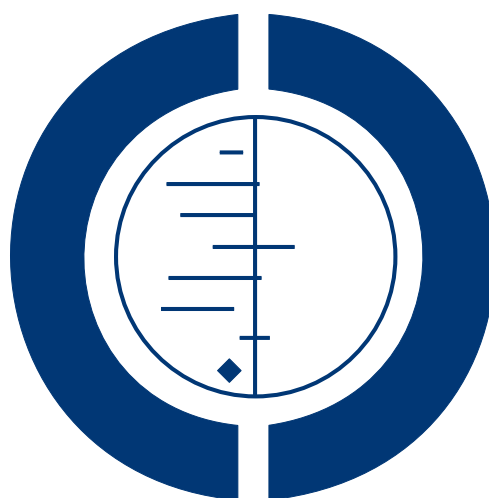# Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria (Review)

Zani B, Gathu M, Donegan S, Olliaro PL, Sinclair D

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Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

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A B S T R A C T

Background

The World Health Organization (WHO) recommends Artemisinin-based Combination Therapy (ACT) for treating uncomplicated *Plasmodium falciparum* malaria. This review aims to assist the decision-making of malaria control programmes by providing an overview of the relative effects of dihydroartemisinin-piperaquine (DHA-P) versus other recommended ACTs.

Objectives

To evaluate the effectiveness and safety of DHA-P compared to other ACTs for treating uncomplicated *P. falciparum* malaria in adults and children.

Search methods

We searched the Cochrane Infectious Diseases Group Specialized Register; the Cochrane Central Register of Controlled Trials (CEN-TRAL) published in *The Cochrane Library*; MEDLINE; EMBASE; LILACS, and the metaRegister of Controlled Trials (mRCT) up to July 2013.

Selection criteria

Randomized controlled trials comparing a three-day course of DHA-P to a three-day course of an alternative WHO recommended ACT in uncomplicated *P. falciparum* malaria.

Data collection and analysis

Two authors independently assessed trials for eligibility and risk of bias, and extracted data. We analysed primary outcomes in line with the WHO 'Protocol for assessing and monitoring antimalarial drug efficacy' and compared drugs using risk ratios (RR) and 95% confidence intervals (CI). Secondary outcomes were effects on gametocytes, haemoglobin, and adverse events. We assessed the quality of evidence using the GRADE approach.

Main results

We included 27 trials, enrolling 16,382 adults and children, and conducted between 2002 and 2010. Most trials excluded infants aged less than six months and pregnant women.

DHA-P versus artemether-lumefantrine

In Africa, over 28 days follow-up, DHA-P is superior to artemether-lumefantrine at preventing further parasitaemia (PCR-unadjusted treatment failure: RR 0.34, 95% CI 0.30 to 0.39, nine trials, 6200 participants, *high quality evidence*), and although PCR-adjusted treatment failure was below 5% for both ACTs, it was consistently lower with DHA-P (PCR-adjusted treatment failure: RR 0.42, 95% CI 0.29 to 0.62, nine trials, 5417 participants, *high quality evidence*). DHA-P has a longer prophylactic effect on new infections which may last for up to 63 days (PCR-unadjusted treatment failure: RR 0.71, 95% CI 0.65 to 0.78, two trials, 3200 participants, *high quality evidence*).

In Asia and Oceania, no differences have been shown at day 28 (four trials, 1143 participants, *moderate quality evidence*), or day 63 (one trial, 323 participants, *low quality evidence*).

Compared to artemether-lumefantrine, no difference was seen in prolonged QTc (*low quality evidence*), and no cardiac arrhythmias were reported. The frequency of other adverse events is probably similar with both combinations (*moderate quality evidence*).

DHA-P versus artesunate plus mefloquine

In Asia, over 28 days follow-up, DHA-P is as effective as artesunate plus mefloquine at preventing further parasitaemia (PCR-unadjusted treatment failure: eight trials, 3487 participants, *high quality evidence*). Once adjusted by PCR to exclude new infections, treatment failure at day 28 was below 5% for both ACTs in all eight trials, but lower with DHA-P in two trials (PCR-adjusted treatment failure: RR 0.41 95% CI 0.21 to 0.80, eight trials, 3482 participants, *high quality evidence*). Both combinations contain partner drugs with very long half-lives and no consistent benefit in preventing new infections has been seen over 63 days follow-up (PCR-unadjusted treatment failure: five trials, 2715 participants, *moderate quality evidence*).

In the only trial from South America, there were fewer recurrent parastaemias over 63 days with artesunate plus mefloquine (PCR-unadjusted treatment failure: RR 6.19, 95% CI 1.40 to 27.35, one trial, 445 participants, *low quality evidence*), but no differences were seen once adjusted for new infections (PCR-adjusted treatment failure: one trial, 435 participants, *low quality evidence*).

DHA-P is associated with less nausea, vomiting, dizziness, sleeplessness, and palpitations compared to artesunate plus mefloquine (*moderate quality evidence*). DHA-P was associated with more frequent prolongation of the QTc interval (*low quality evidence*), but no cardiac arrhythmias were reported.

Authors' conclusions

In Africa, dihydroartemisinin-piperaquine reduces overall treatment failure compared to artemether-lumefantrine, although both drugs have PCR-adjusted failure rates of less than 5%. In Asia, dihydroartemisinin-piperaquine is as effective as artesunate plus mefloquine, and is better tolerated.

PLAIN LANGUAGE SUMMARY

Dihydroartemisinin-piperaquine for treating uncomplicated malaria

This review summarises trials evaluating the effects of dihydroartemisinin-piperaquine (DHA-P) compared to other artemisinin-based combination therapies recommended by the World Health Organization. After searching for relevant trials up to July 2013, we included 27 randomized controlled trials, enrolling 16,382 adults and children and conducted between 2002 and 2010.

What is uncomplicated malaria and how might dihydroartemisinin-piperaquine work

Uncomplicated malaria is the mild form of malaria which usually causes a fever, with or without headache, tiredness, muscle pains, abdominal pains, nausea, and vomiting. If left untreated, uncomplicated malaria can develop into severe malaria with kidney failure, breathing difficulties, fitting, unconsciousness, and eventually death.

DHA-P is one of five artemisinin-based combination therapies the World Health Organization currently recommends to treat malaria. These combinations contain an artemisinin component (such as dihydroartemisinin) which works very quickly to clear the malaria

parasite from the person's blood, and a longer acting drug (such as piperaquine) which clears the remaining parasites from the blood and may prevent new infections with malaria for several weeks.

What the research says

DHA-P versus artemether lumefantrine

In studies of people living in Africa, both DHA-P and artemether-lumefantrine are very effective at treating malaria (*high quality evidence*). However, DHA-P cures slightly more patients than artemether-lumefantrine, and it also prevents further malaria infections for longer after treatment (*high quality evidence*). DHA-P and artemether-lumefantrine probably have similar side effects (*moderate quality evidence*).

DHA-P versus artesunate plus mefloquine

In studies of people living in Asia, DHA-P is as effective as artesunate plus mefloquine at treating malaria (*moderate quality evidence*). Artesunate plus mefloquine probably causes more nausea, vomiting, dizziness, sleeplessness, and palpitations than DHA-P (*moderate quality evidence*).

Overall, in some people, DHA-P has been seen to cause short term changes in electrocardiographs tracing the conduction of the heart rhythm (*low quality evidence*), but these small changes on the electrocardiograph resolved within one week without serious consequences.

S U M M A R Y   O F   F I N D I N G S   F O R   T H E   M A I N   C O M P A R I S O N   [Explanation]

Dihydroartemisinin-piperaquine versus Artemether-lumefantrine for uncomplicated *P. falciparum* malaria in Africa

Patient or population: Patients with uncomplicated *P. falciparum* malaria
Settings: Malaria endemic settings in Africa
Intervention: Dihydroartemisinin-piperaquine (DHA-P)
Comparison: Artemether-lumefantrine (AL6)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	AL6	DHA-P			
Treatment failure Day 28	PCR-unadjusted		RR 0.34 (0.30 to 0.39)	6200 (9 trials)	⊕⊕⊕⊕ high[1,2,3,4]
	23 per 100	8 per 100 (7 to 9)			
	PCR-adjusted		RR 0.42 (0.29 to 0.62)	5417 (9 trials)	⊕⊕⊕⊕ high[1,2,3,5]
	3 per 100	1 per 100 (1 to 2)			
Treatment failure Day 63	PCR-unadjusted		RR 0.71 (0.65 to 0.78)	3200 (2 trials)	⊕⊕⊕⊕ high[1,3,4,6,7]
	45 per 100	32 per 100 (29 to 35)			
	PCR-adjusted		RR 0.72 (0.50 to 1.04)	2097 (2 trials)	⊕⊕⊕⊕ high[1,3,7,8,9]
	6 per 100	4 per 100 (3 to 6)			

*The basis for the **assumed risk** (for example, the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) 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.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.,
Very low quality: We are very uncertain about the estimate.

[1] No serious risk of bias: Trials are generally at low risk of bias. Exclusion of studies at high or unclear risk of selection bias or detection bias did not change the result.

[2] No serious inconsistency: The trials all had similar results and statistical heterogeneity was low.

[3] No serious indirectness: The trials were conducted in different transmission settings in East, West and Southern Africa. Most studies were limited to children.

[4] No serious imprecision: Both limits of the 95% CI imply appreciable benefit, and the overall meta-analysis is adequately powered to detect this result.

[5] No serious imprecision: Although there is a benefit in favour of DHA-P, PCR-adjusted treatment failure was below 5% with both drugs.

[6] No serious inconsistency: At this timepoint there is more inconsistency between trials. Both show a benefit with DHA-P but there is variation in the size of this benefit.

[7] Seven studies from East, West and Southern Africa reported outcomes at day 42. At this timepoint DHA-P still had an advantage over AL6 on PCR-unadjusted treatment failure (RR 0.60, 95% CI 0.53 to 0.67, seven studies, 3301, *high quality evidence*), and PCR-adjusted treatment failure (RR 0.58, 95% CI 0.41 to 0.81, seven studies, 2559 participants, *moderate quality evidence*).

[8] No serious inconsistency: Statistical heterogeneity was low.

[9] No serious imprecision: Both ACTs performed well in these two trials with low levels of treatment failure.

BACKGROUND

Description of the condition

Malaria is a febrile illness caused by infection with the protozoan parasite *Plasmodium*, which is transmitted from person to person by the bite of infected female *Anopheles* mosquitoes. Five *Plasmodium* species are capable of causing malaria in humans, of which *P. falciparum* is responsible for over 90% of malaria cases and almost all of the malaria deaths worldwide (WHO 2012).

Uncomplicated malaria is the mild form of the disease which typically presents as a fever, with or without associated headache, tiredness, muscle pains, abdominal pains, rigors (severe shivering), nausea, and vomiting. If left untreated *P. falciparum* malaria can rapidly develop into severe malaria with consequent renal failure (kidney failure), pulmonary oedema (fluid in the lungs), convulsions (fitting), coma, and eventually death (WHO 2010; Sinclair 2012). A clinical diagnosis of malaria can be confirmed by detection of the malaria parasite in the patient's blood. This has traditionally been done by light microscopy but increasingly rapid diagnostic tests are being used (Abba 2011).

Resistance of *P. falciparum* to the traditional antimalarial drugs (such as chloroquine, sulfadoxine-pyrimethamine, amodiaquine, and mefloquine) is a growing problem and is thought to have contributed to increased malaria mortality in recent years (WHO 2010). Chloroquine resistance has now been documented in all regions except Central America and the Caribbean. There is high-level resistance to sulfadoxine-pyrimethamine throughout South East Asia and increasingly in Africa, and mefloquine resistance is common in the border areas of Cambodia, Myanmar, and Thailand (WHO 2010; WWARN 2013).

To combat the spread of resistance, the World Health Organization (WHO) now recommends that *P. falciparum* malaria is always treated using a combination of two drugs that act at different biochemical sites within the parasite (WHO 2010). If a parasite mutation producing drug resistance arises spontaneously during treatment, the parasite should then be killed by the partner drug, thus reducing or delaying the development of resistance and increasing the useful lifetime of the individual drugs (White 1996; White 1999). The current drug combinations all include a short-acting artemisinin derivative (such as artesunate, artemether, or dihydroartemisinin), partnered with a longer-acting drug in combinations known as 'Artemisinin-based Combination Therapies' (ACTs).

Description of the intervention

The WHO recommends five ACTs for treating uncomplicated *P. falciparum* malaria: dihydroartemisinin-piperaquine (DHA-P); artesunate plus mefloquine (AS+MQ); artemether-lumefantrine - six doses regimen (AL6); artesunate plus amodiaquine (AS+AQ); and artesunate plus sulfadoxine-pyrimethamine (AS+SP) (WHO 2010).

Dihydroartemisinin is the active metabolite of the artemisinin derivatives, and produces faster relief of clinical symptoms and faster clearance of parasites from the blood than other antimalarial drugs (McIntosh 2000; Adjuik 2004; WHO 2010). When used as a monotherapy, the short half-life of the artemisinin derivatives (and rapid elimination from the blood) means that patients must take the drug for at least seven days (Meshnick 1996; Adjuik 2004). Failure to complete the course, due to the rapid improvement in clinical symptoms, can lead to high levels of treatment failure even in the absence of drug resistance. The long-acting partner drug in ACTs therefore allows the artemisinin component to be taken for a shorter duration (White 1999), and the current recommendation is for three days of the artemisinin-derivative to cover two asexual parasite life-cycles (Adjuik 2004; WHO 2010).

The artemisinin derivatives also reduce the development of gametocytes (the sexual form of the *P. falciparum* parasite that is capable of infecting mosquitoes) and consequently the carriage of gametocytes in the peripheral blood (Price 1996; Targett 2001). This reduction in infectivity has the potential to reduce the post-treatment transmission of malaria (particularly in areas of low or seasonal transmission), which may have important public health benefits (WHO 2010).

Artemisinin and its derivatives are generally reported as being safe and well-tolerated, and the safety profile of ACTs may be largely determined by the partner drug (Nosten 2007; WHO 2010). Animal studies of artemisinin derivatives have reported neurotoxicity (brain damage), but this has not been seen in human studies (Price 1999). Animal studies have also shown adverse effects on the early development of the fetus, and consequently the use of artemisinin derivatives in pregnant women has so far been restricted to the second and third trimesters and continues to be evaluated (Nosten 2007). Other reported adverse events include gastrointestinal (GI) disturbance (stomach upset), dizziness, tinnitus (ringing in the ears), neutropenia (low levels of white blood cells), elevated liver enzymes (a marker for liver damage), and electrocardiographic (ECG) abnormalities (changes in cardiac conduction) (Nosten 2007). The incidence of type 1 hypersensitivity (allergic) reactions is reported to be approximately 1 in 3000 patients (Nosten 2007).

Piperaquine is a bisquinoline antimalarial whose mode of action is thought to be similar to that of chloroquine (a 4-aminoquinolone) (Keating 2012). In vitro studies have shown it is effective against chloroquine-resistant *P. falciparum,* although there are reports of some cross-resistance (Keating 2012). Piperaquine has a very long elimination half-life of between two to three weeks, similar to mefloquine but longer than lumefantrine or amodiaquine, and consequently could be expected to provide a long period of post-treatment prophylaxis (Davis 2005; Keating 2012).

In a previous review of DHA-P, Myint 2007 noted an association between DHA-P and prolongation of the QT interval in two small

observational trials (Karunajeewa 2004: N = 62, and Ashley 2004a THA; N = 32). Prolonged QT interval is a cardiac conduction defect which can sometimes lead to fatal arrhythmias.

Assessment of antimalarial drug efficacy

The WHO recommends that first-line antimalarials should have a treatment failure rate of less than 10%, and that failure rates higher than 10% should trigger a change in treatment policy (WHO 2010). Treatment failure can be classified as:

Early treatment failure:
- the development of danger signs or severe malaria on days 1, 2, or 3 in the presence of parasitaemia;
- parasitaemia on day 2 higher than on day 0;
- parasitaemia and axillary temperature > 37.5 °C on day three;
- parasitaemia on day 3 > 20% of count on day 0.

or late treatment failure:
- development of danger signs, or severe malaria, after day three with parasitaemia;
- presence of *P. falciparum* parasitaemia and axillary temperature > 37.5 °C on or after day 4;
- presence of *P. falciparum* parasitaemia after day 7.

The late reappearance of *P. falciparum* parasites in the blood can be due to failure of the drug to completely clear the original parasite (a recrudescence) or due to a new infection, which is especially common in areas of high transmission. A molecular genotyping technique called polymerase chain reaction (PCR) can be used in clinical trials to distinguish between recrudescence and new infection, giving a clearer picture of the efficacy of the drug and its post-treatment prophylactic effect (White 2002; Cattamanchi 2003).

The WHO recommends a minimum follow-up period of 28 days for antimalarial efficacy trials, but longer follow-up may be required for antimalarials with long elimination half-lives (White 2002; Bloland 2003). This is because treatment failure due to true recrudescence of malaria parasites may be delayed until the drug concentration falls below the minimum concentration required to inhibit parasite multiplication, which may be beyond 28 days. The WHO recommends 42 days follow-up for trials involving lumefantrine and piperaquine and 63 days for mefloquine trials (WHO 2010).

Why it is important to do this review

This review aims to assist national decision-making by providing a concise summary of the benefits and harms of DHA-P in comparison to the other recommended ACTs. Other information that is also important when selecting national first or second-line ACTs includes:

- the appropriateness of the partner drug within a locality, based on regional and national overviews of drug resistance and the intensity of malaria transmission;
- the simplicity of the treatment regimen (co-formulated products are generally preferred as they reduce the availability and use of monotherapy, which may in turn reduce the development of resistance); and
- the cost (since the ACT is likely to represent a large percentage of the annual health expenditure in highly endemic countries).

OBJECTIVES

To evaluate the effectiveness and safety of DHA-P compared to other ACTs for the treatment of uncomplicated *P. falciparum* malaria in adults and children.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs). We excluded quasi-RCTs.

Types of participants

Adults and children (including pregnant women and infants) with symptomatic, microscopically confirmed, uncomplicated *P. falciparum* malaria.

We also included trials that recruited participants with *P. vivax* co-infection.

Types of interventions

Intervention

A three-day course of DHA-P.

Control

A three-day course of an alternative WHO recommended ACT.

Types of outcome measures

Primary outcomes

Total failure at days 28, 42, and 63; PCR-adjusted and PCR-unadjusted.

