Comparison of efficacy and safety of dihydroartemisinin- piperaquine versus artemether-lumefantrine for the treatment of uncomplicated falciparum malaria in African children: Systematic review and meta-analysis of randomized control trials

By

Dawit Getachew Assefa, (BSc)

A thesis submitted to Addis Ababa University, College of Health Science, CDT-Africa in partial fulfillment of the requirements for the Master of Science Degree in Clinical Trial.

June, 2021
Addis Ababa, Ethiopia

ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCE

DEPARTMENT OF CDT-AFRICA

Comparison of efficacy and safety of dihydroartemisinin- piperaquine versus artemether-lumefantrine for the treatment of uncomplicated falciparum malaria in African children: Systematic review and meta-analysis of randomized control trials

By

Dawit Getachew Assefa, BSc

Advisors: Prof. Eyasu Makonnen

Dr. Gizachew Yismaw

A thesis submitted to Addis Ababa University, College of Health Science, CDT-Africa in partial fulfillment of the requirements for the Master of Science Degree in Clinical Trial

June, 2021

Addis Ababa, Ethiopia

APPROVAL BY THE BOARD OF EXAMINATION.

This thesis by Dawit Getachew Assefa is accepted in its presence from the board of examiners as satisfying the thesis requirement for the Master of Science Degree in Clinical Trial.

EXAMINERS:

Prof. Asrat Hailu	PhD. Professor	_____	_____
Name	Rank	Signature	Date
Dr. Alemayehu Bekele	PhD.	_____	_____
Name	Rank	Signature	Date

RESEARCH ADVISORS:

1. Prof. Eyasu Makonnen	Professor	_____	_____
Name of principal Advisor	Rank	Signature	Date
2. Dr. Gizachew Yesmaw	PhD	_____	_____
Name of Co-Advisor	Rank	Signature	Date

DEPARTMENT HEAD:

Dr. Abebaw Fikadu	PHD. Associate professor	_____	____
Name	Rank	Signature	Date

Table of Content

List of Tables

List of Figures

List of Acronyms/ Abbreviations

ACT	Artemisinin-Based Combination Therapy
ACPR	Adequate Clinical and Parasitological Response
AEs	Adverse Events
AIC	Akaike Information Criteria
ALAT	Alanine Aminotransferase
AL	Artemether-Lumefantrine
AS+AQ	Artesunate plus Amodiaquine
AS+MQ	Artesunate plus Mefloquine
AS+SP	Artesunate plus Sulfadoxine-Pyrimethamine
ART	Anti-Retroviral Therapy
BW	Body Weight
CDT-Africa	Center for Innovative Drug Development and Therapeutic Trials for Africa
CENTRAL	Cochrane Central Register of Controlled Trials
CMA	Comprehensive Meta-analysis
CI	Confidence Interval
DBSCAN	Density-Based Spatial Clustering of Applications with Noise
DF	Degree of Freedom
DHA	Dihydroartemisinin
DHA-PQ	Dihydroartemisinin-Piperaquine
ETF	Early Treatment Failure
FDA	Food and Drug Authority
GADE	Grading of Recommendations, Assessment, Development, and Evaluations
GOSH	Graphic Display of Heterogeneity
g/dl	Grams per Deciliter
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
ID	Identification

ITT	Intention to Treat
K13	Klecher 13
LCF	Late Clinical Failure
LPF	Late Parasitological Failure
LTF	Loss to Follow-up
MH	Mantel–Haenszel
OIS	Optimal Information Size
PCR	Polymerase Chain Reaction
PICO	Population, Intervention, Comparison, and outcome
PP	Per-Protocol
PQ	Piperaquine
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized Control Trial
RDT	Rapid Diagnostic Test
RMNFS	Recurrent of Malaria by Non-*Falciparum* Species
SAE	Serious Adverse Event
SD	Standard Deviation
SE	Standard Error
SEA	South East Asia
SERCA	Sarco-Endoplasmic Reticulum Calcium Adenosine Triphosphatase
SMD	Standardized Mean Difference
SP	Sulfadoxine–Pyrimethamine
TMP-SMX	Trimethoprim and Sulfonamide Combination
URTI	Upper Respiratory Tract Infection
WHO	World Health Organization

Acknowledgements

First, I would like to thank my God the lord of wisdom and knowledge. Second, I would like to express my gratitude to Addis Ababa University, CDT Africa for funding this study and giving me this chance to join this MSc program and Prof.Eyasu Makonnen and Dr.Gizachew Yesmaw for their continuous follow-up and mentorship.

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. While the concern on resistance in South East Asia but with potential benefits of DHA-PQ over other ACTs, it is necessary to assess if the antimalarial treatment efficacy of this regimen in Africa has changed. 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: An electronic systematic search method was used to search for articles from online databases PubMed/ MEDLINE, Embase, and Cochrane Center for Clinical Trial database (CENTRAL) for repossessing randomized control trials comparing efficacy and safety of DHA-PQ and AL for management of uncomplicated *Plasmodium falciparum* malaria in African children. The search was done from August 2020 to 30 April 2021. Using Rev-Man software (V5.4), R-studio, and Comprehensive Meta-analysis software, the data obtained from the included studies were assembled as risk ratio (RR), MD, and SMD with 95% confidence interval (CI). The per-protocol analysis was used.

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 to 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 risk of treatment failure adjusted by PCR 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. However, DHA-PQ was somewhat coupled with a higher incidence 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 recurrent 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 an alternative first line treatment for uncomplicated *falciparum* malaria in Africa, while use of AL continues.

Keywords: Uncomplicated *Plasmodium falciparum*, children, Randomized control trial, Artemisinin combination therapies, Dihydroartemisinin-piperaquine, Artemether-lumefantrine, Systematic review and meta-analysis, Africa

Chapter one: Introduction

Background

Malaria is the main reason for two third of deaths among children under the age of five though it is a preventable and treatable disease. It is caused by a protozoan *plasmodium* parasite via the bites of infected female *Anopheles* mosquitoes to infect blood cells (1-3). There are five human *plasmodium* species namely *P.falciparum, P.vivax, P.ovale (P.ovale curtisi and P.ovale wallikeri), Plasmodium Knowlesi, and P. malariae* of which *P.falciparum* and *p.vivax* are responsible for majority of malaria cases and deaths worldwide (1, 2). Four species (*P.falciparum, P.vivax, P.ovale, and P. malariae*) account for almost all human infections in Africa (1, 2).

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). Compared to 2018 global malaria case burden (1), the number of malaria cases increased by one million. In 2018, half of the global populations were in danger of malaria, and 93% of the malaria cases and 94% of deaths happened in Africa (4). Furthermore, the relative number of cases and deaths in 2017 were 231 million and 416 000 (1). Globally, 95% of all malaria cases are accounted by 29 countries and five African countries : Nigeria (27%), Democratic Republic of Congo (12%), Uganda (5%), Mozambique (4%), and Niger (3%) accounted for about 51% of all malaria cases and deaths globally (3). Most of these cases and deaths were reported from Sub-Saharan Africa countries (1, 4). However, the global malaria case incidences between 2000-2015 and between 2015 - 2019 were reduced by 27% and less than 2%, respectively (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). Nevertheless, the percentage of total malaria deaths declined by 67% in 2019 (3). *P.falciparum* was observed to be the cause for about 99.7% of malaria cases in Africa (4).

Uncomplicated malaria is a mild form of malaria with no signs of severity and/or sign of vital organ dysfunction and/or positive parasitological test (microscopy or RDT) (2, 5). It will progress to sever disease, if it is left untreated (2). Early diagnosis and prompt treatment of

malaria play a crucial role in reducing mortality and morbidity and also contributes for the reduction of malaria transmission (6).

Before antimalarial treatment is initiated for patients with suspected malaria, confirmatory diagnosis with light microscopy and rapid diagnostic tests are used to detect malaria parasite in the patient's blood (2, 7). However, polymerase chain reaction (PCR) adjusted parasitological cure rate is a recommended method for accurate estimation of anti-malarial drug efficacy in clinical trials conducted in malaria endemic areas (8).

All African counties, where *P. falciparum* malaria is endemic, have introduced the currently recommended Artemisinin-Based Combination (ACT) in the confirmed cases of *P. falciparum* malaria since 2004 (1). 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 (9, 10). 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 (11). Artemisinin and partner drugs protect each other to prevent resistance development. Artemisinin derivatives are safe and well-tolerated by children; therefore, the safety and tolerability of partner drug determine the choice of ACT. This has substantial contribution for reduction of malaria cases worldwide (5, 12-14)**.**

Description of interventions

Artemisinin-based combination therapies (ACTs) recommended for treating uncomplicated *P. falciparum* malaria by the WHO include dihydroartemisinin-piperaquine (DHA-PQ); artesunate plus mefloquine (AS+MQ); artemether-lumefantrine - six doses regimen (AL); artesunate plus amodiaquine (AS+AQ); and artesunate plus sulfadoxine-pyrimethamine (AS+SP) **(6).** All ACTs include a short-acting (rapidly acting) artemisinin derivative (such as artesunate, artemether, or dihydroartemisinin), combined with a longer-acting (more slowly eliminated) drug **(5).**

Artemether-Lumefantrine Combination

Artemether is obtained from the Chinese herb sweet wormwood (Artemisia annua). It interferes with parasite transport proteins, disturb parasite mitochondrial function, and modulate host immune function (15). After oral administration of artemether absorbed rapidly and within two hours after dosing it reaches maximum plasma concentration and clear malaria parasites from circulation (16). It has a half-life of 1-5 hrs. It is quickly bio-transformed to its active metabolite dihydroartemisinin (DHA) (17). It gets peak plasma concentration 2-3 hours after dosing. Both artemether and dihydroartemisinin significantly reduce asexual parasite load by 10,000 fold (4 log) per reproductive cycle, with enhancement of symptoms resolution (18).

Lumefantrine is aryl-amino alcohol (17) that prevents clearing of heme (19). It is abosrbed after two hours of oral administration and reaches the maximum plasma concentration after 3-4 hours (20), and has a half-life of 3–6 days and prevents recurrent malaria parasitemia (21). It keeps clearing the residual parasites remaining after artemether and dihydroartemisinin have been cleared from the body and thus prevents recrudescence (16, 19). Ndebutylation metabolized lumefantrine (17) to desbutyllumefantrine which has 5–8-fold higher antiparasitic effect than lumefantrine (22).

Artemether and lumefantrine act at different sites in the parasite life cycle and their mode of action is different from each other (23, 24). Fat containing foods enhance absorption of lumefantrine (16, 20).

Dihydroartemisinin-piperaquine (DHA-PQ) Combination

Dihydroartemisinin is the main potent metabolite of artemisinin derivative and achieves high concentrations in red blood cells infected with *P. falciparum* (6, 25), and compared to other anti-malaria drugs, it clears parasites from the blood and relieves clinical symptoms faster (6). The endoperoxide bridge of DHA appears to be essential to its antimalarial activity, resulting in free radical damage to parasite membrane systems (25). DHA hampers with mitochondrial electron transport and parasite transport proteins, as well as inhibiting

plasmodial sarco-endoplasmic reticulum calcium adenosine triphosphatase (SERCA), and disrupting parasite mitochondrial function (25, 26).

Piperaquine is a bisquinoline antimalarial drug with close structural similarity to chloroquine with unknown exact mechanism of action (25). It has a very long half-life between 2-3 weeks, i.e., longer than lumefantrine, providing a long period of post treatment prophylaxis (particularly in areas of low or seasonal transmission) (6, 11). Within 3 hrs of each dose food should not be given to the child or it should be administered at least 3 hrs after food and high fat containing foods should be avoided because it accelerate the absorption of piperaquine, thereby increasing the risk of QTc interval prolongation (2, 25).

Literature review

Artemether-lumefantrine and dihydroartemisinin-piperaquine combination

Numerous trials have reported that dihydroartemisinin/piperaquine is highly effective in the treatment of uncomplicated *P. falciparum* malaria (27-31). A previous review reported that pyrexia, early vomiting, diarrhea and prolongation of QT interval on day 2 post treatment were common in patients treated with DHA-PQ (25). Administration of DHA-PQ with food could increase piperaquine exposure and it needs to be administered in fasting state (32-34). However, adverse drug reactions observed for DHA-PQ were generally mild in severity, and the majorities were non-serious. DHA-PQ was efficacious, safe, and well-tolerated in the treatment of uncomplicated malaria (30, 35). In addition to efficacy and safety of anti-malaria drugs, factor like cost has a curtail role for the choice of appropriate ACT (36) and previous cost effectiveness studies reported that DHA-PQ is more cost effective in areas where malaria transmission intensity is low to high (37-39).

The six-dose regimen of artemether/lumefantrine has been effective in many different patient populations worldwide, steadily achieving 28 and 42 days PCR corrected cure rates of >95% in the evaluated population, rapidly clearing parasitemia and fever, and demonstrating a significant gametocidal effect (28, 40-46). Artemether-lumefantrine combination showed good safety and tolerability profile (41, 42, 47). Hence, previous review reported mild or moderate adverse reactions on gastrointestinal tract and nervous systems (48).

A former review reported that the total treatment failure unadjusted by PCR on day 28 in African population was significantly lower in DHA-PQ than AL (13, 49). A similar kind of review also reported that the PCR unadjusted treatment failure on day 42 was significantly lower in the DHA-PQ group than AL (12, 50, 51). In addition, DHA-PQ has shown extended post-treatment prophylactic effect (52), which decreased the risk of new infections after treatment (13). Consistently, the pooled result from analysis of six studies also reported that DHA-PQ has shown excellent post-treatment protection up to 29 days (11). However, in a recent review long post treatment prophylactic effect on recurrent infection which lasts for up to 63 days has been seen on AL (51), and no difference between the two treatment groups has been shown on days 28 and 63 in Papua New Guinea and Asia (13). AL has shown a significant reduction in PCR adjusted treatment failure on day 28 in Asia (12).

A recent study conducted in African pregnant women having uncomplicated malaria reported that DHA-PQ had the best efficacy and an acceptable safety profile, while AL had smallest number of adverse effects with acceptable cure rates and shortest post-treatment prophylaxis effect (53). A recent study conducted in Mali also reported that PCR unadjusted treatment failure on days 28 and 42 in both adults and children was significantly lower in DHA-PQ compared with AL (54). Nevertheless, both treatments can be used safely during the second and third trimester of pregnancy without any adverse effect on the baby (55).

Furthermore, in a study conducted in Cambodia- Thailand border where malaria is endemic with the most severe forms of multi-drug resistant *falciparum* malaria, the 28-day cure rate in DH-PQ groups was superior to AL and patients had good tolerance to both treatment groups (56, 57). Hence, many RCTs conducted in Africa have reported that both AL and DHA-PQ have shown excellent treatment efficacy, with genotype adjusted efficacies generally >95% and safety for the treatment of uncomplicated *P. falciparum* malaria (35, 41, 43, 44, 58-60). However, in South East Asia, high prevalence of *K13* mutations associated with artemisinin resistance was observed at two trial sites (61).

Statement of the problem

The efficacies of artemisinin-based combinations has been excellent in Africa (41, 43), meanwhile the emergence of antimalarial resistance has become a great public health

challenge and remain to be a prominent danger to enduring malaria control efforts (62). The WHO recommended steady efficacy monitoring of artemisinin based combinations intend to be done every 2-3 years (63). Artemisinin resistance, defined as a delayed parasite clearance half-life of ≥5 h cutoff post treatment (14, 64-66) and resistance to ACT in Southeast Asia is becoming the highest concern (67). While there are so far a few reports on artemisinin resistance mediated by mutations *kelch13 (K13)* gene in Greater Mekong Sub-region (68), Sudan (69), higher prevalence (42%) in Myanmar (61), and low frequency of *kelch13 (K13)* gene mutation in 18 Sub-Saharan African countries (Cameroon, Central African Republic, Chad, Comoros Archipelago, the Democratic Republic of the Congo, Ethiopia, Gabon, Gambia, Ghana, Kenya, Madagascar, Malawi, Mali, Rwanda, Senegal, Togo, Uganda, and Zambia) (70, 71).

In addition, over the past ten years a decline in parasitological response in Nigeria (72), decrease in PCR corrected therapeutic efficacy of ACT below 80% in Burkina Faso have been noticed (73), Moreover, increase in copy number of *plasmepsin genes* associated with decrease in effectiveness of piperaquine has been arisen in South East Asia. In Cambodia, high rates of recrudescence after DHA-PQ treatment for uncomplicated malaria, with decreased efficacy of both components of the combination has shown failure of DHA-PQ (64, 74, 75). Furthermore, the emergence and spread of artemisinin resistance has become an emerging danger globally, and it needs an immediate attention (14, 76). To prevent the spread and detect artemisinin resistance early, the WHO recommended regular efficacy monitoring and surveillance (2, 77).

Although ACTs are widely used for malaria treatment in children, there are limited information about the efficacy and safety as well as the dosage of ACTs in young infants And children due to the marked difference in the metabolic characteristics of this group of the population (78). Manual conversion of the formulations that may result in under-dosing for this group and which may also lead them to treatment failure (78).

Significant of the study

While the concern on resistance in South East Asia (64, 66, 75, 79), but with potential benefits of DHA-PQ over other ACTs (13, 52), 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 (80-82), 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, done to evaluate the efficacy and safety of DHA-PQ and AL for treatment of uncomplicated *falciparum* malaria in African children in order to assist policymakers to design appropriate national treatment policies and protocol.

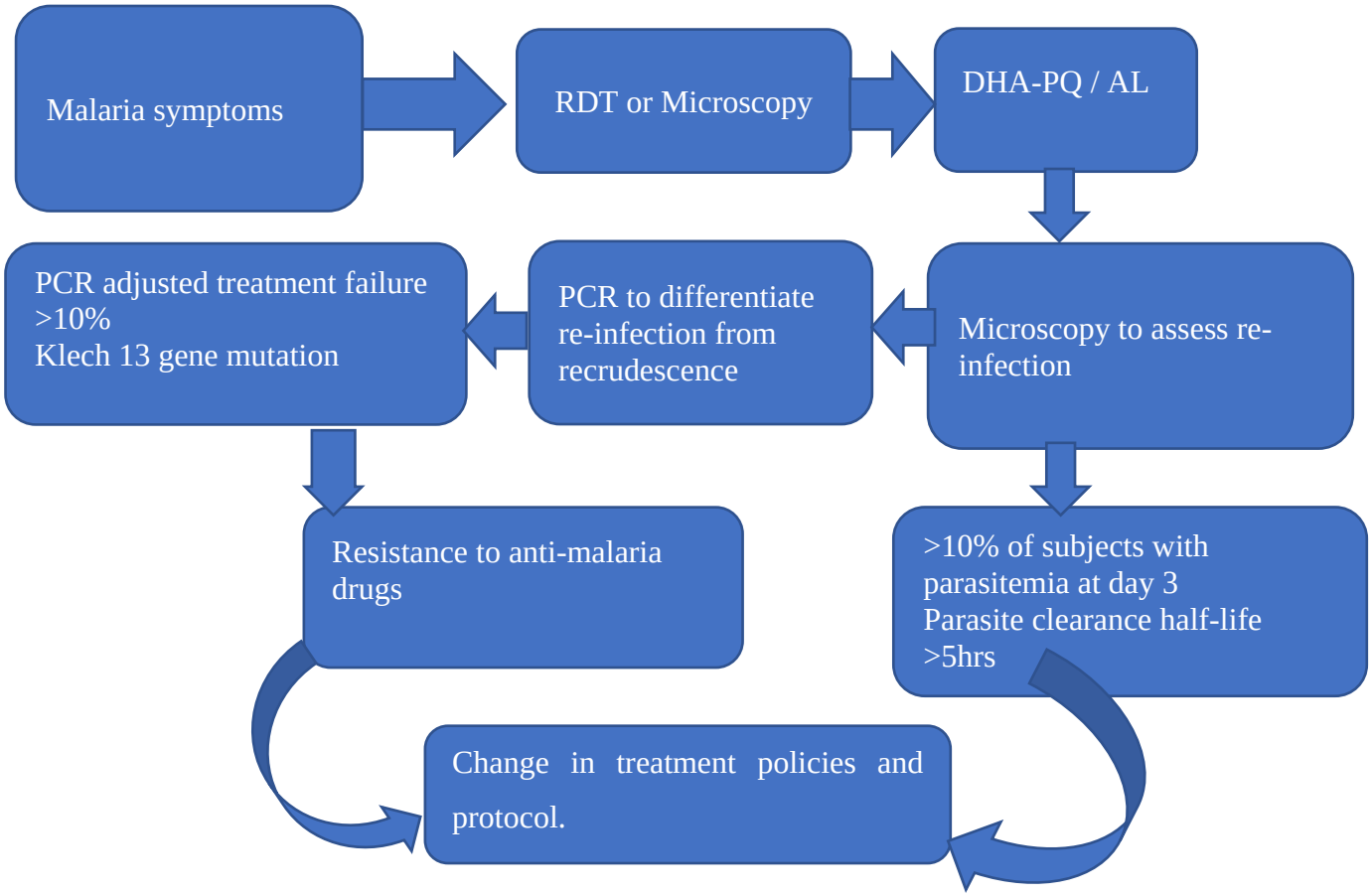

Figure 1: Conceptual framework

Chapter two: Objectives

General Objective

- To compare the efficacy and safety of dihydroartemisinin piperaquine and artemether-lumefantrine for treatment of uncomplicated *p. falciparum* malaria in African children.

Specific Objectives

- To compare the efficacy of dihydroartemisinin-piperaquine and artemether-lumefantrine for treatment of uncomplicated *p. falciparum* malaria in African children.
- To compare the safety of dihydroartemisinin-piperaquine and artemether-lumefantrine for treatment of uncomplicated *p. falciparum* malaria in African children.

Hypothesis

This study was designed to assess the hypothesis that dihydroartemisinin-piperaquine and artemether-lumefantrine have equal efficacy for treatment of uncomplicated *p. falciparum* malaria in African children.

This study was designed to assess the hypothesis that dihydroartemisinin-piperaquine and artemether-lumefantrine are equally safe and tolarable for treatment of uncomplicated *p. falciparum* malaria in African children.

Chapter three: Methods

This protocol has been registered at the International Prospective Register of Systematic Reviews (PROSPERO) database, ID: CRD42020200337 (83). The Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA 2020) guideline was followed to select studies to be included (84), **Appendix 6**.

Eligibility Criteria

Types of studies

Randomized controlled trials (RCTs) conducted in Africa which compares the efficacy and safety of DHA-PQ and AL for treatment of uncomplicated *p. falciparum* malaria in children, inscribed in English, and published between 2004 to April 2021 were included. The PICOS format was used to identify suitable studies **(85).**

Participants involved in the studies

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

Interventions used in the studies

- A fixed dose dihydroarthemisinin-piperaquine combination tablet contains 40mg dihydroartemisinin and 320mg piperaquine (2). The pediatric tablet contains 20mg dihydroartemisinin and 160 mg piperaquine. The target doses (body weight adjusted) for children whose weight was less than 25kg was 4(2-10) mg/kg per day DHA and 24(20-32) mg/kg per day PQ, once a day for 3days (2). Within 3 hrs of each dose food was not given to the child or it was administered at least 3 hrs after food

Comparator

- The 1:6 fixed dose combination tablets consists artemether (20 mg) and lumefantrine (120 mg). Body weight-adjusted doses for children include 25 to 35kg, 3 tablets per dose; 15 to 25kg, 2 tablets per dose; and <15kg, 1 tablet. It was administered twice a day for three days (total six doses). The first two doses was taken eight hours apart,

the third dose is taken after 24 hours of the first dose administration, and then every 12 hours on days 2 and 3 (2). Fat containing foods enhance absorption of lumefantrine (16, 20).

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 (63). It is classified as;

Early treatment failure *(ETF):* Dangerous signs or severe malaria within the first three days in the company of parasitemia; or parasitaemia on the second day higher than on day zero; or on the third day parasitaemia and axillary temperature > 37.5 °C; or parasitaemia on the third day > 20% of count on baseline or incidence of danger signs, or severe malaria after the third day with parasitemia; or occurrence of *falciparum* parasitemia and axillary temperature > 37.5 °C on or after 4^{th} day; or occurrence of *falciparum* parasitemia after 7^{th} day.

Late clinical failure (LCF): Dangerous signs or severe malaria in the company of parasitemia between 4^{th} day and 28 (days 4- 42) in those who did not formerly meet any of the standards for ETF; or occurrence of parasitemia between 4^{th} day and 28 (days 4- 42) with axillary temperature ≥ 37.5 °C in those who did not formerly meet any of the criteria for ETF.

Late parasitological failure (LPF): Having of parasitemia between 7th and 28 (days 7-42) with axillary temperature < 37.5 °C in those who did not formerly meet any of the criteria for ETF or LTF.

Adequate clinical and parasitological response (ACPR): Before and after genotyping by PCR was used to confirm the treatment failure and was defined as nonexistance of parasitemia by the end of treatment (day 28) irrespective of axillary temperature without previously meeting any of the benchmarks of ETF or LCF or LPF.

We used genotyping by PCR to define treatment failure consistent to current World Health Organization (WHO) recommendation (63). Adverse events including serious adverse events were also assessed.

PCR-unadjusted total failure: was calculated as the sum of LTF and ETF (without PCR adjustment). Those who didn't satisfy the inclusion criteria after randomization and those outcomes were not available (for example, those who were lost to follow-up, consent withdrew, infected with another species, or on another antimalarial) excluded from the denominator, **Table 1**.

PCR-adjusted total failure*:* calculated as the sum of ETF plus LTF due to recrudescence confirmed by genotyping. Participants with unknown PCR results, PCR results missing or PCR-proven recurrent infection were measured to be compulsory withdrawals and omitted them from the final analysis. Participants who did not satisfy the inclusion criteria after randomization, participants with (falciparum reinfection, other species mixed with *P. falciparum* recurrent infection, and unknown or PCR missing) and those participants for whom an outcome was not available (for example, those who were lost to follow-up, consent withdrawn, infected with other species, or on another antimalarial), **Table 1**.

Table 1: Primary outcome measure (Total Failure)

Analysis	Participants	PCR[1]-Unadjusted		PCR-Adjusted	
		Numerator	Denominator	Numerator	Denominator
Primary Analysis	Exclusion after enrolment [2]	Excluded[3]	Excluded	Excluded	Excluded
	Missing or indeterminate PCR	Included as failures	Included	Excluded	Excluded
	New infection	Included as failures	Included	Excluded	Excluded

Secondary outcomes

- Fever clearance: the ratio of patients afebrile within the first three days,

[1] PCR: polymerase chain reaction.
[2] Participants who were found to not satisfy the inclusion criteria after randomization are removed from all calculations.
[3] Excluded' means removed from the calculation.

- Parasite clearance: Defined as the number (n) and the proportion (%) of patients with a positive parasite count on days1, 2, and 3 as well as the number (N) of patients evaluated on those days was estimated.
- Gametocyte carriage from baseline to days 42, and
- Change in serum Hgb level from day 0 (zero to minimum 28 days and 42 days follow-up) was also evaluated.

Search methods for identification of studies

Electronic searches

An electronic systematic search method was used took for articles from online databases PubMed/ MEDLINE, Embase, and Cochrane Center for Clinical Trial database (CENTRAL. The search was limited to RCTs, human trials, and published between 2004 and April 2021. The search was conducted corresponding to direction presented in the Cochrane Handbook for Systematic Reviews of Interventions **(85)**.

The search strategies in PubMed for the MeSH terms and text words were ("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 strategy for Cochrane Center for Clinical Trial database (CENTRAL) and Embase are found in Appendix **1**.

Searching other resources

The reference sections of the selected studies and other relevant reviews were also checked for the possibility of any additional papers. In addition online trial registries: such as ClinicalTrials.gov (clinicaltrials.gov), the WHO International Clinical Trials Registry

Platform (www.who.int/ictrp), and the Food and Drug Administration (FDA; www.fda.gov) for ongoing or unpublished trials were searched.

For Dissertation and thesis, we searched online websites: such as Australian thesis (trove.nla.gov.au/), Center for Research Libraries(catalog.crl.edu/search~S5), Open Access Thesis and Dissertations (https://oatd.org/), ProQuest Dissertations & Thesis Global (www.proquest.com/products-services/pqdtglobal.html), Swedish University Dissertations (www.dissertations.se/), and Thesis Canada (www.collectionscanada.gc.ca/thesescanada/) were also searched.

Data collection and analysis

The Cochrane Handbook for Systematic Reviews of Interventions **(86)** was followed. Furthermore, the software package provided by Cochrane (RevMan 5.4) and additionally, R-Studio and Comprehensive Meta-analysis version No.3 (CMA) software's were also used.

Selection of studies

To import the research articles from the electronic databases and remove duplicates, we used ENDNOTE software version X7. The searched literatures and full-text copies of all potentially related trials were independently reviewed by two authors. Also, multiple publications from the same dataset were checked and studies included in this review based on the inclusion criteria. Disagreements were resolved through discussion. The screening and selection process was reported in a PRISMA flow chart **Figure 2**.

Data extraction and management

The title and abstract was produced from the electronic search, and was independently screened by two reviewers based on RCTs that 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 combination ratios. Also, relevant information such as title, journal, year of publication, 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 **Appendix 6**.

Furthermore, the number of participants randomized, and the number analyzed outcomes of each treatment group were also collected. Any discrepancies between the reviewers were settled by consensus. One author independently extracted data and information collected was cross-checked by another investigator. Missing data were requested from the authors whenever necessary though no one replied to our request.

Furthermore, the number of subjects with an event and the total number of subjects in each treatment arm were recorded for dichotomous outcomes and the arithmetic means and standard deviations (SD) for each treatment arm were extracted for continuous outcomes.

Assessment of risk of bias in the 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' **(85)**. To decrease the risk of bias amongst six domains: sequence generation; allocation concealment; blinding (of participants, personnel, and outcome assessors); incomplete outcome data; selective outcome reporting; and other sources of bias, this guidance were used. The ratings were done (i.e. high risk, unclear risk, and low risk) for the risk of bias, and interpretations of the presented data were guided by this information. For unclear judgment, the trial authors were contacted for clarification and differences of opinion were addressed through discussion. In the assessment of the risk of bias, the following definitions were used.

Allocation sequence generation

- **Low risk of bias:** the study performed sequence generation using computer random number-generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice will be considered adequate if an independent person, not otherwise involved in the study, performed them.
- **Unclear risk of bias:** the study authors did not specify the method of sequence generation.
- **High risk of bias:** the sequence generation method was not random.

Allocation concealment

- **Low risk of bias:** the participant allocations could not have been foreseen in advance of, or during enrolment. A central and independent randomization unit controlled allocation. The investigators were unaware of the allocation sequence (as would be if, for example, the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes).
- **Unclear risk of bias:** the study authors did not describe the method used to conceal the allocation, so the intervention allocations may have been foreseen before, or during, enrolment.
- **High risk of bias:** it is likely that the investigators who assigned the participants knew the allocation sequence.

Blinding of participants and personnel

- **Low risk of bias:** any of the blinding of participants and key study personnel ensured, and it was unlikely that the blinding could have been broken; or rarely, no blinding or incomplete blinding, but the review authors judged that the outcome was not likely to be influenced by absence of blinding.
- **Unclear risk of bias:** any of the insufficient information to permit judgments of 'low risk' or 'high risk'; or the trial did not address this outcome.
- **High risk of bias:** any of the unblinding, or incomplete blinding, and the outcome was likely to be influenced by lack of blinding; or blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome was likely to be influenced by lack of blinding.

Blinded outcome assessment

- **Low risk of bias:** any of the blinding of outcome assessment ensured, and unlikely that the blinding could have been broken; or rarely, no blinding of outcome assessment, but the reviewers judged that the outcome measurement was not likely to be influenced by lack of blinding.
- **Unclear risk of bias:** any of the insufficient information to permit judgment of 'low risk' or 'high risk'; or the trial did not address this outcome.

- **High risk of bias:** any of the unblinding of outcome assessment, and the outcome measurement was likely to be influenced by lack of blinding; or blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement was likely to be influenced by lack of blinding.

Incomplete outcome data

- **Low risk of bias:** missing data were unlikely to make treatment effects depart from plausible values. The study used sufficient methods, such as multiple imputations, to handle missing data.
- **Unclear risk of bias:** there was insufficient information to assess whether missing data, in combination with the method used to handle missing data, was likely to bias the results.
- **High risk of bias:** the results were likely to be biased, due to missing data.

Selective outcome reporting

- **Low risk:** the study reports at least one of the primary outcomes.
- **Unclear risk:** the study authors do not report all predefined outcomes fully, or it is unclear whether the study authors recorded data on these outcomes or not.
- **High risk:** the study authors report none of the predefined outcomes.

Other bias

- **Low risk of bias:** the trial appears to be free of other bias domains that could put it at risk of bias.
- **Unclear risk of bias:** the trial may or may not be free of other domains that could put it at risk of bias.
- **High risk of bias:** there are other factors in the trial that could put it at risk of bias.

Overall bias assessment

- **Low risk of bias:** all domains in a trial are classified at low risk of bias according to the definitions described above.

- **High risk of bias:** one or more of the bias domains in a trial are classified at unclear or high risk of bias. A 'Risk of bias' graph and 'Risk of bias' summary was generated to show a summary of this assessment.

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. We planned to use either ITT or Kaplan-Meier reports for our meta-analysis, but majority of the studies reported the Per-protocol analysis result. Modified intention-to-treat analyses that included all participants who met enrollment criteria and completed all follow-up visits up to the time of exclusion were used to PCR unadjusted treatment failure and safety data. Participants who were randomized to therapy but not enrolled in the study on the basis of primary laboratory results were excluded from the analysis. Per- Protocol analysis was used to assess PCR adjusted treatment failure. Those subjects who did not fulfill the inclusion criteria after randomization were excluded from the denominator, Table 1.

Risk ratio (RR) was used to report pooled results of dichotomous outcomes and using both mean differences and standard mean difference for continuous outcomes, because studies reported the outcome with different measurement scales. Risk ratios, mean differences and standard mean difference were escorted by 95% CIs.

Unit of analysis issues

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

Dealing with missing data

When data from the trial reports were insufficient, unclear, or missing, the either the outcomes or the trials were excluded from quantitative analysis.

Assessment of heterogeneity

Heterogeneity between the included trials was evaluated by look at the forest plots (to detect overlapping CI) and the Cochrane Q and I^2 statistic used to quantify heterogeneity among the included studies in each analysis, the Chi^2 test with a $P< 0.10$ used to suggest statistical

significance, and the results were elucidated following Cochrane Handbook for Systematic Reviews of Interventions Version 6.0, Chapter 10: Analyzing data and undertaking meta-analyses **(87).**

- 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

Since between study heterogeneity can also cause by one or more studies with extreme effect, we assessed the distortion in our pooled effect estimate caused by one or more studies with extreme effect sizes which did not quite fit in and studies with low quality or very small studies, we have looked on the pooled effect again by removing outliers from the analysis (88). In addition, to assess if the effect did not depend on one single study and whether there were studies which heavily pushed the effect of our analysis into one direction, we did influence case analysis (88).

