditionalfileS16.docx
- AdditionalfileS17.docx
- AdditionalfileS18.docx
- AdditionalfileS19.docx
- AdditionalfileS20.docx
- AdditionalfileS21.docx