Secondary outcomes

- Gametocyte carriage at day 7 or 14 (preference for day 14 in data analyses);
- Gametocyte development (negative at baseline and positive at follow-up);
- Change in haemoglobin from baseline (minimum 28 day follow-up).

Adverse events

- Deaths occurring during follow-up;
- Serious adverse events (life threatening, causing admission to hospital, or discontinuation of treatment);
- Haematological and biochemical adverse effects (for example, neutropenia, liver toxicity);
- Early vomiting;
- Other adverse events.

Search methods for identification of studies

Electronic searches

We searched the following databases up to 29 July 2013 using the search terms detailed in Table 1: Cochrane Infectious Diseases Group Specialized Register; Cochrane Central Register of Controlled Trials (CENTRAL) published in *The Cochrane Library*; MEDLINE; EMBASE; LILACS. We also examined the *meta*Register of Controlled Trials (*m*RCT) using the search terms 'malaria' and 'arte* OR dihydroarte*'.

Searching other resources

We contacted individual researchers working in the field, organizations including the WHO, and pharmaceutical companies involved in the manufacture of DHA-P (Atlantic, Guilin, Holleykin, HolleyPharm) for information on unpublished trials. In addition, reference lists of all trials identified by the methods described above were checked.

Data collection and analysis

Selection of studies

Babalwa Zani (BZ) and Michael Gathu (MG) independently reviewed the results of the literature search, obtained full-text copies of all potentially relevant trials and checked each trial report for evidence of multiple publications from the same data set.
BZ and MG also independently assessed each trial for inclusion using an eligibility form based on the inclusion criteria and resolved

any disagreements through discussion or, where necessary, by consultation with David Sinclair (DS). We contacted trial authors when further information was necessary. We listed the ineligible trials and the reasons for their exclusion in the 'Characteristics of excluded studies' table.

Data extraction and management

BZ and MG independently extracted data on trial characteristics including methods, participants, interventions, outcomes, dose, and drug ratios of the combinations using a pre-tested data extraction form. We also recorded the number of participants randomized and analysed in each treatment group for each outcome and reported the loss to follow-up in each group.
For dichotomous outcomes, we recorded the number of participants experiencing the event and the total number of participants in each treatment group. For continuous outcomes, the arithmetic means and standard deviations for each treatment group together with the numbers of participants in each group were extracted. Where trials reported the data using geometric means, we recorded this information and extracted standard deviations on the log scale. Where trials gave median values, we extracted medians and ranges.

Primary outcome

Our primary analyses drew on the WHO's protocol for assessing and monitoring antimalarial drug efficacy (Bloland 2003). This protocol has been used to guide most efficacy trials since its publication in 2003, even though it was designed to assess the level of antimalarial resistance in the study area rather than for comparative trials. As a consequence, a high number of randomized participants are excluded from the final efficacy outcome as losses to follow-up or voluntary or involuntary withdrawals. For this reason we conducted a series of sensitivity analyses to restore the integrity of the randomization process and test the robustness of the results to this methodology (For a summary of the methodology and sensitivity analysis see Table 2).

PCR-unadjusted total failure

We calculated PCR-unadjusted total failure (*P. falciparum*) as the sum of early treatment failures and late treatment failures (without PCR adjustment). The denominator excluded participants for whom an outcome was not available (for example, those who were lost to follow-up, withdrew consent, took other antimalarials, or failed to complete treatment) and those participants who were found not to fulfil the inclusion criteria after randomization.

PCR-adjusted total failure

We defined PCR-adjusted total failure (*P. falciparum*) as the sum of early treatment failures, and late treatment failures due to PCR-confirmed recrudescence. Participants with indeterminate PCR results, missing PCR results, or PCR-confirmed new infections

were treated as involuntary withdrawals and excluded from the calculation. The denominator excluded participants for whom an outcome was not available (for example, those who were lost to follow-up, withdrew consent, took other antimalarials, or failed to complete treatment) and those participants who did not fulfil the inclusion criteria after randomization.

These primary outcomes relate solely to failure due to *P. falciparum*. For both PCR-unadjusted and PCR-adjusted total failure, we retained participants who developed confirmed P. vivax infection during follow-up in the calculation if they were treated with chloroquine and continued in follow-up. They were classified as treatment successes if they did not subsequently develop *P. falciparum* parasitaemia. We excluded from the calculation those participants who developed *P. vivax* parasitaemia and were removed from the trial's follow-up.

Assessment of risk of bias in included studies

BZ and MG independently assessed the risk of bias for each trial using 'The Cochrane Collaboration's tool for assessing the risk of bias' (Higgins 2008) and resolved differences of opinion through discussion with DS. We followed the guidance to assess whether adequate steps were taken to reduce the risk of bias across six domains: sequence generation; allocation concealment; blinding (of participants, personnel, and outcome assessors); incomplete outcome data; selective outcome reporting; and other sources of bias.

For sequence generation and allocation concealment, we reported the methods used. For blinding, we described who was blinded and the blinding method. For incomplete outcome data, we reported the percentage and proportion of participants lost to follow-up. For selective outcome reporting, any discrepancies between the methods used and the results were stated in terms of the outcomes measured or the outcomes reported. For other biases, we described any other trial features that could have affected the trial result (for example, if the trial was stopped early).

We categorized our risk of bias judgements as 'low', 'high', or 'unclear'. Where risk of bias was unclear, we attempted to contact the trial authors for clarification and resolved any differences of opinion through discussion.

Measures of treatment effect

We analysed the data using Review Manager (RevMan) and presented and combined dichotomous data using risk ratios (RR). For continuous data summarized by arithmetic means and standard deviations, we combined data using mean differences. RRs and mean differences were accompanied by 95% confidence intervals (CI). We reported medians and ranges in tables.

Unit of analysis issues

We split trials including more than two comparison groups and analysed as individual pair-wise comparisons. When conducting meta-analysis, we ensured that participants and cases in the placebo group were counted only once, by dividing the placebo cases and participants evenly between the intervention groups.

Dealing with missing data

If data from the trial reports were insufficient, unclear, or missing, we attempted to contact the trial authors for additional information. If the missing data rendered the result uninterpretable, we excluded the data from the meta-analysis and clearly stated the reason for exclusion. We explored the potential effects of missing data through a series of sensitivity analyses (Table 2).

Assessment of heterogeneity

We assessed heterogeneity between trials by inspecting the forest plots, applying the Chi² test with a 10% level of statistical significance, and using the I² statistic with a value of 50% to denote moderate levels of heterogeneity.

Assessment of reporting biases

The possibility of publication bias was assessed by examining funnel plots for asymmetry. We noted that funnel plot asymmetry could also be caused by differences in methodological quality or heterogeneity.

Data synthesis

To aid interpretation, we gave the included trials identity codes including the first author, the year of publication, and the three-letter international country code or two-letter continent code (for trials conducted in more than one country). We listed trials in forest plots in chronological order of the year the trial was completed. Using pair-wise comparisons we directly compared treatments. For outcomes that were measured at different time points, we stratified the analysis by the time point. The primary outcome analysis was also stratified by geographical region as a crude marker for differences in transmission and resistance patterns.

We performed meta-analysis within geographic regions where appropriate after assessment and investigation of heterogeneity. In the first instance, we used a fixed-effects model and applied a random-effects model when the Chi² test P value was less than 0.1 or the I² statistic greater than 50%.

Quality of evidence

We assessed the quality of evidence across each outcome measure using the GRADE approach. The quality rating across studies has four levels: high, moderate, low, or very low. RCTs are initially categorized as high quality but can be downgraded after assessment of five criteria: risk of bias, consistency, directness, imprecision, and publication bias. Similarly, observational studies are initially categorized as low quality and can be downgraded by the same

criteria, but in exceptional circumstances may be upgraded by three further criteria; large effect size, all plausible confounders would act to reduce the effect size, and evidence of a dose-response effect (Guyatt 2008).

Subgroup analysis and investigation of heterogeneity

We investigated potential sources of heterogeneity through a series of analyses, sub-grouping the trials by: geographical region, intensity of malaria transmission (low to moderate versus high malaria transmission), known parasite resistance, allocation concealment, participant age, and drug dose (comparing regimens where there are significant variations in drug dose).

Sensitivity analysis

We conducted a series of sensitivity analyses to investigate the robustness of the methodology used in the primary analysis. The aim was to restore the integrity of the randomization process by adding excluded groups back into the analysis in a stepwise fashion (see Table 2 for details).

R E S U L T S

Description of studies

See the Characteristics of included studies and Characteristics of excluded studies section.

Results of the search

We conducted the searches up to 29 July 2013 and identified 90 trials in total. After screening titles and abstracts, we obtained full text copies of 49 trials. Of these, 34 trials met the inclusion criteria and we excluded 15 trials (Figure 1). We included 27 trials as primary references and retained seven trials as secondary references for additional data on secondary outcomes and adverse events. One of the 26 trials had two different recruitment settings which we split and considered as two separate trials (Ashley 2004a THA; Ashley 2004b THA). One trial (Borrmann 2011 KEN (a)) is pending as we await data for a separate recruitment period from the trial authors.

Figure 1. Study flow diagram.
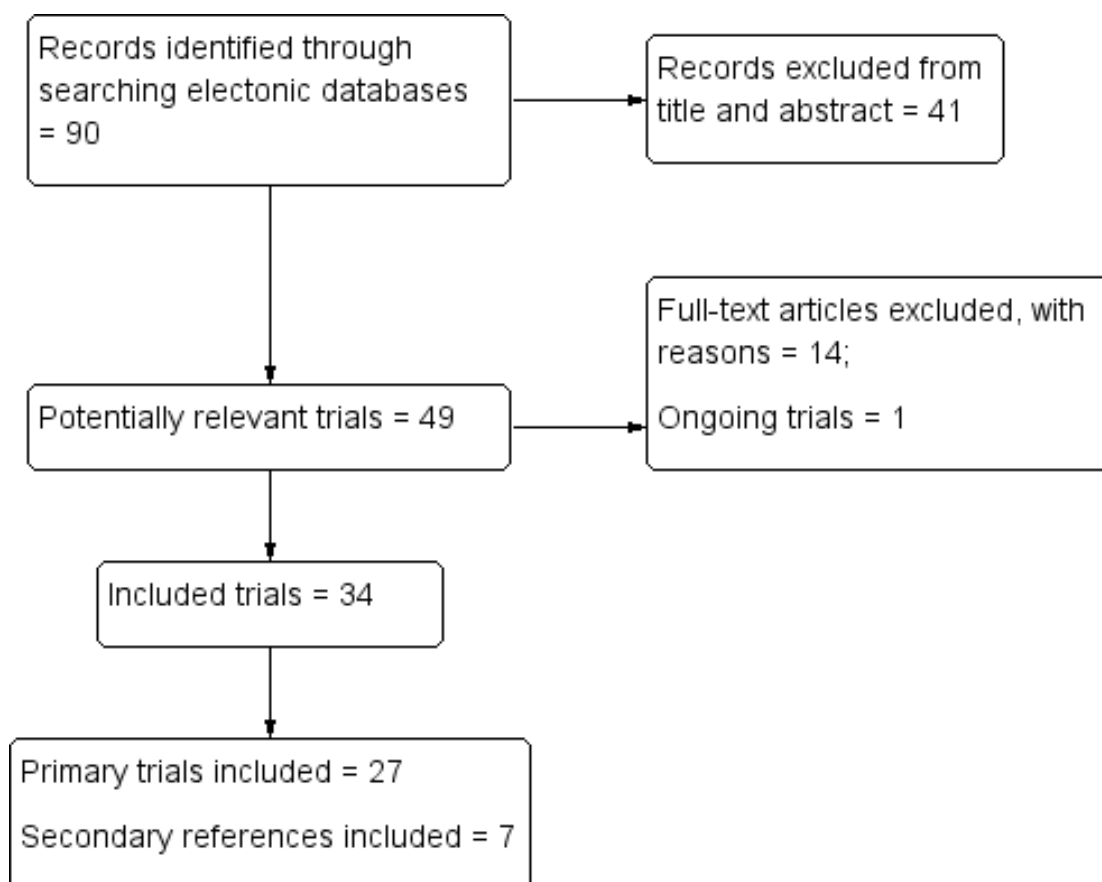
Included studies

We included 27 trials, enrolling 16,382 participants and conducted between 2002 and 2010.

Twelve trials were conducted in Africa; Uganda (three trials), Kenya (three trials), Sudan (one trial), Rwanda (one trial), Burkina Faso (one trial), and three multi-centre trials with sites in Kenya, Uganda, Rwanda, Mozambique, Zambia, Gabon, Burkina Faso, Nigeria, Senegal, Côte d'Ivoire, and Cameroon (Bassat 2009 AF; The 4ABC Study 2011 AF; Yavo 2011 AF). Fourteen trials were conducted in Asia and Oceania; Thailand (five trials), Myanmar (two trials), Laos (one trial), Vietnam (one trial), Cambodia (one trial), Indonesia (two trials), Papua New Guinea (one trial); and one multi-centre trial had sites in Thailand, Laos, and India (Valecha 2010 AS). Only one trial was from South America (Peru).

The African trials focused on children, while Asian trials included older populations and excluded children below one year of age. All trials excluded pregnant and lactating women.

Eleven trials compared DHA-P with AS+MQ, 16 trials compared DHA-P with AL, four trials compared DHA-P with ASAQ, and one trial compared DHA-P with AS+SP. Some trials had more than two arms and compared multiple ACTs.

Three trials (Hasugian 2007 IDN; Ratcliff 2007 IDN; Karunajeewa 2008 PNG) conducted in Asia and Oceania included participants with *P. vivax* mono-infection at baseline. For our primary analysis we obtained data from the trial authors for only those participants who had *P. falciparum* or mixed infection (*P. falciparum* and *P. vivax*) at baseline. Arinaitwe 2009 UGA had an unusual trial design where participants were followed up for more than one episode of malaria. We used data from all malaria episodes in our primary analysis.

We listed the trial details of the included studies in the 'Characteristics of included studies' table.

Excluded studies

The reasons for exclusion are in the 'Characteristics of excluded studies' table.

Risk of bias in included studies

For a summary of the 'Risk of bias' assessments, see Figure 2.

Figure 2.   Risk of bias summary: review authors' judgements about each risk of bias item for each included trial.

Allocation

Nine trials were at low risk of selection bias, with adequate methods for both generation of the randomization sequence and allocation concealment. A further 18 studies were at unclear risk of selection bias due to inadequate descriptions of their methods. For primary outcomes we conducted a sensitivity analysis including only the trials with adequate allocation concealment.

Blinding

Eighteen trials blinded the microscopists to treatment allocation and so were at low risk of performance and detection bias for the primary outcomes. Only four of the included trials blinded the outcome assessors for adverse events.

Incomplete outcome data

We reported the proportion of participants in each treatment arm for whom an outcome was not available and conducted sensitivity analyses to test the possible effect of these losses. Four trials were at high risk of bias due to high dropout rates (> 15%).

Selective reporting

Due to the varying half-lives of drugs, the choice of which day to measure outcomes can influence the comparative effects of the ACTs. If an ACT with a long half-life (DHA-P or AS+MQ) is compared to a drug with a short half-life (AS+AQ or AS+SP), day 28 outcomes may underestimate PCR-adjusted failure with the long half-life drug. At later time points (day 42 and 63), drugs with long half-lives are likely to appear superior in preventing new infections (PCR-unadjusted failure) which represents a prophylactic effect. We noted this while interpreting the data but did not consider this a source of trial bias.

Other potential sources of bias

Pharmaceutical companies provided financial support or study drugs in 13 trials. In the two large trials of the new Eurartesim® formulation (Bassat 2009 AF & Valecha 2010 AS), the pharmaceutical company was fully involved in the design, conduct and analysis of the trials, In one of these (Bassat 2009 AF), it is stated that an independent author had access to the primary dataset and took responsibility for the analyses. We judged this trial to be at unclear risk of bias. In the second trial, this additional safety measure was not described and we judged the trial to be at high risk of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Dihydroartemisinin-piperaquine versus Artemether-lumefantrine for uncomplicated *P. falciparum* malaria in Africa

Comparison 1. DHA-P versus artesunate plus mefloquine

We found 11 trials, 10 in Asia and one in South America, that assessed this comparison; conducted between 2002 and 2009. Allocation concealment was at 'low risk of bias' in only two trials (Mayxay 2006 LAO; Grande 2007 PER). Five trials blinded laboratory staff (outcome assessors) to treatment allocation (Ashley 2004a THA; Ashley 2004b THA; Ashley 2005 THA; Smithuis 2010 MMR; Valecha 2010 AS). Patients were unblinded in all trials, and only one trial blinded outcome assessors for adverse effects (The 4ABC Study 2011 AF).

Total failure

In Asia over 63 days follow-up, recurrent parasitaemias (including both recrudescences and new infections) occurred in less than 15% of all participants, with no differences in PCR-unadjusted treatment failure between groups (day 28: eight trials, 3487 participants, Analysis 1.1; day 42: seven trials, 3421 participants, Analysis 1.3; Day 63: five trials, 2715 participants, Analysis 1.5). Once adjusted by PCR to exclude new infections, treatment failure at day 28 was below 5% for both ACTs in all eight trials for which data was available (eight trials, 3482 participants, Analysis 1.2). Two of the eight trials, conducted in Thailand at trial sites with multi-drug resistant *P. falciparum*, found slightly higher levels of recrudescence following AS+MQ and statistically significant benefits with DHA-P (Ashley 2005 THA; Valecha 2010 AS). Recrudescences remained low in both groups over 63 days of follow-up (day 42: six trials, 2901 participants, Analysis 1.4; day 63: five trials, 2500 participants, Analysis 1.6).

In the one trial from South America, only day 63 data was available (Analysis 1.5; Analysis 1.6). Recrudescences and new infections were very rare with both treatments, but new infections were lower with AS+MQ (RR 6.19, 95% CI 1.40 to 27.35, one trial, 445 participants, Analysis 1.5).

Gametocytes

AS+MQ appears to clear gametocytes from the peripheral blood quicker than DHA-P (Gametocyte carriage on Day 7: RR 1.99, 95% CI 1.57 to 2.51, three trials, 2270 participants, Analysis 1.7; Day 14: RR 5.11, 95% CI 3.26 to 7.99, three trials, 2249 participants, Analysis 1.7). In addition, the number of participants who developed detectable gametocytes (after being negative at baseline)

was low in both groups, but lowest with AS+MQ (RR 3.06, 95% CI 1.13 to 8.33, three trials, 1234 participants, Analysis 1.8). Five trials reported additional data on gametocyte carriage which could not be pooled and are presented in Table 3.