To further investigate the contribution of each study to the overall heterogeneity of our meta-analysis, we used the Baujat Plot (89). The horizontal axis of the plot showed the contribution of each study to the overall heterogeneity as measured by Cochran's Q and the vertical axis showed its influence on the pooled effect size. We considered all studies on the right side (especially in the lower part) of the plot to be causes of the heterogeneity we observed.

GOSH Plot Analysis

To further investigate the pattern of effect sizes and heterogeneity in our data, we used GOSH Plot Analysis (Graphic Display of Heterogeneity (GOSH) plots). In this plot we used all 2^{k-1} possible study combinations models out of all possible randomly selected models within R-studio which fits our model. This model shows the pooled effect size on the x-axis and the between-study heterogeneity at the y-axis. Using this plot, we identified different sub-clusters with different effect size which were candidate for subgroup analysis. A symmetric distribution with one peak from the GOSH plot shows homogenous effect size in our sample. To identify which study caused the pattern and to which sub-cluster it belongs,

we looked at the three algorithms, k-means, DBSCAN and the Gaussian Mixture Model, to detected studies which could contribute to the cluster imbalance (90)**.**

Furthermore, L'Abbe plot was used to visualize the event rate, overall trend of meta-analysis, heterogeneity of effect size, and heterogeneity of event rate. When substantial heterogeneity (I^2> 50%) was recognized, it was reported, and the likely causes were investigated by subgroup analyses.

Subgroup analysis and investigation of heterogeneity

To look into the possible causes of heterogeneity, the following subgroup analyses were used:

- The malaria transmission intensity (low to moderate versus high to very high malaria transmission intensity were compared), and
- Ages of the patients (age less than five years and age between 6 months to 15 years) were compared.
- Studies at low risk of bias were computed with studies at high risk of bias in the overall assessment, because studies at high risk of bias may overrate or underrate the intervention effects.
- The known HIV status of the participant was compared to unknown HIV status in the overall assessment, because HIV infection might have an effect on parasite clearance (91).
- Supervised administration of medication was compared with unsupervised administration of medication, because non-adherence could also contribute to treatment failure.
- Eastern Africa was compared with southern and western Africa.

Meta regression

We used random-effect multiple meta-regression model to investigate the association of study characteristics which causes heterogeneity with treatment effect. To minimize over fitting, we reduced the number of predictors (parsimony) by including predictors which have scientifically proven effect on the treatment failure or based on theoretical questions. To make decision on fit model, we used estimators like *Akaike and Bayesian information criteria*. The covariates were age, HIV status, and malaria transmission intensity, risk of bias,

region, and way of drug administration (night dose). To select the predictors which had an association with effect size, all relevant predictors were forced into the regression model simultaneously. To avoid interaction between predictors, we have done interaction analysis. After checking for interaction, we performed multi-model inference for all possible predictor combinations using all predictors. Finally, we selected predictors which were best fit for the model and had lower *Akaike information criteria* (AIC). The results were presented with figures and tables.

Data synthesis

The meta-analyses was done coherent with the Cochrane recommendations **(86).** To help reading, individual 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. Included studies were listed in forest plots in chronological order of the year which the studies were published. Since the studies were conducted by different researchers and managed independently, the random effect model was used. Because, it could be unlikely that all the studies functional equivalence and had a common effect estimate.

Assessment of reporting biases

To assess the possibility of publication bias, we examined for asymmetry by funnel plots (Egger's test $P<0.05$). When the Egger's test showed publication bias, we used Duval & Tweedie's trim-and-fill procedure to estimate what the actual effect size could have been had the "missing" small studies been published**.** The procedure imputes missing studies into the funnel plot until symmetry was reached again (92). However, this procedure has been shown to be prone to providing inaccurate effect size estimates. We used P-curve 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 (92, 93).

Sensitivity analysis

A series of sensitivity analyses were conducted to explore the potency of the methodology used in the primary analysis and to reinstate the reliability 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 explore the effect 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

'Summary of Findings' tables

Confidence in the evidence were assessed using GRADE criteria and the GRADE pro software (94). We presented the result in a ‘Summary of Findings’ table. Assessments of the evidence were presented using five factors referring to limitations in the study design and implementation of included studies that suggest the quality of the evidence: risk of bias; indirectness of evidence (population, intervention, control, outcomes); unexplained heterogeneity or inconsistency of results; imprecision of results; and a high probability of publication bias. Randomized control trials are initially categorized as high quality but downgraded after assessment of five criteria (95). 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 (96). These grades are defined as follows.

- **High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- **Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

We have judged the imprecision based on the optimal information size criteria and confidence interval (97). We were rate down grade the imprecision;

- If an OIS criterion was not met, we rated down for impression unless the sample size was very high (at least 2000 participants for dichotomous outcome and 400 for continuous outcome).

- If the OIS criteria was met and the 95 % confidence interval excluded no effect (i.e. CI around RR exclude 1.00 for dichotomous outcome and MD exclude 0.00 for continuous outcome), we judged as adequate precision.
- If the OIS criteria was met and confidence interval overlapped no effects (i.e CI include RR of 1.00 for dichotomous and MD exclude 0.00 for continuous), we rated down if the CI fail to exclude important benefit or important harm.
- If the 95% CI included appreciable benefit or harm (RR of under 0.75 or over 1.25), we rated down for imprecision even if the OIS was met.

Operational Definition

Adverse event: any untoward medical occurrence, irrespective of its relationship to the study medications.

Efficacy: nonexistence of parasitaemia by the end of treatment (days 28 or 42 or 63) regardless of axillary temperature without formerly meeting any of the criteria of ETF or LCF or LPF.

Medicine safety: Characteristics of medicine that reflects its potential to cause harm, including the important identified risks of a drug and important potential risks.

Parasite clearance time: Time between first drug administration and the first examination in which no parasites are present in the blood by microscopy.

Recrudescence: Recurrence of asexual parasitemia of the same genotype(s) that caused the original illness, due to incomplete clearance of asexual parasites after antimalarial treatment.

Recurrence: Reappearance of asexual parasitemia after treatment, due to recrudescence, relapse (in P. vivax and P. ovale infections only), or a new infection.

Serious adverse event: any event that resulted in inpatient hospitalization, death, life threatening experience, persistent/significant disability, or specific medical/ surgical intervention to prevent serious outcome.

Treatment failure: failure to clear malarial parasitemia or prevent recrudescence after administration of antimalarial medicine, regardless of whether clinical symptoms are resolved.

Chapter four: Result

Results of the search

We conducted the search from August 2020 to April 2021 and identified a total of 3211 studies. After screening titles and abstracts, we collected the full text copies of 49 studies of which, 24 trials were excluded for reasons mentioned in **Figure 2**. We included 25 studies for both qualitative and quantitative synthesis.

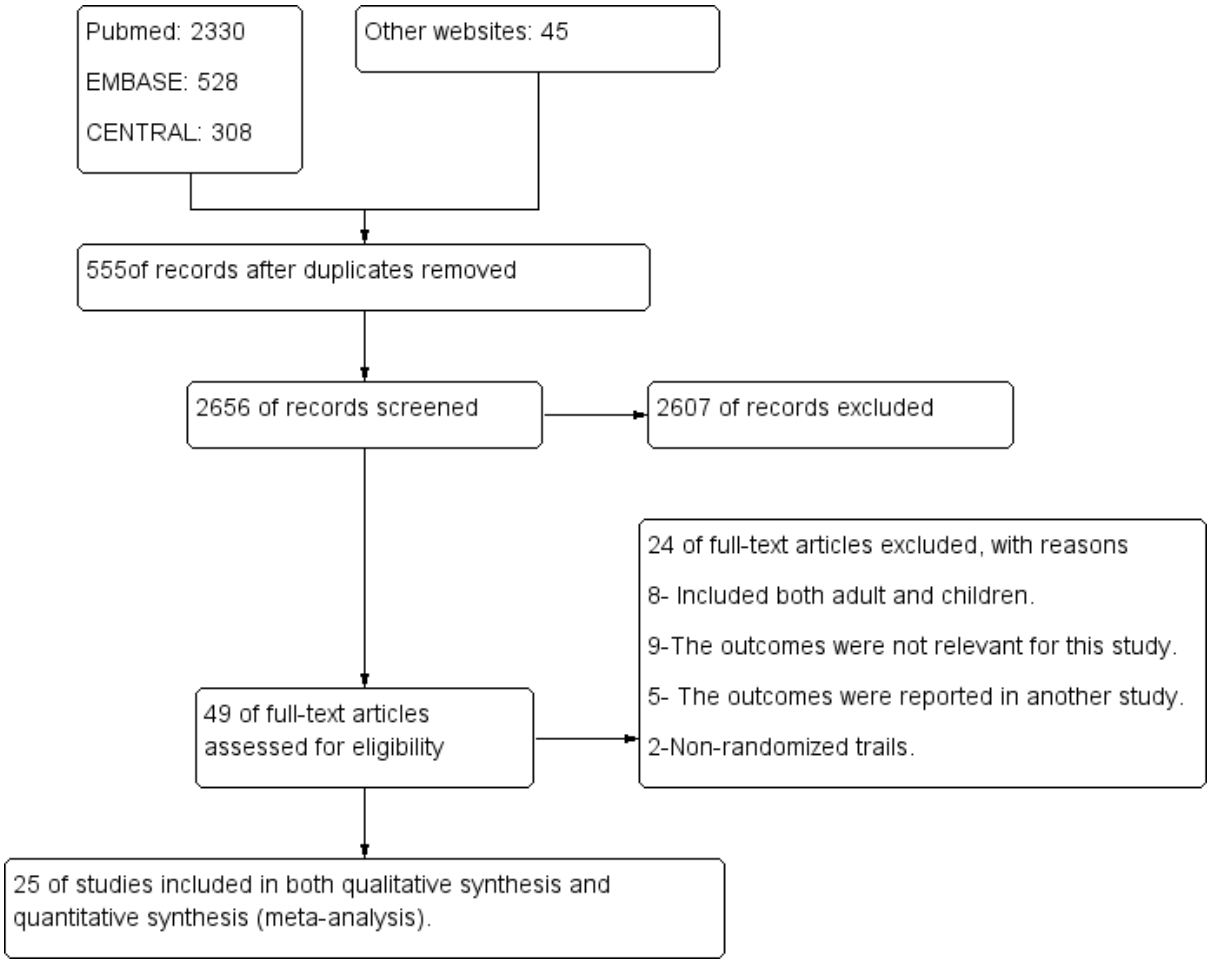

Figure 2: PRISMA study flow diagram.

Included studies

We included 25 trials which enrolled 13,198 subjects with uncomplicated *falciparum* malaria in this review. The trials were conducted in Africa. Most of the trial sites in the thirteen studies were described as having high or very high malaria transmission intensity and two as low or moderate transmission intensity. In addition, two multi-center trials were described as having mesoedemic, perennial, and high malaria transmission intensity and another two trials

sites were described as having low to high and moderate to high malaria transmission intensity, respectively Appendix **2**. Except three studies, twenty-two studies reported the number of female and male enrolled in to the studies. Totally 6798 male and 5828 female were enrolled in to the studies, whereas 3530 males and 3033 females in DHA-PQ group and 3268 males and 2795 females in AL arm were enrolled, respectively.

The included studies enrolled children between the age ranges of 6 weeks to 15 years of who the majority were between the age of 6 months to 5 years, three studies enrolled children who were HIV infected and HIV negative Appendix **2**. These three studies reported that 128 participants to be HIV infected and HIV exposed who were on anti-retroviral therapy and TMP-SMX prophylaxis. Furthermore, in majority of the trials participants were followed for 42 days.

Excluded studies

Twenty-four studies were excluded from primary analysis due to difference in the type of infection or lack of appropriate outcome data, **Appendix 4**.

Risk of bias in included studies

From all the included studies, five were single blind. The risk of bias assessment summary pretested in **Figure 3** and **Figure 4** and authors' judgments presented in the ' characteristics of included studies' table, Appendix 3.

Randomization sequence generation (selection bias)

Twenty studies were judged to be low risk for selection bias, for they adequately described random sequence generation. However, three studies are judged to be unclear for selection bias, for they didn't describe random sequence generation.

Allocation (selection bias)

Eighteen studies were judged to be low risk for selection bias, for they adequately described allocation concealment. Seven studies were judged to be unclear for selection bias, for they didn't describe adequately the allocation concealment.

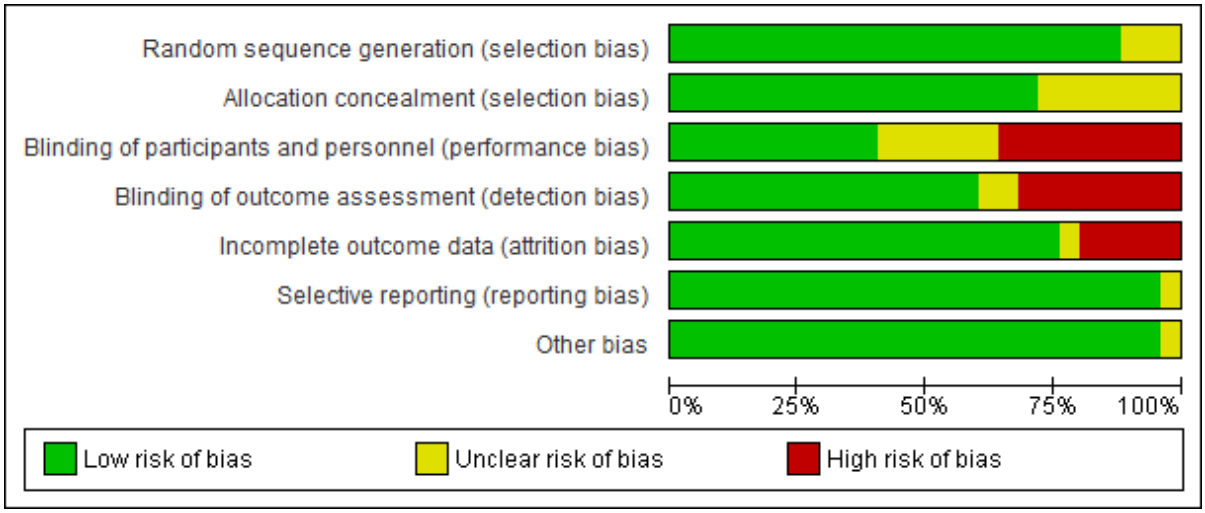

Figure 3: Review authors' judgments about the percentage of each risk of bias item across the included studies.

Blinding of participants and personnel (performance bias)

Nine trials adequately blinded the participants and study personnel were judged to be low risk for performance bias. However, nine studies were judged to be high risk for performance bias, for they didn't blind the participant and personnel and six studies were judged to be unclear risk for performance bias, for they didn't describe blinding of the participant and study personnel.

Blinding of outcome assessor (detection bias)

Fifteen studies adequately blinded the outcome assessors (laboratory staff and study physicians), hence judged to be low risk for detection bias. Eight studies were judged to be high risk for detection bias, for they didn't blind the outcome assessor and two studies were judged to be unclear risk for detection bias, for they didn't describe blinding of the outcome assessors.

Incomplete outcome data (attrition bias)

Nineteen studies were judged to be of low risk for attrition bias, and five studies were judged to be high risk for attrition bias, for they excluded more than 20% of participants from the final analysis. However, the remaining one study is judged to be unclear for attrition bias, for the study didn’t describe how many participants were enrolled and excluded.

Selective reporting (reporting bias)

One study was judged to be unclear for reporting bias, for we couldn't able to find the published protocol. However, in the remaining twenty four studies, we found no evidence of selective reporting in all included trials.

Other potential sources of bias

In majority of the studies both drug manufacturer and non-governmental organizations were involved. However, the company which funded the trial had no engagement in the trial design, data collection, data analysis, data interpretation or writing up.

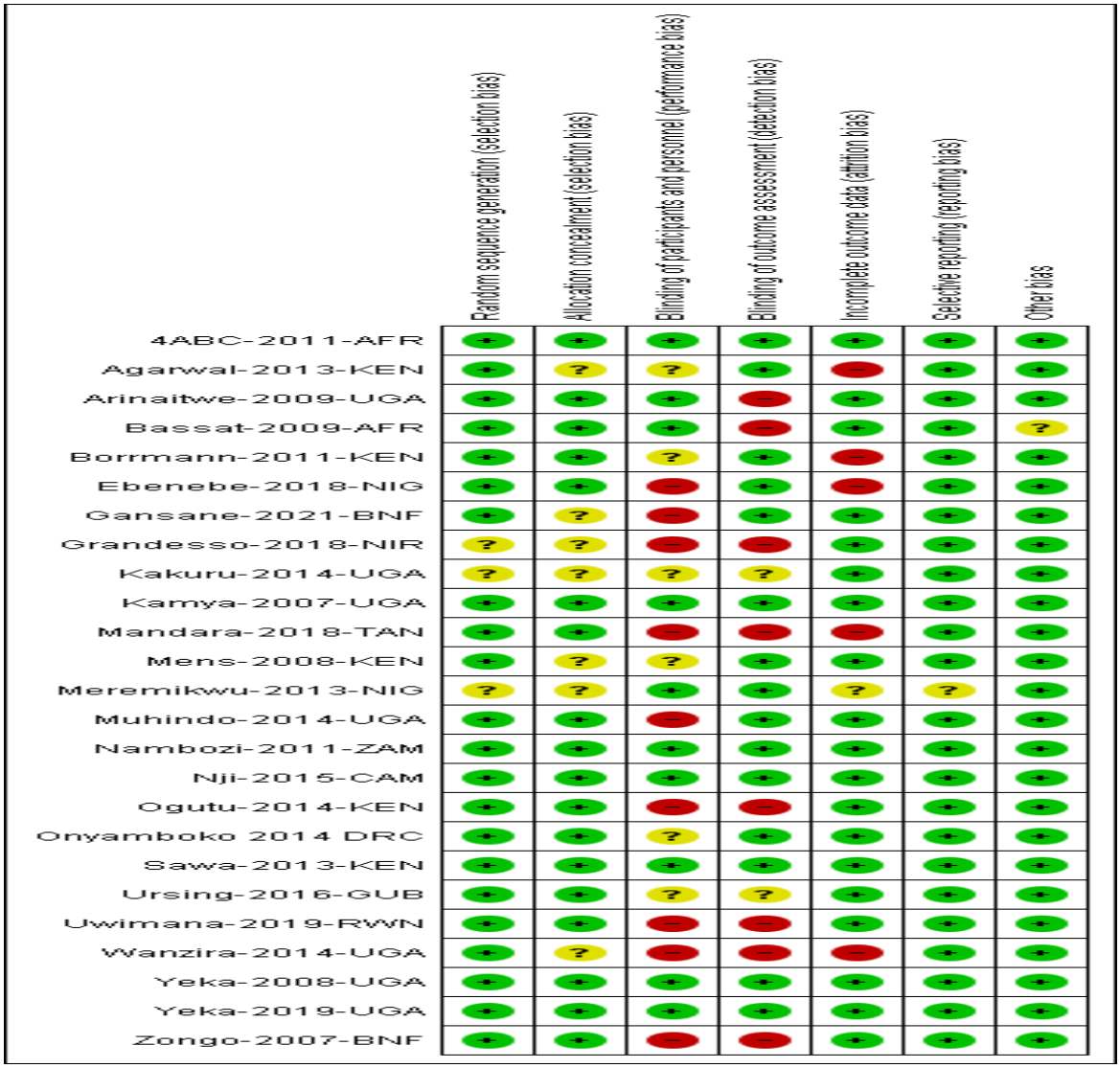

Figure 4: A summary of review authors' appraisals about each risk of bias item for each included study.

Effect of interventions

Treatment failure

PCR-unadjusted total failure on day 28

The PCR uncorrected risk of recurrent *p. falciparum* parasitemia showed considerable heterogeneity between the studies ($Tau^2 = 0.24$; $Chi^2 = 125.66$, df = 16 ($P < 0.00001$); $I^2 = 87\%$, **Figure 6**). We couldn't pool the result.

Outlier assessment and influence analysis.

To investigate the effect of outlier studies on the pooled effect estimate, we did outlier assessment and found four outlier studies. We couldn't find any influence case. However, the pooled result after removing the outliers had considerable heterogeneity ($Tau^2 = 0.1410$; tau = 0.3755; df = 12 ($P< 0.0001$); $I^2 = 73.7\%$). The Baujat plot showed that out of the four outlier studies, three had higher contributions for the heterogeneity in our meta-analysis.

Leave-one-out analysis

The result showed that out of the four outlier studies two had effects on the overall heterogeneity. When we sorted out the result by effect size, two out of the four outlier studies had an effect on the overall effect estimate.

GOSH Plot Analysis

We found two clusters one with high heterogeneity and another with low heterogeneity **Figure 5**.

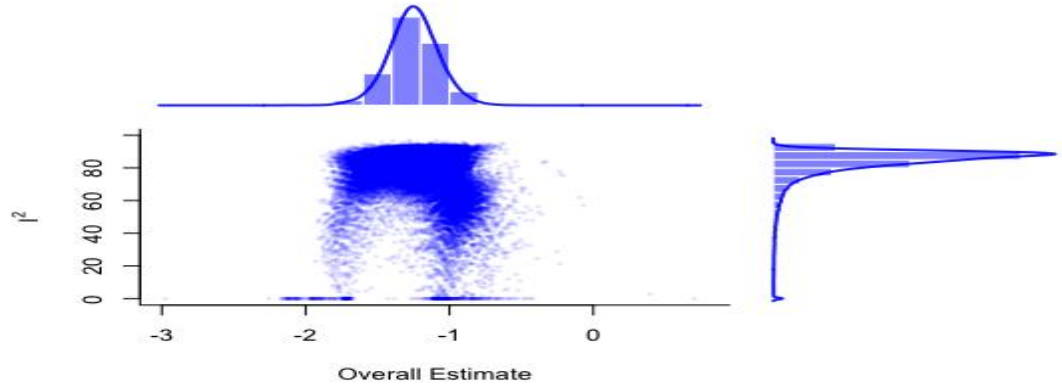

Figure 5: GOSH Plot Analysis of comparison between DHA-PQ and AL for treatment of uncomplicated *p.falciparum* malaria in African children on PCR unadjusted treatment failure on day 28.

Seven studies were detected by DBSCAN algorithm. However, the pooled result after removing those seven studies showed substantial heterogeneity between studies ($Tau^2 = 0.12$; tau= 0.35, df = 7 (P = 0.00016); $I^2 = 70\%$).

Sub-group analysis

The risk of treatment failure uncorrected by genotyping in patients between the age of 6 months to 15 years was (RR 0.14, 95% CI 0.08 to 0.26; participants = 1302; studies = 4; I^2 = 0%, *high quality of evidence*, **Figure 6**). However, the risk of treatment failure uncorrected by genotyping in under five children was heterogonous ($Tau^2 = 0.25$; $Chi^2 = 120.71$, df = 12 (P < 0.00001); $I^2 = 90\%$, *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 twelve 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, we found statistically significant difference between the two subgroups (chi^2= 5.13, df=1, p=0.02, I^2 = 80.5%, **Figure 6**).

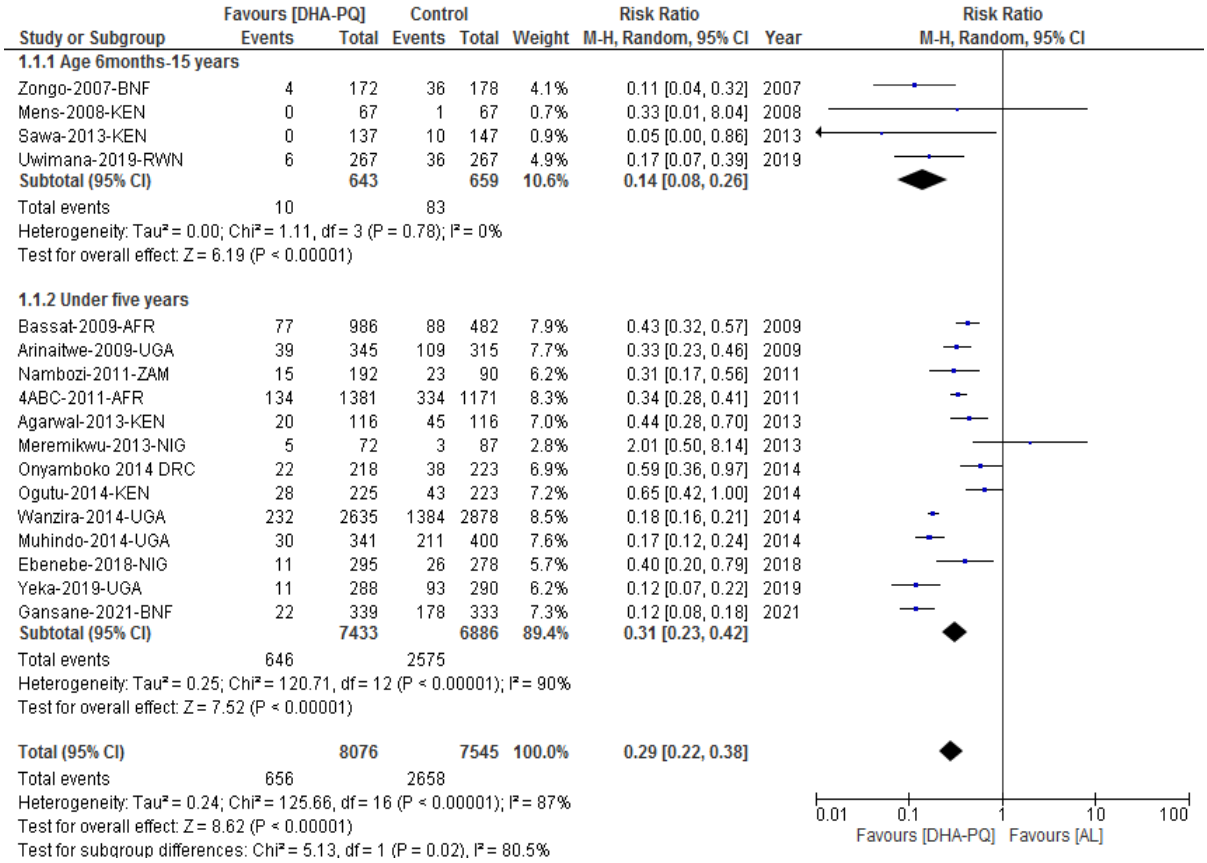

Figure 6: Forest plot of comparison between DHA-PQ and AL for treatment of uncomplicated *p. falciparum* malaria in African children on PCR unadjusted treatment failure on day 28.

Meta regression of day 28 PCR-unadjusted treatment failure

Both participants' age 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, **Figure 7 and Figure 8**). 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 higher by 42.2% compared to children living in high malaria transmission setting, keeping age of children constant **Table 2**. Furthermore, either the age of children or malaria transmission of the countries was related to treatment failure (Q=8.61, df=2, P=0.0135).

The variance in treatment failure about the regression line (Tau^2) was 0.1609, the standard deviation of true effects about the regression line (Tau) is 0.4012. The I^2 statistic is 79.55%, which tells us that 80% of the observed variance about the regression line reflects variation in treatment failure rather than sampling error. The test for heterogeneity yielded a Q-value of 68.47 with 14 degrees of freedom and a corresponding p-value ≤ 0.0000. The risk of treatment failure varied across the studies which means that some studies had high treatment failure and other studies had low treatment failure. Of the total variance in treatment failure, only 32% were explained by participants' age and malaria transmission intensity within the countries.

Table 2: **Meta- regression of PCR-unadjusted treatment failure on 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

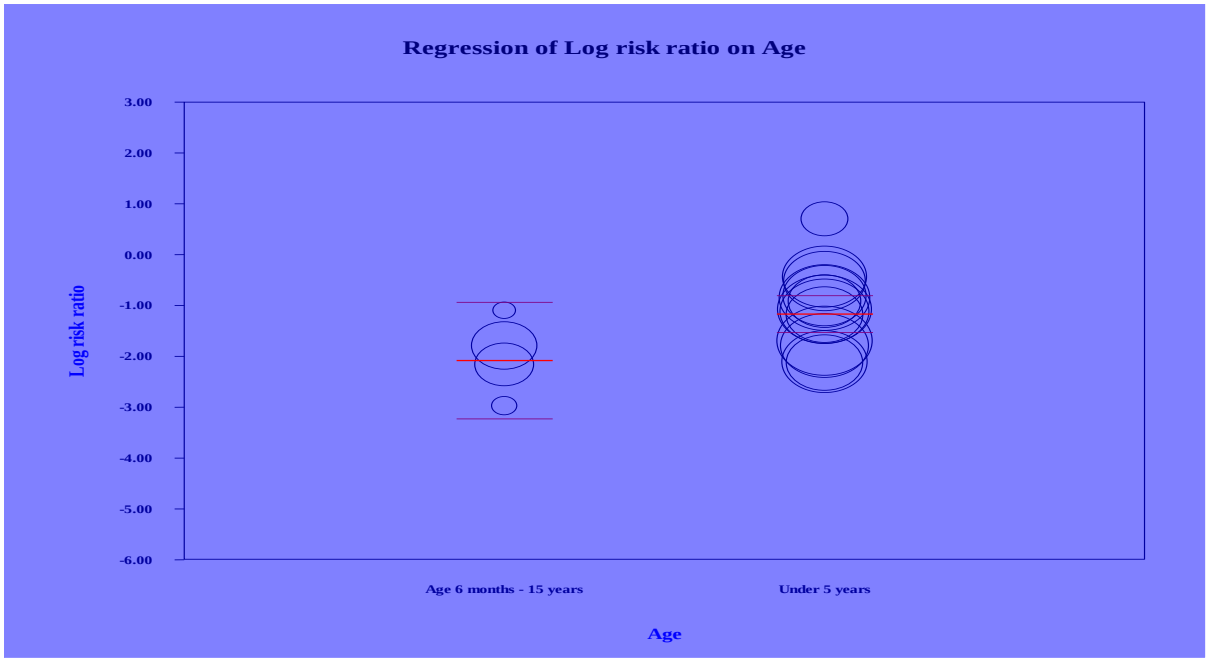

Figure 7: Meta- regression of PCR-unadjusted treatment failure on day 28, association between age of the children and treatment failure.

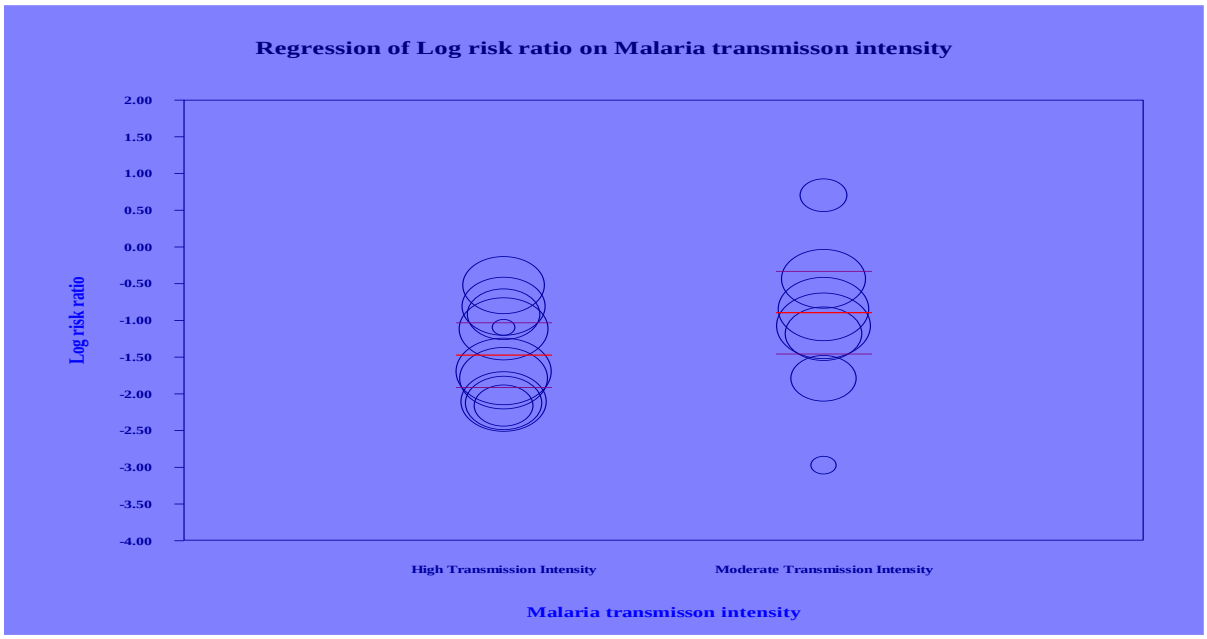

Figure 8: Meta- regression of PCR-unadjusted treatment failure on day 28, association between malaria transmission intensity within the countries and treatment failure.

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: intercept 0.98 (95% CI -1.17, 3.13), P= 0.39, **Figure 9**).

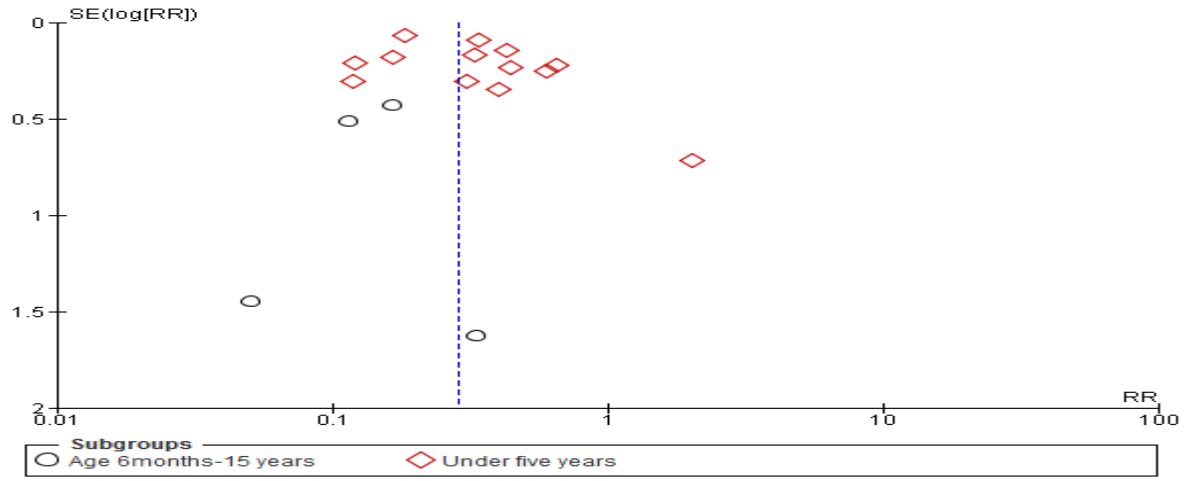

Figure 9: Funnel plot of comparison between DHA-PQ and AL for treatment of uncomplicated *p.falciparum* malaria in African children on PCR unadjusted treatment failure on day 28.

PCR-adjusted total failure on day 28

There were nineteen early treatment failures in the DHA-PQ group arm versus 30 in the AL arm. One study which was conducted in Kenya reported that PCR adjusted treatment failure on day 28 didn't have significant difference (1%) between the two treatment groups and the result of our meta-analysis showed that the risk of recurrent parasitemia due to possible recrudescence (adjusted by genotyping) was below 5% in 14 studies. On the contrary, the PCR adjusted treatment in patients who were treated with AL was 28% in one study from Burkina-Faso (73).

There was no significant difference in the risk of recurrent parasitemia in thirteen studies due to possible recrudescence between the two treatment groups. However, it was significantly lower in DHA-PQ treatment group in one multi-center trial and one study from Burkina Faso (73, 81). However, the pooled result showed that the risk of PCR corrected treatment failure was significantly lower in DHA-PQ group than that of AL on day 28(RR 0.45, 95% CI 0.29 to 0.68; participants = 8508; studies = 16; I^2 = 51%, *high quality of evidence,* **Figure 10**).

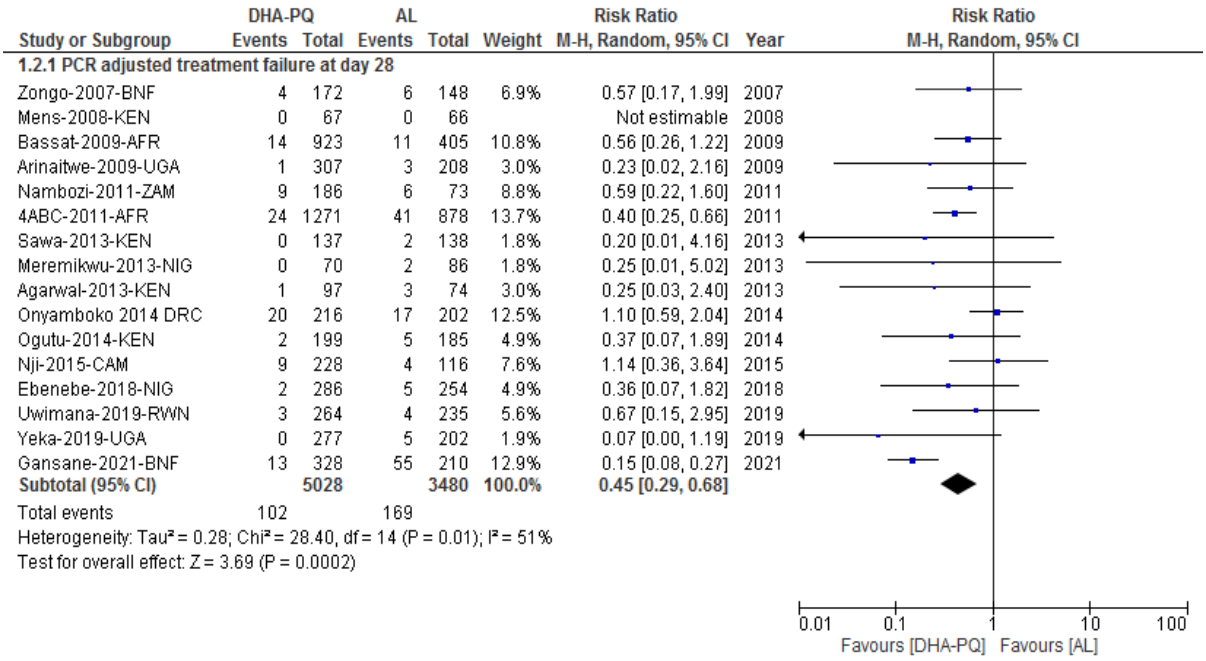

Figure 10: Forest plot of comparison between DHA-PQ and AL for treatment of uncomplicated *p.falciparum* malaria in African children on PCR adjusted treatment failure on day 28.

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, **Figure 11**).

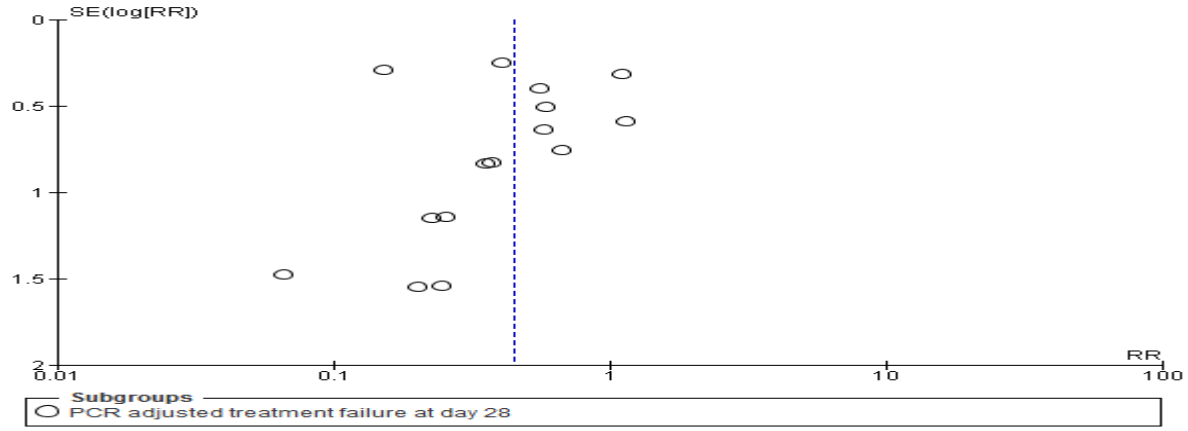

Figure 11: Funnel plot of comparison between DHA-PQ and AL for treatment of uncomplicated *p.falciparum* malaria in African children, outcome on PCR adjusted treatment failure on day 28.

PCR-unadjusted total failure at day 42

Seventeen studies reported this outcome and PCR unadjusted risk of recurrent *falciparum* parasitemia in fourteen studies was significantly lower in participants treated with DHA-PQ than that of AL **Figure 12**. 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*).

Outlier assessment and influence case analysis

Three outlier studies had an effect on the overall effect estimate. The pooled result after removing the outliers had also a considerable heterogeneity (Tau^2 =0.0451; tau = 0.212; df = 13 (P= 0.0005); I^2 = 64.2%). The influence analysis showed no influence case which had an effect on the pooled estimate. The Baujat plot showed that two out of three outlier studies had higher contributions for the heterogeneity and one had an influence on the overall pooled result in our meta-analysis.

Leave-one-out analysis

The leave-one-out analysis result shows that in addition to those three outlier studies, additional three studies had an effect on the overall heterogeneity within our meta-analysis. The leave-one-out analysis which was sorted by effect estimate showed that three studies had an effect on the overall effect estimate.

GOSH Plot Analysis

GOSH Plot Analysis showed only one cluster with high heterogeneity. Nine studies were detected by DBSCAN algorithm. However, the pooled result after removing those nine studies showed substantial heterogeneity between studies (Tau^2 = 0.078; tau= 0.28, df = 7 (P = 0.005); I^2 = 68%).

Individual study data analysis

Considering individual study result, the PCR unadjusted risk of recurrent *falciparum* parasitemia in thirteen studies was significantly lower in DHA-PQ group than AL 0.79 [95% CI 0.65, 0.97, (98)], 0.24 [95% CI 0.14, 0.43, (99)], 0.37 [95% CI 0.25, 0.56, (100)], 0.46 [95% CI 0.27, 0.79, (101)], 0.65 [95% CI 0.54, 0.78, (102)], 0.60 [95% CI 0.41, 0.87, (30)], 0.18 [95% CI 0.07, 0.45, (103)], 0.46 [95% CI 0.31, 0.68, (104)], 0.55 [95% CI 0.43, 0.70, (80)], 0.35 [95% CI 0.22, 0.57, (28)], 0.75 [95% CI 0.56, 0.99, (105)], 0.42 [95% CI 0.26, 0.68, (82)], and 0.56 [95% CI 0.44, 0.70, (106)]. However, in four studies the PCR unadjusted risk of recurrent *falciparum* parasitemia did not have significant difference between the two treatment groups 0.82 [95% CI 0.64, 1.07, (27)], 0.91 [95% CI 0.69, 1.19, (35)], 1.19 [95% CI 0.61, 2.32, (107)], and 0.43 [95% CI 0.14, 1.38, (108)].

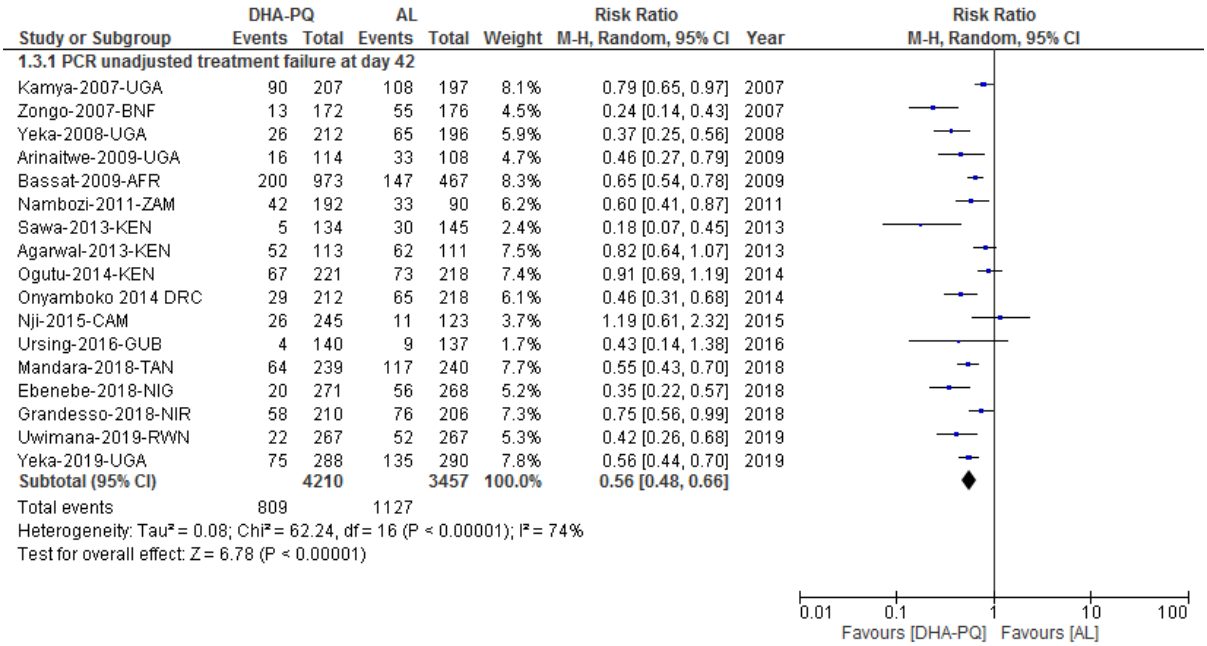

Figure 12: Forest plot of comparison between DHA-PQ and AL for treatment of uncomplicated *p.falciparum* malaria in African children on PCR unadjusted treatment failure on day 42.

Meta- regression of PCR-unadjusted treatment failure on day 42

The meta-regression didn't explain the variation in the treatment failure. So, this variation might be caused due to sampling error.

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). We used the trim-and-fill procedure and the funnel plot which included the imputed studies showed symmetrical distribution of the studies around the pooled estimate.

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 **Figure 13**.

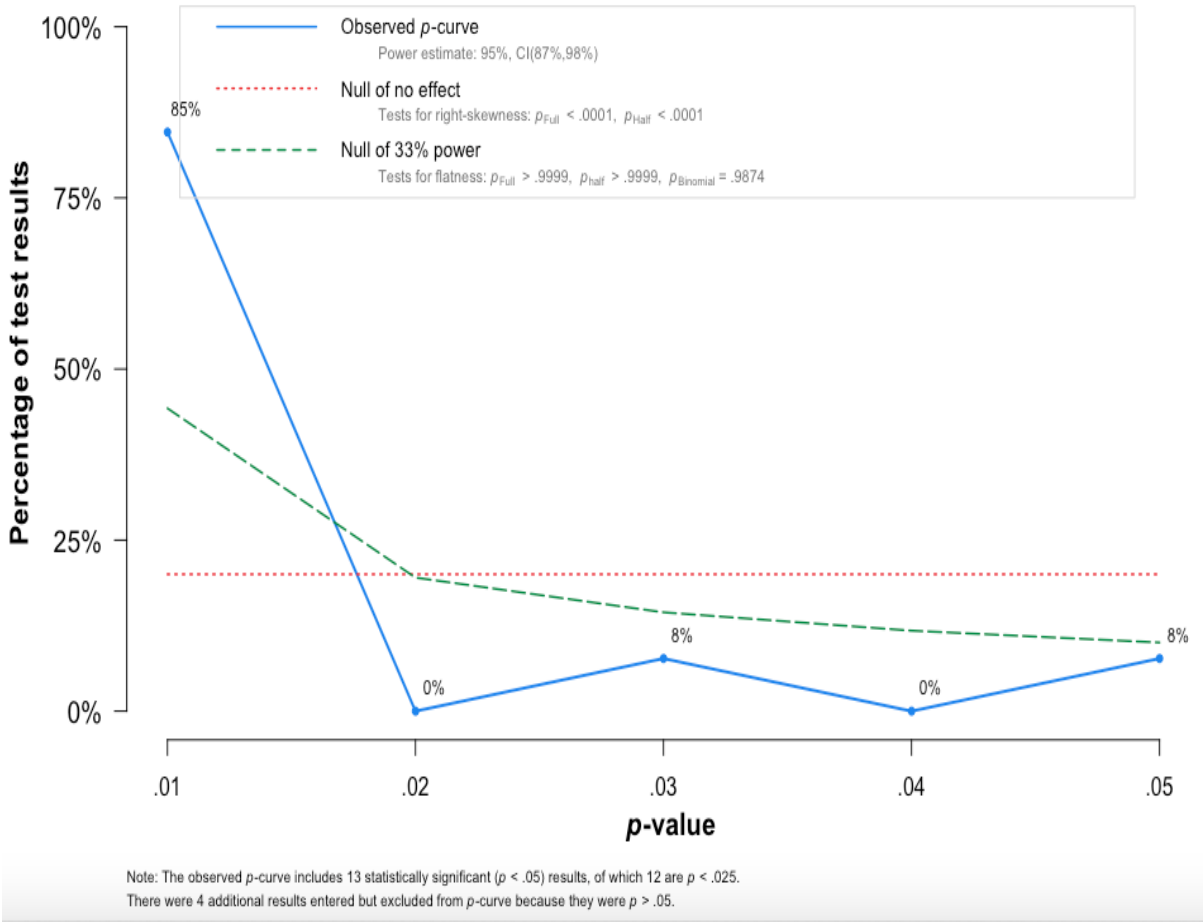

Figure 13: P-curve of comparison between DHA-PQ and AL for treatment of uncomplicated *p. falciparum* malaria in African children on PCR unadjusted treatment failure on day 42.

PCR-adjusted total failure on day 42

The risk of recurrent parasitaemia due to possible recrudescence was significantly lower for participants treated with DHA-PQ than those treated with AL in three studies and no significant difference in risk of genotyping corrected treatment failure was found between the two treatment groups in twelve studies. The overall genotyping adjusted risk of treatment failure due to recrudescence of parasitaemia were lower for patients treated with DHA-PQ than that that of treated with AL (RR 0.60, 95% CI 0.47 to 0.78; participants = 5959; studies = 17; I^2 = 0%, *high quality of evidence*, **Figure 14**).

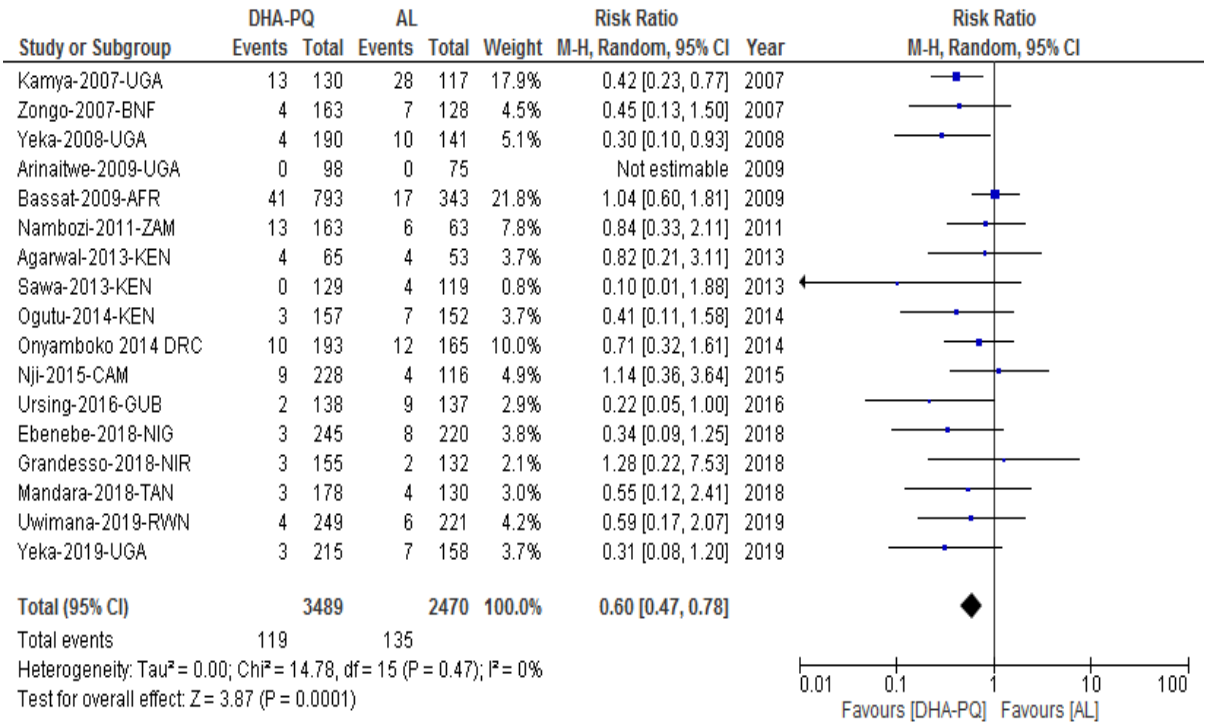

Figure 14: Forest plot of comparison between DHA-PQ and AL for treatment of uncomplicated *p. falciparum* malaria in African children on PCR adjusted treatment failure on day 42.

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, **Figure 15**).

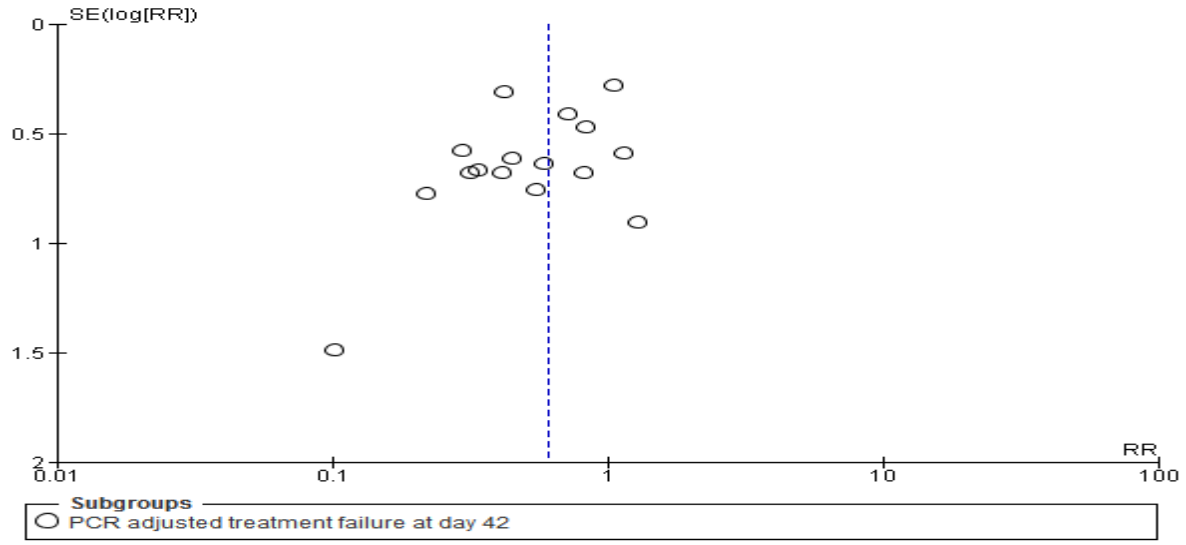

Figure 15: Funnel plot of comparison between DHA-PQ and AL for treatment of uncomplicated *p. falciparum* malaria in African children on PCR adjusted treatment failure on day 42.

PCR-unadjusted total failure on day 63

Three studies with 3365 participants were included in this analysis. The result had considerable heterogeneity (Tau^2 = 0.21; Chi^2 = 18.62, df = 2 (P < 0.0001); I^2 = 89%, *moderate quality of evidence*) and we couldn't pool the result. It is more important to take in to account individual study results. The PCR uncorrected treatment failure in patients treated with DHAPQ was significantly lower than that of treated with AL RR 0.38on day 63 in two studies [95% CI 0.28, 0.52] and RR 0.76 [95% CI 0.70, 0.84]). However, the relative risk of genotyping uncorrected treatment failure was not significantly different between the two treatment groups (109) 1.01 [95% CI 0.32, 3.16], **Figure 16**.

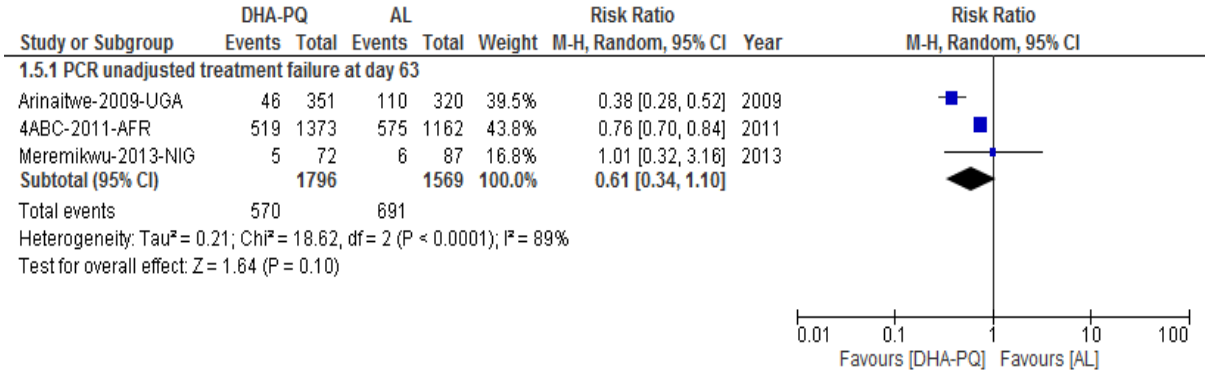

Figure 16: Forest plot of comparison between DHA-PQ and AL for treatment of uncomplicated *p. falciparum* malaria in African children on PCR unadjusted treatment failure on day 63.

PCR-adjusted total failure on day 63

No significant difference between the two groups was observed on day 63. Similarly, the pooled genotyping adjusted risk of treatment failure due to recrudescence of parasitaemia was lower in both treatment arms 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*, **Figure 17**)

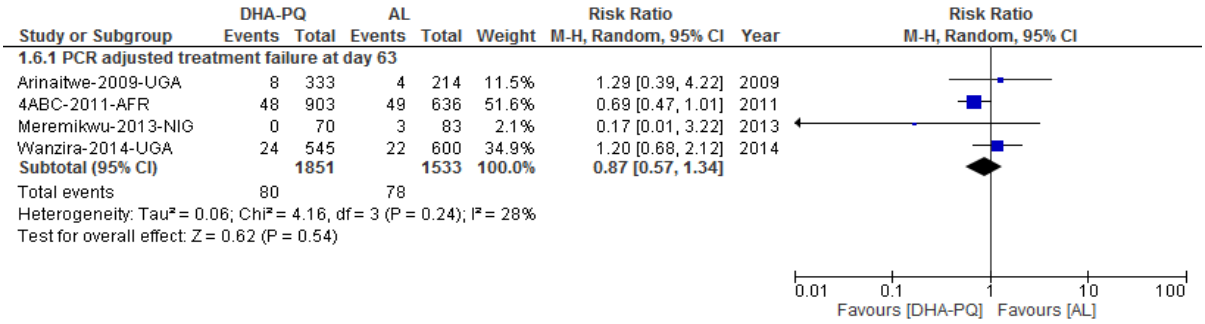

Figure 17: Forest plot of comparison between DHA-PQ and AL for treatment of uncomplicated *p. falciparum* malaria in African children on PCR adjusted treatment failure on day 63.

PCR unadjusted and adjusted treatment failure on day 84

Two studies have followed the patients up to 84 days. The PCR adjusted treatment failure on day 84 was more than 10% in AL treatment group (110) . The number of re-infection was the same in both treatment groups on day 84.

Fever clearance

Fever clearance on Day 1

Twelve studies with 6885 participants reported fever clearance on day 1, but the pooled result showed considerable heterogeneity between studies ($Tau^2 = 0.01$; $Chi^2 = 41.00$, df = 11 ($P < 0.0001$); $I^2 = 73\%$, **Figure 18**. We couldn't figure out the reason for heterogeneity between studies and we could not pool them.

Outlier assessment and influence case analysis

Only one outlier study (111) had an effect on the overall effect estimate. The pooled result after removing the outlier study showed considerable heterogeneity ($Tau^2 = 0.0074$; tau = 0.0858; df = 10 (P= 0.0053); $I^2 = 60.0\%$). The influence analysis showed that one study had influence on the overall effect estimate. The Baujat plot showed that two studies had contributed for heterogeneity between studies and one study had an influence on the overall pooled result of our meta-analysis.

Leave-one-out analysis

The leave-one-out analysis showed that two studies had an influence on the heterogeneity between the included studies**.** The overall effect size of our meta-analysis was influenced in three studies.

GOSH Plot Analysis

The GOSH plot analysis showed that there was one cluster with high heterogeneity between studies and anther one with low heterogeneity between the included studies. We had detected seven outlier studies which might cause the cluster imbalance and performed meta-analysis without including them. Majority of these outlier studies were detected by DBSCAN and the Gaussian Mixture model. However, the pooled result after removing those seven studies showed low heterogeneity between included studies ($Tau^2 = 0$; tau= 0, df = 4 (P = 0.6); $I^2 = 0\%$).

Seven studies reported that fever clearance on day one was higher in DHA-PQ treatment group than AL RR 0.77 [95% CI 0.61, 0.98, (99)], RR 0.81 [95% CI 0.70, 0.95, (100)], RR 0.77 [95% CI 0.65, 0.91, (101)], RR 0.62 [95% CI 0.47, 0.80, (91)], RR 0.53 [95% CI 0.40, 0.70, (111)], RR 0.93 [95% CI 0.86, 1.00, (80)], and RR 0.90 [95% CI 0.82, 1.00]. However, no significant difference in fever clearance was found between the two treatment groups in five studies RR 1.00 [0.87, 1.14,(98)], RR 1.67 [95% CI 0.64, 4.35, (112)], RR 1.00 [95% CI 0.92, 1.09, (102)], RR 0.72 [95% CI 0.30, 1.76, (104)], and RR 0.93 [95% CI 0.82, 1.05(28)]. In addition three studies which were not included in our meta-analysis reported that no significant difference was observed between the two treatments (81, 107, 108). The overall pooled result after excluding the outlier studies showed that fever clearance on day one was higher in patients who were treated with DHA-PQ than AL (RR 0.93, 95% CI 0.89 to 0.98; participants = 2291; studies = 12; $I^2 = 0\%$, **Figure 18**).

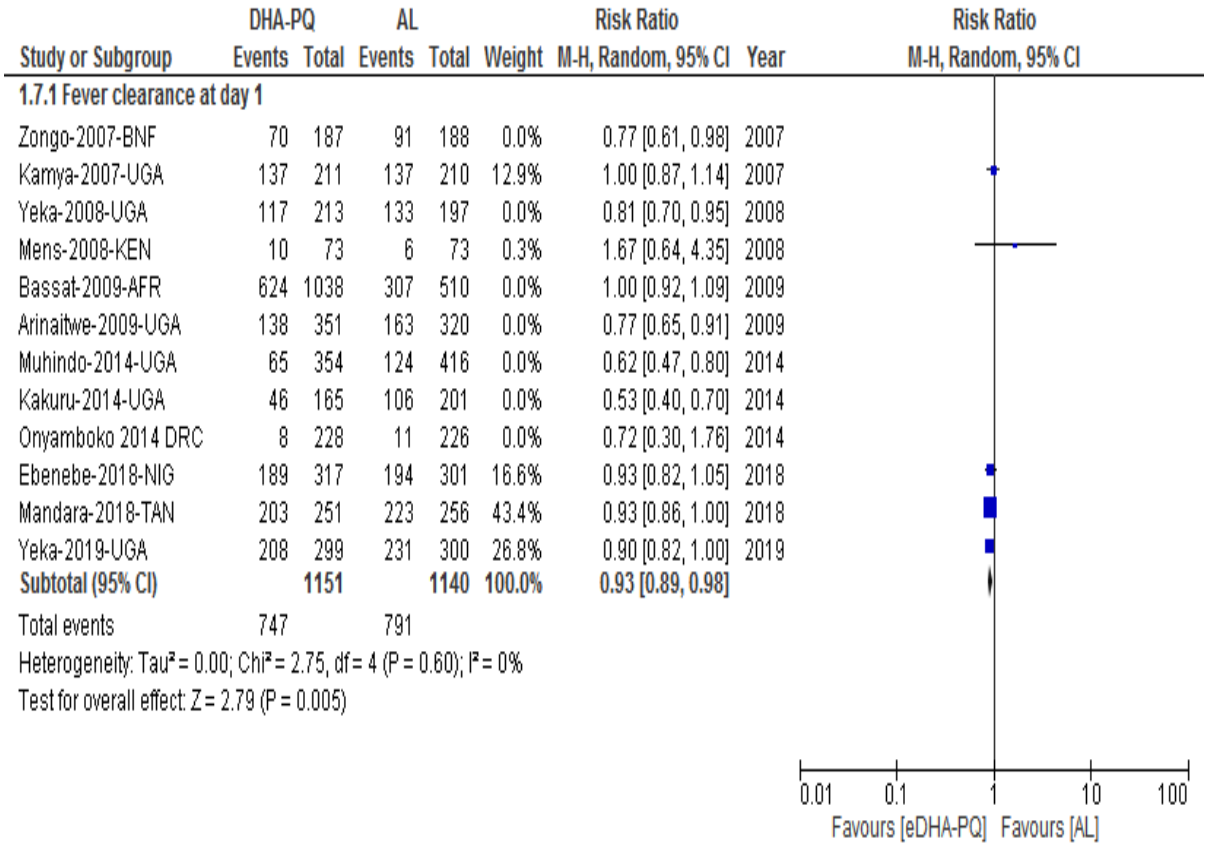

Figure 18: Forest plot of comparison for DHA-PQ and AL for treatment of uncomplicated *p. falciparum* malaria in African children on Fever clearance on day 1.

Meta-regression

HIV infection has inverse relationship with fever clearance (P=0.0001). The relative risk of fever clearance on day one post-treatment was lower by 67.5% in studies with both HIV infected and uninfected children than studies with HIV negative children (Table). The HIV infection was related to fever clearance on days one post treatment (Q=16.20, df=1, P=0.0001), **Table 3**.

The variance in fever clearance on day one post treatment about the regression line (Tau^2) was 0.0034, the standard deviation of true effects about the regression line (Tau) is 0.058. The I^2 statistic was 39.8%, which tells us that some 40% of the observed variance about the regression line reflects variation in fever clearance at day one post treatment rather than sampling error. The test for heterogeneity yields a Q-value of 16.62 with 10 degrees of freedom and a corresponding p-value 0.083. The dispersion of effects about the regression line exceeded the amount we would expect to see based on sampling error alone and the model did not fully explain the variation in effects. Besides, from the total variance in fever

clearance on day one post treatment only 74% of the variability explained by HIV status of the participants, **Figure 19.**

Table 3: Meta-regression analysis of fever clearance on day 1.

Covariate	Coefficient	SE	95% Lower	95% Upper	Z-value	2-sided P-value
Intercept	-0.0802	0.0318	-0.1426	-0.0178	-2.52	0.0118
HIV status: HIV positive and negative children	-0.3249	0.0807	-0.4832	-0.1667	-4.02	0.0001

Fever clearance on Day 2

High resolution of fever observed in majority of the participants without a statistically significant difference between the two treatment arms on day 2 in eleven studies, while those treated with DHA-PQ underwent high resolution of fever in one study (RR 0.86, 95% CI 0.71 to 1.04; participants = 4971; studies = 11; I^2 = 31%, **Figure 20**).

Fever clearance on Day 3

Fever had resolved in the majority of patients irrespective of treatment arms on day 3 in all six trials (RR 1.07, 95% CI 0.85 to 1.34; participants = 4664; studies = 11; I^2 = 0%, **Figure 20**).