Anaemia

Seven trials reported a variety of measures of haematological changes between baseline and the last day of follow-up which we could not pool. None of the individual trials reported differences between groups (see Table 3).

Adverse events

There was no difference in the frequency of serious adverse events (eight trials, 3522 participants, Analysis 1.9; see Appendix 2 for details of serious adverse events).

Nine trials reported some measure of early vomiting (vomiting related to drug administration) and there was no difference shown in any trial (nine trials, 4114 participants, Analysis 1.10). However, subsequent nausea and vomiting were consistently more common with AS+MQ (Nausea: RR 0.68, 95% CI 0.60 to 0.78, nine trials, 4531 participants; vomiting: RR 0.59, 95% CI 0.47 to 0.75, five trials, 2744 participants, Analysis 1.10). Diarrhoea was more common with DHA-P (RR 1.46, 95% CI 1.05 to 2.04, five trials, 2217 participants, Analysis 1.10).

AS+MQ was consistently associated with increased dizziness (RR 0.72, 95% CI 0.66 to 0.78, nine trials, 4531 participants), and sleeplessness (RR 0.49, 95% CI 0.40 to 0.60, six trials, 2551 participants, Analysis 1.11), and increases in headache (four trials), fatigue (two trials), nightmares (one trial), and anxiety (one trial) are reported in the few trials that recorded them (Analysis 1.11). Palpitations were also more common with AS+MQ (RR 0.61, 95% CI 0.45 to 0.82, three trials, 1175 participants, Analysis 1.12), but only one trial performed routine ECGs in both treatment groups (Valecha 2010 AS). In this trial there was a baseline imbalance in the prevalence of borderline prolonged QTc (431 to 450 ms in children and adult men/451 to 470 ms in adult women), using Bazett's correction method (16.6% DHA-P versus 12.2% AS+MQ, P = 0.066; authors' own figures), but not Fridericia's method (2.9% DHA-P versus 1.6% AS+MQ, P > 0.05; authors' own figures).

On day 2, a higher proportion of participants treated with DHA-P had borderline prolonged QTc by both correction methods (Bazett's: 21.4% DHA-P versus 16.3% AS+MQ, P = 0.043; Fridericia's: 13.0% DHA-P versus 5.3% AS+MQ, P < 0.001; authors' own figures). There was also a statistically significant increase in the prevalence of prolonged QTc with DHA-P (> 450 ms in children and adult men, and > 470 ms in adult women), using Bazett's method but not Fridericia's method (one trial, 1148 participants, Analysis 1.12). No consequent arrhythmias were noted, and these differences were no longer present at day seven (for additional data see Table 4).

Four trials conducted biochemical monitoring for either renal or hepatic adverse events. Monitoring was adequate in three trials (Ashley 2004a THA; Tran 2004 VNM; Grande 2007 PER), and inadequate in one (Valecha 2010 AS), but incompletely reported in all four trials. No clinically important toxicities were reported (see Table 5).

Sensitivity analysis

As described in the methods section, we undertook a series of sensitivity analyses to test the robustness of our results to different analysis plans. An example of these is given in Analysis 1.14 & Analysis 1.15. In general, the method of analysis did not change the significance of results and so the remaining sensitivity analyses were deleted.

Comparisons 2 and 3: DHA-P dosing concerns

Two dosing regimens were commonly used in clinical trials of DHA-P versus AS+MQ, which give the same total dose, but divided into three or four doses, given over three days (see Table 6). One trial (Ashley 2005 THA) directly compared the three-dose regimen with the four-dose regimen and found no difference at any time point (one trial, 318 participants, Analysis 2.1; Analysis 2.2).

In comparisons comparing DHA-P to AS+MQ, six trials used the three-dose regimen, four trials used the four-dose regimen, and one trial used both. Stratifying the analysis by dosing regimen did not reveal any important differences in efficacy between the two regimens (Analysis 3.1 to Analysis 3.6).

Comparison 4. DHA-P versus artemether-lumefantrine (six doses)

We found fifteen trials which assessed this comparison; eleven in Africa, three in Asia and one in Oceania; conducted between 2005 and 2011. Eleven of the fifteen trials included children only.

Allocation concealment was at low risk of bias in eight trials (Kamya 2007 UGA; Ratcliff 2007 IDN; Zongo 2007 BFA; Yeka 2008 UGA; Arinaitwe 2009 UGA; Bassat 2009 AF; The 4ABC Study 2011 AF; Yavo 2011 AF). Ten out of 14 trials blinded laboratory staff to treatment allocation.

Total failure

In Africa, PCR-unadjusted treatment failure at day 28 was consistently lower with DHA-P (RR 0.34, 95% CI 0.30 to 0.39, nine trials, 6200 participants, Analysis 4.1). After PCR adjustment to exclude new infections, treatment failure at Day 28 was below 5% with both ACTs in all nine trials, but was consistently lowest with DHA-P (RR 0.42, 95% CI 0.29 to 0.62, nine trials, 5417 participants, Analysis 4.2). Six trials continued follow-up until day 42, and two until day 63. DHA-P appears to have a longer post-

treatment prophylactic effect than AL6 in keeping with its longer elimination half-life (Day 42 PCR-unadjusted treatment failure: RR 0.60, 95% CI 0.53 to 0.67, seven trials, 3301 participants, Analysis 4.3; Day 63 PCR-unadjusted treatment failure: RR 0.71, 95% CI 0.65 to 0.78, two trials, 3200 participants, Analysis 4.5). In Asia and Oceania, PCR-unadjusted treatment failure at day 28 was similar between treatments (four trials, 1143 participants, Analysis 4.1), and with no statistically significant differences after PCR adjustment (three trials, 925 participants, Analysis 4.2). Of note, PCR-adjusted treatment failure at day 28 was above 10% in those treated with DHA-P in the one trial from Papua New Guinea (Karunajeewa 2008 PNG), but this has not been seen elsewhere. No differences were seen in PCR-unadjusted or PCR-adjusted treatment failure at day 42 (two trials, 572 participants, Analysis 4.3; Analysis 4.4), or day 63 (one trial, 323 participants, Analysis 4.5; Analysis 4.6).

Gametocytes

SIx trials, all from Africa, reported the development of gametocytes in those negative at baseline. The results were highly heterogenous and we could not pool them (six trials, 1968 participants) heterogeneity: Chi² test, P = 0.001, I² = 78%, Analysis 4.7). Carriage of gametocytes during the first two weeks was higher with DHA-P (RR 4.32, 95% 1.48 to 12.63, four trials, 1537 participants, Analysis 4.8), but lower with DHA-P during weeks three to six; a finding which may reflect the lower treatment failure rates with DHA-P at later time points (Analysis 4.8). Bassat 2009 AF reports that person-gametocyte weeks was higher in those treated with DHA-P (see Table 7).
In Asia, Karunajeewa 2008 PNG and Ratcliff 2007 IDN report no differences in gametocyte carriage between groups but did not give figures, while Smithuis 2010 MMR reports higher gametocyte carriage with DHA-P (see Table 7).

Anaemia

Six trials reported changes in haemoglobin from baseline to the last day of follow-up (day 28 or 42). There is a trend towards a small benefit with DHA-P which may not be of clinical significance (six trials, 3529 participants, Analysis 4.9).

Adverse events

No difference has been shown in the frequency of serious adverse events, although the trend is towards a small increase in serious adverse events with DHA-P (nine trials, 7246 participants, Analysis 4.10, see Appendix 2 for details of serious adverse events).
DHA-P is associated with a higher frequency of early vomiting (drug-related vomiting), which just reached statistical significance (RR 1.69, 95% CI 1.00 to 2.83, four trials, 2969 participants, Analysis 4.11), but there was no difference in vomiting overall (nine trials, 6761 participants, Analysis 4.11).

Compared to AL6, DHA-P was also associated with a slightly higher frequency of pruritis (RR 1.74, 95% CI 1.03 to 2.92, five trials, 2033 participants, Analysis 4.14), but there were no differences in any other clinical side effects (Analysis 4.11 to Analysis 4.14).
Only one trial conducted ECG monitoring on participants in both treatment groups (Bassat 2009 AF). On day 2, a higher proportion of participants treated with DHA-P had borderline raised QTc intervals (431 to 450 ms) when corrected by Bazett's method (29.1% DHA-P versus 19.8% AL6, P < 0.001; authors' own figures), but not Fridericia's method (1.0% DHA-P versus 1.2% AL6, P = 0.76; authors' own figures). There were no differences in the proportion of patients with prolonged QTc interval (> 450 ms), using either Bazett's or Fridericia's method (one trial, 1548 participants, Analysis 4.13) or reported at day 7 (see Table 4 for additional data).
Three trials conducted biochemical monitoring for either renal or hepatic adverse events (Bassat 2009 AF; The 4ABC Study 2011 AF; Yavo 2011 AF). Monitoring was adequate in all three trials but incompletely reported in one trial. No clinically important toxicities were reported (see Table 8).

Comparison 5. DHA-P versus artesunate plus amodiaquine

We found four trials which assessed this comparison; two in Africa and two in Asia; conducted between 2004 and 2009.
Allocation concealment was assessed as low risk of bias in two trials (Hasugian 2007 IDN; The 4ABC Study 2011 AF) and unclear in the other two. In all four trials laboratory staff were blinded to treatment allocation.

Total failure

In Africa, PCR-unadjusted treatment failure at day 28 was lower following treatment with DHA-P in both trials (RR 0.49, 95% CI 0.41 to 0.59, two trials, 2800 participants, Analysis 5.1). After PCR-adjustment to exclude new infections, the difference between treatments was no longer statistically significant, but treatment failure was below 5% following treatment with DHA-P in both trials, and above 5% following AS+AQ in Rwanda (two trials, 2486 participants, Analysis 5.2). One trial followed participants up to day 63 (The 4ABC Study 2011 AF), and found no differences in PCR-unadjusted or PCR-adjusted treatment failure at this time point (one trial, 2292 participants, Analysis 5.5; Analysis 5.6).
In Asia, PCR-unadjusted treatment failure at day 28 was lower following treatment with DHA-P (RR 0.38 95% CI 0.18 to 0.77, two trials, 482 participants, Analysis 5.1), and remained lower after PCR-adjustment although the number of events was very low (RR 0.08, 95% CI 0.01 to 0.40, two trials, 466 participants, Analysis 5.2). One trial followed participants up to day 42 (Hasugian 2007 IDN), and one to day 63 (Smithuis 2010 MMR), when the differences remained statistically significant in favour of DHA-P (Analysis 5.3 to Analysis 5.6).

Gametocytes

Two trials reported no statistically significant differences in gametocyte carriage during follow-up but did not report the data (see Table 9).

Anaemia

Two trials reported no difference between PCV and haemoglobin levels respectively between the treatment groups (Karema 2006 RWA; Smithuis 2010 MMR; see Table 9). Hasugian 2007 IDN found that the prevalence of anaemia at day 7 (P = 0.02) and 28 (P = 0.006) was higher with AS+AQ (authors' own figures); this may be attributed to the recurrence of parasitaemia with both *P. falciparum* and *P. vivax* being higher in the AS+AQ group.

Adverse events

The frequency of serious adverse events was lower with DHA-P, and despite few events, this reached statistical significance (RR 0.40 95% CI 0.19 to 0.87, two trials, 2805 participants, Analysis 5.7, see Appendix 2 for details of serious adverse events). The 4ABC Study 2011 AF reported 15 serious adverse events in 1003 participants treated with AS+AQ versus 10/1468 with DHA-P. The exact nature of these serious adverse events was unclear, but the authors reported no differences in serious adverse events classified as possibly, probably, or definitely related to the trial drug (4/1003 versus 4/1468).

Hasugian 2007 IDN and Smithuis 2010 MMR found no difference in the number of participants with early vomiting (two trials, 650 participants, Analysis 5.8).

Pyrexia was the only adverse event that was statistically more common with DHA-P (RR 1.18 95% CI 1.02 to 1.37, one trial, 2471 participants, Analysis 5.9).

Two trials conducted biochemical monitoring for renal or hepatic adverse events (Karema 2006 RWA; Smithuis 2010 MMR). Monitoring was adequate in both trials but incompletely reported in one trial. No clinically important toxicities were reported (see Table 10).

Comparison 6. DHA-P versus artesunate plus sulfadoxine-pyrimethamine

One trial conducted in Oceania in 2007 assessed this comparison (Karunajeewa 2008 PNG). The trial authors did not describe any attempt to conceal allocation. Laboratory staff were blinded to treatment allocation.

Total failure

At day 28 PCR-adjusted treatment failure was > 10% in both groups (Analysis 6.2).

There were no statistically significant differences in treatment failure between the two arms (one trial, 223 participants, Analysis 6.1 to Analysis 6.4)

Gametocytes

No significant differences in gametocyte carriage during follow-up were reported (figures not reported).

Anaemia

Trial authors reported haemoglobin levels remained similar in both groups throughout follow-up (figures not reported).

Adverse events

Monitoring for adverse events was undertaken but no differences between the groups were reported.

DISCUSSION

For summaries of the main results for efficacy see; Summary of findings for the main comparison; Table 11; Table 12; Table 13; Table 14; Table 15), and for adverse effects see Appendix 3.

Summary of main results

DHA-P versus artemether lumefantrine

In Africa, during 28 days follow-up, DHA-P is superior to AL6 at preventing further parasitaemia (*high quality evidence*), and although PCR-adjusted treatment failure was below 5% for both ACTs it was consistently lower with DHA-P (*high quality evidence*). DHA-P has a longer prophylactic effect on new infections which may last for up to 63 days (*high quality evidence*).

In Asia and Oceania, no differences in treatment failure have been shown at day 28 (*moderate quality evidence*), or day 63 (*low quality evidence*).

DHA-P and AL6 appear to have similar adverse effect profiles (*moderate quality evidence*). DHA-P was associated with borderline prolongation of QTc interval but no difference was seen in prolonged QTc (*low quality evidence*) and no cardiac arrhythmias were reported.

DHA-P versus artesunate plus mefloquine

In Asia, during 28 days follow-up, DHA-P is as effective as AS+MQ at preventing further parasitaemia (*high quality evidence*). Once adjusted by PCR to exclude new infections, treatment failure at day 28 was below 5% for both ACTs in all eight trials, but lower with DHA-P in two trials from sites with multi-drug resistant *P. falciparum* (*high quality evidence*). Both combinations contain partner drugs with very long half-lives and no consistent difference in preventing new infections has been seen between drugs over 63 days follow-up (*moderate quality evidence*).

In the only trial from South America, there were fewer recurrent parasitaemias over 63 days with AS+MQ (*low quality evidence*), but there was no difference between treatments once adjusted by PCR for new infections (*low quality evidence*).

Compared to AS+MQ, DHA-P is associated with reduced nausea, vomiting, dizziness, sleeplessness, and palpitations (*moderate quality evidence*). The only notable adverse event associated with DHA-P was an increased frequency of prolongation of the QTc interval (*low quality evidence*), however no cardiac arrhythmias were reported in these trials.

Overall completeness and applicability of evidence

DHA-P is one of the most studied ACTs, and we included 27 trials in this review, which enrolled 16,382 adults and children with uncomplicated malaria. Notably, these trials excluded infants aged less than six months and pregnant women, and further safety data is required for these groups.

The efficacy of DHA-P against uncomplicated *P. falciparum* malaria in adults and children however is now well established, and although there is only limited data from South America, it is likely that the findings of this review can be applied worldwide.

Despite the high efficacy against asexual parasitaemia, DHA-P appears to have a reduced efficacy against gametocytes. Compared to DHA-P, both AS+MQ and AL6 reduce the carriage of gametocytes during the first 14 days post-treatment. This deficiency has been discussed in the literature, and it is likely due to a relative underdosing of the artemisinin derivative in the combination. The clinical significance of this effect remains unclear as gametocyte carriage is only an indirect measure of transmission potential. Furthermore, any increased risk of transmission in the early period after treatment may be offset by the later improved prophylactic effect of DHA-P.

DHA-P has been available and in use for several years despite the lack of a WHO prequalified formulation manufactured according to Good Manufacturing Practices Standards (GMP), and concerns about the stability and shelf-life of the dihydroartemisinin combination (Jansen 2010; Schmatz 2010). However, the Eurartesim® formulation evaluated by Bassat 2009 AF and Valecha 2010 AS has now been registered and approved for use by the European Medicines Agency (EMA) (European Medicines Agency 2011).

The potential for prolongation of the QTc interval is the most notable adverse effect. This was noted in the EMA's report where they advised that DHA-P should not be used in people who have, or are at risk of, QTc interval prolongation or cardiac arrhythmias, and should not be taken with other drugs which prolong the QTc interval (European Medicines Agency 2011). No participants were reported to have experienced confirmed cardiac arrhythmias in these studies.

Systematic reviews in infectious diseases also need to consider the possibility of changing drug effects over time as drug resistance patterns change and develop. In this review, we partially explored this possibility by presenting all forest plots with trials arranged in chronological order, but we found no evidence of a decline in efficacy over time. However, a systematic review may not be the most appropriate way to examine these effects, as RCTs tend to be conducted for new drugs with little research interest once they are well established. Selection of first and second line antimalarials should therefore take into account other knowledge on antimalarial resistance, such as that produced by the WorldWide Antimalaria Resistance Network (WWARN 2013).

Quality of the evidence

We assessed the quality of the evidence in this review using the GRADE approach and presented the evidence in six summary of findings tables for efficacy (Summary of findings for the main comparison; Table 12; Table 13; Table 11; Table 14; Table 15), and in three summary of findings tables for adverse events (in Appendix 3).

The evidence that DHA-P is at least as effective as AS+MQ in Asia was of high quality. There was some statistical heterogeneity, with two trials (predominantly from trial sites in Thailand) finding slightly higher levels of treatment failure with AS+MQ. This may be a consequence of resistance to mefloquine in the area and was not considered sufficient to downgrade the evidence.

The evidence for superiority of DHA-P over AL6 in Africa was of high quality, with no reason to downgrade for risk of bias, inconsistency, indirectness, or imprecision. It should be noted that both DHA-P and AL6 performed better than the WHO standard of 5% PCR-adjusted treatment failure at day 28 in all trials. The choice between DHA-P and AL6 may therefore be based more on considerations of adherence and cost, rather than efficacy.

We also assessed the quality of evidence on comparative adverse effects and presented these in Appendix 3. In general, the evidence was of moderate to low quality, meaning we can have reasonable confidence in some of these effects.

Agreements and disagreements with other studies or reviews

We found three recent systematic reviews of DHA-P (Keating 2012; Naing 2013 & WWARN 2013b), and reviewed the public assessment report of Eurartesim® by the EMA (European Medicines Agency 2011).

The most recent systematic review (Naing 2013) includes 26 of the 27 trials we included in this review and reaches very similar conclusions: "DHA-P is non-inferior to other currently used ACTs such as AS+MQ and AL6" and "the better safety profile of DHA-P and once-daily dosage improves adherence. For these reasons, DHA-P has the potential to become a first-line antimalarial drug".

The second review (Keating 2012) is more narrative and focuses on the Eurartesim® formulation registered with the EMA. The review contains an extensive discussion of the effects of the formulation on the QTc interval, and the author concludes that "there are currently no data signalling that DHA-P is associated with clinically significant arrhythmias". Similarly, the EMA public report concludes that "Treatment emergent QTc prolongation was asymptomatic in all cases", and "The magnitude of QTc prolongation is reduced if dosing occurs between meals". Conditional for registration, the pharmaceutical company agreed to undertake further post-marketing evaluation of the effects of DHA-P on the QTc interval and the potential for arrhythmias (European Medicines Agency 2011).

The third review (WWARN 2013b) was based on individual patient data from 24 published and two unpublished studies. The analysis paid particular attention to the relationship between age, the drug dose administered, and treatment efficacy. The authors report that treatment failure following DHA-P was highest in young children (aged between one and five years), and conclude that this is related to significant underdosing of both dihydroartemisinin and piperaquine in this age group, and to different pharmacokinetics in young children. On this basis, some further dose optimization of this combination is underway.

AUTHORS' CONCLUSIONS

Implications for practice

In Africa, DHA-P seems to reduce treatment failure compared to AL6, although it should be noted that AL6 also performed above the WHO standard of 95% cure rate in all these trials. DHA-P therefore represents an effective alternative with a simplified dosing regimen, and a longer post-treatment prophylactic effect.

In Asia, DHA-P appears to be as effective as the widely used AS+MQ, and is better tolerated. This may promote DHA-P to become the first line treatment option.

Implications for research

The efficacy of DHA-P is now well established. Future research should concentrate on safety surveillance, particularly in infants and pregnant women, and further appraisal of the potential effects on cardiac conduction.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Adam 2010 SDN

Methods	Trial design: An open label RCT Follow-up: Temperature and blood smears on days 1, 2, 3, 7, 14, 21, and 28. Haemoglobin concentrations (Hb) measured on days 0 and 28 Adverse event monitoring: Participants requested to attend the health centre any time they felt unwell. During follow-up participants were asked about the presence of adverse effects that might be expected from treatment (for example, nausea, vomiting). These were considered treatment-related if they had not been reported at the participant's first presentation
Participants	Number of participants: 160 Inclusion criteria: Age ≥ 6 months, uncomplicated *P. falciparum* mono-infection, axillary temperature > 37.5°C or a history of fever within the preceding 24 hrs, able to take oral treatment, informed consent Exclusion criteria: Severe or complicated malaria, severe concomitant pathology or other illness needing medical follow-up incompatible with the trial, allergy to one of the trial drugs, use of one of the trial drugs in the preceding 28 days, pregnancy
Interventions	1. DHA-P, fixed dose combination, 40 mg/320 mg adult tablets, 20 mg/160 mg children's tablets (Duo-Cotecxin: Beijing) • 5 to 9 kg half an adult tablet (or 1 children's tablet) each day for 3 days • 10 to 19.9 kg 1 adult tablet (or 2 children's tablets) each day for 3 days • 20 to 40 kg 2 adult tablets (or 4 children's tablets) each day for 3 days • > 40 kg 3 adult tablets (or 6 children's tablet) each day for 3 days • (Equivalent to daily doses of about 2.4 mg dihydroartemisinin/kg and 20 mg piperaquine/kg) 2. Artemether-lumefantrine, fixed dose combination, 20 mg/120 mg (Coartem: Novartis) • 5 to 14 kg 1 tablet twice daily for 3 days • 15 to 24 kg 2 tablets twice daily for 3 days • 25 to 34 kg 3 tablets twice daily for 3 days • ≥ 35 kg 4 tablets twice daily for 3 days All doses were supervised.
Outcomes	1. ACPR at day 28, PCR-adjusted and PCR-unadjusted 2. Gametocyte carriage 3. Adverse events Not included in this review: 1. Fever clearance time 2. Parasite clearance time
Notes	Country: Sudan Setting: Elmouraf health centre, Sinnar Transmission: Unstable transmission Resistance: "Multiple drug resistance"

Adam 2010 SDN (*Continued*)

	Dates: Dec 2009 to Feb 2010 Funding: Beijing Holley-Cotec Pharmaceuticals	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Block-randomization using a concealed envelope system was used to allocate each patient to one of the two treatment arms". Block size was unclear
Allocation concealment (selection bias)	Unclear risk	Used concealed envelopes, unclear if they were sequentially numbered or opaque
Blinding for microscopy outcomes (performance bias and detection bias)	Low risk	"all the slides were double-checked blindly".
Blinding for adverse events (performance and detection bias)	High risk	Trial described as "open".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low losses to follow-up in both groups (6. 3% DHA-P versus 7.5% AL6)
Selective reporting (reporting bias)	Low risk	The WHO recommends 42 day follow-up in studies of AL6. Day 28 outcomes may underestimate treatment failure with AL6
Other bias	Unclear risk	The role of the trial sponsor was not described.

Agarwal 2013 KEN

Methods	Trial design: An open label RCT Follow-up: Followed up for 42 days and asked to return on days 1, 2, 3, 7, 14, 21, 28, 35, and 42 after enrolment or at any day if ill. Clinical assessment and blood smear at each visit. Hb measured on days 0, 7, 14, 28, and 42 Adverse event monitoring: Not reported. "Adverse events investigated and addressed"
Participants	Number of participants: 274 Inclusion criteria: Children aged 6 to 59 months with axillary temperature $\geq$ 37.5 °C or history of fever in preceding 48 hrs, weight $\geq$ 5.0 kg, parasitaemia, residing within 10 km of Siaya District Hospital, written informed consent Exclusion criteria: Lethargy, convulsions, persistent vomiting, inability to drink, signs of severe malaria, severe anaemia (Hb < 5 g/dL), known hypersensitivity to trial drugs, presence of chronic medical conditions, treatment with any anti-malarial in preceding two weeks, previous enrolment in any malaria trial, severe malnutrition (weight-for-age $\leq$ 3 standard deviations below mean for gender according to WHO standards)

Interventions	1. DHA-P, fixed dose combination, 20 mg/160 mg tablets (DuoCotexin: Beijing Holley-Cotec) • 5 to 6 kg: one half tablet daily • 7 to 9 kg: one tablet daily • 10 to 14 kg: two tablets on day 0 then one tablet on days 1 and 2 • 15 to 19 kg: two tablets daily 2. Artemether-lumefantrine, fixed dose combination, 20 mg/120 mg (Coartem: Novartis) • 5 to 14 kg 1 tablet twice daily for 3 days • 15 to 24 kg 2 tablets twice daily for 3 days • 25 to 34 kg 3 tablets twice daily for 3 days All doses, except AL evening doses, administered under direct supervision
Outcomes	1. ACPR at days 28 and 42, PCR-unadjusted and PCR-adjusted 2. Mean change in Hb from baseline to day 28 3. Adverse events Not included in this review: 1. Fever clearance 2. Parasite clearance
Notes	Country: Kenya Setting: district hospital in western Kenya Transmission: Holoendemic with high transmission and two seasonal peaks, April to July and November to December Resistance: Not reported Dates: Oct 2010 to Aug 2011 Funding: KEMRI/CDC Research and Public Health Collaboration, Beijing Holley-Cotec provided DHA-P free of charge

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"children were block randomized in fixed blocks of ten to treatment"
Allocation concealment (selection bias)	Unclear risk	None described.
Blinding for microscopy outcomes (performance bias and detection bias)	Low risk	"All microscopists were blinded to the treatment arm".
Blinding for adverse events (performance and detection bias)	Unclear risk	No other blinding reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	Percentage withdrawn from analysis high in both treatment groups (17.5% DHA-P versus 18.2% AL)

Agarwal 2013 KEN *(Continued)*

Selective reporting (reporting bias)	Low risk	All WHO outcomes reported.
Other bias	Low risk	No other forms of bias identified.

Arinaitwe 2009 UGA

Methods	Trial design: An open label RCT Follow-up: Blood smears taken on days 0, 2, 3, 7, 14, 21, and 28 after each episode and any time they felt ill. Follow-up continued for up to one year Adverse event monitoring: Clinicians assessed participants for adverse events using standardized criteria at each follow-up visit. Passive monitoring was carried out for up to 63 days after treatment. Adverse events were defined as any untoward medical occurrence, regardless of its suspected relationship to the trial drugs, as per International Conference of Harmonization guidelines. Adverse events were graded as mild, moderate, severe, or life threatening
Participants	Number of participants: 232, with 671 episodes of uncomplicated falciparum malaria treated. All episodes treated were included in the analysis Inclusion criteria: For enrolment in the trial cohort: age 6 weeks to 12 months, HIV status of mother and child documented, living within a 30 km radius of the trial clinic, currently breast-feeding if HIV exposed, and informed consent including consent to come to the trial clinic for any illness and avoid medications given outside of the trial. For randomization: uncomplicated malaria diagnosed by positive blood smear after documented fever of $\geq$ 38.0 °C or history of fever in the past 24 hrs, age $\geq$ 4 months, weight $\geq$ 5 kg Exclusion criteria: Active medical problems requiring inpatient evaluation. For withdrawal from trial cohort: movement outside trial area, inability to tolerate trial drugs, withdrawal of informed consent, inability to be located for > 60 days, or inability to adhere to trial procedures and schedule

Interventions	1. DHA-P, fixed dose combination, 40 mg/320 mg tablets (Duocotecxin: Holley Pharm)
	    ● Target daily dose 6.4 mg/kg dihydroartemisinin and 51.2 mg/kg piperaquine given in three equally divided daily doses to the nearest quarter tablet.
	2. Artemether-lumefantrine, fixed dose combination, 20 mg/120 mg (Coartem: Novartis)
	    ● 5 to 14 kg 1 tablet twice daily for 3 days
	    ● 15 to 24 kg 2 tablets twice daily for 3 days
	Only the first daily dose supervised. Subsequent episodes of malaria occurring > 14 days after a previous episode were treated with the assigned trial drug

Outcomes	1. Recurrent falciparum parasitaemia at day 28, 42, 63, PCR-unadjusted and PCR-adjusted 2. Gametocyte carriage 3. Mean change in Hb from baseline to day 28 4. Adverse events Not included in this review: 1. Incidence of malaria after randomization 2. Fever clearance

Arinaitwe 2009 UGA (*Continued*)

	3. Parasite clearance
Notes	Country: Uganda Setting: Enrolled from local antenatal clinics in Tororo Transmission: High transmission Resistance: Not reported Dates: Aug 2007 to Jul 2008 Funding: Doris Duke Charitable Foundation and Puget Sound Partners in Global Health. Holleypharm provided DHA-P free of charge

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A 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 for microscopy outcomes (performance bias and detection bias)	Low risk	No blinding of microscopists reported, but all slides were re-read by a second microscopist, and a third microscopist resolved discrepancies
Blinding for adverse events (performance and detection bias)	High risk	Described as "open-label".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar low drop out in both groups (1.7% DHA-P versus 1.6% AL6)
Selective reporting (reporting bias)	Low risk	All listed outcomes reported.
Other bias	Low risk	This trial randomized individuals to an ACT and then followed them up through multiple treatment episodes. The data presented is for the all malaria episodes reported during the trial period

Ashley 2004a THA

Methods	Trial design: A 3-arm RCT
	Follow-up: All patients admitted to hospital for 28 days, oral temperature taken every 6 hrs, parasite counts 12-hourly until negative then daily for 28 days
	Adverse event monitoring: Adverse events defined as signs or symptoms that occurred or became more severe after treatment started. All patients had full blood counts, urea, electrolytes, creatinine, and liver function tests at days 0 and 7
Participants	Number of participants: 134
	Inclusion criteria: Age > 14 yrs, weight > 40 kg, symptoms of malaria, *P. falciparum* parasitaemia, informed consent.
	Exclusion criteria: Pregnancy or lactation, signs or symptoms of severe malaria, > 4% of red blood cells parasitized, contraindication to mefloquine, treatment with mefloquine in the previous 60 days, sulphonamides or 4-aminoquinolones present in urine on admission
Interventions	1. DHA-P, fixed dose combination (Artekin: Holleykin)
	• Total dose: 6 mg/kg DHA and 48 mg/kg P in 4 divided doses at 0, 8, 24, and 48 hrs
	2. Artesunate plus mefloquine, loose combination (Artesunate: Guilin, Mequin: Atlantic)
	• AS 4 mg/kg once daily for 3 days
	• MQ 8 mg/kg once daily for 3 days
	All doses were supervised.
Outcomes	1. Cure rate at day 28, all reappearances of parasites presumed to be recrudescences as patients hospitalized for duration
	2. Adverse events
	Not included in this review:
	1. Fever clearance time
	2. Parasite clearance time
Notes	Country: Thailand
	Setting: Bangkok Hospital for Tropical Diseases
	Transmission: Low transmission
	Resistance: Multiple-drug resistance
	Dates: Jul 2002 to Apr 2003
	Funding: Mahidol University, Tak Malaria Initiative Project, supported by Bill and Melinda Gates Foundation, Wellcome Trust of Great Britain

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomisation was computer generated (STATA; version 7; Statacorp)". Randomized in blocks of six
Allocation concealment (selection bias)	Unclear risk	"The treatment allocation was concealed in sealed envelopes labelled with the study code", unclear if these were sequentially

Ashley 2004a THA   (*Continued*)

		numbered or opaque
Blinding for microscopy outcomes (performance bias and detection bias)	Low risk	"Laboratory staff reading the blood smears had no knowledge of the treatment received"
Blinding for adverse events (performance and detection bias)	Unclear risk	No other blinding described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar loss to follow-up in all groups (10. 6% DHA-P versus 11.9% AS+MQ)
Selective reporting (reporting bias)	Low risk	The WHO recommends 63 days follow-up in studies of AS+MQ. Day 28 outcomes are likely to underestimate treatment failure with AS+MQ and DHA-P
Other bias	Low risk	No other sources of bias identified.

Ashley 2004b THA

Methods	Trial design: A RCT Follow-up: Temperature and blood smears daily until clearance of fever and parasites, then weekly attendance until day 63 Adverse event monitoring: Adverse events defined as signs or symptoms that occurred or became more severe after treatment started. A subset of 55 patients in the DHA-P group had full blood counts, urea, electrolyte, creatinine and liver function tests at days 0 and 7. Thirty-two patients from the DHA-P group also had ECG monitoring before and after treatment
Participants	Number of participants: 355 Inclusion criteria: Age 1 to 65 yrs, symptomatic *P. falciparum* parasitaemia, informed consent Exclusion criteria: Pregnancy or lactation, signs or symptoms of severe malaria, > 4% of red blood cells parasitized, contraindication to mefloquine, treatment with mefloquine in the previous 60 days

Interventions	1. DHA-P, fixed dose combination (Artekin: Holleykin)
	   • Total dose: 6 mg/kg DHA and 48 mg/kg P in 4 divided doses at 0, 8, 24, and 48 hrs
	 2. Artesunate plus mefloquine, loose combination (Artesunate: Guilin, Mequin: Atlantic)
	   • AS 4 mg/kg once daily for 3 days
	   • MQ 8 mg/kg once daily for 3 days
	 All doses were supervised.

Outcomes	1. Cure rate at day 63, PCR-adjusted and PCR-unadjusted 2. *P. vivax* during follow-up, and mean time to reappearance 3. Gametocyte development during follow-up 4. Mean haematocrit at days 0 and 7

Ashley 2004b THA (*Continued*)

  5. Adverse events
Not included in this review:
  1. Fever clearance time
  2. Parasite clearance time

Notes	Country: Thailand Setting: Four clinics on the Thai-Myanmar border Transmission: Unstable low and seasonal transmission Resistance: Multiple-drug resistance Dates: Jul 2002 to Apr 2003 Funding: Wellcome Trust of Great Britain

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomisation was computer generated (STATA; version 7; Statacorp)". Randomized in blocks of 9
Allocation concealment (selection bias)	Unclear risk	"The treatment allocation was concealed in sealed envelopes labelled with the study code", unclear if these were sequentially numbered or opaque
Blinding for microscopy outcomes (performance bias and detection bias)	Low risk	"Laboratory staff reading the blood smears had no knowledge of the treatment received"
Blinding for adverse events (performance and detection bias)	Unclear risk	No other blinding described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar losses to follow-up in all groups (12. 8% DHA-P versus 13.6% AS+MQ)
Selective reporting (reporting bias)	Low risk	All WHO outcomes reported.
Other bias	Low risk	No other sources of bias identified.