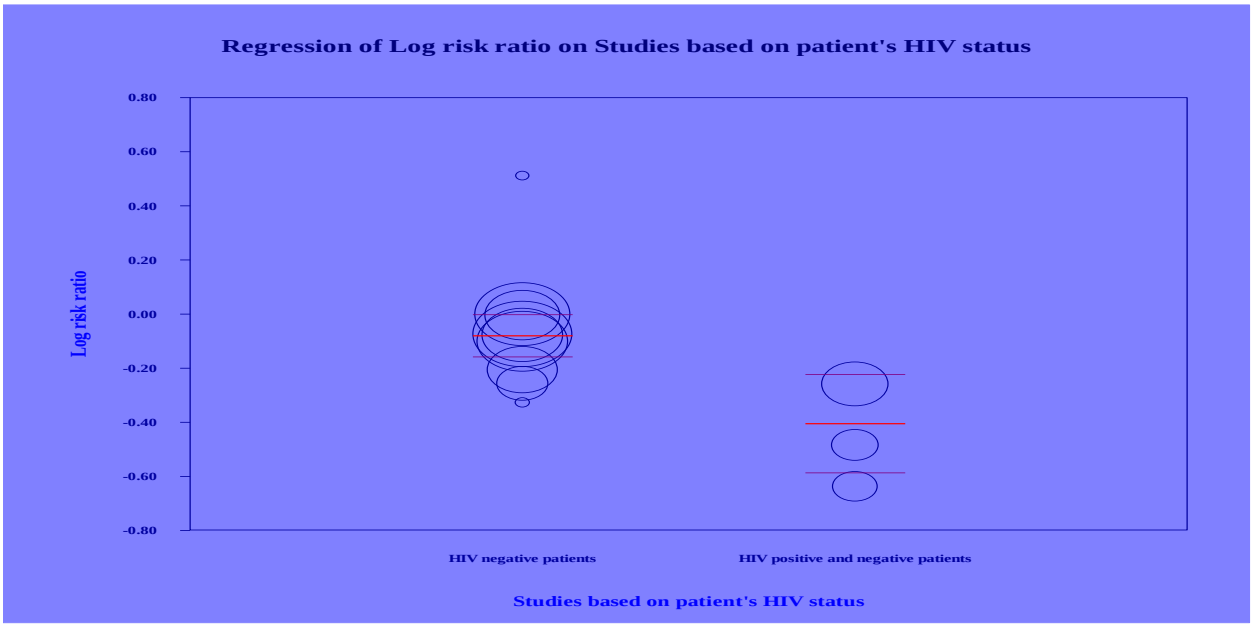

Figure 19: Meta-regression of comparison between DHA-PQ and AL for treatment of uncomplicated *p. falciparum* malaria in African children on Fever clearance on day 1.

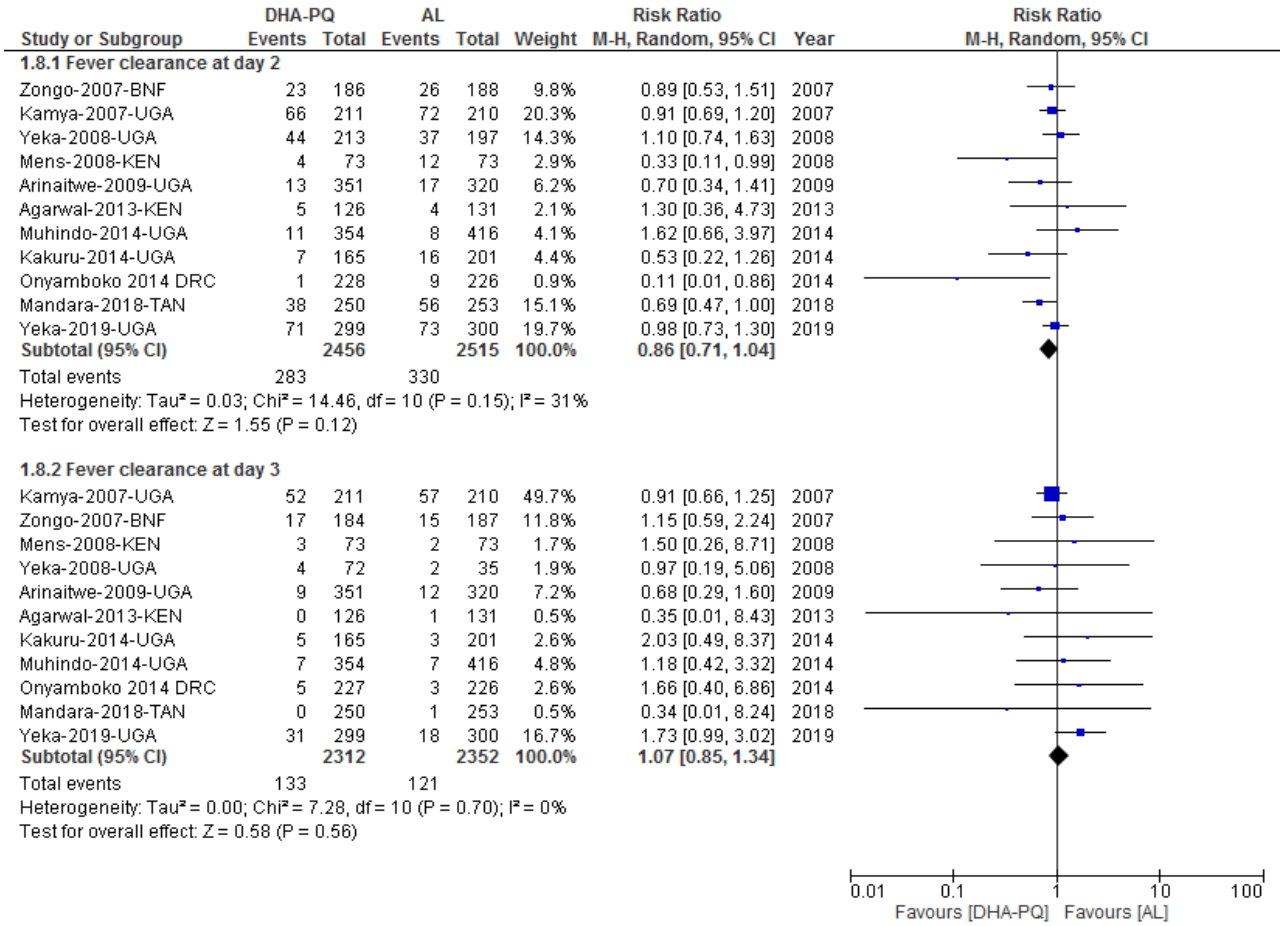

Figure 20: Forest plot of comparison between DHA-PQ and AL for treatment of uncomplicated *p. falciparum* malaria in African children on fever clearance.

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%, **Figure 21**). We couldn't pool the result.

Outlier assessment and influence case analysis

We observed no outlier study in this outcome. The influence analysis showed that one (110) study had an influence on the overall effect estimate of our meta-analysis. The Baujat plot also showed that one study had a significant contribution for the heterogeneity between the included studies.

Leave-one-out analysis

The leave-one-out analysis also showed that the above study had a significant contribution for the heterogeneity between the included studies. As we saw on Baujat plot a study conducted in Tanzania had an effect on the overall effect estimate.

Sub-group analysis

We did subgroup analysis and found a significant difference between the two sub-groups ($Chi^2 = 4.40$, df = 1 (P = 0.04), $I^2 = 77.3\%$). By day one, the proportion of participants with parasitaemia in under five children was significantly lower in the DHA-PQ treatment group than AL (RR 0.82, 95% CI 0.75 to 0.90; participants = 2450; studies = 4; $I^2 = 65\%$, **Figure 21**). Similarly, the prevalence of parasitemia was significantly lower in DHA-PQ treatment arm than that of AL in children between the age of six months to 15 years (RR 0.93, 95% CI 0.86 to 1.00; participants = 507; studies = 1; $I^2 = 0\%$, **Figure 21**).

Parasite clearance on Day 2

The percentage of patient with paracitemia on day two was significantly lower in patient treated with DHA-PQ than that of AL. In ten studies, we found no significant difference between the two treatment arms. The pooled result showed that the percentage of patients with parasitemeia on day 2 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; $I^2 = 12\%$, **Figure 22**).

Parasite clearance on Day 3

In majority of the studies, the proportion of participants with detected parasitemia was lower in both treatment arms without significant difference on day 3 (RR 0.99, 95% CI 0.50 to 1.98; participants = 6635; studies = 13; $I^2 = 0\%$, **Figure 22**) and none of the patients in both treatment groups had parasite in their blood in four studies (98-100, 110). Studies which were not included in our meta-analysis reported that no significant difference was found in parasite clearance between the two treatments on day 3 (28, 81, 107, 108). However, in one study, the majority of the children from DHA-PQ treatment group had parasite clearance on day 3 (110).

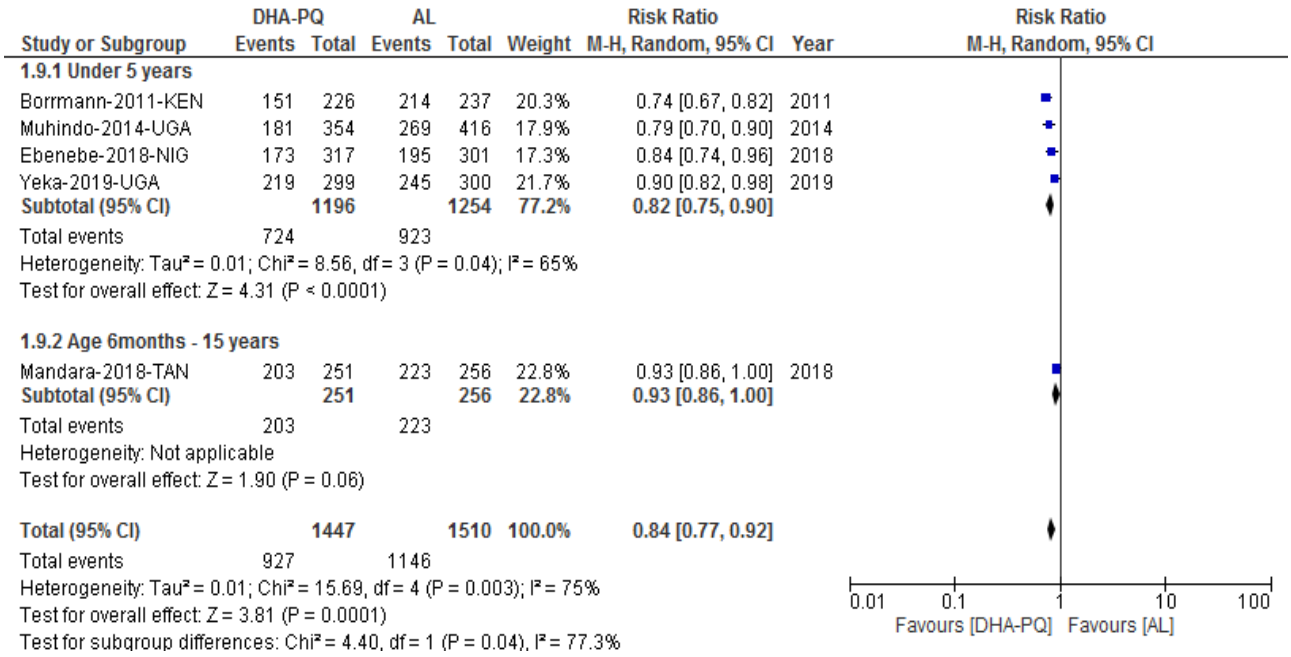

Figure 21: Forest plot of comparison between DHA-PQ and AL for treatment of uncomplicated *p. falciparum* in African Children on parasite clearance on day 1.

Gametocytes

Gametocyte Carriage at Baseline

In one multi-center study the appearance of gametocytes at baseline was lower in patients treated with AL than DHA-PQ (81), and we no statistically significant difference in the emergence of gametocyte between two treatments in other studies. The pooled result showed that the emergence of gametocyte had no significant difference between the two treatment arms (RR 1.00, 95% CI 0.82 to 1.22; participants = 9283; studies = 14; I^2 = 40%, **Figure 23**).

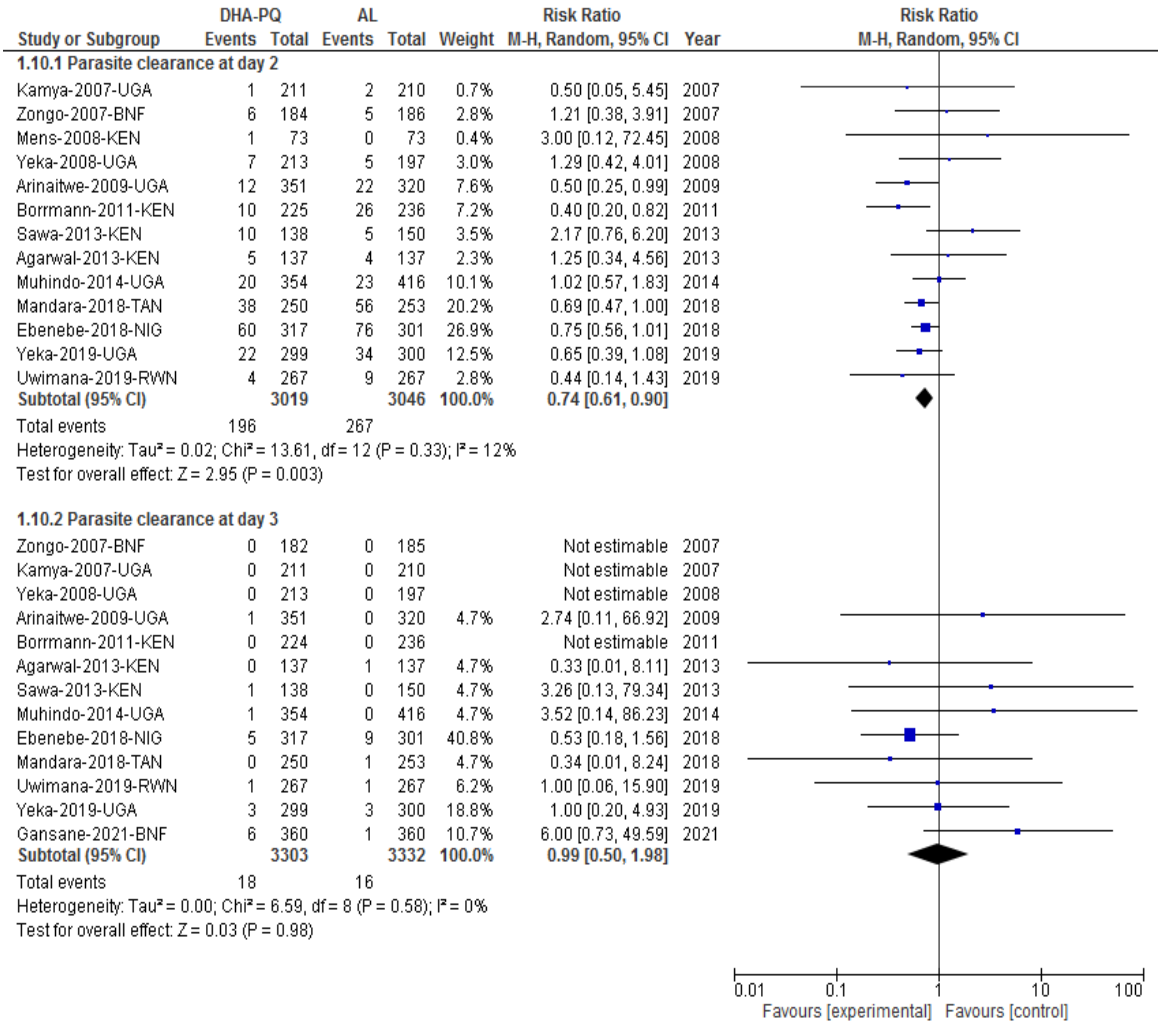

Figure 22: Forest plot of comparison between DHA-PQ and AL for treatment of uncomplicated *p .falciparum* malaria in African children on parasite clearance on days 2 and 3.

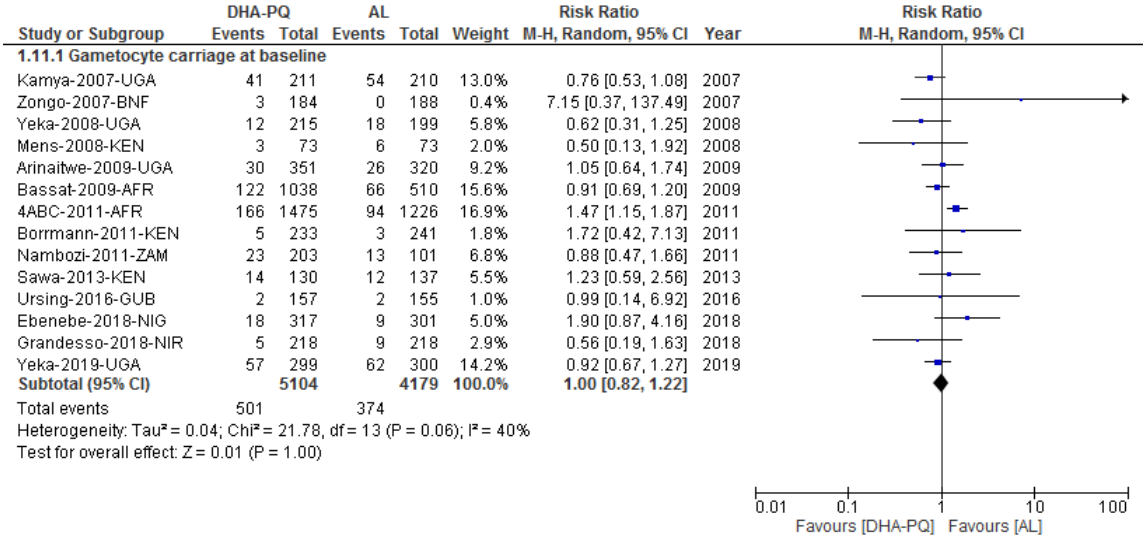

Figure 23: Forest plot of comparison between DHA-PQ and AL for treatment of uncomplicated *p. falciparum* malaria in African children on Gametocyte carriage at Baseline.

Gametocyte carriage on days 1-14

The appearance of gametocyte was lower in patients treated with AL than DHA-P in one trial (101), and it was lower in both treatment groups in the other three trials. The overall gametocyte appearance on days 1-14 was significantly lower in both treatment arms without significant difference (RR 1.78, 95% CI 0.65 to 4.90; participants = 2294; studies = 5; I^2 = 39%, **Figure 24**).

Gametocyte carriage on day 15-28

On days 15-28, no significant difference was found in the emergence of gametocyte between the two treatment arms (RR 0.50, 95% CI 0.09 to 2.89; participants = 2042; studies = 4; I^2 = 54%, **Figure 24**).

Gametocyte carriage on day 29-42

Between days 29-42, the appearance of gametocyte was lower in DHA-PQ treatment group than AL in one study (100). But, no significant difference was found in the emergence of gametocyte between the two treatment arms in the other two studies. Similarly, the pooled result showed that the emergence of gametocyte was the same in both treatment groups (RR 0.40, 95% CI 0.13 to 1.24; participants = 1218; studies = 3; I^2 = 43%, **Figure 24**).

Gametocyte carriage on day 0-84 days

Between 0-84 days several studies also reported the emergence of gametocyte. All the studies reported consistent result that the emergence of gametocyte was lower in both treatment arms (RR 2.00, 95% CI 0.18 to 21.90; participants = 456; studies = 1, day 0-35, (104)), (RR 0.77, 95% CI 0.49 to 1.21; participants = 599; studies = 1, day 1-3, (106)), (RR 2.35, 95% CI 0.62 to 8.93; participants = 375; studies = 1, day 1-42, (99)), (RR 0.43, 95% CI 0.11 to 1.65; participants = 599; studies = 1, day 4-42, (106)) and (RR 2.59, 95% CI 0.51 to 13.20; participants = 474; studies = 1,day 7-84, (110)).

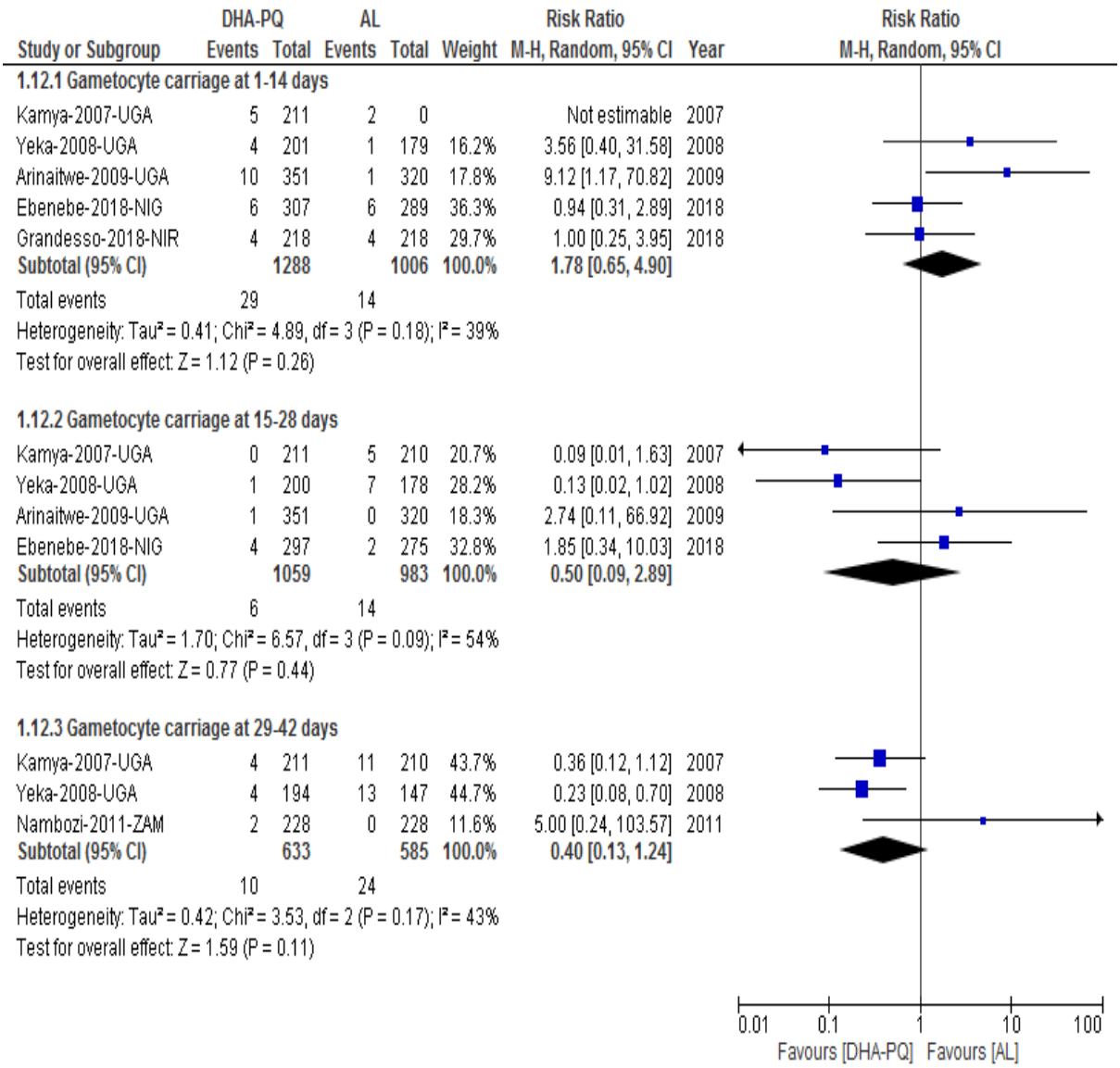

Figure 24: Forest plot of comparison between DHA-PQ and AL for treatment of uncomplicated *p. falciparum* malaria in African children on Gametocyte carriage.

Anemia

Mean Hemoglobin at baseline

There was no significant difference in the mean hemoglobin level at baseline in both treatment arms (SMD 0.00, 95% CI -0.06 to 0.06; participants = 10080; studies = 18; I^2 = 45%, **Figure 25**). Similar result was obtained in a study conducted in Kenya (27).

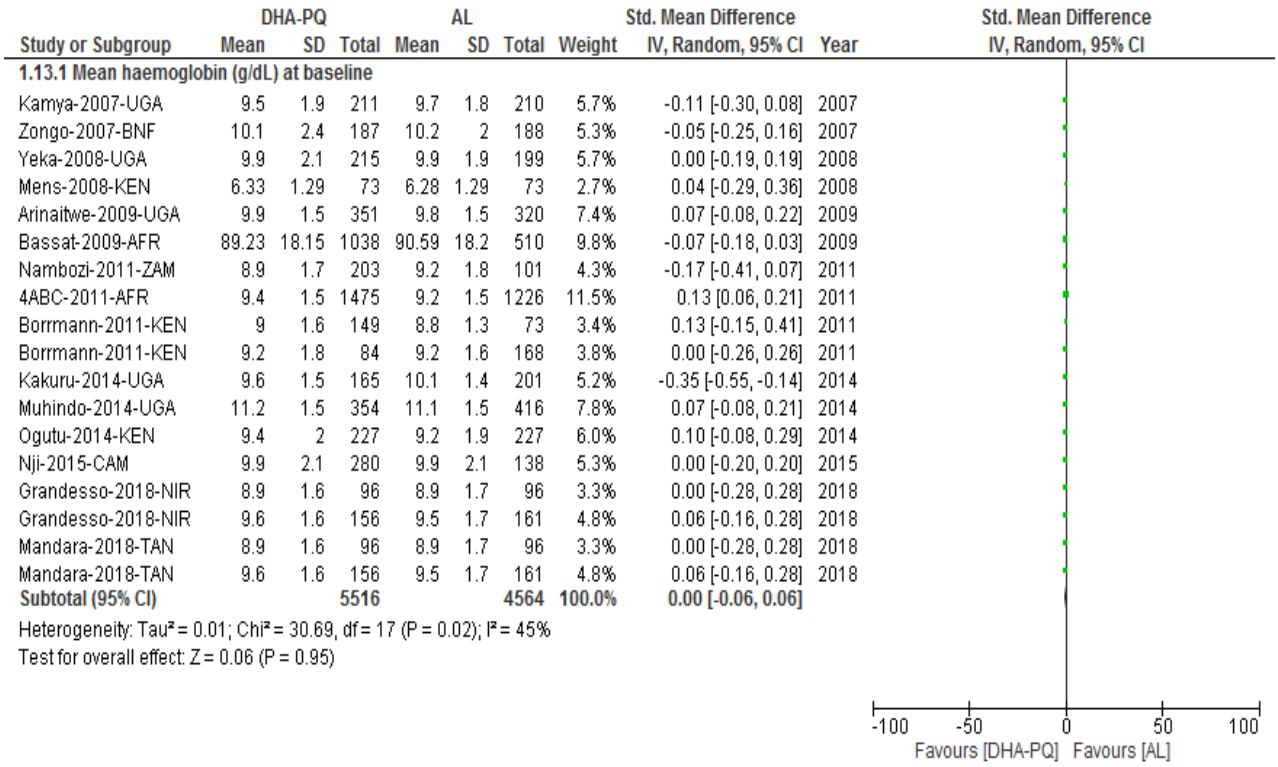

Figure 25: Forest plot of comparison between DHA-PQ and AL for treatment of uncomplicated *p. falciparum* malaria in African children on Anemia.

Mean Hemoglobin change on day 28 from the baseline

The mean change on hemoglobin on day 28 from the baseline was significantly higher in patients treated with 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*, **Figure 26***)*. A study from Zambia also reported the same result (30).

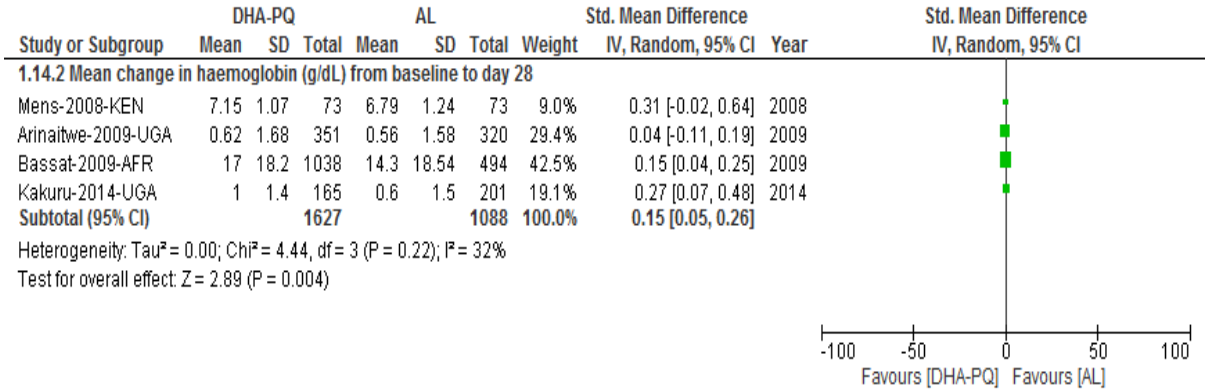

Figure 26: Forest plot of comparison between DHA-PQ and AL for treatment of uncomplicated *p. falciparum* malaria in African children on Anemia.

Mean Hemoglobin change from baseline to Day 0-7

The mean change in Hemoglobin from baseline was the same in both treatment groups (MD 0.09, 95% CI -0.26 to 0.44; participants = 418; studies = 1, day 0-7, (107)) and the mean(g/dl) hemoglobin level was also the same in both arms (MD 0.36, 95% CI -0.02 to 0.74; participants = 146; studies = 1, day 28, (112) and (MD 0.40, 95% CI 0.08 to 0.72; participants = 375; studies = 1, day 42,(99)).

Mean Hemoglobin change on day 42 from the baseline

The mean change in Hemoglobin on day 42 from the baseline was significantly higher in participants who were treated with DHA-PQ than that of treated with AL (MD 0.35, 95% CI 0.12 to 0.59; participants = 1434; studies = 3; I^2 = 35%, *high quality of evidence*, **Figure 27**).

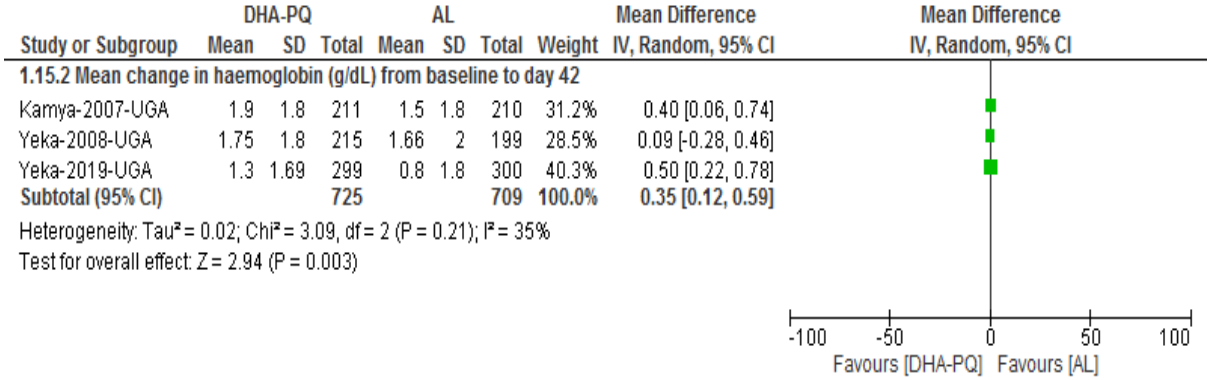

Figure 27: Forest plot of comparison between DHA-PQ and AL for treatment of uncomplicated *p. falciparum* malaria in African children on anemia.

Adverse events

Most of the adverse events were coherent with symptoms due to malaria and they were mild or moderate. However, some respiratory, gastrointestinal, and neuropsychiatry adverse events like cough, early vomiting, anorexia, diarrhea, vomiting, and weakness were the most common adverse events within the included studies in the safety analysis. In addition, there was a significant difference in the prevalence of patients who experienced some adverse events of mild and moderate severity between the two treatment arms.

Three studies which were not included in the meta-analysis also reported adverse events. Both treatments were well tolerated in study from Kenya and adverse events were not related

with the study drugs. Studies from Nigeria reported convulsion, joint pain, diarrhea, stomach pain, itch, rash, palpitation, inability to eat, sleep, and drink were reported within the first 3 days and also, in one study from Guinea-Bissau, cough and running nose were the most commonly reported AEs. Other AEs like fever, anorexia, vomiting, abdominal pain, diarrhea, weakness, poor sleep, and headache also reported. However, high numbers of AEs were reported from DHA-PQ treatment group.

Gastrointestinal adverse events

Early vomiting

The relative risk of early vomiting was higher in patients treated with 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*, **Figure 29**).

Publication Bias

The funnel plot shows that all studies lied symmetrically around the pooled effect estimate implying that there was no publication bias (P= 0.5, **Figure 28**).

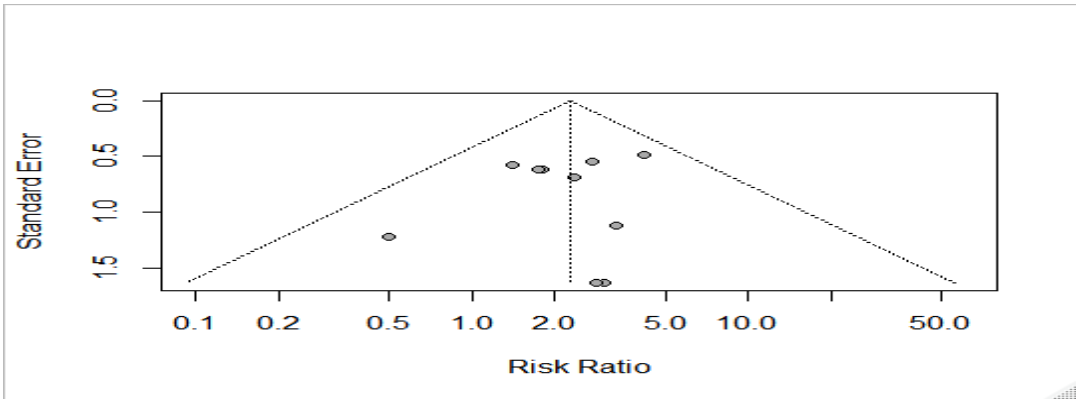

Figure 28: Funnel plot of comparison between DHA-PQ and AL for treatment of uncomplicated *p. falciparum* malaria in African children on gastrointestinal adverse events (early vomiting).

Diarrhea

Similarly, the relative risk of diarrhea was higher in patients treated with 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*, **Figure 29**).

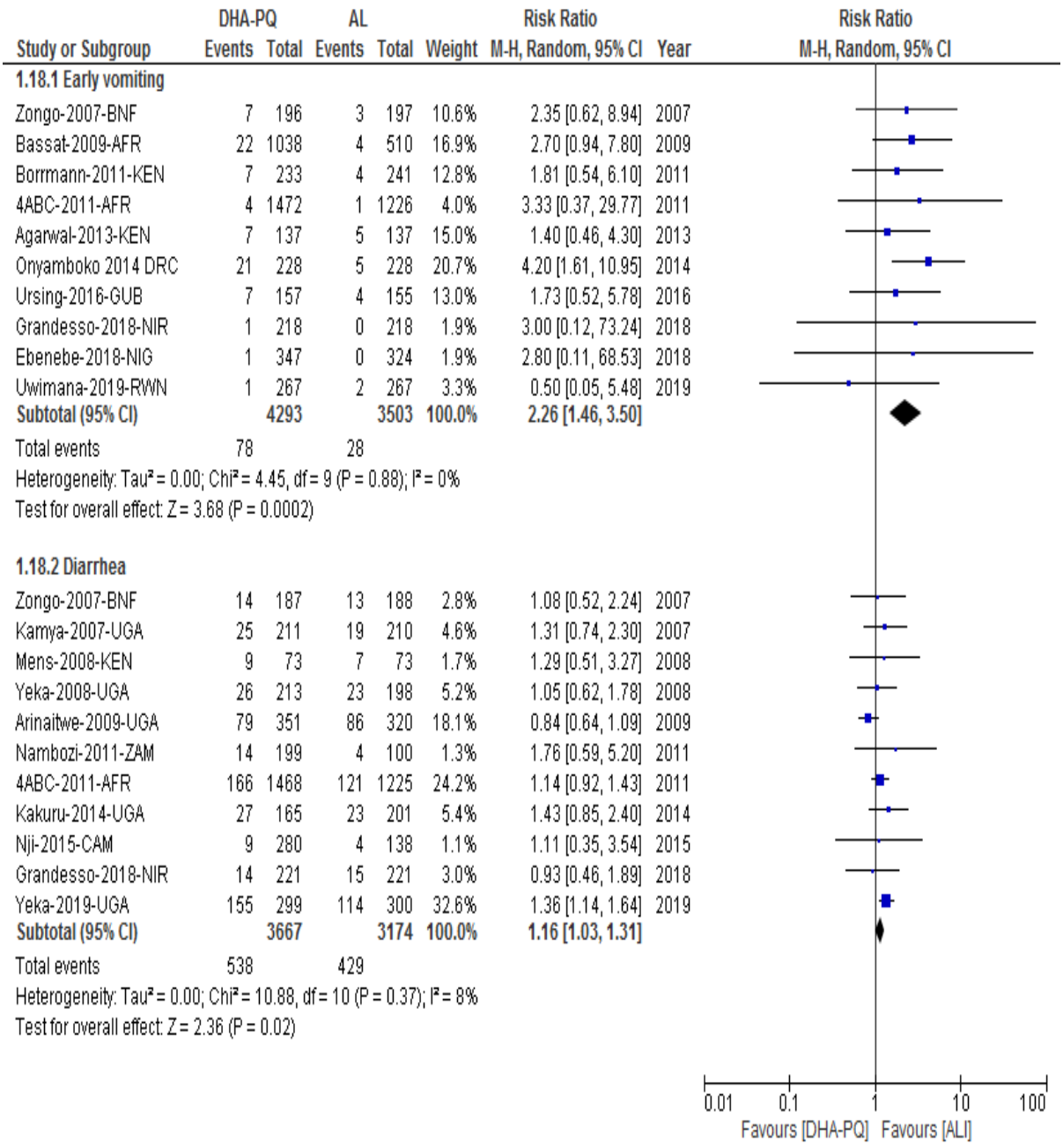

Figure 29: Forest plot of comparison between DHA-PQ and AL for treatment of uncomplicated *p. falciparum* malaria in African children on gastrointestinal adverse events.

Publication bias

The funnel plot showed that all studies lie symmetrically around the pooled effect estimate implying that there was no publication bias (P= 0.9, **Figure 30**).

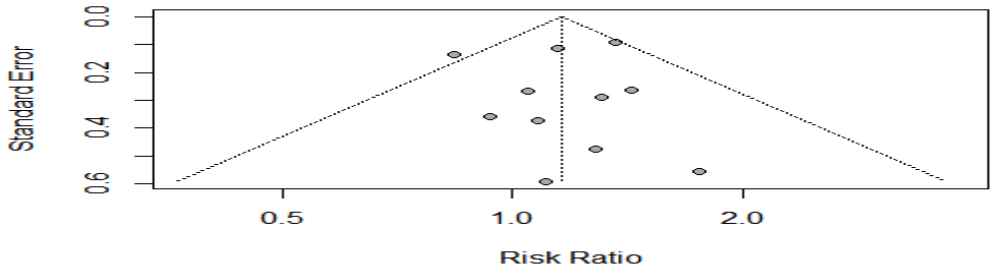

Figure 30: Funnel plot of comparison between DHA-PQ and AL for treatment of uncomplicated *p. falciparum* malaria in African children on gastrointestinal adverse events (diarrhea).

Vomiting

Thirteen studies reported vomiting as an adverse event and in one study more patients from DHA-PQ group experienced vomiting (104). However, there was no 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*, **Figure 31**).

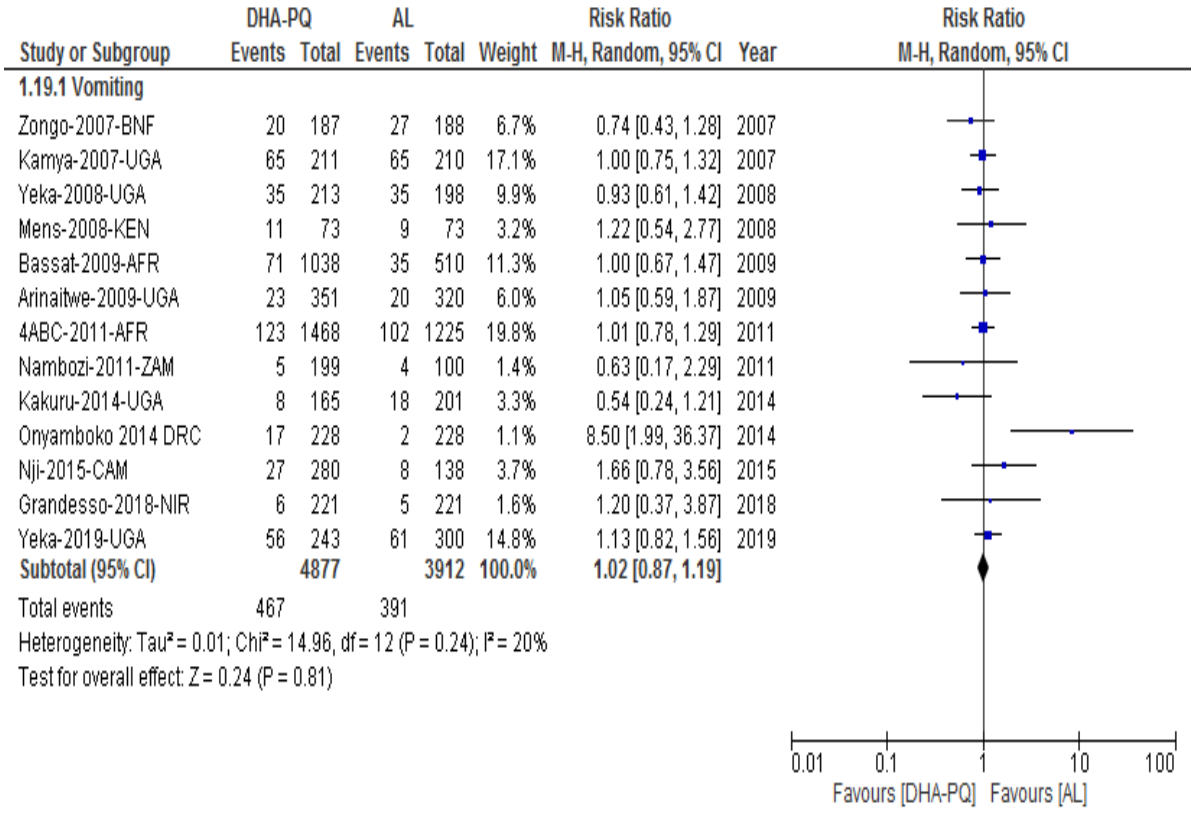

Figure 31: Forest plot of comparison between DHA-PQ and AL for treatment of uncomplicated *p. falciparum* malaria in African children on vomiting.

Publication bias

The funnel plot showed that all studies lied symmetrically around the pooled effect estimate implying that there was no publication bias (P= 0.47, **Figure 32**).

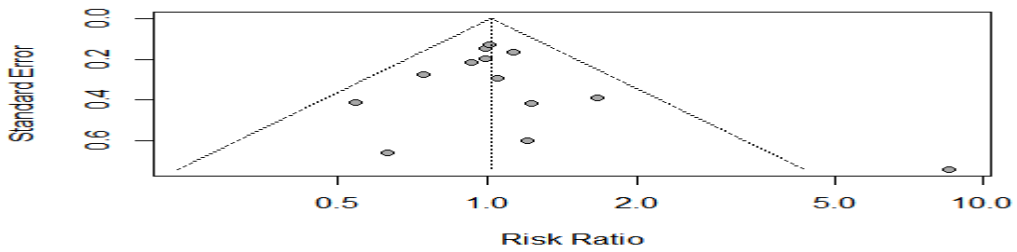

Figure 32: Funnel plot of comparison between DHA-PQ and AL for treatment of uncomplicated *p. falciparum* malaria in African children on vomiting.

Anorexia

Eleven studies reported anorexia as an adverse event, and significant difference in the risk of anorexia between the two treatment groups was not found (RR 0.95, 95% CI 0.84 to 1.07; participants = 6841; studies = 11; I^2 = 0%, *high quality of evidence*, **Figure 33**). Also, eight studies reported abdominal pain as an adverse event, and in two studies more patients from AL treatment group developed abdominal pain in two studies. In one study, more patients developed abdominal pain from DHA-PQ treatment group (73). However, the relative risk of abdominal pain didn't have significant difference between the treatment groups (RR 0.80, 95% CI 0.57 to 1.11; participants = 2732; studies = 8; I^2 = 53%, *high quality of evidence*, **Figure 33**).

Other gastrointestinal adverse events

There was no significant difference between the two arms in the relative risk of gastroenteritis and loss of appetite (RR 0.57, 95% CI 0.19 to 1.68; participants = 469; and RR 2.06, 95% CI 0.52 to 8.14; participants = 469; studies = 1, (35)), respectively.

Biochemistry tests for liver and renal function before and after treatment

ALAT with clinically significant values above normal range between days and 28

Two studies (81, 102) reported clinically significant elevation ALAT value above the normal range. It was significantly higher in patients treated with DHA-PQ than AL (102). However,

no significant difference seen between the two treatment arms in the overall result (RR 0.52, 95% CI 0.32 to 0.84; participants = 4116; studies = 2; I^2 = 0%, **Figure 34**).

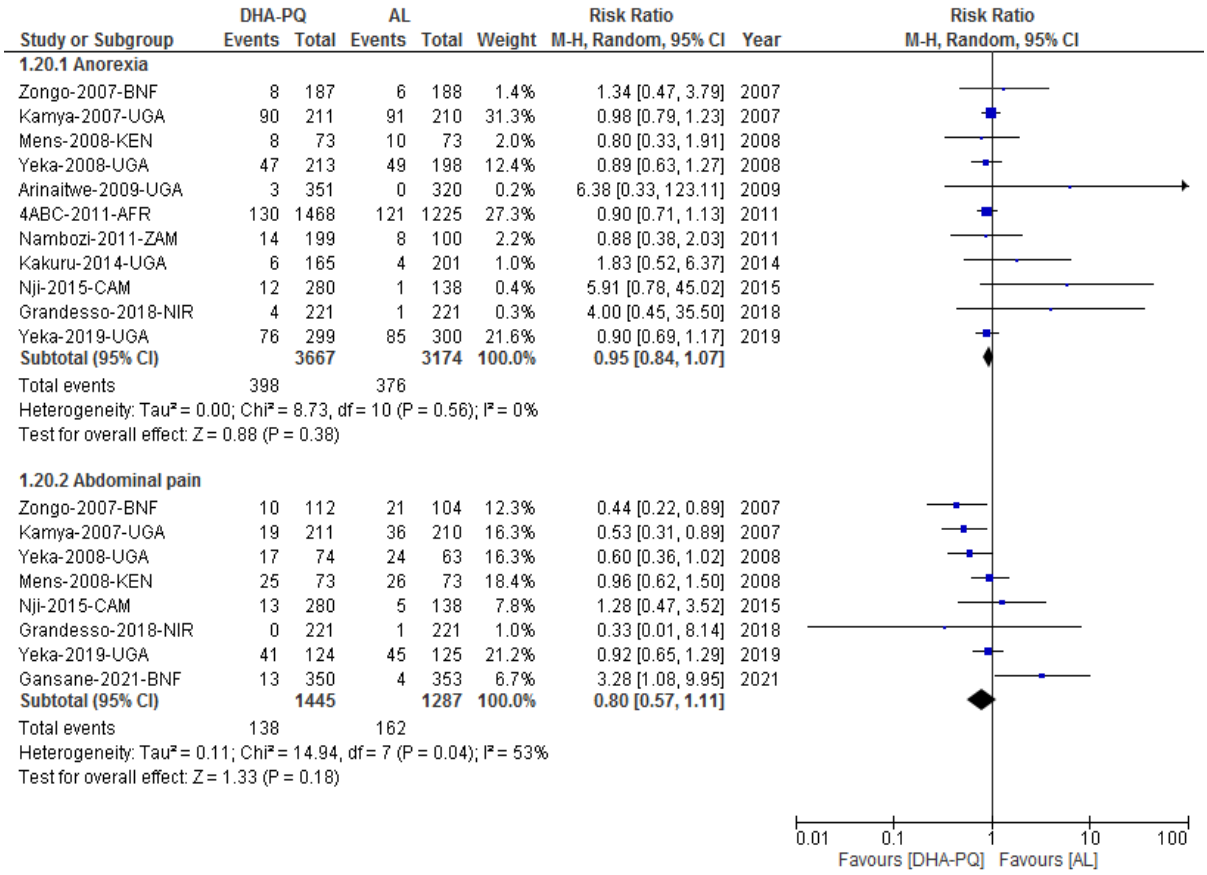

Figure 33: Forest plot of comparison between DHA-PQ and AL for treatment of uncomplicated *p. falciparum* malaria in African children on Gastrointestinal Adverse event.

One study reported clinically significant elevation ALAT value above the normal range on days 7 and 28, and the relative risk of having clinically significant elevation ALAT value above the normal range did not have significant difference between the treatment arms (RR 0.61, 95% CI 0.14 to 2.74; participants = 2392; studies = 1) and (RR 2.93, 95% CI 0.33 to 26.14; participants = 2161; studies = 1), respectively.

Creatinine with clinically significant values above normal range between days 0 and 28

In one study a clinically significant elevation in creatinine values above normal range. However, the relative risk of developing a clinically significant elevation in creatinine values above normal range did not have significant difference between the treatment arms (RR 4.25, 95% CI 0.20 to 88.36; participants = 2537; studies = 1) and (RR 0.15, 95% CI 0.01 to 3.16; participants = 2108; studies = 1), respectively.

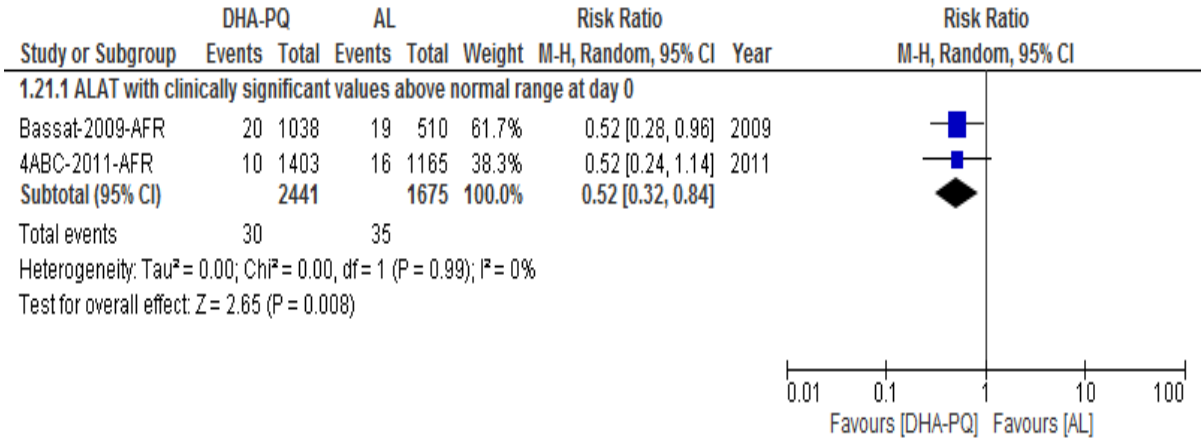

Figure 34: Forest plot of comparison between DHA-PQ and AL for treatment of uncomplicated *p. falciparum* malaria in African children on liver and renal functions tests before and after treatment.

Cardio-respiratory adverse events

Cough

Cough was the most common cardio-respiratory adverse event, and significantly higher number of patients from DHA-PQ treatment arm had cough (RR 1.06, 95% CI 1.01 to 1.11; participants = 8013; studies = 13; I^2 = 0%, *high quality of evidence*, **Figure 36**).

Publication bias

The funnel plot showed that all studies lie symmetrically around the pooled effect estimate implying that there was no publication bias (P= 0.84, **Figure 35**).

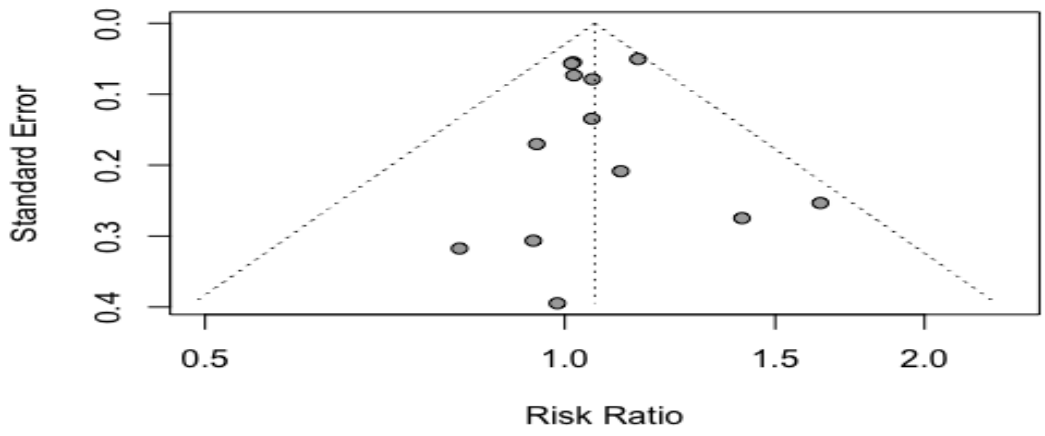

Figure 35: Funnel plot of comparison between DHA-PQ and AL for treatment of uncomplicated *p. falciparum* malaria in African children on cough.

Other cardiorespiratory and hematological adverse events

The relative risk of developing coryza was significantly higher in DHA-PQ treatment group than AL in one study, but no significant difference between the two treatment arms was seen in the pooled result (RR 1.00, 95% CI 0.92 to 1.10; participants = 832; studies = 2; I^2 = 0%, **Figure 36**). 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 arms (RR 1.59, 95% CI 0.89 to 2.83; participants = 442; studies = 1, (105)), (RR 1.23, 95% CI 0.59 to 2.57; participants = 299; studies = 1, (30)), (RR 3.35, 95% CI 1.11 to 10.12; participants = 469; studies = 1, (35)), 95% CI 0.91 to 1.92; participants = 1548; studies = 1,(102)).

Two studies reported anemia as an adverse event, and the pooled result had considerable heterogeneity (Tau^2 = 0.75; Chi^2 = 7.06, df = 1 (P = 0.008); I^2 = 86%). We couldn't pool the result. The relative risk of developing anemia as an adverse event was the same in both treatment groups RR 3.10 [95% CI 2.18, 4.39,(81)] and RR 0.82 [95% CI 0.33, 2.05, (35)], **Figure 36**. In addition, Hematological adverse events such as decrease in hemoglobin level and neutropenia didn't also have significant difference between the two arms (RR 1.04, 95% CI 0.78 to 1.37; participants = 2693; studies = 1, (81)) and (RR 0.74, 95% CI 0.36 to 1.52; participants = 1548; studies = 1, (102)), and (RR 1.70, 95% CI 0.87 to 3.31; participants = 599; studies = 1, (106)), respectively. Similarly, the relative risk of cardiac adverse events like QTc interval prolongation and QTc interval prolongation (Fridericia's correction and Bazett's correction) a significant difference didn't also seen between the two treatment arms (RR 0.98, 95% CI 0.51 to 1.90; participants = 1548; studies = 1, (102) 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, (102)).

Neuropsychiatry adverse event

weakness/malaise

There was no significant difference in the relative risk of developing weakness or malaise between the two treatment arms (RR 0.88, 95% CI 0.74 to 1.03; participants = 3407; studies = 8; I^2 = 0%, *high quality of evidence*, **Figure 37**). Also, there was no significant difference in the relative risk of headache between the two treatment arms (RR 0.81, 95% CI 0.47 to 1.38; participants = 598; studies = 3; I^2 = 72%, **Figure 37**).

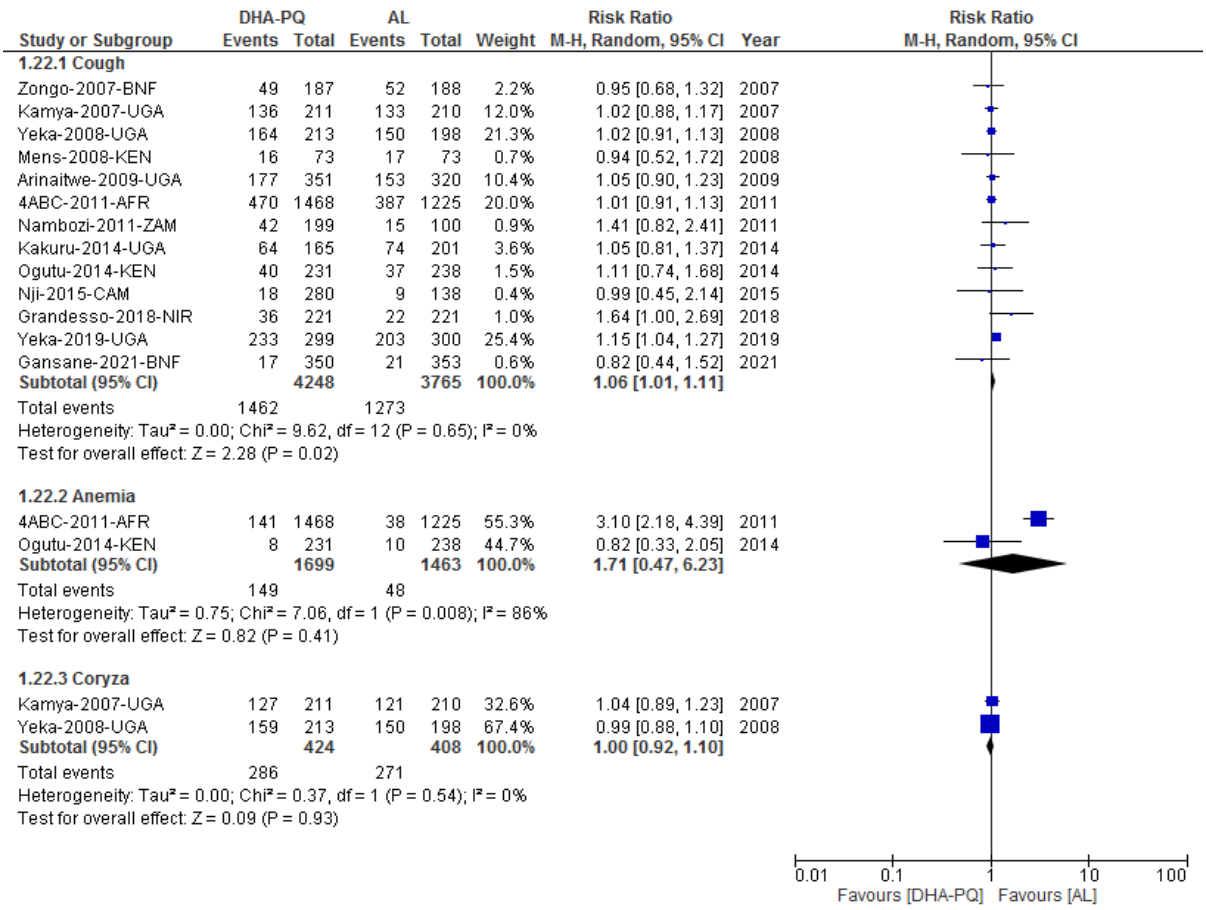

Figure 36: Forest plot of comparison between DHA-PQ and AL for treatment of uncomplicated *p. falciparum* malaria in African children on cardio-respiratory adverse events.

Musculoskeletal/dermatological adverse events

Pruritus

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*, **Figure 38**). Also, there was no significant difference in the relative risk of developing skin rash between the two treatment groups (RR 1.40, 95% CI 0.99 to 1.96; participants = 1720; studies = 3; I^2 = 0%, **Figure 38**).

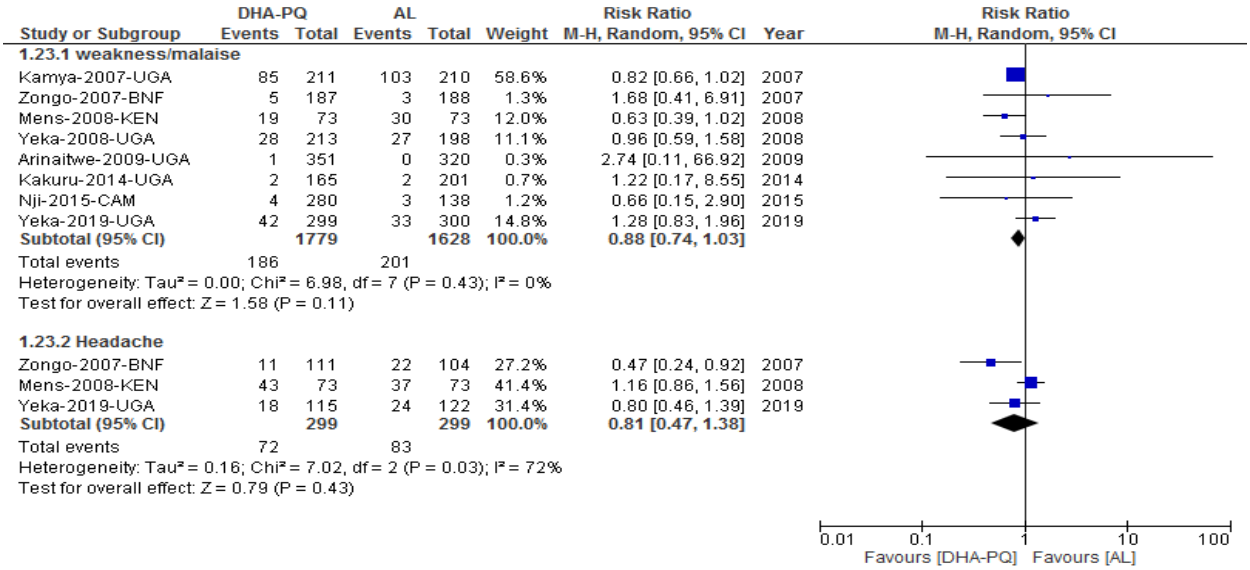

Figure 37: Forest plot of comparison between DHA-PQ and AL for treatment of uncomplicated *p. falciparum* malaria in African children on Neuropsychiatry adverse event.

Other Musculoskeletal/dermatological adverse events

There was no significant difference in the relative risk of developing musculoskeletal or dermatological adverse events such as skin and subcutaneous disorder, urticarial, hypersensitivity, pyoderma, conjunctivitis, joint pain, tinea-capitis, itchiness, frunculosis; (RR 1.19, 95% CI 0.78 to 1.80; participants = 1548; studies = 1, (102)), (RR 0.25, 95% CI 0.02 to 2.70; participants = 1548; studies = 1, (102)), (RR 0.98, 95% CI 0.09 to 10.81; participants = 1548; studies = 1, (102)), (RR 1.00, 95% CI 0.33 to 3.05; participants = 442; studies = 1, (105)), (RR 0.47, 95% CI 0.19 to 1.12; participants = 442; studies = 1, (105)), (RR 0.49, 95% CI 0.07 to 3.46; participants = 418; studies = 1, (107)), (RR 1.24, 95% CI 0.54 to 2.81; participants = 469; studies = 1, (35)), (RR 0.34, 95% CI 0.01 to 8.22; participants = 703; studies = 1,(73)) and (RR 3.03, 95% CI 0.12 to 74.02; participants = 703; studies = 1, (73)), 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%, **Figure 39**). 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%, **Figure 39**).

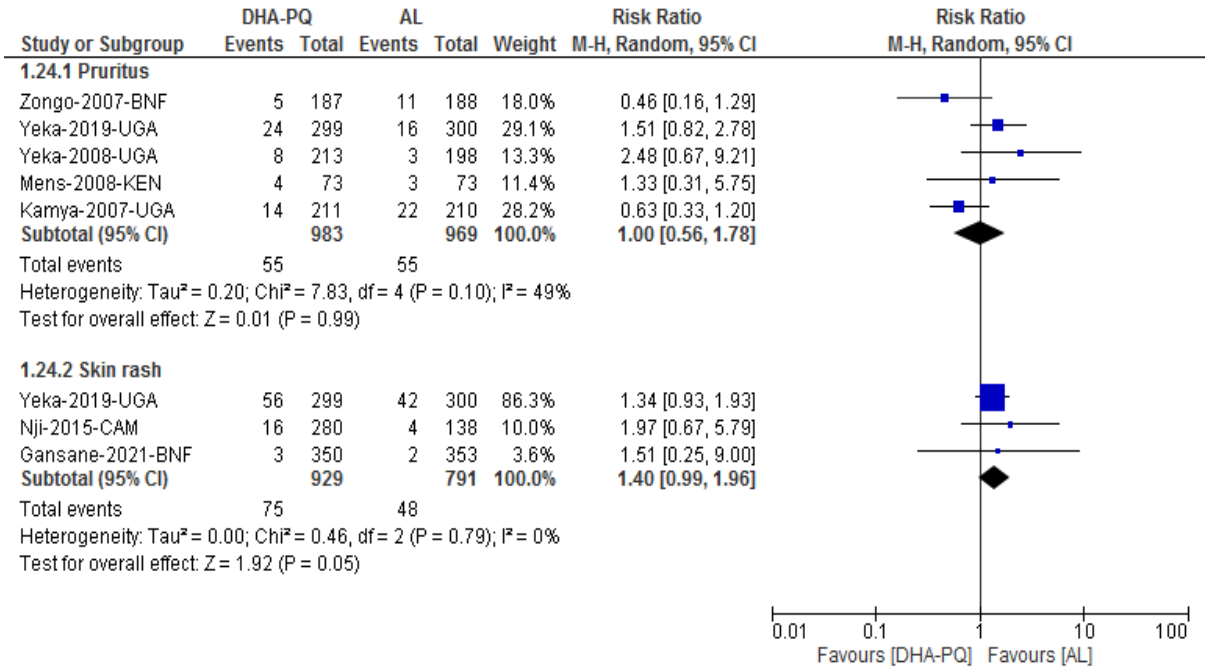

Figure 38: Forest plot of comparison between DHA-PQ and AL for treatment of uncomplicated *p. falciparum* malaria in African children on Musculoskeletal or dermatological adverse events.

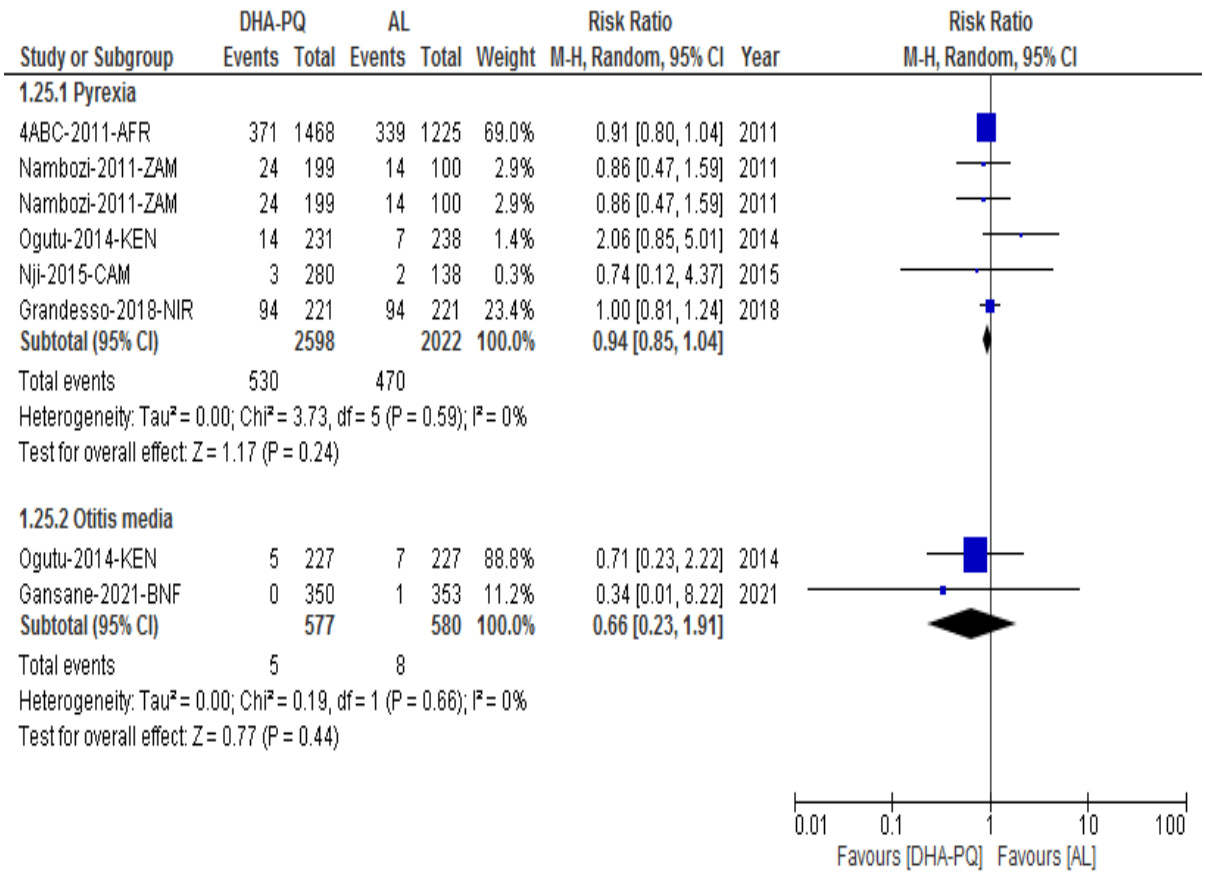

Figure 39: Forest plot of comparison between DHA-PQ and AL for treatment of uncomplicated *p. falciparum* malaria in African children on Other Adverse events.

Serious adverse event

Fifty nine serious adverse events (SAEs) from DHA-PQ and 35 SAEs from the AL treatment arm were reported from fourteen studies. However, there was no significant difference in the distributions of SAEs the two treatment arms (RR 1.27, 95% CI 0.83 to 1.96; participants = 9558; studies = 14; I^2 = 0%, *high quality of evidence*, **Figure 40**). Eight deaths were reported from two multi-center trials and the cause of death for seven of them were 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.