Ashley 2005 THA

Methods	Trial design: A 3-arm RCT Follow-up: Temperature and blood smears daily until clearance of fever and parasites, then weekly attendance for examination, symptom enquiry, malaria smear and haematocrit until day 63 Adverse event monitoring: Adverse events defined as signs or symptoms that occurred or became more severe after treatment started. Symptoms were screened at each visit
Participants	Number of participants: 499 Inclusion criteria: Age 1 to 65 yrs, symptomatic *P. falciparum* mono-infection or mixed infections, informed consent Exclusion criteria: Pregnancy or lactation, signs or symptoms of severe malaria, > 4% of red blood cells parasitized, treatment with mefloquine in the previous 60 days
Interventions	1. DHA-P, fixed dose combination (Artekin: Holleykin) • Total dose: 6.4 mg/kg DHA and 51.2 mg/kg P in 4 divided doses at 0, 8, 24, and 48 hrs 2. DHA-P, fixed dose combination (Artekin: Holleykin) • Total dose: 6.4 mg/kg DHA and 51.2 mg/kg P in 3 divided doses at 0, 24, and 48 hrs 3. Artesunate plus mefloquine, loose combination (Artesunate: Guilin, Mequin: Atlantic) • AS 4 mg/kg once daily for 3 days • MQ 8 mg/kg once daily for 3 days All doses supervised.
Outcomes	1. Cure rate at day 63, PCR-adjusted and PCR-unadjusted 2. *P. vivax* during follow-up, and mean time to reappearance 3. Gametocyte development during follow-up 4. Mean haematocrit at days 0 and 7 5. Adverse events Not included in this review: 1. Fever clearance time 2. Parasite clearance time
Notes	Country: Thailand Setting: Six clinics on the Thai-Myanmar border Transmission: Unstable low and seasonal transmission Resistance: Multiple-drug resistance Dates: Nov 2004 to Jun 2005 Funding: DnDi, European Union International Co-operation programme, Médecins sans Frontières, WHO/TDR, Wellcome Trust of Great Britain

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomisation list was generated using STATA; version 7 (Stata)". Randomized in blocks of nine

Ashley 2005 THA *(Continued)*

Allocation concealment (selection bias)	Unclear risk	"The treatment allocation was concealed in sealed envelopes labelled with the study code", unclear if these were sequentially numbered or opaque
Blinding for microscopy outcomes (performance bias and detection bias)	Low risk	"Laboratory staff reading the blood smears had no knowledge of the treatment received"
Blinding for adverse events (performance and detection bias)	Unclear risk	No other blinding described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up were low in all groups (4.2% DHA-P versus 4.8% AS+MQ)
Selective reporting (reporting bias)	Low risk	All WHO outcomes reported. Two patients were considered to be early treatment failures by the reviewers and reclassified as such. This was not clearly stated in the paper
Other bias	Low risk	No other sources of bias identified.

Bassat 2009 AF

Methods	Trial design: An open label RCT (non-inferiority). Follow-up: Children were kept at the health facility for the three day treatment period, and then returned on days 7, 14, 21, 28, 35, and 42, and any time symptoms occurred, for clinical assessment and blood smears. Haematological and biochemical assessments were carried out at enrolment, days 3, 28, and 42 and at clinician request Adverse event monitoring: Monitoring and recording of adverse events was carried out throughout the trial. A 12-lead ECG was performed at enrolment and on days 2 and 7 to assess any QT/QTc interval prolongation
Participants	Number of participants: 1553 Inclusion criteria: Uncomplicated malaria, age 6 to 59 months, body weight > 5 kg, fever (axillary temperature ≥ 37.5 °C) or history of fever in the preceding 24 hrs, microscopically confirmed *P. falciparum* mono-infection, asexual parasite densities between 2,000 and 200,000/μL, informed consent Exclusion criteria: severe malaria or other danger signs, acute malnutrition (weight for height < 70% of the median National Center for Health Statistics/WHO reference), any other concomitant illness or underlying disease, contra-indication to trial drugs, ongoing antimalarial prophylaxis, ECG abnormality requiring urgent management
Interventions	1. DHA-P, fixed dose combination, 40 mg/320 mg tablets and 20 mg/160 mg tablets (Eurartesim®, Sigma-Tau) • Daily dose of 2.25 mg/kg dihydroartemisinin and 18 mg/kg piperaquine, rounded up to the nearest half tablet

Bassat 2009 AF *(Continued)*

	2. Artemether-lumefantrine, fixed dose combination, 20 mg/120 mg (Coartem: Novartis) • 5 to 14 kg 1 tablet twice daily for 3 days • 15 to 24 kg 2 tablets twice daily for 3 days • 25 to 34 kg 3 tablets twice daily for 3 days All doses were supervised.
Outcomes	1. Adequate clinical and parasitological response on days 14, 28, and 42, PCR-adjusted and PCR-unadjusted 2. Gametocyte presence and clearance 3. Hb changes from baseline to day 28 4. Adverse events Not included in this review: 1. Fever clearance time 2. Parasite clearance time
Notes	Country: Burkina Faso, Kenya, Mozambique, Uganda, and Zambia Setting: Four rural sites and one peri-urban site. Transmission: Malaria mesoendemic at all sites. Two sites had high transmission in one period of the year (Jun to Dec or Nov to May), three others had perennial malaria with two sites having two peak seasons and one with marked seasonality (Oct to Apr) Resistance: Documented resistance to chloroquine ranged from 35% in Burkina Faso to 81% in Uganda Dates: Aug 2005 to Jul 2006 Funding: Medicine for Malaria Venture and Sigma-Tau I.F.R. SpA (Rome)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A randomisation list stratified by country was generated by an independent off site contract research organisation"
Allocation concealment (selection bias)	Low risk	"Each treatment allocation concealed in opaque sealed envelopes that were opened only after the patient's recruitment"
Blinding for microscopy outcomes (performance bias and detection bias)	Low risk	"assessment of the primary end-point were made by staff blinded to the treatment assignment and before availability of the PCR results"
Blinding for adverse events (performance and detection bias)	High risk	Described as 'open label'. ECG assessment were interpreted in a blinded manner
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number excluded from primary analysis similar between groups (7.5% DHA-P versus 9.7% AL6)

Bassat 2009 AF   *(Continued)*

Selective reporting (reporting bias)	Low risk	All outcomes listed in the trial protocol were assessed.
Other bias	Unclear risk	"Employees of Sigma-Tau participated in study design, data entry, collection and analysis of data". "An author independent of the sponsor, Umberto D'Alessandro, had access to the primary dataset and takes responsibility for the analyses and manuscript as a whole"

Grande 2007 PER

Methods	Trial design: An open-label RCT Follow-up: Days 0, 1, 2, 3, 7, 14, 21, 28, 35, 42, 49, 56, and 63 or any other day they became ill, for a clinical assessment and malaria film. PCV measurement day 0, 7, 14 and 63. *P. vivax* treated with CQ. Adverse event monitoring: Assessed at each follow-up visit, an adverse event defined as any unfavourable and unintended sign, symptom or disease temporally associated with the drug administered. Complete blood count, liver, and renal function tests at days 0 and 7
Participants	Number of participants: 522 Inclusion criteria: Age 5 to 60 yrs, fever > 37.5 °C or history of fever in the previous 24 hrs, *P. falciparum* mono-infection 1000 to 200,000/μL. Exclusion criteria: Pregnancy or lactation, severe malaria, any concomitant illness or underlying disease, contraindication to any of the trial drugs, history of treatment with mefloquine in the previous 60 days or chloroquine, primaquine or quinine in previous 14 days
Interventions	1. DHA-P, fixed dose combination (Artekin: Holleykin) 　● Total dose: 6.3 mg/kg DHA and 50.4 mg/kg PQP in 3 divided doses, given once daily for 3 days 2. Artesunate plus mefloquine, loose combination (Artesunate: Guilin, Lariam: Hoffman La-Roche) 　● AS 4 mg/kg once daily for 3 days 　● MQ 8 mg/kg once daily for 3 days All doses were supervised.
Outcomes	1. Day 63 cure rate PCR-adjusted and PCR-unadjusted 2. *P. vivax* during follow-up 3. Gametocyte prevalence at day 0, 7, 14, 21, and 28 4. Gametocyte development during follow-up 5. Adverse events Not included in this review: 1. Fever clearance 2. Parasite clearance

Grande 2007 PER (*Continued*)

Notes	Country: Peru Setting: Nine rural health posts Transmission: Low malaria transmission Resistance: High CQ and SP resistance Dates: July 2003 to July 2005 Funding: Directorate-General for Development and Cooperation of the Belgian Government

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomized in blocks of 10". No further details given.
Allocation concealment (selection bias)	Low risk	"Sealed opaque envelopes were opened only after the final decision to recruit the patient had been made"
Blinding for microscopy outcomes (performance bias and detection bias)	Unclear risk	No comment on blinding of laboratory staff.
Blinding for adverse events (performance and detection bias)	High risk	An open-label trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar loss to follow-up in both groups (8. 7% DHA-P versus 5.9% AS+MQ)
Selective reporting (reporting bias)	Low risk	All WHO outcomes reported.
Other bias	Low risk	No other sources of bias identified.

Hasugian 2007 IDN

Methods	Trial design: An open label RCT Follow-up: Daily until fever and parasites cleared then weekly until day 42, for a physical examination, a symptom questionnaire and malaria film. Hb measured on days 0, 7, and 28 Adverse event monitoring: Assessed at each follow-up visit
Participants	Number of participants: 340 Inclusion criteria: Age > 1 yr, weight > 5 kg, slide confirmed malaria (*P. falciparum*, *P. vivax* or both), fever or history of fever in the preceding 48 hrs Exclusion criteria: Pregnancy or lactation, danger signs or signs of severe malaria, > 4% red blood cells parasitized, concomitant disease that required hospital admission

Hasugian 2007 IDN   *(Continued)*

Interventions	1. DHA-P, fixed dose combination (Artekin: Holley)
	  • Total dose: 6.75 mg/kg DHA and 54 mg/kg PQP in 3 divided doses given once daily for 3 days
	2. Artesunate plus amodiaquine, loose combination (Arsumax: Guilin, Flavoquine: Aventis)
	  • AS 4 mg/kg once daily for 3 days
	  • AQ 10 mg/kg once daily for 3 days
	All doses supervised

Outcomes	1. Parasitological failure on days 42 and 28, PCR-adjusted and PCR-unadjusted 2. Parasitological failure with *P. vivax* on days 42 and 28 3. Gametocyte carriage after treatment 4. Anaemia at days 0, 7, and 28 5. Adverse events Not included in the review: 1. Fever clearance 2. Parasite clearance
Notes	Country: Indonesia Setting: Rural clinics Transmission: Unstable Resistance: Chloroquine and SP resistance Dates: Jul 2005 to Dec 2005 Funding: Wellcome Trust - National Health and Medical Research Council

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A randomisation list was generated in blocks of 20 by an independent statistician"
Allocation concealment (selection bias)	Low risk	"Treatment allocation concealed in an opaque, sealed envelope that was opened once the patient had been enrolled"
Blinding for microscopy outcomes (performance bias and detection bias)	Low risk	"All slides were read by a certified microscopist who was blinded to treatment allocation"
Blinding for adverse events (performance and detection bias)	High risk	An open-label trial.
Incomplete outcome data (attrition bias) All outcomes	High risk	The primary outcome data are unpublished data including only participants with *P. falciparum* mono or co-infection at baseline. High losses to follow-up in both groups at day 42 (21% DHA-P versus 24.5 % AL6),

Hasugian 2007 IDN (*Continued*)

		moderate at day 28 (16.6% DHA-P versus 18.8 % AL6)
Selective reporting (reporting bias)	Low risk	All WHO outcomes reported. Day 42 outcomes may underestimate failure with DHA-P due to its long half-life
Other bias	Low risk	No other sources of bias identified.

Janssens 2007 KHM

Methods	Trial design: An open label RCT Follow-up: Monitored daily until fever and parasites cleared then weekly to day 63. Temperature, symptom questionnaire, malaria film, and haematocrit at each visit Adverse event monitoring: An adverse event defined as any new sign or symptom appearing after treatment started. At each visit a symptom questionnaire was completed
Participants	Number of participants: 464 Inclusion criteria: Age > 1 yr, axillary temp > 37.5 °C or history of fever, signs and symptoms of uncomplicated malaria, *P. falciparum* mono or mixed infections, written informed consent Exclusion criteria: Pregnancy or lactation, signs or symptoms of severe malaria, > 4% red blood cells parasitized, a history of convulsions or neuropsychiatric disorder, treatment with mefloquine in the past 60 days

Interventions	1. DHA-P, fixed dose combination, 40 mg/320 mg tablets (Artekin: Holleykin)
	   • Adult total dose: 6 mg/kg DHA and 48 mg/kg P in 4 divided doses, given at 0, 8, 24, and 48 hrs
	   • Children total dose: 6.4 mg/kg DHA + 51.2 mg/kg P in 4 divided doses, given at 0, 8, 24, 48 hrs
	2. Artesunate plus mefloquine, loose combination (Artesunate: Guilin, Mefloquine: Mepha)
	   • Adults: 100 mg AS plus 500 mg MQ twice daily on day 0, then 200 mg AS once daily on day 1 and day 2
	   • Children: AS 4 mg/kg once daily for 3 days plus 25 mg/kg MQ split into 2 doses on day 0
	All doses supervised.

Outcomes	1. Cure rate at days 63, 42, and 28, PCR-adjusted and PCR-unadjusted
	  2. *P. vivax* parasitaemia during follow-up
	  3. Mean haematocrit at day 0 and 63
	  4. Adverse effects
	Not included in the review:
	  1. Fever clearance
	  2. Parasite clearance

Notes	Country: Cambodia Setting: Rural health centres and outreach malaria clinics Transmission: Low and seasonal

Janssens 2007 KHM   (*Continued*)

| | | Resistance: Multiple-drug resistance
Dates: Oct 2002 to March 2003
Funding: Médecins sans Frontières |

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer generated randomisation (STATA version 8, Statacorp)"
Allocation concealment (selection bias)	Unclear risk	"Treatment allocations were concealed in sealed envelopes". No further details
Blinding for microscopy outcomes (performance bias and detection bias)	Unclear risk	No comment on blinding of laboratory staff.
Blinding for adverse events (performance and detection bias)	High risk	An open-label trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up balanced and low in both groups (9.3% DHA-P versus 10% AS+MQ)
Selective reporting (reporting bias)	Low risk	All WHO outcomes reported.
Other bias	Low risk	No other sources of bias identified.

Kamya 2007 UGA

Methods	Trial design: A single blind (outcome assessors) RCT Follow-up: Standardized history and examination and malaria film on days 0, 1, 2, 3, 7, 14, 21, 28, 35, 42 and any other day they felt unwell. Hb measured at day 0 and day 42 or day of failure. Anaemia was treated with ferrous sulphate and anthelminthics according to IMCI guidelines Adverse event monitoring: Assessed for any new or worsening event at each visit. An adverse event defined as any untoward medical occurrence, irrespective of its suspected relationship to the trial medications
Participants	Number of participants: 509 Inclusion criteria: Age 6 months to 10 yrs, weight > 5 kg, axillary temp > 37.5 °C or history of fever in the past 24 hrs, *P. falciparum* mono-infection 2000 to 200,000/μL, informed consent Exclusion criteria: Danger signs or signs of severe malaria, evidence of concomitant febrile illness, history of serious side effects to trial medication

Interventions	1. Artemether-lumefantrine, fixed dose combination, 20 mg/120 mg tablets (Coartem: Novartis)
	• 5 to 14 kg 1 tablet twice daily for 3 days
	• 15 to 24 kg 2 tablets twice daily for 3 days
	• 25 to 34 kg 3 tablets twice daily for 3 days
	• > 35 kg 4 tablets twice daily for 3 days
	2. DHA-P, fixed dose combination, 40 mg/320 mg tablets (Duocotexin: HolleyPharm)
	• Total dose: DHA 6.4 mg/kg + P 51.2 mg/kg in 3 divided doses, given once daily for 3 days
	• Plus placebo tablet in the evening to simulate twice daily dosing
	All doses supervised. All participants received a glass of milk after each dose
Outcomes	1. Risk of treatment failure at day 42, PCR-adjusted and unadjusted
	2. Non *falciparum* species during follow-up
	3. Gametocyte development during follow-up
	4. Mean increase in Hb at last day of follow-up
	5. Adverse events
	Not included in the review:
	1. Fever clearance
	2. Parasite clearance
Notes	Country: Uganda
	Setting: Rural health centre
	Transmission: Perennial holoendemic malaria with very high transmission intensity
	Resistance: Not reported
	Dates: Mar 2006 to July 2006
	Funding: US Centres for Disease Control, Malaria Consortium Drugman, DFID, DHA-P supplied by HolleyPharm

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A randomisation 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 randomisation list"
Blinding for microscopy outcomes (performance bias and detection bias)	Low risk	"Study physicians and laboratory personnel involved in assessing outcomes were blinded to treatment assignments"
Blinding for adverse events (performance and detection bias)	Low risk	Placebos were used to blind participants to treatment allocation. Trial physicians were also blinded

Kamya 2007 UGA *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Low losses to follow-up in both groups (0. 9% AL6 versus 0.9% DHA-P). A large number of participants were excluded after randomization for failing to meet the entry criteria
Selective reporting (reporting bias)	Low risk	All WHO outcomes reported. Day 42 outcomes may underestimate failure with DHA-P due to its long half-life
Other bias	Low risk	No other sources of bias identified.

Karema 2006 RWA

Methods	Trial design: A 3-arm open label RCT Follow-up: History, clinical signs and symptoms, and malaria film on days 0, 1, 2, 3, 7, 14, 21, and 28 and any other day they felt unwell. PCV measured at days 0 and 14 Adverse event monitoring: An adverse event defined as any unfavourable and unintended sign associated temporally with the use of the drug administered. Differential WBC count (and liver function tests at 1 site only) assessed at days 0 and 14
Participants	Number of participants: 762 Inclusion criteria: Age 12 to 59 months, weight > 10 kg, axillary temp > 37.5 °C or history of fever in the preceding 24 hrs, *P. falciparum* mono-infection 2000 to 200,000/ μL. Exclusion criteria: Severe malaria, any other concomitant illness or underlying disease, known allergy to trial drugs, clear history of adequate antimalarial treatment in the previous 72 hrs, PCV < 15%
Interventions	1. DHA-P, fixed dose combination, 40 mg/320 mg tablets (Artekin: Holleypharm) • Total dose: DHA 4.8 to 9.3 mg/kg + P 38.4 to 73.8 mg/kg in 3 divided doses, given once daily for 3 days 2. Artesunate plus amodiaquine, loose combination (Arsumax: Sanofi) • AS 4 mg/kg once daily for 3 days • AQ 10 mg/kg once daily for 3 days All doses supervised
Outcomes	1. ACPR at day 28, PCR-adjusted and PCR-unadjusted 2. Gametocyte prevalence during follow-up 3. Mean PCV at baseline and day 14 4. Adverse events Not included in this review: 1. Fever clearance 2. Parasite clearance
Notes	Country: Rwanda Setting: Peri-urban and rural health centres Transmission: Not reported

Karema 2006 RWA *(Continued)*

	Resistance: Not reported Dates: Oct 2003 to Apr 2004 Funding: Belgian Development Co-operation in collaboration with the Prince Leopold Institute of Tropical Medicine. DHA-P provided by Holleypharm

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomly allocated in blocks of 15", computer generated sequence (information from author)
Allocation concealment (selection bias)	Unclear risk	"Allocation of treatment was concealed until final recruitment'. No further details
Blinding for microscopy outcomes (performance bias and detection bias)	Low risk	"Laboratory technicians reading malaria slides did not know the treatment received"
Blinding for adverse events (performance and detection bias)	High risk	An open-label trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Very low losses to follow-up in all groups (0.8% DHA-P versus 0.4% AS+AQ)
Selective reporting (reporting bias)	Low risk	All WHO outcomes reported. Day 28 outcomes may underestimate failure with DHA-P due to its long half-life
Other bias	Low risk	No other sources of bias identified.

Karunajeewa 2008 PNG

Methods	Trial design: A 4-arm open label RCT Follow-up: Standardized follow-up including temperature and malaria film on days 0, 1, 2, 3, 7, 14, 28, and 42. Drug levels assayed on day 7 Adverse event monitoring: None described
Participants	Number of participants: 372 Inclusion criteria: Age 0.5 to 5 yrs, axillary temp > 37.5 °C or history of fever in the preceding 24 hrs, > 1000/µL asexual *P. falciparum* or > 250/µL asexual *P. vivax,P. ovale*, or *P. malariae*, informed consent Exclusion criteria: Features of severe malaria, evidence of another infection or coexisting condition including malnutrition, intake of trial drug in previous 14 days
Interventions	1. Artesunate plus sulfadoxine-pyrimethamine, loose combination (Sanofi-Aventis, Roche) • AS 4 mg/kg once daily for 3 days

	• SP 25/1.25 mg/kg once on the first day
	2. DHA-P, fixed dose combination, 40 mg/320 mg tablets (Beijing Holley-Cotec)
	  • DHA 2.5 mg/kg once daily for 3 days
	  • P 20 mg/kg once daily for 3 days
	3. Artemether-lumefantrine, fixed dose combination, 20 mg/120 mg tablets (Novartis), given with milk
	  • A 1.7 mg/kg twice daily for 3 days
	  • L 10 mg/kg twice daily for 3 day
	All doses supervised except the evening dose of AL6

Outcomes	1. ACPR (*P. falciparum*) at days 28 and 42, PCR-adjusted and PCR-unadjusted 2. ACPR (*P. vivax*) at day 42 3. Gametocyte prevalence during follow-up 4. Adverse events Not included in this review: 1. Fever clearance 2. Parasite clearance 3. Drug levels day 7
Notes	Country: Papua New Guinea Setting: Health centres Transmission: Holoendemic Resistance: CQ and SP Dates: Apr 2005 to Jul 2007 Funding: WHO Western Pacific Region, Rotary against Malaria in Papua New Guinea, National Health and Medical Research Council of Australia

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated randomised assignment with blocks of 24 for each site"
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding for microscopy outcomes (performance bias and detection bias)	Low risk	Microscopists were unaware of treatment assignments.
Blinding for adverse events (performance and detection bias)	High risk	An open label trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Moderate losses to follow-up in all groups (11.5% AS+SP versus 13.0% DHA-P versus 14.2% AL6)
Selective reporting (reporting bias)	Low risk	All WHO outcomes reported. Day 42 outcomes may underestimate failure with DHA-P due to its long half-life

Karunajeewa 2008 PNG *(Continued)*

Other bias	Low risk	No other sources of bias identified.

Krudsood 2007 THA

Methods	Trial design: An open label RCT Follow-up: Blood smears every 12 hrs until found to be negative and daily for 28 days. Haematological and biochemical samples, and urine examined on day 0, 1 and 3 and weekly for the 4 weeks trial period Adverse event monitoring: Regular physical examinations were conducted and assessment was done using non-suggestive questioning by investigators
Participants	Number of participants: 191 Inclusion criteria: Male and female patients with uncomplicated malaria confirmed by positive falciparum asexual blood smear, age $\geq$ 13 years, body weight $\geq$ 35kg, ability to take oral medication, agreement to stay in hospital for at least 28 days, informed consent Exclusion criteria: Pregnant or lactating women, severe malaria per WHO criteria, vomiting not allowing oral medication, concomitant systemic disease or disorder other than malaria requiring therapy, history of ingestion of antimalarials in preceding 14 days or with sulphonamides or 4-aminoquinolones in urine
Interventions	1. DHA-P, fixed dose combination, 40 mg/320 mg tablets (Artekin: Holleypharm) • Daily dose: DHA 2.0 mg/kg + P 15 mg/kg, given once daily for 3 days 2. Artemether-lumefantrine, fixed dose combination (Coartem: Novartis) • Daily dose: A 1.6 mg/kg + L 9.6 mg/kg, given twice daily for 3 days All doses supervised
Outcomes	1. Cure rate at day 28, PCR-unadjusted 2. Adverse events Not included in this review: 1. Fever clearance 2. Parasite clearance
Notes	Country: Thailand Setting: Hospital for tropical diseases Transmission: "No known malaria transmission" Resistance: Some resistance to *P. falciparum* reported in Southeast Asia reported Dates: Nov 2005 to June 2006 Funding: Mahidol University Research Grant

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported in the trial.
Allocation concealment (selection bias)	Unclear risk	Not reported.

Krudsood 2007 THA *(Continued)*

Blinding for microscopy outcomes (performance bias and detection bias)	Unclear risk	Blinding of microscopists not reported.
Blinding for adverse events (performance and detection bias)	High risk	Trial is 'open-label'.
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss to follow-up in one treatment group was high (15.5% DHA-P versus 13.8% AL6)
Selective reporting (reporting bias)	Low risk	All listed outcomes are reported.
Other bias	Low risk	No other sources of bias identified.

Mayxay 2006 LAO

Methods	Trial design: An open label RCT Follow-up: Temperature was measured every 6 hrs and patient reviewed daily until fever and parasites cleared then weekly until day 42 or anytime they felt unwell. At each visit a malaria film and haematocrit measurement was taken Adverse event monitoring: Potential adverse events were recorded at each visit
Participants	Number of participants: 220 Inclusion criteria: Age > 1 year, axillary temp > 37.5 °C or history of fever in the previous 3 days, *P. falciparum* mono-infection 1000 to 200,00/µL, were likely to stay in hospital until parasite clearance and complete 42 days follow-up, informed consent Exclusion criteria: Pregnancy or lactation, signs of severe malaria, antimalarials in the previous 3 days, contraindications to the trial drugs

Interventions	1. DHA-P, fixed dose combination, 40 mg/320 mg tablets (Artekin: Holleykin)
	  • Total dose: DHA 6.3 mg/kg + P 50.4 mg/kg in 3 divided doses, given once daily for 3 days
	2. Artesunate plus mefloquine, loose combination (Artesunate: Guilin, Lariam: Roche)
	  • AS 4 mg/kg once daily for 3 days
	  • MQ 15 mg base/kg on day 1 and 10 mg base/kg on day 2
	All doses supervised.

Outcomes	1. Cure rate at day 42, PCR-adjusted and PCR-unadjusted 2. *P. vivax* during follow-up 3. Adverse events Not included in the review: 1. Fever clearance time 2. Parasite clearance time 3. Gametocyte carriage after treatment
Notes	Country: Lao People's Democratic Republic (Laos) Setting: District clinic Transmission: Not reported

Mayxay 2006 LAO *(Continued)*

Resistance: Not reported
Dates: May 2004 to Sept 2004
Funding: Western Pacific Regional office of WHO, Wellcome Trust of Great Britain,
Artekin provided by Holleykin Pharmaceuticals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomized in blocks of 10". No further details given.
Allocation concealment (selection bias)	Low risk	"The treatment choice was kept in a sealed opaque envelope, which was opened only after the decision to recruit"
Blinding for microscopy outcomes (performance bias and detection bias)	Unclear risk	No comment on blinding of laboratory staff.
Blinding for adverse events (performance and detection bias)	High risk	An open-label trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low losses to follow-up in both groups (3. 6% DHA-P versus 1.8% AS+MQ)
Selective reporting (reporting bias)	Low risk	The WHO recommends 63 days follow-up in studies of AS+MQ. Day 42 outcomes are likely to overestimate the efficacy of the two drugs
Other bias	Low risk	No other sources of bias identified.

Mens 2008 KEN

Methods	Trial design: An open label RCT Follow-up: Malaria film and Hb level on days 0, 1, 2, 3, 7, 14, and 28, plus QT-NASBA for detection of sub-microscopic gametocytaemia Adverse event monitoring: Adverse events were recorded at each visit in the case record form. An adverse event defined as any unfavourable and unintended sign
Participants	Number of participants: 146 Inclusion criteria: Age 6 months to 12 years, axillary temp > 37.5 °C or history of fever, *P. falciparum* mono-infection 1000 to 200,000/μL, informed consent Exclusion criteria: Severe malaria, any other underlying illness
Interventions	1. DHA-P, fixed dose combination, 20 mg/160 mg tablets (Sigma-Tau) • 4 to 7 kg ½ tablet once daily for 3 days • 7 to 13 kg 1 tablet once daily for 3 days

Mens 2008 KEN   (*Continued*)

	• 13 to 24 kg 2 tablets once daily for 3 days • 24 to 35 kg 4 tablets once daily for 3 days 2. Artemether-lumefantrine, fixed dose combination, 20/120 mg tablets (Novartis) • 5 to 14 kg 1 tablet twice daily for 3 days • 15 to 24 kg 2 tablets twice daily for 3 days • 25 to 34 kg 3 tablets twice daily for 3 days All doses supervised and given with a glass of milk.
Outcomes	1. Recurrent parasitaemia at day 28, PCR-adjusted and PCR-unadjusted 2. Gametocyte prevalence during follow-up 3. Mean Hb at day 28 4. Adverse events Not included in this review: 1. Fever clearance 2. Parasite clearance
Notes	Country: Kenya Setting: Health centre Transmission: High transmission Resistance: Not reported Dates: Apr 2007 to Jul 2007 Funding: The Knowledge and Innovation Fund, Koninklijk Instituut voor de Tropen/ Royal Tropical Institute. DHA-P provided free of charge by Sigma-Tau

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A computer generated randomisation list".
Allocation concealment (selection bias)	Unclear risk	None described.
Blinding for microscopy outcomes (performance bias and detection bias)	Low risk	Microscopists were blinded to treatment allocation.
Blinding for adverse events (performance and detection bias)	Unclear risk	No other blinding described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low losses to follow-up in both groups (8. 2% DHA-P versus 8.2% AL6)
Selective reporting (reporting bias)	Low risk	The WHO recommends 42 days follow-up in studies of AL6. Day 28 outcomes may underestimate treatment failure with AL6 and DHA-P
Other bias	Low risk	No other sources of bias identified.

Ratcliff 2007 IDN

Methods	Trial design: An open-label RCT Follow-up: A symptom questionnaire, physical examination, malaria film and Hb measurement daily until fever and parasites cleared then weekly to day 42 Adverse event monitoring: A symptom questionnaire at each visit
Participants	Number of participants: 774 Inclusion criteria: Weight > 10 kg, fever or a history of fever in the preceding 48 hrs, slide confirmed malaria (*P. falciparum, P. vivax* or mixed infections) Exclusion criteria: Pregnancy or lactation, danger signs or signs of severity, parasitaemia > 4%, concomitant disease requiring hospital admission

Interventions	1. DHA-P, fixed dose combination, 40 mg/320 mg tablets (Artekin: Holleykin)
	  • Total dose: DHA 6.75 mg/kg + P 54 mg/kg in 3 divided doses, given once daily for 3 days
	2. Artemether-lumefantrine, fixed dose combination, 20 mg/120 mg tablets (Coartem: Novartis)
	  • 10 to 15 kg 1 tablet twice daily for 3 days
	  • 15 to 25 kg 2 tablets twice daily for 3 days
	  • 25 to 35 kg 3 tablets twice daily for 3 days
	  • > 35 kg 4 tablets twice daily for 3 days
	Only the first dose of each day was supervised. All participants advised to take each dose with a biscuit or milk

Outcomes	1. Parasitological failure at days 42 and 28, PCR-adjusted and PCR-unadjusted 2. *P. vivax* during follow-up 3. Gametocyte carriage after treatment 4. Anaemia during follow-up 5. Adverse events Not included in the review: 1. Fever clearance 2. Parasite clearance
Notes	Country: Indonesia Setting: Rural outpatient clinics Transmission: Unstable Resistance: Multiple-drug resistance Dates: Jul 2004 to Jun 2005 Funding: Wellcome Trust UK and National Health and Medical Research Council Australia

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A randomisation list was generated in blocks of 20 patients by an independent statistician"

Ratcliff 2007 IDN   (*Continued*)

Allocation concealment (selection bias)	Low risk	"With each treatment allocation concealed in an opaque sealed envelope". No further details given
Blinding for microscopy outcomes (performance bias and detection bias)	Low risk	The microscopists were blinded to treatment allocation.
Blinding for adverse events (performance and detection bias)	High risk	An open label trial.
Incomplete outcome data (attrition bias) All outcomes	High risk	The primary outcome data are unpublished data including only participants with *P. falciparum* mono or co-infection at baseline. Losses to follow-up were high in both groups at day 42 (28.4 % DHA-P versus 25.6 % AL6) and moderate at day 28 (19% DHA-P versus 17.6% AL6)
Selective reporting (reporting bias)	Low risk	All WHO outcomes reported. Day 42 outcomes may underestimate failure with DHA-P due to its long half-life
Other bias	Low risk	No other sources of bias identified.

Sawa 2013 KEN

Methods	Trial design: RCT Follow-up: Clinical assessment on days 1, 2, 3, 7, 14, 28, and 42 and any other time when child became ill. Blood smears taken on all follow-up days except day 1 Adverse event monitoring: Not reported
Participants	Number of participants: 298 Inclusion criteria: Microscopically confirmed *P. falciparum* infection with asexual parasite density of 1,000 to 200,000 parasites/μL, tympanic temperature of ≥ 37.5 °C or history of fever in preceding 24 hrs, age 6 months to 10 years, informed consent Exclusion criteria: Hb level of < 5 g/dL, presence of any other *Plasmodium* species, presence of other febrile disease, severe malaria, history of adverse events with trial drugs

Interventions	1. DHA-P, fixed dose combination, 40 mg/320 mg tablets (Duocotexin: Holley Pharm)
	  • Total dose: DHA 6.4 mg/kg + P 51.2 mg/kg in 3 equally divided doses, given once daily for 3 days
	  • Dose rounded off to nearest half tablet
	2. Artemether-lumefantrine, fixed dose combination, 20 mg/120 mg tablets (Coartem: Novartis)
	  • Half tablet per 5 kg body weight
	  • Dose rounded to nearest half tablet
	All doses were supervised. All participants advised to take each dose with fatty food to facilitate absorption

Sawa 2013 KEN (*Continued*)

Outcomes	1. Parasitological efficacy at days 42 and 28, PCR-adjusted and PCR-unadjusted 2. Gametocyte carriage after treatment Not included in the review: 1. Malaria transmission to mosquitoes
Notes	Country: Kenya Setting: Community setting Transmission: Moderate transmission intensity Resistance: None reported Dates: Apr to Jun 2009 Funding: Grants from the European Community's Seventh Framework Programme and the Bill and Melinda Gates Foundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A randomization list was generated for different age strata (<2 years, 2-5 years, and 5-10 years), using MS Excel"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment is not reported.
Blinding for microscopy outcomes (performance bias and detection bias)	Low risk	"Except for those involved in administering medication, all staff members engaged in the trial were blinded to the treatment arm to which each child was assigned"
Blinding for adverse events (performance and detection bias)	Low risk	All staff blinded were except those administering drugs.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low number of patients without outcomes in both groups (DHA-P 7.6%, AL6 5.2%)
Selective reporting (reporting bias)	Low risk	All WHO outcomes are reported.
Other bias	Low risk	No other sources of bias identified.

Smithuis 2006 MMR

Methods	Trial design: A 4-arm open-label RCT Follow-up: A symptom questionnaire, malaria film, and gametocyte count on days 0, 1, 2, 3, 7, 14, 21, 28, 35, and 42. Hb was measured on days 0 and 28 Adverse event monitoring: A symptom questionnaire at each visit
Participants	Number of participants: 652 Inclusion criteria: Age > 1 year, axillary temperature > 37.5 °C or history of fever in

Smithuis 2006 MMR (*Continued*)

	the previous 48 hrs, *P. falciparum* mono-infection 500 to 100,000 parasites/μL or co-infection with *P. vivax*, informed consent. Exclusion criteria: Pregnancy, signs of severe malaria, signs or symptoms of other diseases, history of taking mefloquine in the previous 2 months or any other antimalarial in the previous 48 hrs, history of psychiatric disease

Interventions	1. DHA-P, fixed dose combination, 40 mg/320 mg tablets (Artekin: Holleykin)
	  • Total dose: DHA 6.3 mg/kg + P 50.4 mg/kg in 3 divided doses, given once daily for 3 days
	    • Supervised
	2. DHA-P, fixed dose combination, 40 mg/320 mg tablets (Artekin: Holleykin)
	  • Total dose: DHA 6.3 mg/kg + P 50.4 mg/kg in 3 divided doses, given once daily for 3 days
	    • Unsupervised
	3. Artesunate plus mefloquine, loose combination (artesunate: Guilin, Lariam: Hoffman-La Roche)
	    • AS 4 mg/kg once daily for 3 days
	    • MQ 25 mg base/kg as a single dose on day 0
	    • Supervised
	4. Artesunate plus mefloquine, loose combination (artesunate: Guilin, Lariam: Hoffman-La Roche)
	    • AS 4 mg/kg once daily for 3 days
	    • MQ 25 mg base/kg as a single dose on day 0
	    • Unsupervised

Outcomes	1. Failure Rate at days 42 and 28, 42 PCR-unadjusted and PCR-adjusted 2. *P. vivax* during follow-up and median time to appearance 3. Gametocyte carriage at days 0, 7, 14, 21, and 28 4. Mean change in Hb from day 0 to day 28 5. Adverse events Not included in the review: 1. Fever clearance 2. Parasite clearance 3. New gametocyte appearance at day 7 and day 14
Notes	Country: Myanmar Setting: Rural village tracts Transmission: Seasonal with peaks in the monsoon season Nov to Jan and sometimes in the early monsoon, May to June Resistance: Very high rates of CQ and SP resistance Dates: Nov 2003 to Feb 2004 Funding: Médecins sans Frontières (Holland)

Risk of bias

Bias	Authors' judgement	Support for judgement

Smithuis 2006 MMR (*Continued*)

Random sequence generation (selection bias)	Low risk	Unmarked and sealed envelopes, containing the treatment allocation were drawn from a box
Allocation concealment (selection bias)	Unclear risk	"Unmarked and sealed envelopes". No further details given.
Blinding for microscopy outcomes (performance bias and detection bias)	Unclear risk	No comment on blinding of laboratory staff.
Blinding for adverse events (performance and detection bias)	High risk	An open label trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Very low losses to follow-up in both groups.
Selective reporting (reporting bias)	Low risk	The WHO recommends 63 days follow-up in studies of AS+MQ. Day 42 outcomes are likely to overestimate the efficacy of the two drugs
Other bias	Low risk	No other sources of bias identified.