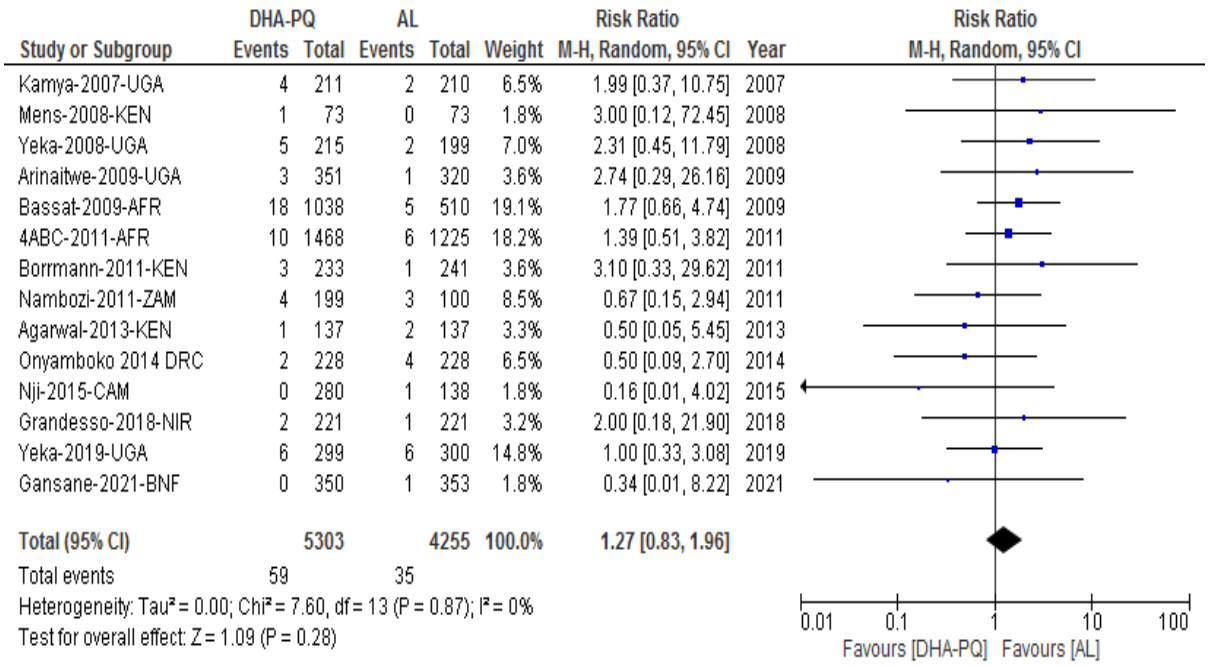

Figure 40: Forest plot of comparison between DHA-PQ and AL for treatment of uncomplicated *p. falciparum* malaria in African children on serious adverse event (including death).

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, **Figure 41**).

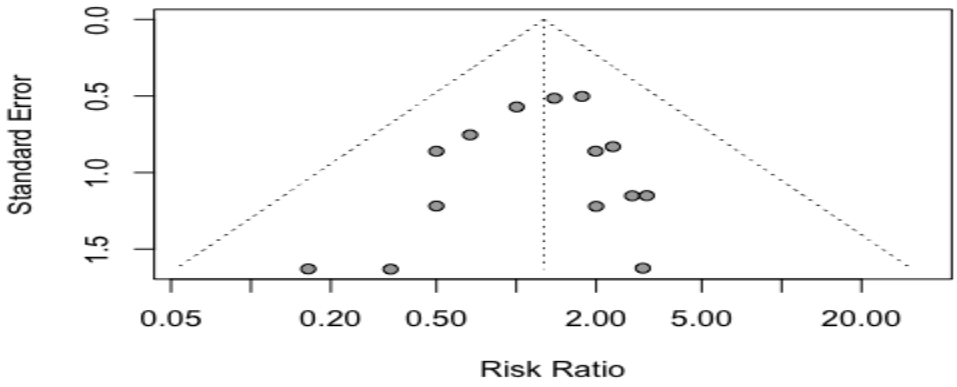

Figure 41: Funnel plot of comparison between DHA-PQ and AL for treatment of uncomplicated *p. falciparum* malaria in African children on serious adverse event (including death).

Sensitivity analysis

To explore the robustness of the methodology applied in the main analysis, a series of sensitivity analyses was done. This analysis aimed to restore the reliability of the randomization process. We have done the analysis by adding removed groups back into the analysis in a stepwise fashion and by removing studies classified as high risk of bias. Furthermore, to assess the influence of small-study effects on the results of our meta-analysis, we have compared random-effects and fixed-effect estimates of the intervention effect. However, we haven't seen any change in the result of the primary outcome.

Quality of the evidence

The quality of the evidence was explored in this review using the GRADE approach and summary of findings tables for efficacy, hemoglobin recovery, and safety (Summary of findings for the main comparison; Appendix **5**) were used to present the result.

The evidence that DHA-PQ was more effective than that of AL on day 28 and 42 uncorrected by genotyping was of *high and moderate quality of evidence*. There was considerable heterogeneity between studies on the pooled result of PCR uncorrected treatment failure on days 28 and 42. In addition, DHA-PQ consistently superiority over AL on days 28 and 42 corrected by PCR was *of high quality of evidence* and both DHA-PQ and AL achieved superior than the WHO standard of 95% genotyping corrected treatment success on day 28 in majority of the studies *(high quality of evidence)*. Nevertheless, the hemoglobin recoveries from the baseline were significantly higher in patients who were treated with DHA-PQ than that of AL (*high quality of evidence*). Also, the assessment of the quality of evidence on comparative AEs and SAEs; early vomiting, diarrhea, vomiting, and cough were somewhat more common in DHA-PQ treatment group (*high quality of evidence)*. In General, the quality of evidence of safety of the two treatments groups were high quality.

Chapter five: Discussion

Summary of findings

This study was designed to explore the therapeutic efficacy and safety of DHA-PQ and AL for management of uncomplicated *falciparum* malaria in African children. In this study, the 28 and 42 days PCR uncorrected treatment failure of 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*). The genotyping adjusted treatment failure on day 28 was below 5% in both treatment groups and similar result was seen in DHA-PQ treatment arm on day 42. On the contrary, a study from Burkina Faso 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*).

Patients in the DHA-PQ treatment group cleared their fever quicker than those in the AL group on post treatment day. This difference between the two treatment groups, however, implies that patients taking DHA-PQ were relieved of the symptom much faster compared to those treated with AL, and this did not influence the outcome of treatment. However, majority of the patients in both treatment groups cleared their fever on day 3. Furthermore, many under five children treated with DHA-PQ had parasite clearance on day 1. Consistently, participants from 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 treated with DHA-PQ compared to that of AL (*high quality of evidence*) on days 28 and 42. 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 in patients treated with DHA-PQ than that of AL (*high quality of evidence*). All SAEs were not associated to study drugs. Eight deaths were also reported. All SAEs 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 list 28 days post treatment and the appearance of 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 recommend a change in national malaria treatment policy (2).

In the majority of African countries, the first-line drug for uncomplicated malaria is generally AL or AS/AQ, with DHA-PQ as a second line one in many countries (9, 10). The observed lower PCR unadjusted treatment failure on days 28 and 42 in DHA-PQ treatment arm was similar with that of former reviews from Africa (12, 13). As seen in Myanmar, Papua New Guinea, Angola, and elsewhere in Africa, recurrent parasitaemia due to recrudescence occurs significantly more frequently in those patients treated with AL in the first 28 days (61, 113-117). 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 (13). 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 (22) 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 (20, 118). 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 (119), but due to the sub-therapeutic drug levels, selection for resistant parasite may occur (120). For patients who live in areas where malaria transmission is low, the benefit of drug's longer post treatment prophylactic period is low and the probability of developing drug resistance is higher (121). 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 (60, 122). Similarly, a former review reported that in no significant difference between the two treatment groups was seen on days 28 and day 63 in Papua New Guinea and Asia (13). 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 (12, 61, 123). Fever is one of the usual symptom of malaria that commonly causes discomfort. Thus, it was encouraging that in many studies from Africa, Ocean and Asia that the resolution of fever on days 2 and 3 was excellent in both treatment groups without a statistically significant difference (51, 122, 124, 125).

According to WHO (2, 70), 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 (113) and elsewhere in Africa (51, 126, 127) reported that artemisinin resistance has not emerged in Africa and Ocean. Furthermore, some molecular studies in Africa indicated nonappearance of the known mutations in *klecher-13(K-13) gene* which associated with artemisinin resistance in SEA (68, 128, 129), meaning that this drugs are quiet effective and their capacity of parasite clearance has not been changed. However, artemisinin resistance has been spreading in SEA (64, 130), to prevent the potential emergence artemisinin resistance, African countries have to be cautious through continuous monitoring of the parasite clearance and efficacy of artemisinin combination therapies, and surveillance of polymorphism in the *klecher-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 (91). 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 (91).

Young children presented with acute malaria and high parasitaemia have the highest risk of anemia (131). Especially, *p.falciparum* has a strong association with anemia in a place where malaria transmission intensity is moderate (132). In the first two days after treatment majority of the patients experience decrease in hemoglobin level, followed by a linear increase afterward (131). Similarly, patients from both treatment groups experienced significant drip in hemoglobin level within the first seven days after treatment (113, 126), and hemoglobin level significantly improved in both treatment arms on days 28 and 42 (122). 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 (113). 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 (80, 131, 133-135).

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 (113). A recent review on the efficacy and safety of the two ACT's also reported that vomiting, diarrhea, anorexia, and cough were the most frequent AEs. In this review more patients from DHA-PQ treatment arm had cough than that of AL (51) 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 (36, 136-138). Studies from Thiland-Mynamar border (33, 139) and elsewhere in Africa (32, 34, 140, 141) 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) (138), efavirenz-based ART (142), and administration of DHA-PQ with food could increase piperaquine exposure and it needs to be administered in fasting state (32-34).

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 prophylactic effect of the two drugs up to day 63.

Conclusion

This systematic review and meta-analysis show higher efficacy of DHA-PQ on days 28 and 42 than that of AL and association with gastrointestinal and respiratory adverse events. However, both treatments were safe and tolerable. While AL may continue to be used, DHA-PQ may be recommended as an alternative first line treatment for uncomplicated falciparum malaria in Africa.

Recommendations

- DHA-PQ better be the first line treatment.
- Trials that explore the long-term efficacy of DHA-PQ and AL with 42 and 63 days follow up better be carried out.
- To assess the safety profile of DHA-PQ well supervised study better be carried out.
- To identify molecular markers which are related to ACT resistance, comprehensive study using molecular technique better be conducted.

Reference

1. WHO. World Malaria Report 2019: Geneva, World Health Organization, 2019. Available from: Available from: https://www.who.int/malaria/publications/world-malaria-report-2019/en/.
2. WHO. Guidelines for treatment of malaria, 3rd edn. Geneva, World Health Organization, 2015. Available from: Available from: https://www.who.int/malaria/publications/atoz/9789241549127/en/.
3. World malaria report 2020: 20 years of global progress and challenges. Geneva: World Health Organization; 2020. . Available from: Available from: https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2020.
4. WHO. Malaria fact sheets. Geneva, World Health Ogranization, 2020. Available from: Available from: https://www.who.int/news-room/fact-sheets/detail/malaria.
5. WHO. World Malaria Report 2014. Geneva, World Health Organization, 2014. Available from: Available from: https://www.who.int/malaria/publications/world_malaria_report_2014/en.
6. WHO. Global Malaria Programme. Guidelines for the treatment of malaria. Geneva, World Health Organization, 2010. Available from: Available from: https://www.ncbi.nlm.nih.gov/books/NBK254223/pdf/Bookshelf_NBK254223.pdf.
7. Abba K, Kirkham AJ, Olliaro PL, Deeks JJ, Donegan S, Garner P, et al. Rapid diagnostic tests for diagnosing uncomplicated non-falciparum or Plasmodium vivax malaria in endemic countries. The Cochrane database of systematic reviews. 2014;2014(12):Cd011431.
8. Juliano JJ GN, Sutherland CJ, Meshnick SR. . The perils of PCR: can we accurately 'correct' antimalarial trials? Trends in parasitology. 2010;26(3):19-24.
9. WHO. World Malaria Report 2017. World Health Organization,Geneva, Switzerland Avilable at: https://wwwwhoint/malaria/publications/world-malaria-report-2017/report/en/. November 2017.
10. Health TRoUMo. Uganda Clinical Guidelines. National Guidelines for Management of Common Conditions. Available from: http://libraryhealthgoug/publications/guidelines/uganda-clinical-guidelines-2016. 2016:195-9.
11. Bretscher MT, Griffin JT, Hugo P, Baker M, Ghani A, Okell L. A comparison of the duration of post-treatment protection of artemether-lumefantrine, dihydroartemisinin-piperaquine and artesunate-amodiaquine for the treatment of uncomplicated malaria. Malaria Journal. 2014;13(Suppl 1):P19-P.
12. Sinclair D, Zani B, Donegan S, Olliaro P, Garner P. Artemisinin-based combination therapy for treating uncomplicated malaria. The Cochrane database of systematic reviews. 2009;2009(3):Cd007483.
13. Zani B, Gathu M, Donegan S, Olliaro PL, Sinclair D. Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria. The Cochrane database of systematic reviews. 2014;2014(1):Cd010927.
14. Fairhurst RM, Dondorp AM. Artemisinin-Resistant Plasmodium falciparum Malaria. Microbiology spectrum. 2016;4(3).

15. J. Golenser JHW, M. Krugliak, N. H. Hunt, and G. E. Grau. Current perspectives on the mechanism of action of artemisinins. International Journal for Parasitology. 2006; vol. 36(no. 14):pp. 1427–41.
16. White NJ, van Vugt M, Ezzet F. Clinical pharmacokinetics and pharmacodynamics and pharmacodynamics of artemether-lumefantrine. Clinical pharmacokinetics. 1999;37(2):105-25.
17. German PI, Aweeka FT. Clinical pharmacology of artemisinin-based combination therapies. Clinical pharmacokinetics. 2008;47(2):91-102.
18. Djimde A, Lefevre G. Understanding the pharmacokinetics of Coartem. Malaria Journal. 2009;8 Suppl 1:S4.
19. Kokwaro G, Mwai L, Nzila A. Artemether/lumefantrine in the treatment of uncomplicated falciparum malaria. Expert opinion on pharmacotherapy. 2007;8(1):75-94.
20. Ezzet F, van Vugt M, Nosten F, Looareesuwan S, White NJ. Pharmacokinetics and pharmacodynamics of lumefantrine (benflumetol) in acute falciparum malaria. Antimicrob Agents Chemother. 2000;44(3):697-704.
21. Travassos MA, Laufer MK. Resistance to antimalarial drugs: molecular, pharmacologic, and clinical considerations. Pediatric research. 2009;65(5 Pt 2):64R-70R.
22. COARTEM®(artemether and lumefantrine) tablets fouNPC. Available from: Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=7866ec19-dfac-47d4-a53f-511a12643cbf.
23. Abdulla S, Sagara I. Dispersible formulation of artemether/lumefantrine: specifically developed for infants and young children. Malaria Journal. 2009;8 Suppl 1:S7.
24. Abdulla S, Sagara I, Borrmann S, D'Alessandro U, Gonzalez R, Hamel M, et al. Efficacy and safety of artemether-lumefantrine dispersible tablets compared with crushed commercial tablets in African infants and children with uncomplicated malaria: a randomised, single-blind, multicentre trial. Lancet (London, England). 2008;372(9652):1819-27.
25. Agency EM. Eurartesim (dihydroartemisinin/piperaquine) 20 mg/160 mg and 40 mg/320 mg film-coated tablets: EU summary of product characteristics [online]

26. Eckstein-Ludwig U, Webb RJ, Van Goethem ID, East JM, Lee AG, Kimura M, et al. Artemisinins target the SERCA of Plasmodium falciparum. Nature. 2003;424(6951):957-61.
27. Agarwal A, McMorrow M, Onyango P, Otieno K, Odero C, Williamson J, et al. A randomized trial of artemether-lumefantrine and dihydroartemisinin-piperaquine in the treatment of uncomplicated malaria among children in western Kenya. Malaria Journal. 2013;12:254.
28. Ebenebe JC, Ntadom G, Ambe J, Wammanda R, Jiya N, Finomo F, et al. Efficacy of artemisinin-based combination treatments of uncomplicated falciparum malaria in under-five-year-old Nigerian children ten years following adoption as first-line antimalarials. The American Journal of Tropical Medicine and Hygiene. 2018;99(3):649-64.
29. Gargano N, Madrid L, Valentini G, D'Alessandro U, Halidou T, Sirima S, et al. Efficacy and Tolerability Outcomes of a Phase II, Randomized, Open-Label, Multicenter Study of a New Water-Dispersible Pediatric Formulation of Dihydroartemisinin-Piperaquine for the Treatment of Uncomplicated Plasmodium falciparum Malaria in African Infants. Antimicrobial agents and chemotherapy. 2018;62(1).
30. Nambozi M, Van Geertruyden JP, Hachizovu S, Chaponda M, Mukwamataba D, Mulenga M, et al. Safety and efficacy of dihydroartemisinin-piperaquine versus artemether-

lumefantrine in the treatment of uncomplicated *Plasmodium falciparum* malaria in Zambian children. Malaria Journal. 2011;10:50.
31. Dama S, Niangaly H, Djimde M, Sagara I, Guindo CO, Zeguime A, et al. A randomized trial of dihydroartemisinin–piperaquine versus artemether–lumefantrine for treatment of uncomplicated Plasmodium falciparum malaria in Mali. Malaria Journal. 2018;17.
32. Funck-Brentano C, Bacchieri A, Valentini G, Pace S, Tommasini S, Voiriot P, et al. Effects of Dihydroartemisinin-Piperaquine Phosphate and Artemether-Lumefantrine on QTc Interval Prolongation. Scientific reports. 2019;9(1):777.
33. Manning J, Vanachayangkul P, Lon C, Spring M, So M, Sea D, et al. Randomized, double-blind, placebo-controlled clinical trial of a two-day regimen of dihydroartemisinin-piperaquine for malaria prevention halted for concern over prolonged corrected QT interval. Antimicrobial Agents and Chemotherapy. 2014;58(10):6056-67.
34. Oduro AR, Owusu-Agyei S, Gyapong M, Osei I, Adjei A, Yawson A, et al. Post-licensure safety evaluation of dihydroartemisinin piperaquine in the three major ecological zones across Ghana. PLoS ONE. 2017;12(3).
35. Ogutu BR, Onyango KO, Koskei N, Omondi EK, Ongecha JM, Otieno GA, et al. Efficacy and safety of artemether-lumefantrine and dihydroartemisinin-piperaquine in the treatment of uncomplicated Plasmodium falciparum malaria in Kenyan children aged less than five years: results of an open-label, randomized, single-centre study. Malaria Journal. 2014;13:33.
36. Yavo W, Faye B, Kuete T, Djohan V, Oga SA, Kassi RR, et al. Multicentric assessment of the efficacy and tolerability of dihydroartemisinin-piperaquine compared to artemether-lumefantrine in the treatment of uncomplicated Plasmodium falciparum malaria in sub-Saharan Africa. Malaria Journal. 2011;10:198.
37. Mori AT, Ngalesoni F, Norheim OF, Robberstad B. Cost-effectiveness of dihydroartemisinin-piperaquine compared with artemether-lumefantrine for treating uncomplicated malaria in children at a district hospital in Tanzania. Malaria Journal. 2014;13(1).
38. Pfeil J, Borrmann S, Bassat Q, Mulenga M, Talisuna A, Tozan Y. An economic evaluation of the posttreatment prophylactic effect of dihydroartemisinin-piperaquine versus artemether-lumefantrine for first-line treatment of plasmodium falciparum malaria across different transmission settings in Africa. American Journal of Tropical Medicine and Hygiene. 2015;93(5):961-6.
39. Pfeil J, Borrmann S, Tozan Y. Dihydroartemisinin-piperaquine vs. artemether-lumefantrine for first-line treatment of uncomplicated malaria in African children: A cost-effectiveness analysis. PLoS ONE. 2014;9(4).
40. Dorkenoo AM, Yehadji D, Agbo YM, Layibo Y, Agbeko F, Adjeloh P, et al. Therapeutic efficacy trial of artemisinin-based combination therapy for the treatment of uncomplicated malaria and investigation of mutations in k13 propeller domain in Togo, 2012–2013. Malaria Journal. 2016;15.
41. Davlantes E, Dimbu PR, Ferreira CM, Florinda Joao M, Pode D, Félix J, et al. Efficacy and safety of artemether–lumefantrine, artesunate–amodiaquine, and dihydroartemisinin–piperaquine for the treatment of uncomplicated *Plasmodium falciparum* malaria in three provinces in Angola, 2017. Malaria Journal. 2018;17:144.
42. Ebstie YA, Zeynudin A, Belachew T, Desalegn Z, Suleman S. Assessment of therapeutic efficacy and safety of artemether-lumefantrine (Coartem®) in the treatment of

uncomplicated Plasmodium falciparum malaria patients in Bahir Dar district, Northwest Ethiopia: an observational cohort study. Malaria Journal. 2015;14.
43. Plucinski MM, Dimbu PR, Macaia AP, Ferreira CM, Samutondo C, Quivinja J, et al. Efficacy of artemether–lumefantrine, artesunate–amodiaquine, and dihydroartemisinin–piperaquine for treatment of uncomplicated *Plasmodium falciparum* malaria in Angola, 2015. Malaria Journal. 2017;16:62.
44. Warsame M, Hassan AM, Hassan AH, Jibril AM, Khim N, Arale AM, et al. High therapeutic efficacy of artemether–lumefantrine and dihydroartemisinin–piperaquine for the treatment of uncomplicated falciparum malaria in Somalia. Malaria Journal. 2019;18.
45. Samad R, Rahman MR, Yunus EB, Hussain MA, Arif SM, Islam MN, et al. An open randomized controlled trial to compare the efficacy of two fixed dose combinations of artemesinin based combinations for uncomplicated falciparum malaria in Bangladesh. Bangladesh Medical Research Council bulletin. 2013;39(3):109-15.
46. Derbie A, Mekonnen D, Adugna M, Yeshitela B, Woldeamanuel Y, Abebe T. Therapeutic Efficacy of Artemether-Lumefantrine (Coartem®) for the Treatment of Uncomplicated Falciparum Malaria in Africa: A Systematic Review. Journal of parasitology research. 2020;2020:7371681.
47. Makanga M, Bassat Q, Falade CO, Premji ZG, Krudsood S, Hunt P, et al. Efficacy and Safety of Artemether-Lumefantrine in the Treatment of Acute, Uncomplicated Plasmodium falciparum Malaria: A Pooled Analysis. The American Journal of Tropical Medicine and Hygiene. 2011;85(5):793-804.
48. Falade C, Manyando C. Safety profile of Coartem®: the evidence base. Malaria Journal. 2009;8(Suppl 1):S6.
49. Whegang Youdom S, Tahar R, Basco LK. Comparison of anti-malarial drugs efficacy in the treatment of uncomplicated malaria in African children and adults using network meta-analysis. Malaria Journal. 2017;16(1).
50. Abdulla S, Adam I, Adjei GO, Adjuik MA, Alemayehu B, Allan R, et al. Clinical determinants of early parasitological response to ACTs in African patients with uncomplicated falciparum malaria: A literature review and meta-analysis of individual patient data. BMC medicine. 2015;13(1).
51. Assefa DG, Zeleke ED, Bekele D, Tesfahunei HA, Getachew E, Joseph M, et al. Efficacy and safety of dihydroartemisinin–piperaquine versus artemether–lumefantrine for treatment of uncomplicated Plasmodium falciparum malaria in Ugandan children: a systematic review and meta-analysis of randomized control trials. Malaria Journal. 2021;20(1):174.
52. Akpaloo W, Purssell E. Does the use of dihydroartemisinin-piperaquine in treating patients with uncomplicated falciparum malaria reduce the risk for recurrent new falciparum infection more than artemether-lumefantrine? Malaria research and treatment. 2014;2014.
53. Group PS, Pekyi D, Ampromfi AA, Tinto H, Traore-Coulibaly M, Tahita MC, et al. Four artemisinin-based treatments in African pregnant women with malaria. Malawi medical journal : the journal of Medical Association of Malawi. 2016;28(3):139-49.
54. Dama S, Niangaly H, Djimde M, Sagara I, Guindo CO, Zeguime A, et al. A randomized trial of dihydroartemisinin-piperaquine versus artemether-lumefantrine for treatment of uncomplicated Plasmodium falciparum malaria in Mali. Malaria Journal. 2018;17(1):347.

55. Nambozi M, Tinto H, Mwapasa V, Tagbor H, Kabuya J-BB, Hachizovu S, et al. Artemisinin-based combination therapy during pregnancy: outcome of pregnancy and infant mortality: a cohort study. Malaria Journal. 2019;18(1):105.
56. Song J, Socheat D, Tan B, Seila S, Xu Y, Ou F, et al. Randomized trials of artemisinin-piperaquine, dihydroartemisinin-piperaquine phosphate and artemether-lumefantrine for the treatment of multi-drug resistant falciparum malaria in Cambodia-Thailand border area. Malaria Journal. 2011;10:231.
57. Wang SQ, Christophel E, Lin SG, Meng F, Hu XM, Wang GZ, et al. Efficacy of dihydroartemisinin-piperaquine and artemether-lumefantrine in the treatment of uncomplicated falciparum malaria in Hainan, China. Zhongguo ji sheng chong xue yu ji sheng chong bing za zhi = Chinese journal of parasitology & parasitic diseases. 2008;26(1):50-2.
58. Ogutu B. Artemether and lumefantrine for the treatment of uncomplicated Plasmodium falciparum malaria in sub-Saharan Africa. Expert opinion on pharmacotherapy. 2013;14(5):643-54.
59. Sow D, Ndiaye JL, Sylla K, Ba MS, Tine RC, Faye B, et al. [Evaluation of the efficacy and safety of three 2-drug combinations for the treatment of uncomplicated Plasmodium falciparum malaria in Senegal: artesunate-amodiaquine, dihydroartemisinin-piperaquine, and artemether-lumefantrine]. Medecine et sante tropicales. 2016;26(1):45-50.
60. Sylla K, Abiola A, Tine RCK, Faye B, Sow D, Ndiaye JL, et al. Monitoring the efficacy and safety of three artemisinin based-combinations therapies in Senegal: Results from two years surveillance. BMC infectious diseases. 2013;13(1).
61. Han KT, Lin K, Myint MK, Thi A, Aye KH, Han ZY, et al. Artemether-lumefantrine and dihydroartemisinin-piperaquine retain high efficacy for treatment of uncomplicated plasmodium falciparum malaria in Myanmar. American Journal of Tropical Medicine and Hygiene. 2020;102(3):598-604.
62. Hamainza B, Masaninga F, Moonga H, Mwenda M, Chanda-kapata P, Chalwe V, et al. Therapeutic efficacy of artemether-lumefantrine on treatment of uncomplicated Plasmodium falciparum mono-infection in an area of high malaria transmission in Zambia. Malaria Journal. 2014;13:430.
63. WHO. Methods for surveillance of antimalarial drug efficacy. Geneva, World Health Organization, 2009. Available from: Available from: https://www.who.int/malaria/publications/atoz/9789241597531/en/.
64. Ashley EA, Dhorda M, Fairhurst RM, Amaratunga C, Lim P, Suon S, et al. Spread of artemisinin resistance in Plasmodium falciparum malaria. The New England journal of medicine. 2014;371(5):411-23.
65. Noedl H, Se Y, Schaecher K, Smith BL, Socheat D, Fukuda MM. Evidence of artemisinin-resistant malaria in western Cambodia. The New England journal of medicine. 2008;359(24):2619-20.
66. Dondorp AM, Nosten F, Yi P, Das D, Phyo AP, Tarning J, et al. Artemisinin resistance in *Plasmodium falciparum* malaria. The New England journal of medicine. 2009;361(5):455-67.
67. von Seidlein L, Dondorp A. Fighting fire with fire: mass antimalarial drug administrations in an era of antimalarial resistance. Expert review of anti-infective therapy. 2015;13(6):715-30.
68. Menard D, Khim N, Beghain J, Adegnika AA, Shafiul-Alam M, Amodu O, et al. A Worldwide Map of Plasmodium falciparum K13-Propeller Polymorphisms. The New England journal of medicine. 2016;374(25):2453-64.

69. Mohamed AO, Hussien M, Mohamed A, Suliman A, Elkando NS, Abdelbagi H, et al. Assessment of Plasmodium falciparum drug resistance molecular markers from the Blue Nile State, Southeast Sudan. Malaria Journal. 2020;19(1).
70. WHO. Artemisinin and artemisinin-based combination therapy resistance. Status report. Geneva, World Health Organization, 2017
Available from: Available from: https://www.who.int/malaria/publications/atoz/artemisinin-resistance-april2017/en/.
71. Chebore W, Zhou Z, Westercamp N, Otieno K, Shi YP, Sergent SB, et al. Assessment of molecular markers of anti-malarial drug resistance among children participating in a therapeutic efficacy study in western Kenya. Malaria Journal. 2020;19(1).
72. Sowunmi A, Ntadom G, Akano K, Ibironke FO, Ayede AI, Agomo C, et al. Declining responsiveness of childhood Plasmodium falciparum infections to artemisinin-based combination treatments ten years following deployment as first-line antimalarials in Nigeria. Infectious Diseases of Poverty. 2019;8(1):69.
73. Gansané A, Moriarty LF, Ménard D, Yerbanga I, Ouedraogo E, Sondo P, et al. Anti-malarial efficacy and resistance monitoring of artemether-lumefantrine and dihydroartemisinin-piperaquine shows inadequate efficacy in children in Burkina Faso, 2017–2018. Malaria Journal. 2021;20(1).
74. Witkowski B, Amaratunga C, Khim N, Sreng S, Chim P, Kim S, et al. Novel phenotypic assays for the detection of artemisinin-resistant Plasmodium falciparum malaria in Cambodia: in-vitro and ex-vivo drug-response studies. The Lancet Infectious Diseases. 2013;13(12):1043-9.
75. Amaratunga C LP, Suon S, et al. Dihydroartemisinin-piperaquine resistance in Plasmodium falciparum malaria in Cambodia: a multi site prospective cohort study. The Lancet Infectious Diseases. 2016;16:357-65.
76. Zhao SM, Wang MY. [Artemisinin resistance in Plasmodium falciparum: global status and basic research]. Zhongguo ji sheng chong xue yu ji sheng chong bing za zhi = Chinese journal of parasitology & parasitic diseases. 2014;32(5):380-4.
77. Wilson DW, Langer C, Goodman CD, McFadden GI, Beeson JG. Defining the timing of action of antimalarial drugs against Plasmodium falciparum. Antimicrob Agents Chemother. 2013;57(3):1455-67.
78. Okebe J, Bojang K, D'Alessandro U. Use of artemisinin and its derivatives for the treatment of malaria in children. The Pediatric infectious disease journal. 2014;33(5):522-4.
79. Witkowski B, Khim N, Chim P, Kim S, Ke S, Kloeung N, et al. Reduced artemisinin susceptibility of *Plasmodium falciparum* ring stages in western Cambodia. Antimicrob Agents Chemother. 2013;57(2):914-23.
80. Mandara CI, Kavishe RA, Gesase S, Mghamba J, Ngadaya E, Mmbuji P, et al. High efficacy of artemether-lumefantrine and dihydroartemisinin-piperaquine for the treatment of uncomplicated falciparum malaria in Muheza and Kigoma Districts, Tanzania. Malaria Journal. 2018;17(1):261.
81. Four Artemisinin-Based Combinations Study G. A head-to-head comparison of four artemisinin-based combinations for treating uncomplicated malaria in African children: a randomized trial. PLoS Medicine. 2011;8(11):e1001119.
82. Uwimana A, Penkunas MJ, Nisingizwe MP, Warsame M, Umulisa N, Uyizeye D, et al. Efficacy of artemether-lumefantrine versus dihydroartemisinin-piperaquine for the treatment of uncomplicated malaria among children in Rwanda: an open-label, randomized

controlled trial. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2019;113(6):312-9.
83. Dawit Assefa EZ, Eyasu Makonnen, Gizachew Yismaw. . Systematic review and meta-analysis of the efficacy and safety of Dihydroartemisinin Piperaquine versus Artemether-Lumefantrine for the treatment of uncomplicated falciparum malaria in African children. PROSPERO 2020. Available from: Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020200337.
84. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Bmj. 2021;372:n71.
85. Higgins JPT, Green S., Eds. Cochrane Handbook for Systematic Reviews of Interventions, 2011.
. Available from: Available from: www.cochrane-handbook.org.
86. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from: Available from: www.training.cochrane.org/handbook.
87. Deeks JJ, Higgins JPT, Altman DG. Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., Eds. Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from: Available from: www.training.cochrane.org/handbook.
88. Viechtbauer W, Cheung MW. Outlier and influence diagnostics for meta-analysis. Research synthesis methods. 2010;1(2):112-25.
89. Baujat B, Mahé C, Pignon J-P, Hill C. A graphical method for exploring heterogeneity in meta-analyses: application to a meta-analysis of 65 trials. Statistics in medicine. 2002;21(18):2641-52.
90. Olkin I, Dahabreh IJ, Trikalinos TA. GOSH - a graphical display of study heterogeneity. Research synthesis methods. 2012;3(3):214-23.
91. Muhindo MK, Kakuru A, Jagannathan P, Talisuna A, Osilo E, Orukan F, et al. Early parasite clearance following artemisinin-based combination therapy among Ugandan children with uncomplicated *Plasmodium falciparum* malaria. Malaria Journal. 2014;13:32.
92. Simonsohn U, Nelson LD, Simmons JP. p-Curve and Effect Size: Correcting for Publication Bias Using Only Significant Results. Perspectives on psychological science : a journal of the Association for Psychological Science. 2014;9(6):666-81.
93. Simonsohn U, Simmons JP, Nelson LD. Better P-curves: Making P-curve analysis more robust to errors, fraud, and ambitious P-hacking, a Reply to Ulrich and Miller (2015). Journal of experimental psychology General. 2015;144(6):1146-52.
94. McMaster University GRADEproGDT. McMasterUniversity (developed by Evidence Prime), 2020. Available from: Available from: https://gradepro.org/.
95. Schünemann, Brożek, Guyatt, Oxman. Introduction to GRADE Handbook (Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach), 2013. Available from: Available from: https://gradepro.org.
96. HigginsJPT, SavovicJ, PageMJ, ElbersRG, Sterne JAC . Chapter 8: Assessing risk of bias in a randomized trial.Cochrane Handbook for Systematic Reviews ofInterventions version 6.0 (updated July 2019). Cochrane, 2019. Available from: Available from: www.training.cochrane.org/handbook.

97. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. Journal of clinical epidemiology. 2011;64(12):1283-93.
98. Kamya MR, Yeka A, Bukirwa H, Lugemwa M, Rwakimari JB, Staedke SG, et al. Artemether-lumefantrine versus dihydroartemisinin-piperaquine for treatment of malaria: a randomized trial. PLoS clinical trials. 2007;2(5):e20.
99. Zongo I, Dorsey G, Rouamba N, Dokomajilar C, Sere Y, Rosenthal PJ, et al. Randomized comparison of amodiaquine plus sulfadoxine-pyrimethamine, artemether-lumefantrine, and dihydroartemisinin-piperaquine for the treatment of uncomplicated Plasmodium falciparum malaria in Burkina Faso. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2007;45(11):1453-61.
100. Yeka A, Dorsey G, Kamya MR, Talisuna A, Lugemwa M, Rwakimari JB, et al. Artemether-lumefantrine versus dihydroartemisinin-piperaquine for treating uncomplicated malaria: a randomized trial to guide policy in Uganda. PLoS ONE. 2008;3(6):e2390.
101. Arinaitwe E, Sandison TG, Wanzira H, Kakuru A, Homsy J, Kalamya J, et al. Artemether-lumefantrine versus dihydroartemisinin-piperaquine for falciparum malaria: a longitudinal, randomized trial in young Ugandan children. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2009;49(11):1629-37.
102. Bassat Q, Mulenga M, Tinto H, Piola P, Borrmann S, Menendez C, et al. Dihydroartemisinin-piperaquine and artemether-lumefantrine for treating uncomplicated malaria in African children: a randomised, non-inferiority trial. PLoS ONE. 2009;4(11):e7871.
103. Sawa P, Shekalaghe SA, Drakeley CJ, Sutherland CJ, Mweresa CK, Baidjoe AY, et al. Malaria transmission after artemether-lumefantrine and dihydroartemisinin-piperaquine: a randomized trial. The Journal of Infectious Diseases. 2013;207(11):1637-45.
104. Onyamboko MA, Fanello CI, Wongsaen K, Tarning J, Cheah PY, Tshefu KA, et al. Randomized comparison of the efficacies and tolerabilities of three artemisinin-based combination treatments for children with acute *Plasmodium falciparum* Malaria in the Democratic Republic of the Congo. Antimicrob Agents Chemother. 2014;58(9):5528-36.
105. Grandesso F, Guindo O, Woi Messe L, Makarimi R, Traore A, Dama S, et al. Efficacy of artesunate-amodiaquine, dihydroartemisinin-piperaquine and artemether-lumefantrine for the treatment of uncomplicated *Plasmodium falciparum* malaria in Maradi, Niger. Malaria Journal. 2018;17(1):52.
106. Yeka A, Wallender E, Mulebeke R, Kibuuka A, Kigozi R, Bosco A, et al. Comparative Efficacy of Artemether-Lumefantrine and Dihydroartemisinin-Piperaquine for the Treatment of Uncomplicated Malaria in Ugandan Children. The Journal of Infectious Diseases. 2019;219(7):1112-20.
107. Nji AM, Ali IM, Moyeh MN, Ngongang EO, Ekollo AM, Chedjou JP, et al. Randomized non-inferiority and safety trial of dihydroartemisin-piperaquine and artesunate-amodiaquine versus artemether-lumefantrine in the treatment of uncomplicated Plasmodium falciparum malaria in Cameroonian children. Malaria Journal. 2015;14:27.
108. Ursing J, Rombo L, Rodrigues A, Kofoed PE. Artemether-Lumefantrine versus Dihydroartemisinin-Piperaquine for Treatment of Uncomplicated Plasmodium falciparum Malaria in Children Aged Less than 15 Years in Guinea-Bissau - An Open-Label Non-Inferiority Randomised Clinical Trial. PLoS ONE. 2016;11(9):e0161495.
109. Meremikwu MM, Odey F, Donegan S, Oringanje C, Oyo-Ita A, Elemi I, et al. Artemether-lumefantrine, artesunate+amodiaquine and dihydroartemisininpiperaquine for treating uncomplicated plasmodium falciparum malaria in under-five Nigerian children: A

randomized controlled trial. American Journal of Tropical Medicine and Hygiene. 2013;89(5):387.
110. Borrmann S, Sasi P, Mwai L, Bashraheil M, Abdallah A, Muriithi S, et al. Declining responsiveness of Plasmodium falciparum infections to artemisinin-based combination treatments on the Kenyan coast. PLoS ONE. 2011;6(11):e26005.
111. Kakuru A, Achan J, Muhindo MK, Ikilezi G, Arinaitwe E, Mwangwa F, et al. Artemisinin-based combination therapies are efficacious and safe for treatment of uncomplicated malaria in HIV-infected Ugandan children. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2014;59(3):446-53.
112. Mens PF, Sawa P, van Amsterdam SM, Versteeg I, Omar SA, Schallig HD, et al. A randomized trial to monitor the efficacy and effectiveness by QT-NASBA of artemether-lumefantrine versus dihydroartemisinin-piperaquine for treatment and transmission control of uncomplicated Plasmodium falciparum malaria in western Kenya. Malaria Journal. 2008;7:237.
113. Tavul L, Hetzel MW, Teliki A, Walsh D, Kiniboro B, Rare L, et al. Efficacy of artemether–lumefantrine and dihydroartemisinin–piperaquine for the treatment of uncomplicated malaria in Papua New Guinea. Malaria Journal. 2018;17(1):350.
114. Plucinski MM, Dimbu PR, Macaia AP, Ferreira CM, Samutondo C, Quivinja J, et al. Efficacy of artemether-lumefantrine, artesunate-amodiaquine, and dihydroartemisinin-piperaquine for treatment of uncomplicated Plasmodium falciparum malaria in Angola, 2015. Malaria Journal. 2017;16(1).
115. Plucinski MM, Talundzic E, Morton L, Dimbu PR, Macaia AP, Fortes F, et al. Efficacy of artemether-lumefantrine and dihydroartemisinin-piperaquine for treatment of uncomplicated malaria in children in Zaire and Uige Provinces, angola. Antimicrob Agents Chemother. 2015;59(1):437-43.
116. Adam I, Salah MT, Eltahir HG, Elhassan AH, Elmardi KA, Malik EM. Dihydroartemisinin-piperaquine versus artemether-lumefantrine, in the treatment of uncomplicated Plasmodium falciparum malaria in central Sudan. Annals of tropical medicine and parasitology. 2010;104(4):319-26.
117. Warsame M, Hassan AM, Hassan AH, Jibril AM, Khim N, Arale AM, et al. High therapeutic efficacy of artemether-lumefantrine and dihydroartemisinin-piperaquine for the treatment of uncomplicated falciparum malaria in Somalia. Malaria Journal. 2019;18(1):231.
118. Hung TY, Davis TM, Ilett KF, Karunajeewa H, Hewitt S, Denis MB, et al. Population pharmacokinetics of piperaquine in adults and children with uncomplicated falciparum or vivax malaria. British journal of clinical pharmacology. 2004;57(3):253-62.
119. Price RN, Douglas NM. Artemisinin Combination Therapy for Malaria: Beyond Good Efficacy. Clinical Infectious Diseases. 2009;49(11):1638-40.
120. Stepniewska K, White NJ. Pharmacokinetic determinants of the window of selection for antimalarial drug resistance. Antimicrob Agents Chemother. 2008;52(5):1589-96.
121. Pongtavornpinyo W, Yeung S, Hastings IM, Dondorp AM, Day NPJ, White NJ. Spread of anti-malarial drug resistance: Mathematical model with implications for ACT drug policies. Malaria Journal. 2008;7(1):229.
122. Dama S, Niangaly H, Djimde M, Sagara I, Guindo CO, Zeguime A, et al. A randomized trial of dihydroartemisinin-piperaquine versus artemether-lumefantrine for treatment of uncomplicated Plasmodium falciparum malaria in Mali. Malaria Journal. 2018;17(1):347.

123. Diallo MA, Yade MS, Ndiaye YD, Diallo I, Diongue K, Sy SA, et al. Efficacy and safety of artemisinin-based combination therapy and the implications of Pfkelch13 and Pfcoronin molecular markers in treatment failure in Senegal. Scientific reports. 2020;10(1):8907.
124. Menan H, Faye O, Same-Ekobo A, Oga AS, Faye B, Kiki Barro CP, et al. Comparative study of the efficacy and tolerability of dihydroartemisinin-piperaquine-trimethoprim versus artemether-lumefantrine in the treatment of uncomplicated Plasmodium falciparum malaria in Cameroon, Ivory Coast and Senegal. Malaria Journal. 2011;10:185.
125. Tavul L, Hetzel MW, Teliki A, Walsh D, Kiniboro B, Rare L, et al. Efficacy of artemether-lumefantrine and dihydroartemisinin-piperaquine for the treatment of uncomplicated malaria in Papua New Guinea. Malaria Journal. 2018;17(1).
126. Menan H, Faye O, Same-Ekobo A, Oga ASS, Faye B, Kiki Barro CP, et al. Comparative study of the efficacy and tolerability of dihydroartemisinin - Piperaquine - trimethoprim versus artemether - Lumefantrine in the treatment of uncomplicated Plasmodium falciparum malaria in Cameroon, Ivory Coast and Senegal. Malaria Journal. 2011;10.
127. Davlantes E, Dimbu PR, Ferreira CM, Florinda Joao M, Pode D, Félix J, et al. Efficacy and safety of artemether-lumefantrine, artesunate-amodiaquine, and dihydroartemisinin-piperaquine for the treatment of uncomplicated Plasmodium falciparum malaria in three provinces in Angola, 2017. Malaria Journal. 2018;17(1).
128. Kamau E, Campino S, Amenga-Etego L, Drury E, Ishengoma D, Johnson K, et al. K13-propeller polymorphisms in Plasmodium falciparum parasites from sub-Saharan Africa. The Journal of Infectious Diseases. 2015;211(8):1352-5.
129. Taylor SM, Parobek CM, DeConti DK, Kayentao K, Coulibaly SO, Greenwood BM, et al. Absence of putative artemisinin resistance mutations among Plasmodium falciparum in Sub-Saharan Africa: a molecular epidemiologic study. The Journal of Infectious Diseases. 2015;211(5):680-8.
130. Leang R, Mairet-Khedim M, Chea H, Huy R, Khim N, Mey Bouth D, et al. Efficacy and Safety of Pyronaridine-Artesunate plus Single-Dose Primaquine for Treatment of Uncomplicated Plasmodium falciparum Malaria in Eastern Cambodia. Antimicrob Agents Chemother. 2019;63(3).
131. Zwang J, D'Alessandro U, Ndiaye JL, Djimdé AA, Dorsey G, Mårtensson AA, et al. Haemoglobin changes and risk of anaemia following treatment for uncomplicated falciparum malaria in sub-Saharan Africa. BMC infectious diseases. 2017;17(1).
132. Halliday KE, Karanja P, Turner EL, Okello G, Njagi K, Dubeck MM, et al. Plasmodium falciparum, anaemia and cognitive and educational performance among school children in an area of moderate malaria transmission: baseline results of a cluster randomized trial on the coast of Kenya. Tropical medicine & international health : TM & IH. 2012;17(5):532-49.
133. Sousa-Figueiredo JC, Gamboa D, Pedro JM, Fancony C, Langa AJ, Magalhaes RJ, et al. Epidemiology of malaria, schistosomiasis, geohelminths, anemia and malnutrition in the context of a demographic surveillance system in northern Angola. PLoS ONE. 2012;7(4):e33189.
134. Ngui R, Lim YA, Chong Kin L, Sek Chuen C, Jaffar S. Association between anaemia, iron deficiency anaemia, neglected parasitic infections and socioeconomic factors in rural children of West Malaysia. PLoS neglected tropical diseases. 2012;6(3):e1550.
135. Magalhaes RJ, Clements AC. Mapping the risk of anaemia in preschool-age children: the contribution of malnutrition, malaria, and helminth infections in West Africa. PLoS Medicine. 2011;8(6):e1000438.

136. Myint HY, Ashley EA, Day NP, Nosten F, White NJ. Efficacy and safety of dihydroartemisinin-piperaquine. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2007;101(9):858-66.
137. Kakolwa MA, Mahende MK, Ishengoma DS, Mandara CI, Ngasala B, Kamugisha E, et al. Efficacy and safety of artemisinin-based combination therapy, and molecular markers for artemisinin and piperaquine resistance in Mainland Tanzania. Malaria Journal. 2018;17(1):369.
138. Creek D, Bigira V, Arinaitwe E, Wanzira H, Kakuru A, Tappero J, et al. Increased risk of early vomiting among infants and young children treated with dihydroartemisinin-piperaquine compared with artemether-lumefantrine for uncomplicated malaria. The American Journal of Tropical Medicine and Hygiene. 2010;83(4):873-5.
139. Saito M, Yotyingaphiram W, Cargill Z, Gilder ME, Min AM, Phyo AP, et al. Electrocardiographic effects of four antimalarials for pregnant women with uncomplicated malaria on the Thailand-Myanmar border: a randomised controlled trial. Antimicrobial agents and chemotherapy. 2021.
140. Kabanywanyi AM, Baiden R, Ali AM, Mahende MK, Ogutu BR, Oduro A, et al. Multi-country evaluation of safety of dihydroartemisinin/piperaquine post-licensure in african public hospitals with electrocardiograms. PLoS ONE. 2016;11(10).
141. Mhamilawa LE, Wikström S, Mmbando BP, Ngasala B, Mårtensson A. Electrocardiographic safety evaluation of extended artemether-lumefantrine treatment in patients with uncomplicated Plasmodium falciparum malaria in Bagamoyo District, Tanzania. Malaria Journal. 2020;19(1).
142. Sevene E, Banda CG, Mukaka M, Maculuve S, Macuacua S, Vala A, et al. Efficacy and safety of dihydroartemisinin–piperaquine for treatment of Plasmodium falciparum uncomplicated malaria in adult patients on antiretroviral therapy in Malawi and Mozambique: an open label non-randomized interventional trial. Malaria Journal. 2019;18(1):277.
143. Lefebvre C GJ, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, Noel-Storr A, Rader T, Shokraneh F, Thomas J, Wieland LS. Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from: Available from: www.training.cochrane.org/handbook.
144. Wanzira H, Kakuru A, Arinaitwe E, Bigira V, Muhindo MK, Conrad M, et al. Longitudinal outcomes in a cohort of Ugandan children randomized to artemether-lumefantrine versus dihydroartemisinin-piperaquine for the treatment of malaria. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2014;59(4):509-16.
145. Conrad MD, LeClair N, Arinaitwe E, Wanzira H, Kakuru A, Bigira V, et al. Comparative impacts over 5 years of artemisinin-based combination therapies on Plasmodium falciparum polymorphisms that modulate drug sensitivity in Ugandan children. Journal of Infectious Diseases. 2014;210(3):344-53.
146. Green JA, Mohamed K, Goyal N, Bouhired S, Hussaini A, Jones SW, et al. Pharmacokinetic interactions between tafenoquine and dihydroartemisinin-piperaquine or artemether-lumefantrine in healthy adult subjects. Antimicrobial Agents and Chemotherapy. 2016;60(12):7321-32.

147. Ishengoma DS, Mandara CI, Francis F, Talundzic E, Lucchi NW, Ngasala B, et al. Efficacy and safety of artemether-lumefantrine for the treatment of uncomplicated malaria and prevalence of Pfk13 and Pfmdr1 polymorphisms after a decade of using artemisinin-based combination therapy in mainland Tanzania. Malaria Journal. 2019;18(1):88.
148. Kakolwa MA, Mahende MK, Ishengoma DS, Mandara CI, Ngasala B, Kamugisha E, et al. Efficacy and safety of artemisinin-based combination therapy, and molecular markers for artemisinin and piperaquine resistance in Mainland Tanzania ACTRN12615000159550 ACTRN. Malaria Journal. 2018;17(1).
149. Kakuru A, Jagannathan P, Arinaitwe E, Wanzira H, Muhindo M, Bigira V, et al. The effects of ACT treatment and TS prophylaxis on Plasmodium falciparum gametocytemia in a cohort of young Ugandan children. American Journal of Tropical Medicine and Hygiene. 2013;88(4):736-43.
150. Katrak S, Gasasira A, Arinaitwe E, Kakuru A, Wanzira H, Bigira V, et al. Safety and tolerability of artemether-lumefantrine versus dihydroartemisinin-piperaquine for malaria in young HIV-infected and uninfected children. Malaria Journal. 2009;8(1).
151. Omondi P, Burugu M, Matoke-Muhia D, Too E, Nambati EA, Chege W, et al. Gametocyte clearance in children, from western Kenya, with uncomplicated Plasmodium falciparum malaria after artemether-lumefantrine or dihydroartemisinin-piperaquine treatment. Malaria Journal. 2019;18(1).
152. Taylor AR, Flegg JA, Holmes CC, Guérin PJ, Sibley CH, Conrad MD, et al. Artemether-lumefantrine and dihydroartemisinin-piperaquine exert inverse selective pressure on plasmodium falciparum drug sensitivity-associated haplotypes in Uganda. Open forum infectious diseases. 2017;4(1).
153. van der Pluijm RW, Tripura R, Hoglund RM, Pyae Phyo A, Lek D, ul Islam A, et al. Triple artemisinin-based combination therapies versus artemisinin-based combination therapies for uncomplicated Plasmodium falciparum malaria: a multicentre, open-label, randomised clinical trial. The Lancet. 2020;395(10233):1345-60.
154. Verret WJ, Arinaitwe E, Wanzira H, Bigira V, Kakuru A, Kamya M, et al. Effect of nutritional status on response to treatment with artemisinin-based combination therapy in young Ugandan children with malaria. Antimicrobial Agents and Chemotherapy. 2011;55(6):2629-35.
155. Yeka A, Tibenderana J, Achan J, D'Alessandro U, Talisuna AO. Efficacy of quinine, artemether-lumefantrine and dihydroartemisinin-piperaquine as rescue treatment for uncomplicated malaria in Ugandan children. PLoS ONE. 2013;8(1):e53772.

Appendix 1: Detailed search strategy

Search set	CENTRAL [a]	MEDLINE	EMBASE
1.	malaria	malaria	malaria
2.	arte*	arte*	arte*
3.	dihydroarte*	dihydroarte*	dihydroarte*
4.	amodiaq*	amodiaq*	amodiaq*
5.	lumefantrine	lumefantrine	lumefantrine
6.	Coartem*	Coartem*	Coartem*
7.	mefloquine	mefloquine	mefloquine
8.	2 or 3	2 or 3	2 or 3
9.	4 or 5 or 6 or 7	4 or 5 or 6 or 7	4 or 5 or 6 or 7
10.	1 and 8 and 9	1 and 8 and 9	1 and 8 and 9
11.	Limit 10 to date between 2004-2021	Limit 10 to humans	Limit 10 to humans
12.		Limit 10 to randomized control trial	Limit 10 to randomized control trial
13.		Limit 10 to date between 2004-2021	Limit 10 to date between 2004-2021

[a]Cochrane Infectious Diseases Group Specialized Register.
[b]Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Lefebvre C 2021 (143)) upper case: MeSH or EMTREE heading; lower case: free text term

Appendix 2: Characteristics of included studies

S. No	Study ID	Study design	Study setting and period	Transmission	Follow up	Subjects			Patient important outcome	DHA-PQ	AL
						Number of participants		Inclusion age			
						DHA-PQ	AL				
1	**Kamya-2007-UGA (98)**	Single-blind, RCT	Rural health center, March,2006-July, 2006	High transmission	42 days	253	256	6 months-10 years	Loss to follow up	0	0
									ETF	0	0
									LCF	19	30
									LPF	73	89
									ACPR	117	89
									Fever clearance at day 1 [b]	137	137
									Fever clearance at day 2	66	72
									Fever clearance at day 3	52	57
									Parasite clearance at day 2	1	2
									Parasite clearance at day 3	0	0
									Gametocyte carriage at baseline	9	18
									Gametocyte carriage day 1-14	5	2
									Gametocyte carriage at day 15-28	0	5

									Gametocyte carriage at day 29-41	4	11
									Hgb at baseline mean(SD) g/dl	9.5(1.8)	9.7(1.9)
									Hgb g/dl at day 42 mean(SD)[a] g/dl	1.9(1.8)	1.5(1.8)
									Vomiting	65	65
									Diarrhea	25	19
									Anorexia	90	91
									Abdominal pain	19	20
									weakness/malaise	85	103
									Cough	136	133
									Coryza	127	121
									Pruritus	14	22
									SAE	4	2
2	**Zongo-2007-BNF** (99)	Single blind RCT	Government health dispensaries, August 2006-January 2007	High transmission	42 days	196	197	6 months-10 years	Withdrawn	24	21
									ETF	2	2
									LCF	8	34
									LPF	3	19
									ACPR	159	121
									Fever on day 1	70	91
									Fever on day 2	23	26
									Fever on day 3	17	15
									Parasite clearance at day 2	6	5
									Parasite clearance at day 3	0	0
									Gametocyte	3	0

									carriage at baseline		
									Gametocyte carriage at day 1-42	7	3
									Mean haemoglobin (g/dL) (SD) at baseline	10.1(2.4)	10.2(2)
									Mean haemoglobin (g/dL) (SD) at day 42	11.6(1.6)	11.2(1.6)
									Early vomiting	7	3
									Vomiting	20	27
									Diarrhea	14	13
									Anorexia	8	6
									Abdominal pain	10	21
									Cough	49	52
									Weakness/Malaise	5	3
									Pruritus	5	11
									Headache	11	22
3	**Mens-2008-KEN** (112)	Open label RCT	Health center, Apr 2007 to Jul 2007	High transmission	28 days	73	73	6 months-12 years	Withdrawn	6	6
									Re-infection at day 28	0	1
									Recrudescence at day 28	0	0
									Fever clearance	10	6

									at day 1 [b]		
									Fever clearance at day 2	4	12
									Fever clearance at day 3	3	2
									Parasite clearance at day 2	1	0
									Gametocyte at baseline	3	6
									Hgb mmol/l at baseline mean (SD)	6.33(1.29)	6.28 (1.27)
									Hgb mmol/l at day 28 mean (SD)[a]	7.15(1.07)	6.79 (1.24)
									Headache	43	39
									Abdominal pain	25	26
									Weakness	19	30
									Anorexia	8	10
									Diarrhea	9	7
									Cough	16	17
									Vomiting	11	9
									Pruritus	4	3
									SAE	1	0
4	**Yeka-2008-UGA (100)**	Single-blind, RCT	Health center, August 2006- April 2007	N/A	42 days	234	227	6 months-10 years	Los to follow up	3	3
									ETF	0	1
									LCF	9	23
									LPF	17	41
									ACPR	186	131
									Fever clearance at day 1 [b]	117	133
									Fever clearance at day 2	44	37

								Fever clearance at day 3	22	22
								Parasite clearance at day 2	7	5
								Parasite clearance at day 3	0	0
								Gametocyte carriage at baseline	12	18
								Gametocyte carriage day 1-14	4	1
								Gametocyte carriage at day 15-28	1	7
								Gametocyte carriage at day 29-41	4	13
								Hgb at baseline mean (SD) g/dl	9.9(2.1)	9.9(1.8)
								Hgb at day 42 mean (SD)[a] g/dl	1.8(1.8)	1.7(2.0)
								Vomiting	35	35
								Diarrhea	26	23
								Anorexia	47	49
								Abdominal pain	17	24
								Weakness/malaise	28	27
								Cough	164	150
								Coryza	159	150
								Pruritus	8	3
								SAE	5	2
5	**Bassat-2009-**	Open-label,	Four rural sites and one peri-urban site, August 2005 and July 2006.	Mesoendemic	1038	510	6–59 months	Withdrawn	61	36
								Treatment failure	77	88

AFR (102)	RCT	at day 28		
		Recrudescence at day 28	14	11
		Treatment failure at day 42	200	147
		Recrudescence at day 42	41	16
		Hgb in g/L at baseline mean(SD)	89.2(18.2)	90.6(18.2)
		Mean change in Hgb (g/dL) from baseline to day 28	17(18.2)	14.3 (18.5)
		Early vomiting	22	4
		Vomiting	71	35
		Splenomegaly	41	19
		Hepatomegaly	6	3
		5 Prolonged QTc interval (Fridericia's correction)	2	1
		Electrocardiogram QT prolonged	26	13
		Urticarial	1	2
		Hypersensitivity	2	1
		Neutropenia	18	12
		Alanine	20	19

									aminotransferase increased		
									Electrocardiogram QT prolonged	26	13
									SAE	18	5
6	**Arinaitwe-2009-UGA** (101)	Open-label RCT	Local antenatal clinics in Tororo, August 2007-July 2008	High transmission	63 days	119	111	6 weeks- 12 months	No treatment outcome	6	5
									ETF	0	0
									LCF at day 28	13	45
									LPF at day 28	26	64
									ACPR at day 28	306	205
									PCR unadjusted Rx failure at day 42	16	33
									PCR adjusted Rx failure at day 42	0	0
									PCR unadjusted Rx failure at day 63	46	110
									PCR adjusted Rx failure at day 63	8	4
									Fever clearance at day 1 [b]	138	163
									Fever clearance at day 2	13	17
									Fever clearance	9	12

at day 3		
Parasite clearance at day 2	12	22
Parasite clearance at day 3	1	0
Gametocyte carriage at baseline	30	26
Gametocyte carriage day 1-14	10	1
Gametocyte carriage at day 15-28	1	0
Hgb at baseline mean(SD) g/dl	9.9(1.5)	9.8(1.5)
Hgb at day 28 mean(SD)[a] g/dl	0.6(1.68)	0.6(1.56)
Vomiting	23	20
Diarrhea	79	86
Anorexia	3	0
Weakness	1	0
Cough	177	153

									Pruritus	0	0
									SAE	3	1
7	**Borrmann-2011 –KEN (110)**	Not described, RCT	Pingilikani study site, September 2005 to April 2008	Perennial transmission	84 days	233	241	6–59 months	withdrawn	40	25
									ETF	2	2
									Early vomiting	7	4
									Mean(SD) g/dl hemoglobin at baseline	9(1.6)	8.8(1.3)
									Mean(SD) g/dl hemoglobin at baseline	9.2(1.8)	9.2(1.6)
									Parasite clearance at day 1	151	214
									Parasite clearance at day 2	10	26
									Parasite clearance at day 3	0	0
									Gametocyte carriage at baseline	5	3
									Gametocyte carriage at 7-84	5	2

									days		
8	**Nambozi-2011- ZAM** (30)	Open-label, RCT	Peri-urban health centers, September 2005 and May 2006	Mesoendemic	42 days	203	101	6-59 months	Withdrawn	11	11
									LCF PCR un adjusted at day 28	6	10
									LPF PCR un adjusted at day 28	9	13
									ACPR PCR un adjusted at day 28	177	67
									LCF PCR- adjusted at day 28	0	3
									LPF PCR- adjusted at day 28	9	3
									ACPR PCR- adjusted at day 28	183	84
									LCF PCR un adjusted at day 42	11	13
									LPF PCR un adjusted at day	31	20

42		
ACPR PCR un adjusted at day 42	150	57
LCF PCR- adjusted at day 42	4	3
LPF PCR adjusted at day 42	9	3
ACPR PCR adjusted at day 42	179	84
Gametocyte carriage at baseline	23	13
Anorexia	14	8
Cough	42	15
Diarrhea	14	4
Fever	24	14
Respiratory tract Infection	22	9
Vomiting	5	4
SAE	4	3

9	**4ABC-2011-AFR** (81)	Open label, RCT	Rural, urban or health facilities, 9 July 2007 and 19 June 2009	Mesoendemic, perennial and high transmission	63 days	1475	1226	6 to 59 months	Withdrawn	103	66
									ETF	2	0
									New infections at day 28	98	268
									Recrudescence at day 28	22	41
									Death up to day 63	1	3
									New infections at day 63	277	166
									Recrudescence at day 63	23	8
									Day 28: no PCR results	12	25
									Day 63: no PCR result	83	67
									Hepatomegaly	5	8
									Splenomegaly	88	80

Anemia	141	38
Diarrhea	166	142
Vomiting	123	102
Pyrexia	371	339
Hgb decrease	103	83
Anorexia	130	121
Cough	470	387
ALAT above normal range at day 0	10	16
ALAT above normal range at day 7	3	4
ALAT above normal range at day 28	4	1
Creatinine above normal range at day 0	2	0
Creatinine above	0	0

									normal range at day 7		
									Creatinine above normal range at day 28	0	2
									SAE	10	6
10	**Agarwal - 2013-KEN (27)**	An open label RCT	District hospital, October 2010 to August 2011	High transmission	42 days	137	137	6 to 59 months	Withdrawn	24	26
									LCF at day 28	4	13
									LPF at day 28	16	32
									LCF at day 42	11	21
									LPF at day 42	41	41
									Recrudescence at day 28	1	3
									Recrudescence at day 42	4	4
									Fever clearance at day 2 [b]	5	4
									Fever clearance at day 3	0	1
									Early vomiting	7	5
									SAE	1	2
11	**Meremikwu-2013-NIG** (109)	Open label, RCT	N/A	N/A	63 days	77	92	6 to 59months	Withdrawn	5	5
									PCR unadjusted treatment failure	5	3

									at day 28		
									PCR adjusted treatment failure at day 28	0	2
									PCR unadjusted treatment failure at day 63	5	6
									PCR adjusted treatment failure at day 63	0	3
12	**SAWA-2013 –KEN (103)**	Single-blind, RCT	Community setting, April to June 2009	Moderate transmission	42 days	145	153	6 months to 10 years	Withdrawn	11	8
									Recrudescence at day 28	0	2
									New infection at day 28	0	8
									Undetermined PCR at day 28	0	0
									Recrudescence at day42	0	4
									New infection at day 42	3	23
									Undetermined PCR at day 42	2	3
									Parasite clearance at day 2	10	5
									Parasite clearance at day 3	1	0
									Gametocyte carriage at baseline	14	12
13	**Muhindo-2014-UGA (91)**	Open-label, RCT	Post-natal clinic at Tororo District Hospital, October 2011 to December	High-transmission	28 days	106	96	6 weeks to 12 months	Withdrawn	13	16
									ETF	1	0
									LCF	7	74
									LPF	22	137

			2012						ACPR	311	189
									Fever clearance at day 1	65	124
									Fever clearance at day 2	11	8
									Fever clearance at day 3	7	7
									Parasite clearance at day 1	181	269
									Parasite clearance at day 2	20	23
									Parasite clearance at day 3	1	0
									Hgb at baseline mean(SD) g/dl	11.2(1.5)	11.1(1.5)
14	**Ogutu-2014-KEN** (35)	Open-label, RCT	Nyando District hospital, March, 2010- 30 November, 2011	Not described	42 days	227	227	6 to 59 months	Withdrawn	2	4
									PCR uncorrected treatment failure at day 28	28	43
									PCR corrected treatment failure at day 28	2	5
									PCR uncorrected treatment failure at day 42	67	73
									PCR corrected treatment failure at day 42	3	7
									Cough	40	37
									Anemia	8	10
									Fever	14	7
									Tinea capitis	12	10

									Rhinitis	13	4
									Gastroenteritis	5	9
									Loss of appetite	6	3
									Otitis media	5	7
15	**Onyamboko-2014-DRC** (104)	Open label, RCT	Urban district of Kinshasa (DRC) (Hospitals), September 2011 and November 2012	Intense and perennial	42 days	228	228	3 to 59 months	Withdrawn	16	10
									ETF at day 42	1	1
									LCF at day 42	10	12
									LPF at day 42	18	52
									PCR Unadjusted ACPR at day 28	206	190
									PCR adjusted ACPR at day 28	208	211
									Fever clearance at day 1 [b]	8	11
									Fever clearance at day 2	1	9
									Fever clearance at day 3	5	3
									Gametocyte carriage at day 0-35 days	2	1
									Gametocyte carriage at day 35-42 days	2	0
									Early vomiting	21	5
									Vomiting	17	2
16	**Wanzira-2014- UGA** (144)	Open-label, RCT	Tororo District Hospital, February 2009- 2012	Very high transmission	28 days	154	158	6 weeks to 9 months	Withdrawn	25	26
									ETF	2	15
									LCF	48	475
									LPF	182	894

									ACPR	2403	1494
									Recrudescence at day 63	24	22
17	**Kakuru-2014-UGA** (111)	Not described, RCT	District Hospital, August 2007 and April 2008	High transmission	28 days	21	22	6 weeks -12 months	Fever clearance at day 1 [b]	46	106
									Fever clearance at day 2	7	16
									Fever clearance at day 3	5	3
									Hgb g/dl at baseline mean(SD)	9.6(1.5)	10.1(1.4)
									Hgb g/dl at day 28 mean(SD)[a]	1.0(1.4)	0.6(1.5)
									Vomiting	8	18
									Diarrhea	27	23
									Anorexia	6	4
									weakness/malaise	2	2
									Cough	64	74
18	**Nji-2015-CAM** (107)	Open-label, RCT	Two distinct ecological regions, 2009 to April 2013	Low to moderate transmission	42 days	288	144	6 months-10 years	Withdrawn	43	21
									PCR adjusted ETF at day 28	2	0
									PCR adjusted LCF at day 28	4	1
									PCR adjusted LPF at day 28	3	3
									ACPR at day 28	236	119

									PCR unadjusted treatment failure at day 42	26	11
									PCR adjusted treatment failure at day 42	9	4
									Mean(SD) g/dl hemoglobin at baseline	9.9(2.1)	9.9(2.1)
									Mean(SD) g/dl hemoglobin at 0-7 days [a]	0.55 (1.79)	0.46 (1.67)
									Abdominal pain	13	5
									Anorexia	12	1
									Diarrhea	9	4
									Vomiting	27	8
									Fatigue	4	3
									Fever	3	2
									Cough	18	9
									Joint pain	2	2
									Rash	16	4
									SAE	0	1
19	**Ursing-2016-GUB** (108)	Open-label, RCT	Bandimand Belem Health Centers, November 2012 and July 2015	Low to high transmission	42 days	157	155	6 months-15 years	Withdrawn	17	18
									ETF	2	6
									LCF at day 42	0	3
									New infection at day 42	2	0
									Gametocyte carriage at baseline	2	2
									Early vomiting	7	4

20	**Ebenebe-2018-NIG** (28)	Open label, RCT	Hospitals and clinics, June 2014 and December 2015	High transmission	42 days	347	324	6 - 59 months	Withdrawn	55	44
									Parasite clearance at day 1	173	195
									Parasite clearance at day 2	60	76
									Parasite clearance at day 3	5	9
									Fever clearance at day 1 [b]	189	194
									ETF	2	1
									Reinfection at day 28	11	26
									Recrudescence at day 28	0	4
									Reinfection at day 42	18	55
									Recrudescence at day 42	1	7
									Gametocyte carriage at baseline	18	9
									Gametocyte carriage at day 0-14	6	6
									Gametocyte carriage at day 15-28	4	2
21	**Grandesso-2018-NIG**	Open label, RCT	Health center, 7 June 2013 and 22	Not reported	42 days	221	221	6–59 months	Withdrawn	11	15
									Early vomiting	1	0