Smithuis 2010 MMR

Methods	Trial design: A 5-arm open-label RCT Follow-up: Assessment done weekly for 9 weeks and at any other time they became ill. Hb was only measured on day 63 Adverse event monitoring: Specific procedures not reported.
Participants	Number of participants: 811 Inclusion criteria: Acute uncomplicated malaria (parasite density 500 - 200,000 parasites/µL) or mixed infection, weight > 5 kg, age > 6 months, informed consent Exclusion criteria: Pregnancy, severe malaria, severe acute malnutrition (weight-for-height below 70% of median with or without symmetrical peripheral oedema), history of antimalarial treatment within preceding 48 hrs, history of taking mefloquine in past 8 weeks, known history of hypersensitivity to trial drugs
Interventions	1. DHA-P, fixed dose combination, 40 mg/320 mg adult tablets, 20 mg/160mg children's tablets • DHA 2.5 mg/kg + P 20 mg/kg daily, given once daily for 3 days • Supervised 2. Artemether-lumefantrine, fixed dose combination, 20 mg/120mg tablets • A 3.3 mg/kg + L 19.8 mg/kg daily, twice daily for 3 days • Only first dose was supervised • Patients were advised to take some fatty food. Mothers were encouraged to breastfeed treated infants before each dose 3. Artesunate amodiaquine, fixed dose combination, 25 mg/67.5mg tablets, 50 mg/135

Smithuis 2010 MMR   (*Continued*)

	mg tablets, 100 mg/270mg tablets
	    • AS 4 mg/kg + AQ 10.8 mg base/kg daily, once daily for 3 days
	    • Supervised
	4. Artesunate plus mefloquine, fixed dose combination, 25 mg/55 mg tablets, 100mg/220mg tablets
	    • AS 4 mg/kg + MQ 8.8 mg/kg daily, once daily for 3 days
	    • Supervised
	5. Artesunate plus mefloquine, loose combination
	    • AS 4 mg/kg once daily for 3 days
	    • MQ 25 mg base/kg as a single dose on day 0
	    • Supervised
	    • Dose rounded off to nearest quarter tablet
	For children, tablets were crushed and syrup added.

Outcomes	1. Recurrence of *P. falciparum* after antimalarial treatment on days 28 and 63 PCR-unadjusted and PCR-adjusted 2. *P. vivax* during follow-up and median time to appearance 3. Gametocyte carriage at days 0, 7, 14, 21, and 28 4. Mean change in Hb from day 0 to day 28 5. Adverse events Not included in the review: 1. New gametocyte appearance at day 7 2. Gametocyte carriage after single dose of primaquine
Notes	Country: Myanmar Setting: Three clinics in Rakhine state Transmission: Seasonal and generally low Resistance: No resistance reported Dates: Dec 2008 to Mar 2009 Funding: Médecins sans Frontières (Holland) and the Wellcome Trust Mahidol University Oxford Tropical Medicine Research Programme

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"random assignment was achieved by patients drawing an envelope from a box after enrolment"
Allocation concealment (selection bias)	Unclear risk	"Treatment allocations were put in sealed envelopes in blocks of 50 for each age-group"
Blinding for microscopy outcomes (performance bias and detection bias)	Low risk	"Microscopists examining blood films were unaware of treatment allocation"
Blinding for adverse events (performance and detection bias)	High risk	Described as "open-label".

Smithuis 2010 MMR *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Low losses to follow-up in each treatment group (AA 3.2%, AL6 5.6%, AM-F 4.1%, AM-L 7.5%, DP 3.7%)
Selective reporting (reporting bias)	Unclear risk	Some WHO outcomes are not reported (for example, LTF, ETF).
Other bias	Low risk	No other sources of bias identified.

Tangpukdee 2005 THA

Methods	Trial design: An open label RCT Follow-up: The patients were admitted to hospital for 28 days. Clinical evaluation and parasite counts were performed 12-hourly until parasites cleared then daily for 28 days Adverse event monitoring: Assessed daily using non-suggestive questioning. Side effects were defined as signs and symptoms which occurred or became more severe after treatment started. Routine haematology, biochemistry, and urinalysis were conducted and baseline and weekly during follow-up
Participants	Number of participants: 180 Inclusion criteria: Age >14 years, weight > 40 kg, *P. falciparum* on blood smear, ability to take oral medicines, agree to stay in hospital for 28 days, informed consent Exclusion criteria: Pregnancy or lactation, severe malaria, severe vomiting, concomitant systemic diseases, other antimalarials in the previous 14 days or the presence of sulphonamides or 4-aminoquinolones in the urine
Interventions	1. DHA-P, fixed dose combination, 40 mg/320 mg tablets (Artekin: Holleykin) • Total dose: DHA 6 mg/kg + P 45 mg/kg in 3 divided doses, given once daily for 3 days 2. Artesunate plus mefloquine, loose combination • AS 4 mg/kg once daily for 3 days • MQ 8 mg/kg once daily for 3 days All doses supervised
Outcomes	1. Cure rate at day 28. PCR analysis not performed as all patients hospitalised for duration of follow-up, so all recurrent parasitaemias presumed to be recrudescence 2. Adverse events Not included in the review: 1. Fever clearance time 2. Parasite clearance time
Notes	Country: Thailand Setting: Bangkok Hospital for Tropical Diseases Transmission: Low Resistance: Multiple-drug resistance Dates: Not given Funding: Mahidol University Research Grant, Artekin supplied by Holleykin Pharmaceuticals

Tangpukdee 2005 THA *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly treated at a ratio of 1:2". No further details given
Allocation concealment (selection bias)	Unclear risk	None described.
Blinding for microscopy outcomes (performance bias and detection bias)	Unclear risk	No comment on blinding of laboratory staff.
Blinding for adverse events (performance and detection bias)	High risk	An open label trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up were low and similar between groups (10.8% DHA-P versus 10% AS+MQ)
Selective reporting (reporting bias)	Low risk	Day 28 outcomes may overestimate the efficacy of drugs with long half-lives such as AS+MQ and DHA-P
Other bias	Low risk	No other sources of bias identified.

The 4ABC Study 2011 AF

Methods	Trial design: An open label multicenter RCT Follow-up: The patients were admitted to hospital for 3 days in some facilities while in some, they were kept for only 1h to check for vomiting. They were asked to return on days 3, 7, 14, 21, and 28. Clinical assessment and blood smears taken at each visit and when clinically judged to be necessary. Haematological samples were taken at enrolment and on days 3, 7, 14, and 28. Samples for biochemistry tests (liver and renal function) were taken at enrolment and on days 7 and 28 Adverse event monitoring: Monitored throughout the trial. Method of monitoring not specified
Participants	Number of participants: 4116 Inclusion criteria: Suspected uncomplicated malaria, age 6 to 59 months, body weight > 5 kg, microscopically confirmed *P. falciparum* mono-infection with asexual parasite density between 2,000 and 200,000/μL, fever (axillary temperature ≥ 37.5 °C) or history of fever in preceding 24 hrs, Hb ≥ 7.0 g/dL, informed consent Exclusion criteria: Participation in another investigational drug trial in previous 30 days, known hypersensitivity to study drugs, severe malaria or other danger signs for example not able to breast-feed or drunk, vomiting (more than twice in 24 hrs), recent history of convulsions (more than once in 24 hrs), unconscious state, unable to stand or sit, severe malnutrition (weight for height < 70% of median National Center for Health Statistics/

	WHO reference) or other concomitant illness or underlying disease, contra-indication to receive trial drugs, or ongoing prophylaxis with drugs having antimalarial activity
Interventions	1. DHA-P, fixed dose combination, 40 mg/320 mg adult tablets, 20 mg/160 mg paediatric tablets (Eurartesim®: Sigma Tau) • DHA 2.25 mg/kg + P 18 mg/kg daily, given once daily for 3 days • Dose rounded off to nearest half tablet 2. Artemether-lumefantrine, fixed dose combination (Coartem: Novartis) • 5 to 14 kg 1 tablet twice daily for 3 days • 15 to 24 kg 2 tablets twice daily for 3 days • 25 to 34 kg 3 tablets twice daily for 3 days • Administered with a fatty food (for example, milk or groundnuts) 3. Artesunate-amodiaquine, fixed dose combination, 25 mg/67.5 mg tablets, 50 mg/135 mg tablets, 100 mg/270 mg tablets (Coarsucam: Sanofi Aventis) • AS 2.8-5.5 mg/kg + AQ 7.5-15 mg/kg, given once daily for 3 days • < 9 kg 1 tablet of 25 mg/67.5 mg formulation per day • 9 to 17.9kg 1 tablet of 50 mg/135 mg formulation per day • 18 to 35.9kg 1 tablet of 100 mg/270 mg formulation per day All doses supervised.
Outcomes	1. ACPR at day 28, PCR-unadjusted and PCR-adjusted 2. ACPR at day 63, PCR-unadjusted and PCR-adjusted 3. Presence and clearance of gametocytes 4. Hb changes from baseline to days 3, 7, 14, and 28 5. Adverse events Not included in the review: 1. Fever clearance time 2. Parasite clearance time
Notes	Country: Seven sub-Saharan African countries (Burkina Faso, Gabon, Nigeria, Rwanda, Uganda, Zambia, and Mozambique) Setting: We were unable to identify the trial sites as rural, urban or health facilities Transmission: Varied across trial regions. Trial regions in Gabon and Nigeria had perennial and high malaria transmission; trial regions in Burkina Faso and Rwanda had seasonal but high transmission; trial regions in Zambia included areas with seasonal, mesoendemic transmission; trial regions in Mozambique had perennial, mesoendemic transmission; Jinja and Tororo trial regions in Uganda had perennial, low transmission while Mbarara in Uganda had mesoendemic transmission. Resistance: All sites had notable CQ and SP resistance. CQ resistance ranged from 24% in Burkina Faso to 100% in Gabon while SP resistance ranged from 4% in Burkina Faso to 49% in Jinja, Uganda. Dates: Jul 2007 to Jun 2009 Funding: European Developing Countries Clinical Trials Partnership (EDCTP) and the Medicine for Malaria Venture (MMV)

Risk of bias

Bias	Authors' judgement	Support for judgement

The 4ABC Study 2011 AF *(Continued)*

Random sequence generation (selection bias)	Low risk	"A randomization list was produced for each recruiting site by the National Institute for Health Research Medicines for Children Research Network Clinical Trials Unit, University of Liverpool, UK"
Allocation concealment (selection bias)	Low risk	"Each treatment allocation concealed in opaque sealed envelopes that were opened only after the patient's recruitment"
Blinding for microscopy outcomes (performance bias and detection bias)	Low risk	Trial is described as "open-label" but the clinician or other staff following up the patient and assessing the end points blinded to the treatment assignment whenever possible
Blinding for adverse events (performance and detection bias)	Low risk	"the clinician or other staff following up the patient and assessing the end points blinded to the treatment assignment whenever possible"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low loss to follow-up in each treatment group (3.5% ASAQ, 2.5% DHA-P, 2.4% AL6)
Selective reporting (reporting bias)	Low risk	All WHO outcomes are reported.
Other bias	Low risk	No other sources of bias identified.

Tran 2004 VNM

Methods	Trial design: An open label RCT Follow-up: Malaria film on days 0, 2, and 7. Participants followed up to day 56 but further details not described Adverse event monitoring: Not described
Participants	Number of participants: 243 Inclusion criteria: Age > 2 yrs, microscopically confirmed uncomplicated *P. falciparum* malaria Exclusion criteria: Pregnancy, evidence of organ dysfunction, unable to tolerate oral medication, unable to return for follow-up, resident in Dac O for > 2 years
Interventions	1. DHA-P, fixed dose combination, 40 mg/320 mg tablets (Artekin: Holleykin) • Adults: 2 tablets at 0, 6, 24, and 48 hrs • Children < 15 yrs: 1 tablet at 0, 6, 24, and 48 hrs 2. Artesunate plus mefloquine, loose combination (artesunate: Guilin, Lariam: Hoffman-La Roche) • AS 4 mg/kg once daily for 3 days

Tran 2004 VNM (*Continued*)

	• MQ 25 mg base/kg as 2 divided doses 6 hrs apart on day 3
Outcomes	1. Parasitological failure at days 42 and 28, PCR-adjusted and PCR-unadjusted 2. Adverse events Not included in this review: 1. Fever clearance 2. Parasite clearance
Notes	Country: Vietnam Setting: Health station Transmission: Low and seasonal Resistance: Multiple-drug resistance Dates: Nov 2001 to Mar 2002 Funding: Wellcome Trust of Great Britain

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomly allocated one of three treatments in a ratio of 2:2:1". No further details given
Allocation concealment (selection bias)	Unclear risk	"Drugs were kept in identically numbered opaque envelopes". No further details
Blinding for microscopy outcomes (performance bias and detection bias)	Unclear risk	No comment on blinding of laboratory staff.
Blinding for adverse events (performance and detection bias)	High risk	An open label trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"There were no losses to follow-up".
Selective reporting (reporting bias)	Unclear risk	It is unclear from the paper whether it is only clinical failure that is being reported
Other bias	Low risk	No other sources of bias identified.

Valecha 2010 AS

Methods	Trial design: An open-label (non-inferiority) RCT Follow-up: Particiopants were managed as outpatients unless local practice dictated otherwise (some centres used hospital stays of between 3 and 28 days). Outpatients were asked to return on days 1, 2, 3, 7, 14, 21, 28, 35, 42, 49, 56, and 63, and any time they felt unwell. Blood smears were performed at each visit Adverse event monitoring: Blood and urine samples were taken for analysis on days 0, 28, 63 (if abnormal on day 28) and on the day of any recurrent parasitaemia. Twelve-lead ECGs were performed at days 0, 2, 7, 28 (if abnormal on day 7), 63 and on the day of any recurrent parasitaemia
Participants	Number of participants: 1150 Inclusion criteria: Age 3 months to 65 years (≥18 years in India), *P. falciparum* mono-infection (80 to 200,000 parasites/µL) or mixed infection, weight ≥ 5 kg, fever (≥ 37. 5 °C) or history of fever, informed consent Exclusion criteria: Severe malaria, treatment with MQ in the 60 days before screening, treatment with DHA-P in the 3 months before screening, > 4% parasitised red blood cells, pregnancy or lactation
Interventions	1. DHA-P, fixed dose combination, adult tablets 40 mg/320 mg, child tablets 20 mg/ 160 mg (Eurartesim®: Sigma Tau) • One dose daily for 3 days • 2.25 mg/kg DHA and 18 mg/kg piperaquine per dose • Dose rounded up to the nearest half tablet 2. Artesunate plus mefloquine, loose dose combination, AS 50mg tablets, MQ 250 mg tablets (Mepha Ltd) • AS 4mg/kg once daily for 3 days • MQ none on day 0, then 15 mg/kg once on day 1 and 10 mg/kg once on day 2 All doses supervised.
Outcomes	1. Cure rate at days 28, 42, and 63, PCR corrected and uncorrected 2. Mean change in Hb day 0 to day 63 3. Gametocyte carriage 4. Person-gametocyte-weeks 5. Adverse events Not included in this review: 1. Fever clearance 2. Parasite clearance
Notes	Country: Thailand (six sites), Laos (two centres), and India (three centres) Setting: Hospitals and research units. Transmission: Varied across trial regions. Trial regions in Thailand had unstable, low and seasonal malaria transmission; trial regions in Laos had seasonal transmission with a peak just after the heavy rainy months of July to August; trial regions in India included areas with perennial transmission, perennial transmission with a seasonal peak from June to September, and transmission active in post monsoon months Resistance: All sites had notable CQ resistance (estimates of 28 day treatment failure at the Indian sites ranged from 32% to 67% between 2002 and 2007). The Thai sites also had multi-drug resistant *P. falciparum*. Dates: Jun 2005 to Feb 2007.