	(105)		September 2014						Reinfection at day 42	51	64
									Undetermined PCR at day 42	4	10
									PCR adjusted LCF	1	1
									PCR adjusted LPF	2	1
									Baseline hemoglobin mean(SD) g/dl	9.7(1.7)	9.7(1.7)
									Gametocyte carriage at baseline	5	9
									Fever	94	94
									Cough	36	22
									Rhinorrhea	27	17
									Diarrhea	14	15
									Conjunctivitis	7	15
									Pyoderma	6	6
									Vomiting	6	5
									Anorexia	4	1
									Abdominal pain	0	1
									Hepatomegaly	1	0
									Splenomegaly	2	1
									Another AE	40	45
									SAE	2	1
22	**Mandara-2018-TAN** (80)	Open label, RCT	District Hospital and Health Centre, May 2014 and January 2015	Low to moderate transmission	63 days	255	257	6 months-10years	Withdrawn	16	17
									PCR unadjusted LCF at day 42	15	42
									PCR adjusted LPF at day 42	49	75
									PCR adjusted LCF at day 42	1	3
									PCR unadjusted	2	1

									LPF at day 42		
									Undetermined PCR	6	8
									Parasite clearance at day 1	203	223
									Parasite clearance at day 2	38	56
									Parasite clearance at day 3	0	1
									Baseline hemoglobin Mean(SD)g/dl	8.9(1.6)	8.9(1.7)
									Baseline hemoglobin Mean(SD)g/dl	9.6(1.6)	9.5(1.7)
23	**Uwimana-2019-RWA** (82)	Open label, RCT	Health centers, September 2013 and December 2015	Moderate transmission	42 days	269	267	1–14 years	Withdrawn	2	0
									ETF	2	2
									PCR unadjusted LCF day 28	2	16
									PCR unadjusted LPF day 28	2	18
									PCR adjusted LCF day 28	1	2
									PCR adjusted LPF day 28	0	0
									PCR unadjusted LCF day 42	10	24
									PCR unadjusted LPF day 42	10	26
									PCR adjusted LCF day 42	1	3
									PCR adjusted	1	1

									LPF day 42		
									Early vomiting	1	2
24	**Yeka-2019-UGA** (106)	Single-blind RCT	Health center and Hospital, October 2015-December, 2016	High transmission	42 days	299	300	6-59 months	Withdrawn	11	10
									ETF	0	0
									LCF	32	50
									LPF	43	85
									ACPR	213	155
									Fever clearance at day 1[b]	208	231
									Fever clearance at day 2	71	73
									Fever clearance at day 3	31	18
									Parasite clearance at day 1	219	245
									Parasite clearance at day 2	22	34
									Parasite clearance at day 3	3	3
									Gametocyte carriage at baseline	59	60
									Gametocyte carriage at day 1-42	43	46
									Hgb at day 42 mean(SD)[a]	1.3(1.7)	0.8(1.8)
									Vomiting	56	61
									Diarrhea	155	114
									Anorexia	12	3
									Abdominal pain	41	45

									Headaches	18	24
									weakness/malaise	42	33
									Cough	233	203
									Pallor	22	13
									Skin rash	56	42
									Pruritus	24	16
									SAE	6	6
25	**Gansane-2021-BNF** (73)	Open label, RCT	Primary health facility and district hospital, November 2017 to September 2018	Moderate to high transmission	42 days	360	360	6-59 months	Withdrawn	21	27
									Parasite clearance at day 3	6	1
									ETF	6	1
									LCF at day 28	6	73
									LCF at day 28	10	104
									Recrudescence at day 28	7	54
									Re-infection at day 28	10	107
									Undetermined PCR at day 28	1	16
									Itchiness	0	1
									Otitis media	0	1
									Cough	17	21
									Abdominal pain	13	4
									Skin rash	3	2
									Furunculosis	1	0
									Vomiting	33	54
									SAE	0	1

Abbreviations: ETF= early treatment failure, LCT= late clinical failure, LPF= late parasitological failure, ACPR= Adequate clinical and parasitological response, AL= artemether-lumefantrine; DHA-PQ= dihydroartemisinin-piperaquine, Hgb= hemoglobin, SD= standard deviation, PCR= polymerase chain reaction, SAE= serious adverse event, N/A= not available.
AFA= Africa, **BNF**= Burkina Faso, **CAM**= Cameroon, **DRC**= Democratic Republic of Congo, **GUB**= Guinea Bissau, **KEN**= Kenya, **NIG**= Nigeria, **NIJ** = Niger, **RWN**= Rwanda, **TAN**= Tanzania, **UGA**= Uganda, **ZAM**= Zambia
[a] The mean increase in hemoglobin values from the baseline.
[b] Subjective fever during the previous 24 hrs or temperature >38^{o}C

Appendix 3: Risk of bias assessment of the included studies

Agarwal-2013-KEN (27)		
Domain	**Author's Judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	Block randomized was used
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Unclear risk	Not described
Blinding of outcome assessment (detection bias)	Low risk	All laboratory technologists were blinded to the treatment arm.
Incomplete outcome data (attrition bias)	High risk	High number of patients withdrawn both treatment groups (17.5% DHA-PQ versus 18.2% AL)
Selective outcome reporting	Low risk	All outcomes were reported.
Other bias	Low risk	No other source of bias.

Arinaitwe-2009-UGA (101)		
Domain	**Author's Judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	Computer generated randomization by an off-site investigator.
Allocation concealment (selection bias)	Low risk	The allocation concealed using sealed envelope.

Blinding of participants and personnel (performance bias)	Low risk	The second and third micropist were blind.
Blinding of outcome assessment (detection bias)	High risk	Described as "open-label".
Incomplete outcome data (attrition bias)	Low risk	Small number of patients withdrawn (1.7% DHA-PQ versus 1.6% AL).
Selective outcome reporting	Low risk	All outcomes were reported.
Other bias	Low risk	No other source of bias.

Bassat-2009-AFR (102)		
Domain	**Author's Judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	Stratified randomization by an independent off-site CRO.
Allocation concealment(selection bias)	Low risk	Allocation concealed using opaque sealed envelopes.
Blinding of participants and personnel (performance bias)	Low risk	All the staffs were blinded.
Blinding of outcome assessment(detection bias)	High risk	Open label
Incomplete out come data(attrition bias)	Low risk	Few number of patients were withdrawn (7.5% DHA-P versus 9.7% AL)
Selective outcome reporting	Low risk	All outcomes were reported.
Other bias	Unclear risk	One of the researchers was former employee of the sponsoring organization.

Borrmann-2011-KEN (110)		
Domain	**Author's Judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	"A randomization list was generated by an independent off-site contract research organization (CRO)."
Allocation concealment (selection bias)	Low risk	"Sealed envelopes containing treatment allocation was used to randomize eligible patients."
Blinding of participants and personnel (performance bias)	Unclear risk	Not described

Blinding of outcome assessment (detection bias)	Low risk	"Microscopist was blinded."
Incomplete outcome data (attrition bias)	High risk	17.2% from DHA-PQ and 14.5 % AL were excluded from analysis.
Selective outcome reporting	Low risk	All outcomes were reported.
Other bias	Low risk	No other kinds of source of bias.

Ebenebe-2018-NIG (28)		
Domain	**Author's Judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	"Randomization was computer-generated for each site."
Allocation concealment (selection bias)	Low risk	"Treatment codes were sealed in individual envelopes."
Blinding of participants and personnel (performance bias)	High risk	Open label
Blinding of outcome assessment (detection bias)	Low risk	"The microscopist didn't know the treatment allocation."
Incomplete outcome data (attrition bias)	High risk	30(8.6%) and 25(7.8%) prematurely withdrawn from DHA-PQ and AL group.
Selective outcome reporting	Low risk	All outcomes were reported.
Other bias	Low risk	No other source of bias.

Four ABC-2011-AFR (81)		
Domain	**Author's Judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	The randomization list prepared off-site organization.
Allocation concealment (selection bias)	Low risk	Allocation concealed using opaque sealed envelopes.
Blinding of participants and personnel (performance bias)	Low risk	Clinician and other staffs were blinded.
Blinding of outcome assessment (detection bias)	Low risk	Clinician or other staffs were blinded.
Incomplete outcome data (attrition bias)	Low risk	Few patients withdrawn (2.5% DHA-P, 2.4% AL).

Selective outcome reporting	Low risk	All outcomes are reported.
Other bias	Low risk	No other sources of bias.

Gansane-2021-BNF (73)		
Domain	**Authors Judgment**	**Support for judgment**
Random sequence generation *(selection bias)*	**Low risk**	"Permuted block randomization. 1:1 randomization of 2 groups, blocks will be size 10"
Allocation concealment *(selection bias)*	**Low risk**	"Sealed opaque envelopes"
Blinding of participants and personnel *(performance bias)*	**High risk**	Open label
Blinding of outcome assessment *(detection bias)*	**High risk**	Open label
Incomplete outcome data *(attrition bias)*	**Low risk**	27(7.5%) from DHA-PQ and 23 (6.4%) from AL were excluded
Selective outcome reporting?	**Low risk**	All outcomes were reported.
Other bias	**Low risk**	No other source of bias.

Grandesso-2018-NIG (105)		
Domain	**Author's Judgment**	**Support for judgment**
Random sequence generation (selection bias)	Unclear risk	Randomized but method of randomization not described.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	High risk	Open label
Blinding of outcome assessment (detection bias)	High risk	Open label
Incomplete outcome data (attrition bias)	Low risk	8 from DHA-PQ and 10 from AL group loss follow up.

Selective outcome reporting	Low risk	All outcomes were reported.
Other bias	Low risk	No other source of bias

Kakuru-2014-UGA (111)		
Domain	**Author's Judgment**	**Support for judgment**
Random sequence generation (selection bias)	Unclear risk	Randomized but the method of randomization not described.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Unclear risk	Not described
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Low risk	
Selective outcome reporting	Low risk	All outcomes were reported.
Other bias	Low risk	No other source of bias.

Kamya-2007-UGA (98)		
Domain	**Author's Judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	Computer generated randomization list by an off-site investigator.
Allocation concealment (selection bias)	Low risk	Allocation concealed using sealed envelopes.
Blinding of participants and personnel (performance bias)	Low risk	Physicians and laboratory personnel were blinded.
Blinding of outcome assessment (detection bias)	Low risk	Placebos were used to blind participants to treatment allocation. Study physicians were also blinded.
Incomplete outcome data (attrition bias)	Low risk	Few patients have withdrawn (0.9% AL6 versus 0.9% DHA-P).
Selective outcome reporting	Low risk	All outcomes reported.
Other bias	Low risk	No other sources of bias.

Mandara-2018-TAN (80)		
Domain	**Author's Judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	"Randomization list was computer generated for different age-strata using Microsoft Excel."
Allocation concealment (selection bias)	Low risk	"Sequentially numbered, sealed envelopes containing the treatment group assignments were prepared from the randomization list for each age category."
Blinding of participants and personnel (performance bias)	High risk	Open label
Blinding of outcome assessment (detection bias)	High risk	Open label
Incomplete outcome data (attrition bias)	High risk	Adverse events were not reported.
Selective outcome reporting	Low risk	16 from DHA-PQ and 17 from AL were withdrawn.
Other bias	Low risk	No other source of bias.

Meremikwu-2013-NIG (109)		
Domain	**Author's Judgment**	**Support for judgment**
Random sequence generation (selection bias)	Unclear risk	Randomized but way of randomization not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias)	High risk	Open label
Blinding of outcome assessment (detection bias)	High risk	Open label
Incomplete outcome data (attrition bias)	Unclear risk	Not described.
Selective outcome reporting	Unclear risk	Not described.
Other bias	Low risk	No other source of bias

Mens-2008-KEN (112)		
Domain	**Author's Judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	Randomization list generated using computer.
Allocation concealment (selection bias)	Unclear risk	None described.
Blinding of participants and personnel (performance bias)	Unclear risk	None described.

Blinding of outcome assessment (detection bias)	Low risk	Laboratory personnel were blinded.
Incomplete outcome data (attrition bias)	Low risk	Few patients were withdrawn (8.2% DHA-PQ versus 8.2% AL).
Selective outcome reporting	Low risk	All outcomes were reported.
Other bias	Low risk	No other sources of bias.

Muhindo-2014-UGA (91)		
Domain	**Author's Judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	"Randomization list was computer generated by an off-site investigator."
Allocation concealment (selection bias)	Low risk	"Sequentially numbered, sealed envelopes containing the treatment group assignments were prepared from the randomization list. The study nurse assigned treatment numbers sequentially and allocated treatment by opening the envelope corresponding to the treatment number."
Blinding of participants and personnel (performance bias)	High risk	Open label
Blinding of outcome assessment (detection bias)	Low risk	"Laboratory technicians were blinded to the study participants' treatment assignments."
Incomplete outcome data (attrition bias)	Low risk	16 (3.9%) from AL and 13 (3.7%) from DHA-PQ were loss to follow up.
Selective outcome reporting	Low risk	All listed outcomes reported.
Other bias	Low risk	No other source of bias.

Nambozi-2011-ZAM (30)		
Domain	**Author's Judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	An independent off-site contract research organization (CRO) was generated a randomization list.
Allocation concealment (selection bias)	Low risk	Allocation concealed using opaque sealed envelopes.
Blinding of participants and personnel	Low risk	All the staffs were blinded.

(performance bias)		
Blinding of outcome assessment (detection bias)	Low risk	All the staffs were blinded.
Incomplete outcome data (attrition bias)	Low risk	All outcomes were reported.
Selective outcome reporting	Low risk	From each treatment group 13 patients either withdrawn or loss to follow up.
Other bias	Low risk	No other source of bias.

Nji-2015-CAM (107)		
Domain	**Author's Judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	"Randomization allocation schedule generated by a computer-based randomization program."
Allocation concealment (selection bias)	Low risk	"Allocation of participants was concealed in opaque envelopes that were opened sequentially by the study physician once consent was provided."
Blinding of participants and personnel (performance bias)	Low risk	"The randomization number was recorded on the case report form as the study identification code and used in labeling all study-related laboratory samples."
Blinding of outcome assessment (detection bias)	Low risk	"The randomization number was recorded on the case report form as the study identification code and used in labeling all study-related laboratory samples."
Incomplete outcome data (attrition bias)	Low risk	43 from DP and 21 from al treatment group were loss to follow up.
Selective outcome reporting	Low risk	All outcomes were reported
Other bias	Low risk	No other source of bias

Ogutu-2014-KEN (35)		
Domain	**Author's Judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	"Used random tables"
Allocation concealment (selection bias)	Low risk	"Sealed opaque envelopes"
Blinding of participants and personnel	High risk	Open-label (Masking Not Used)

(performance bias)		
Blinding of outcome assessment (detection bias)	High risk	Open-label (Masking Not Used)
Incomplete outcome data (attrition bias)	Low risk	2 from DHA-PQ and 4 from al arm withdrawn.
Selective outcome reporting	Low risk	All outcomes were reported.
Other bias	Low risk	No other kinds of source of bias.

Onyamboko-2014-DRC (104)		
Domain	**Author's Judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	"Randomization sequence, in blocks of 15, was computer generated and numerically sequenced."
Allocation concealment (selection bias)	Low risk	"Opaque envelopes containing the study drug name were prepared at the Mahidol Oxford Tropical Medicine Research Unit (MORU), Bangkok, Thailand."
Blinding of participants and personnel (performance bias)	Unclear bias	Not described.
Blinding of outcome assessment (detection bias)	Low risk	"The laboratory technicians were blinded to the treatment received by individual patients."
Incomplete outcome data (attrition bias)	Low risk	Forty-two patients (6.1%) discontinued the study.
Selective outcome reporting	Low risk	All outcomes were reported.
Other bias	Low risk	No other source of bias

SAWA-2013-KEN (103)		
Domain	**Author's Judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	Different age strata (<2 years, 2-5 years, and 5-10 years), using MS Excel used to generate a randomization list
Allocation concealment(selection bias)	Unclear risk	Allocation concealment is not described.
Blinding of participants and personnel (performance bias)	Low risk	All the staffs were blinded.
Blinding of outcome assessment (detection bias)	Low risk	All staffs were blinded.

Incomplete outcome data (attrition bias)	Low risk	Few participants were withdrawn (DHA-PQ 7.6%, AL 5.2%)."
Selective outcome reporting	Low risk	All outcomes were reported.
Other bias	Low risk	No other sources of bias

Ursing-2016-GUB (108)		
Domain	**Author's Judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	"Randomization was achieved by mothers drawing a sealed card with either Eurartesim or Coartem written on it from an envelope containing 10 of each card."
Allocation concealment (selection bias)	Low risk	Cards and envelopes were prepared by the investigators.
Blinding of participants and personnel (performance bias)	Unclear risk	Not described
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data(attrition bias)	Low risk	In the AL and DP arms loss to follow up by day 42 was 10% (n = 15) and 8% (n = 12), respectively. Losses to follow up were due to children travelling.
Selective outcome reporting	Low risk	All outcomes were reported.
Other bias	Low risk	No other source of bias.

Uwimana-2019-RWN (82)		
Domain	**Author's Judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	Treatment assignment was randomized.
Allocation concealment(selection bias)	Low risk	Blinded through sealed envelopes.
Blinding of participants and personnel (performance bias)	High risk	Open label
Blinding of outcome assessment (detection bias)	High risk	Open label

Incomplete outcome data (attrition bias)	Low risk	Only 2 patients withdrawn from DHA-PQ arm with reason.
Selective outcome reporting	Low risk	ALL WHO outcomes were reported
Other bias	Low risk	No other source of bias.

Wanzira-2014-UGA (144)		
Domain	**Author's Judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	"Computerized randomization list."
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	High risk	Open label
Blinding of outcome assessment (detection bias)	High risk	Open label
Incomplete outcome data (attrition bias)	High risk	24% (44 from AL and 32 from DHA-PQ) arms were excluded.
Selective outcome reporting	Low risk	All outcomes were reported.
Other bias	Low risk	No other source of bias.

Yeka-2008-UGA (100)		
Domain	**Author's Judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	A randomization list generated using computer by an off-site investigator.
Allocation concealment (selection bias)	Low risk	Allocation concealment was sealed in opaque envelopes.
Blinding of participants and personnel (performance bias)	Low risk	All staffs were blinded.
Blinding of outcome assessment (detection bias)	Low risk	All study personnel were blinded.
Incomplete outcome data (attrition bias)	Low risk	3 participants loss to follow up from each treatment group
Selective outcome reporting	Low risk	All outcomes were reported
Other bias	Low risk	No other source of bias.

Yeka-2019-UGA (106)		
Domain	**Author's Judgment**	**Support for judgment**

Random sequence generation (selection bias)	Low risk	"A computer-generated randomization."
Allocation concealment (selection bias)	Low risk	"Sequentially numbered, sealed, opaque envelopes containing the treatment assignment were prepared and secured in a locked cabinet accessible to the study nurse."
Blinding of participants and personnel (performance bias)	Low risk	"Patients and providers other than the study nurse was not informed of treatment assignments. A placebo tablet was used for the evening dose among children enrolled in the DHA-PQ arm, to simulate AL dosing, although the placebo was not matched to the appearance of AL."
Blinding of outcome assessment (detection bias)	Low risk	"Microscopists were blinded to clinical information Patients and providers other than the study nurse were not informed of treatment assignments."
Incomplete outcome data (attrition bias)	Low risk	11 from DHA-PQ and 10 from al arm loss to follow up.
Selective outcome reporting	Low risk	All outcomes were reported.
Other bias	Low risk	No other source of bias.

Zongo-2007-BNF (99)		
Domain	**Author's Judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	"Randomization list generated using computer by an off-site Investigator."
Allocation concealment (selection bias)	Low risk	"A study nurse, who was not involved in enrollment or assessment of treatment outcomes, assigned the treatment."
Blinding of participants and personnel (performance bias)	High risk	The study was open label.
Blinding of outcome assessment (detection bias)	High risk	The study was open label.
Incomplete outcome data (attrition bias)	Low risk	Few participants were withdrawn (8% DHA-PQ versus 6.4% AL6.
Selective outcome reporting	Low risk	All outcomes were reported.
Other bias	Low risk	No other sources of bias.

Appendix 4: Characteristics of excluded studies

No	Studies	Reason for exclusion
1.	Adam-2010-SUD (116)	Both children and adults were enrolled in this trial. Children's outcome didn't report.
2.	Conrad-2014-UGA (145)	The outcomes were not relevant for this study.
3.	Creek-2010-UGA(138)	The outcomes were reported in another study.
4.	Dama-2018-MAL (31)	Both children and adults were enrolled in this trial. Children's outcome didn't report.
5.	Davlantes-2018-ANG (127)	Both children and adults were enrolled in this trial. Children's outcome didn't report.
6.	Diallo-2020-SEN (123)	Both children and adults were enrolled in this trial. Children's outcome didn't report.
7.	Funck -2019 (32)	The outcomes were not relevant for this study.
8.	Green-2016 (146)	The outcomes were not relevant for this study.
9.	Ishengoma-2019-TAN (147)	The outcomes were not relevant for this study.
10.	Kakolwa-2018-TAN (148)	The outcomes were not relevant for this study.
11.	Kakuru-2013-UGA (149)	The outcomes were reported in another study.
12.	Katrak-2009-UGA (150)	The outcomes were reported in another study.
13.	Menan-2011- AFR (145)	Both children and adults were enrolled in this trial. Children's outcome didn't report.
14.	Omondi-2019-KEN (151)	The outcomes were not relevant for this study.
15.	Plucinski-2015-ANG (115)	Non-randomized trial.
16.	Plucinski-2017-ANG (114)	Non-randomized trial.
17.	Sylla-2013-SEN (60)	The outcomes were not relevant for this study.
18.	Sow-2016-SEN (59)	Both children and adults were enrolled in this trial. Children's outcome didn't report.
19.	Tylor-2017-UGA (152)	The outcomes were not relevant for this study.
20.	Van-2020-MCT (153)	The outcomes were not relevant for this study.
21.	Verret-2009-UGA (154)	The outcomes were reported in another study.
22.	Warsame-2019-SOM (117)	Both children and adults were enrolled in this trial. Children's outcome didn't report.
23.	Yavo-2011-SSA (36)	Both children and adults were enrolled in this trial. Children's outcome didn't report.
24.	Yeka-2013-UGA (155)	The outcomes were reported in another study.

Appendix 5: Summary of finding tables

Table 4: Treatment failure

Dihydroartemisinin-piperaquine compared to artemether-lumefantrine for the treatment of uncomplicated *plasmodium falciparum* malaria in African children.

Patient or population: **African children with uncomplicated *plasmodium falciparum* malaria**
Setting: **Malaria endemic setting in Africa.**
Intervention: **Dihydroartemisinin-piperaquine**
Comparison: **Artemether-lumefantrine**

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with artemether-lumefantrine	**Risk with dihydroartemisinin-piperaquine**				
PCR unadjusted treatment failure at day 28 - Age 6months-15 years	126 per 1,000	**18 per 1,000** (10 to 33)	**RR 0.14** (0.08 to 0.26)	1302 (4 RCTs)	⊕⊕⊕⊕ HIGH [a]	
PCR unadjusted treatment failure at day 28 - Under five years	374 per 1,000	**116 per 1,000** (86 to 157)	**RR 0.31** (0.23 to 0.42)	14319 (13 RCTs)	⊕⊕⊕◯ MODERATE [a,b]	
PCR adjusted treatment failure at day 28 - PCR adjusted treatment failure at day 28	49 per 1,000	**22 per 1,000** (14 to 33)	**RR 0.45** (0.29 to 0.68)	8508 (16 RCTs)	⊕⊕⊕⊕ HIGH [a]	
PCR unadjusted treatment failure at day 42 - PCR unadjusted treatment failure at day 42	326 per 1,000	**183 per 1,000** (156 to 215)	**RR 0.56** (0.48 to 0.66)	7667 (17 RCTs)	⊕⊕◯◯ LOW [a,c,d]	
PCR adjusted treatment failure at day 42 - PCR adjusted treatment failure at day 42	55 per 1,000	**33 per 1,000** (26 to 43)	**RR 0.60** (0.47 to 0.78)	5959 (17 RCTs)	⊕⊕⊕⊕ HIGH [a]	
PCR unadjusted treatment failure at day 63 - PCR unadjusted treatment failure at day 63	440 per 1,000	**269 per 1,000** (150 to 484)	**RR 0.61** (0.34 to 1.10)	3365 (3 RCTs)	⊕⊕⊕◯ MODERATE [a,b,e]	

Table 4: Treatment failure

Dihydroartemisinin-piperaquine compared to artemether-lumefantrine for the treatment of uncomplicated *plasmodium falciparum* malaria in African children.

Patient or population: **African children with uncomplicated *plasmodium falciparum* malaria**
Setting: **Malaria endemic setting in Africa.**
Intervention: **Dihydroartemisinin-piperaquine**
Comparison: **Artemether-lumefantrine**

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with artemether-lumefantrine	**Risk with dihydroartemisinin-piperaquine**				
PCR adjusted treatment failure at day 63 - PCR adjusted treatment failure at day 63	51 per 1,000	**44 per 1,000** (29 to 68)	**RR 0.87** (0.57 to 1.34)	3384 (4 RCTs)	⊕⊕⊕⊕ HIGH [a,f]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Excluding studies with a high risk of bias didn't change the result.
b. There is considerable heterogeneity between the included studies.
c. There is considerable heterogeneity between the included studies and the subgroup analysis didn't explain its source.
d. There was significant publication bias.
e. There is no significant difference between the two treatment groups.
f. The outcome fulfilled the IOS criteria and the effect size is between 0.75 and 1.25.

Table 5: Hemoglobin recovery from baseline

Dihydroartemisinin-piperaquine compared to artemether-lumefantrine for treatment of uncomplicated *plasmodium falciparum* malaria in African children.

Patient or population: African children with uncomplicated *plasmodium falciparum* malaria
Setting: Malaria endemic setting in Africa.
Intervention: Dihydroartemisinin-piperaquine
Comparison: Artemether-lumefantrine

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with artemether-lumefantrine	**Risk with dihydroartemisinin-piperaquine**				
Anemia - Mean change in haemoglobin (g/dL) from baseline to day 28	-	SMD **0.15 higher** (0.05 higher to 0.26 higher)	-	2715 (4 RCTs)	⨁⨁⨁⨁ HIGH [a]	
Anemia - Mean change in haemoglobin (g/dL) from baseline to day 42	The mean anemia - Mean change in haemoglobin (g/dL) from baseline to day 42 was **0**	MD **0.35 higher** (0.12 higher to 0.59 higher)	-	1434 (3 RCTs)	⨁⨁⨁⨁ HIGH [a,b]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio; **SMD:** Standardized mean difference; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Excluding studies with a high risk of bias didn't change the result.
b. There is a significant difference between the two treatment groups

Table 6: Adverse events and serious adverse event

Dihydroartemisinin-piperaquine compared to artemether-lumefantrine for treatment of uncomplicated *plasmodium falciparum* malaria in African children

Patient or population: African children with uncomplicated plasmodium falciparum malaria
Setting: Malaria endemic setting in Africa.
Intervention: Dihydroartemisinin-piperaquine
Comparison: Artemether-lumefantrine

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with artemether-lumefantrine	**Risk with dihydroartemisinin-piperaquine**				
Gastrointestinal adverse events - Early vomiting	8 per 1,000	**18 per 1,000** (12 to 28)	**RR 2.26** (1.46 to 3.50)	7796 (10 RCTs)	⊕⊕⊕⊕ HIGH [a]	
Gastrointestinal adverse events - Diarrhea	135 per 1,000	**157 per 1,000** (139 to 177)	**RR 1.16** (1.03 to 1.31)	6841 (11 RCTs)	⊕⊕⊕⊕ HIGH [a]	
Vomiting - Vomiting	100 per 1,000	**102 per 1,000** (87 to 119)	**RR 1.02** (0.87 to 1.19)	8789 (13 RCTs)	⊕⊕⊕⊕ HIGH [a,c]	
Gastrointestinal Adverse event - Anorexia	118 per 1,000	**113 per 1,000** (100 to 127)	**RR 0.95** (0.84 to 1.07)	6841 (11 RCTs)	⊕⊕⊕⊕ HIGH [a,c]	
Gastrointestinal Adverse event - Abdominal pain	126 per 1,000	**101 per 1,000** (72 to 140)	**RR 0.80** (0.57 to 1.11)	2732 (8 RCTs)	⊕⊕⊕⊕ HIGH [a,c]	
Cardio-respiratory adverse events - Cough	338 per 1,000	**358 per 1,000** (341 to 375)	**RR 1.06** (1.01 to 1.11)	8013 (13 RCTs)	⊕⊕⊕⊕ HIGH [a]	
Neuropsychiatry adverse event - weakness/malaise	123 per 1,000	**109 per 1,000** (91 to 127)	**RR 0.88** (0.74 to 1.03)	3407 (8 RCTs)	⊕⊕⊕⊕ HIGH [a,c]	
Musculoskeletal/dermatological adverse events - Pruritus	57 per 1,000	**57 per 1,000** (32 to 101)	**RR 1.00** (0.56 to 1.78)	1952 (5 RCTs)	⊕⊕⊕◯ MODERATE [a,b]	
Other Adverse events - Pyrexia	232 per 1,000	**218 per 1,000** (198 to 242)	**RR 0.94** (0.85 to 1.04)	4620 (5 RCTs)	⊕⊕⊕⊕ HIGH [a,c]	

Table 6: Adverse events and serious adverse event

Dihydroartemisinin-piperaquine compared to artemether-lumefantrine for treatment of uncomplicated *plasmodium falciparum* malaria in African children

Patient or population: African children with uncomplicated plasmodium falciparum malaria
Setting: Malaria endemic setting in Africa.
Intervention: Dihydroartemisinin-piperaquine
Comparison: Artemether-lumefantrine

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with artemether-lumefantrine	**Risk with dihydroartemisinin-piperaquine**				
Serious adverse event (including death) - Serious adverse event (including death)	8 per 1,000	**10 per 1,000** (7 to 16)	**RR 1.27** (0.83 to 1.96)	9558 (14 RCTs)	⨁⨁⨁◯ MODERATE [a,b]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Excluding studies with a high risk of bias didn't change the result.
b. There is no significant difference between the two treatment groups.
c. The outcome fulfilled the IOS criteria and the effect size is between 0.75 and 1.25.

Appendix 6: PRISMA 2020 checklist.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Front page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	XI
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	1
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	8
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	9-11
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	12-13
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	12 and 80
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	12-13
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	13-14
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	12-13
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	12-13
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	14
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	16
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	16
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	17
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	17

Section and Topic	Item #	Checklist item	Location where item is reported
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	17
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	19
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	20
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	21
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	23
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	117
Study characteristics	17	Cite each included study and present its characteristics.	81
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	24-26
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	81
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	24-26
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	27-61
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	27-61
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	62
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	105-116
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	118
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	63
	23b	Discuss any limitations of the evidence included in the review.	67
	23c	Discuss any limitations of the review processes used.	67

Section and Topic	Item #	Checklist item	Location where item is reported
	23d	Discuss implications of the results for practice, policy, and future research.	64-67
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	9
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	9
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	X
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	126

Appendix 7: Data collection form

General Information

Study ID *(e.g. author name, year)*			
Form completed by			
Study author contact details			
Publication type *(e.g. full report, abstract, letter)*			
List of included publications			
Characteristics of included studies			
Author and year of publication:			
Country			
Setting			
Transmission			
Resistance			
Start & end dates			
Study funding sources *(including role of funders)*			
Possible conflicts of interest			
Methods	**Design**		
	Unit of allocation		
	Aim of study		
	Follow up		
	Adverse event monitoring		
Notes:			
Participants	Total no. randomized		
		DHA-PQ	*AL*

	Age (mean ± SD)		
	Sex (proportion male)		
	Sex (proportion male)		
	Other relevant socio-demographics		
	Temperature at baseline		
	Inclusion criteria		
	Exclusion criteria		
	No. randomized per group	*DHA-PQ*	*AL*
	No. missing		
	Reasons missing		
	Parasite density		
Intervention	Treatment group	DHA-PQ	AL
	Dose		
	Duration of treatment period		
	Timing		
	Delivery		
	Providers		
	Co-interventions		
Note			

Risk of Bias assessment

Domain	**Risk of bias** Low High Unclear	**Support for judgment**	**Location in text or source** *(pg & ¶/fig/table/other)*
Random sequence generation *(selection bias)*	☐ ☐ ☐		
Allocation concealment *(selection bias)*	☐ ☐ ☐		
Blinding of participants and personnel *(performance bias)*	☐ ☐ ☐	**Outcome group: All/**	
Blinding of outcome assessment *(detection bias)*	☐ ☐ ☐	**Outcome group: All/**	
Incomplete outcome data *(attrition bias)*	☐ ☐ ☐	**Outcome group: All/**	
Selective outcome reporting?	☐ ☐ ☐		
Other bias	☐ ☐ ☐		

Treatment outcome

Study ID			
	Treatment group	**Comparator group**	**Time**
Loss to follow up			

Another type of malaria			
Another anti-malaria use			
Recurrent			
ETF			
LCF			
LPF			
Recrudescence			
New infection			
Genotyping unsuccessful			
PCR unadjusted treatment failure			
PCR adjusted treatment failure			

	Intervention group		**Comparator group**	
Fever clearance	**Event**	**Total Number**	**Event**	**Total Number**
Day 1				
Day 2				
Day 3				
Parasite clearance				
Day 1				
Day 2				
Day 3				

	Treatment group		**Comparator**	
Gametocyte carriage	**Event**	**Total Number**	**Event**	**Total Number**
Gametocyte at baseline				
Day 1-14				
Day 15-28				
Day 29-42				
Day 4-48				
Day 4-42				
Any other				

Hemoglobin Mg/dl	**Treatment group**			**Comparator group**		
	Mean	**SD**	**Total No.**	**Mean**	**SD**	**Total No.**
Baseline						
Day						

Day						
Day						
Day						

Adverse event

System	Name of AE	Treatment group		Comparator group	
		Event	Total No.	Event	Total No.
Gastrointestinal					
Neuropsychiatry					
Cardio-respiratory					
Musculoskeletal/dermatological					
Serious Adverse event					
Note					

Other information

	Description as stated in report/paper	**Location in text or source** *(pg & ¶/fig/table/other)*

Key conclusions of study authors		
References to other relevant studies		
Correspondence required for further study information *(from whom, what and when)*		
Notes:		