Valecha 2010 AS   *(Continued)*

	Funding: Medicines for Malaria Venture, Sigma Tau, and Oxford University

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomisation list was generated by an external contract research organisation (MDS Pharma Services) using the plan procedure of SAS (Cary, NC, USA)"
Allocation concealment (selection bias)	Unclear risk	"Randomisation was conducted under blinded conditions: the blind to the investigator and patient in the randomisation process was maintained by the use of sealed envelopes" Envelopes are not described as opaque.
Blinding for microscopy outcomes (performance bias and detection bias)	Low risk	"Evaluation of the PCR test results was blinded".
Blinding for adverse events (performance and detection bias)	High risk	Trial is described as "open label".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Proportion of participants not completing the trial was low in both groups (6.6% DHA-P versus 6.0% AS+MQ)
Selective reporting (reporting bias)	Low risk	All listed outcomes reported.
Other bias	High risk	"A committee representing members of the DHA-PQP Joint Development Team and trial site Principal Investigators developed the protocol. Sigma Tau conducted the study, collected and analysed data. All authors had access to the primary data and take responsibility for data reporting accuracy and completeness. The corresponding author had responsibility for the final decision to submit for publication"

Yavo 2011 AF

Methods	Trial design: An open-label (non-inferiority) RCT Follow-up: Clinical and physical assessment and blood smears taken on follow-up days 1, 2, 3, 4, 7, 14, 21, and 28 after swallowing first antimalarial. Haematological and biochemical assessment conducted at baseline and on day 4 Adverse event monitoring: Recorded on the case report forms and graded as mild, moderate or severe
Participants	Number of participants: 384 Inclusion criteria: At least 2 years of age, *P. falciparum* mono-infection with parasitaemia from 2,000 to 200,000/µL of blood in Cameroon and Côte d'Ivoire and 1,000 to 100, 000/µL of blood in Sénégal, fever with axillary temperature ≥ 37.5 °C, written informed consent Exclusion criteria: History of side-effects to trial drugs, evidence of concomitant febrile illness, severe malaria or danger signs, treatment with 4-amino quinolones, SP, MG or halofantrine in previous 7 days or quinine, artemisinin or cyclins in previous 3 days, pregnancy or nursing, ongoing antimalarial treatment
Interventions	1. DHA-P, fixed dose combination, 40 mg/320 mg tablets (Duocotecxin: Beijing Holley-Cotect Pharmaceutical Co.) • One dose daily for 3 days • 5 to 9 kg half tablet • 10 to 14 kg ¾ tablet • 15 to 19 kg 1 tablet • 20 to 24 kg 1¼ tablets • 25 to 29 kg 1 ½ tablets • 30 to 34 kg 1 ¾ tablets • 35 to 39 kg 2 tablets • 40 to 44 kg 2 ¼ tablets • 45 to 49 kg 2 ½ tablets • ≥ 50 kg 3 tablets • Dose rounded up to the nearest quarter tablet 2. Artemether-lumefantrine, fixed dose combination, 20 mg/120 mg (Coartem: Novartis) • 5 to 14 kg 1 tablet twice daily for 3 days • 15 to 24 kg 2 tablets twice daily for 3 days • 25 to 34 kg 3 tablets twice daily for 3 days • > 35 kg 4 tablets twice daily for 3 days All doses supervised.
Outcomes	1. ACPR at day 28, PCR-adjusted and PCR-unadjusted 2. Mean change in Hb day 0 to day 63 3. Change in gametocyte carrier status 4. Adverse events Not included in this review: 1. Fever clearance 2. Parasite clearance
Notes	Country: Senegal, Côte d'Ivoire, Cameroon Setting: health facilities Transmission: Not reported

Yavo 2011 AF (*Continued*)

Resistance: "CQ and SP resistance reported in most parts of the continent"
Dates: November 2006 to May 2008
Funding: Beijing Holley-Cotec Pharmaceutical Co. Ltd which also supplied DHA-P free of charge

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"In each study site computer generated randomization codes were prepared by an independent individual"
Allocation concealment (selection bias)	Low risk	"These codes were enclosed in sequentially numbered opaque sealed envelopes, each of which contained the treatment allocation"
Blinding for microscopy outcomes (performance bias and detection bias)	Unclear risk	Blinding of microscopists not described.
Blinding for adverse events (performance and detection bias)	High risk	Trial described as "open label".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low percentage of patients without outcomes (3.0% in DHA-P and 2.1% in AL6)
Selective reporting (reporting bias)	Low risk	All WHO outcomes are reported. Day 28 outcomes may underestimate effect of DHA-P
Other bias	Low risk	No other sources of bias identified.

Yeka 2008 UGA

Methods	Trial design: A single blind RCT Follow-up: Standardized history, physical exam, and malaria film on days 0, 1, 2, 3, 7, 14, 21, 28, 35, and 42 and any other day they were unwell. Hb on days 0 and 42 or the day of failure. Anaemia was treated with ferrous sulphate and anthelmintics according to IMCI guidelines Adverse event monitoring: Assessed at each visit including neurological examination. Adverse events described as any untoward medical occurrence
Participants	Number of participants: 461 Inclusion criteria: Age 6 months to 10 yrs, weight > 5 kg, axillary temp > 37.5 °C or history of fever in the previous 24 hrs, *P. falciparum* mono-infection 2000 to 200,000/µL, informed consent Exclusion criteria: Danger signs or evidence of severe malaria, concomitant febrile illness, history of serious side effects to the trial medications

Interventions	1. DHA-P, fixed dose combination, 40 mg/320 mg tablets (Duocotexin: HolleyPharm)
	  • Total dose: DHA 6.4 mg/kg + P 51.2 mg/kg in 3 divided doses, given once daily for 3 days
	  • Plus placebo in the evenings to simulate twice daily dosing
	2. Artemether-lumefantrine, fixed dose combination, 20 mg/120 mg tablets (Coartem: Novartis)
	  • 5 to 14 kg 1 tablet twice daily for 3 days
	  • 15 to 24 kg 2 tablets twice daily for 3 days
	  • 25 to 34 kg 3 tablets twice daily for 3 days
	  • > 35 kg 4 tablets twice daily for 3 days
	All doses supervised and given with a glass of milk

Outcomes	1. ACPR at day 42, PCR-adjusted and PCR-unadjusted 2. Gametocytes development during follow-up 3. Mean increase in Hb at last day of follow-up 4. Adverse events Not included in this review: 1. Fever clearance 2. Parasite clearance
Notes	Country: Uganda Setting: Health centre Transmission: Moderate transmission Resistance: Not stated Dates: Aug 2006 to Apr 2007 Funding: CDC, DfID, DHA-P supplied by Holleypharm, AL6 supplied by Uganda Ministry of Health

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A randomisation list was computer generated by an off-site investigator"
Allocation concealment (selection bias)	Low risk	"Sealed opaque envelopes containing the study number and assigned treatment were secured in a locked cabinet"
Blinding for microscopy outcomes (performance bias and detection bias)	Low risk	"Only the study nurse was aware of assignments. All other study personnel were blinded"
Blinding for adverse events (performance and detection bias)	Low risk	"Patients were not informed of their treatment regimen". "Only the study nurse was aware of assignments and adverse events assessed by clinicians. All other study personnel were blinded"

Incomplete outcome data (attrition bias) All outcomes	Low risk	Low losses to follow-up in both groups (1. 4% DHA-P versus 1.5% AL6)
Selective reporting (reporting bias)	Low risk	All WHO outcomes reported. Day 42 outcomes may underestimate treatment failure with DHA-P due to its long half-life
Other bias	Low risk	No other sources of bias identified.

Zongo 2007 BFA

Methods	Trial design: A 3-arm RCT Follow-up: A standardized history, examination, and malaria film on days 0, 1, 2, 3, 7, 14, 21, 28, 35, and 42. Hb measured on days 0 and 42 or day of clinical failure. Children with Hb < 10 g/dL were treated with ferrous sulphate and antihelminthic treatment Adverse event monitoring: Assessed at each visit. Adverse events defined as untoward medical occurrences
Participants	Number of participants: 580 Inclusion criteria: Age > 6 months, weight > 5 kg, axillary temp > 37.5 °C or history of fever in the last 24 hrs, *P. falciparum* mono-infection 2000 to 200,000/µL, the ability to participate in 42 days follow-up, informed consent Exclusion criteria: Danger signs or signs of severe malaria, history of serious adverse effects related to trial medications, evidence of concomitant febrile illness, antimalarial use other than chloroquine in previous two weeks, Hb < 5 g/dL
Interventions	1. DHA-P, fixed dose combination, 40 mg/320 mg tablets (Duocotexin: HolleyPharm) • Total dose: DHA 6.4 mg/kg + PQP 51.2 mg/kg in 3 divided doses, given once daily for 3 days 2. Artemether-lumefantrine, fixed dose combination, 20 mg/120 mg tablets (Coartem: Novartis) • 5 to 14 kg 1 tablet twice daily for 3 days • 15 to 24 kg 2 tablets twice daily for 3 days • 25 to 34 kg 3 tablets twice daily for 3 days • > 35 kg 4 tablets twice daily for 3 days 3. Amodiaquine plus sulfadoxine-pyrimethamine, loose combination (Flavoquine: Aventis, Fansidar: Roche) • AQ 10 mg/kg once daily on days 0 and 1, then 5 mg/kg once on day 2 • SP 25/1.25 mg/kg on day 0 All doses supervised
Outcomes	1. Risk of treatment failure at days 42 and 28, PCR-adjusted and PCR-unadjusted 2. Gametocyte development during follow-up 3. Hb (mean g/dL) on day 0 and last day of follow-up 4. Adverse events Not included in this review: 1. Fever clearance 2. Parasite clearance

Zongo 2007 BFA   (*Continued*)

Notes	Country: Burkino Faso Setting: Health dispensaries Transmission: Holoendemic, transmission principally in the rainy season May to Oct Resistance: Not reported Dates: Not reported Funding: Doris Duke Charitable Foundation, Holley Cotec Pharmaceuticals, International Atomic Energy Agency, National Budget of the Institut de Recherche en Sciences de la Sante

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomly assigned on the basis of a computer-generated code provided by an off-site investigator"
Allocation concealment (selection bias)	Low risk	"Referred for treatment allocation by a study nurse not involved in enrolment or assessment of treatment outcomes"
Blinding for microscopy outcomes (performance bias and detection bias)	High risk	"The study was not blinded".
Blinding for adverse events (performance and detection bias)	High risk	As above.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low losses to follow-up in all groups (8% DHA-P versus 6.4% AL6 versus 8.2% AQ+SP)
Selective reporting (reporting bias)	Low risk	All WHO outcomes reported. Day 42 outcomes may underestimate treatment failure with DHA-P due to its long half-life
Other bias	Low risk	No other sources of bias identified.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Chinh 2009	Comparison not relevant to this review: two fixed-dose combinations of DHA-P were compared
Guo 1990	Conference presentation. Comparison not relevant to this review: artesunate versus piperaquine

Gupta 2010	Molecular genotyping analysis based on Kamya 2007 UGA and Yeka 2008 UGA. Contains no new efficacy data.
Karema 2005	Conference presentation of Karema 2006 RWA.
Somé 2010	Polymorphism selection analysis based on Zongo 2007a BFA. Contains no new efficacy data
Song 2011 KHM	Comparison not relevant to this review: DHA-P-phosphate (2 day dosage) versus artemether-lumefantrine
Sutanto 2013	Comparison not relevant to this review: DHA-P + primaquine versus DHA-P
Tarning 2008	Pharmacokinetic analysis based on Ashley 2005 THA. Contains no new efficacy data.
Thanh 2009	Quasi-RCT.
Tjitra 2012	Comparison not relevant to this review: Artemisinin-naphthoquine versus DHA-P
Tran 2012	Comparison not relevant to this review: AS monotherapy versus DHA-P
Verret 2011	Nutritional status analysis based on Arinaitwe 2009 UGA. Contains no new efficacy data.
Wang 2008	Quasi-RCT.
Yeka 2013	A comparison of DHA-P versus artemether-lumefantrine as rescue treatments based on The 4ABC Study 2011 AF. Contains no new efficacy data.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Borrmann 2011 KEN (a)

Methods	Trial design: A non-inferiority RCT Follow-up: Clinical assessment and blood smears taken on days 0, 1, 2, and 3 then weekly until day 63 and finally on day 84 Adverse event monitoring: Monitoring done on days 0, 1, 2, and 3 then weekly until day 63 and finally on day 84
Participants	Number of participants: 474 Inclusion criteria: Uncomplicated malaria, age 6 to 59 months, body weight ≥ 5kg, microscopically confirmed falciparum mono-infection with asexual parasite density of 2,000 to 200,000 µL, reported or documented axillary temperature ≥ 37.5 °C, informed consent Exclusion criteria: Known allergies, severe malaria or danger signs, ECG abnormalities that require urgent management, participation in another investigational drug study within previous 30 days
Interventions	1. DHA-P, fixed dose combination, 40 mg/320 mg tablets and 20 mg/160 mg tablets (Eurartesim®, Sigma-Tau) • Daily dose of 2.25 mg/kg dihydroartemisinin and 18 mg/kg piperaquine, given once daily for 3 days, rounded up to the nearest half tablet 2. Artemether-lumefantrine, fixed dose combination, 20 mg/120 mg (Coartem: Novartis) • A 2 mg/kg twice daily for 3 days

	• L 12 mg/kg twice daily for 3 days All doses were supervised.
Outcomes	1. 28-day cure rate, PCR-adjusted and PCR-unadjusted 2. Risk of recrudescent primary or secondary (re-) infections 3. Gametocyte carrier rate 4. Hb recovery Not included in this review: 1. Fever clearance time 2. Parasite clearance time
Notes	Country: Kenya Setting: One hospital site. Transmission: Perennial with peaks trailing two typical annual rainy seasons Resistance: None reported Dates: Sep 2005 to Apr 2008 Funding: DFG and MMV grants, European Developing Countries Clinical Trials Partnership (EDCTP) and the Wellcome Trust

Characteristics of ongoing studies   *[ordered by study ID]*

Tekete 2012 AF

Trial name or title	EDCTP Longitudinal study
Methods	Trial design: An open-label RCT Follow-up: Patients will receive same study drug for subsequent episodes of uncomplicated malaria for up to 2 years after first randomization. Haematology, biochemistry and clinical safety will be assessed over this two year period
Participants	Number of participants: 4032 Inclusion criteria: Acute uncomplicated malaria, age > 6 months, weight ≥ 5 kg with no clinical sign of severe malnutrition, axillary temp > 37.5 °C, oral/rectal/tympanic temperature > 38 °C or history of fever in the last 24 hrs, microscopically confirmed *P. falciparum* with parasite density less than 200,000/μL, ability to swallow oral medication, no documented malaria treatment in preceding 2 weeks or 4 weeks for re-inclusion, the ability to participate in the scheduled follow-up visits, written informed consent Exclusion criteria: Signs and symptoms of severe/complicated malaria, severe vomiting (more than 3 times in preceding 24hrs) or inability to tolerate oral medication, severe diarrhoea (3 or more watery stools per day), known history of clinically significant disorders such as cardiovascular (QTc interval > 450 ms), respiratory (including active tuberculosis), history of jaundice, renal, hepatic, gastrointestinal, immunological (including active HIV), neurological, endocrine, or other major psychiatric disorders, history of convulsions or other abnormality (including recent head trauma), Hb < 7 g/dL, concomitant febrile illness, hypersensitivity to study drugs, use of any other antimalarial in preceding 2 weeks before enrolment, pregnant or lactating women, known or suspected chronic alcohol abuse, active Hepatitis A, B or C, liver function tests > 2 times upper limit of normal, known significant renal impairment indicated by serum creatinine more than 1.5 x ULN

Tekete 2012 AF (*Continued*)

Interventions	1. DHA-P, fixed dose combination, adult tablets 40 mg/320 mg, child tablets 20 mg/160 mg (Eurartesim®: Sigma Tau)
	  • One dose daily for 3 days
	2. Artemether-lumefantrine, fixed dose combination, 20 mg/120 mg tablets (Coartem: Novartis)
	  • Dose based on body weight between 2 to 4 tablets/day
	  • Children given dispersible tablets
	  • Once daily for 3 days
	3. Artesunate-Amodiaquine, fixed dose combination, 3 strengths: 25 mg/67.5 mg, 50 mg/135 mg, 100 mg/270 mg (Winthrop: Sanofi-aventis)
	  • Once daily for 3 days
	4, Artesunate-Amodiaquine, fixed dose combination (Pyramax: Shin Poong)
	  • Dose based on body weight between 1 to 4 tablets/sachets per day
	  • Once daily for 3 days

Outcomes	1. Incidence rate of malaria 2. Repeated treatment safety over 2 years 3. Efficacy of study drugs according to WHO guidelines
Starting date	01 June 2011
Contact information	Principal investigator - Dr Abdoulaye Djimde - adjimde@mrtcbko.org
Notes	Country: Burkino Faso (2 centres), Mali (1 centre), Guinea (1 centre) Dates: 01 June 2011 to 29 June 2014 Funding: Medicines for Malaria Venture and European & Developing Countries Clinical Trials Partnership (EDCTP)

DATA AND ANALYSES

Comparison 1.   Dihydroartemisinin-piperaquine versus Artesunate plus mefloquine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total failure (*P. falciparum*) Day 28 PCR-unadjusted	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Asia	8	3487	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.28, 3.72]
2 Total failure (*P. falciparum*) Day 28 PCR-adjusted	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Asia	8	3482	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.21, 0.80]
3 Total failure (*P. falciparum*) Day 42 PCR-unadjusted	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Asia	7	3421	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.54, 1.50]
4 Total failure (*P. falciparum*) Day 42 PCR-adjusted	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Asia	6	2901	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.26, 0.88]
5 Total failure (*P. falciparum*) Day 63 PCR-unadjusted	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Asia	5	2715	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.69, 1.03]
5.2 South America	1	445	Risk Ratio (M-H, Fixed, 95% CI)	6.19 [1.40, 27.35]
6 Total failure (*P. falciparum*) Day 63 PCR-adjusted	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Asia	5	2500	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.30, 0.84]
6.2 South America	1	435	Risk Ratio (M-H, Fixed, 95% CI)	9.55 [0.52, 176.35]
7 Gametocyte carriage	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Gametocyte carriage day 0	3	2322	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.66, 1.73]
7.2 Gametocyte carriage day 7	3	2270	Risk Ratio (M-H, Random, 95% CI)	1.99 [1.57, 2.51]
7.3 Gametocyte carriage day 14	3	2249	Risk Ratio (M-H, Random, 95% CI)	5.11 [3.26, 7.99]
7.4 Gametocyte carriage day 21	3	2218	Risk Ratio (M-H, Random, 95% CI)	9.44 [0.80, 110.80]
7.5 Gametocyte carriage day 28	3	2199	Risk Ratio (M-H, Random, 95% CI)	9.55 [1.80, 50.61]
8 Gametocyte development (in those negative at baseline)	3	1234	Risk Ratio (M-H, Fixed, 95% CI)	3.06 [1.13, 8.33]
9 Serious adverse events (including deaths)	8	3522	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.59, 2.42]
10 Other adverse events: Gastrointestinal	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Early vomiting	9	4114	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.71, 1.15]
10.2 Nausea	9	4531	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.60, 0.78]
10.3 Vomiting	5	2744	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.47, 0.75]
10.4 Anorexia	6	3497	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.73, 1.02]
10.5 Diarrhoea	5	2217	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [1.05, 2.04]
10.6 Abdominal pain	7	3887	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.82, 1.20]
11 Other adverse events: Neuro-psychiatric	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

11.1 Headache	4	2039	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.64, 1.00]
11.2 Dizziness	9	4531	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.66, 0.78]
11.3 Sleeplessness	6	2551	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.40, 0.60]
11.4 Fatigue	2	872	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.23, 0.73]
11.5 Nightmares	1	220	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.01, 0.69]
11.6 Anxiety	1	522	Risk Ratio (M-H, Fixed, 95% CI)	0.10 [0.03, 0.33]
11.7 Blurred vision	1	464	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.24, 1.02]
11.8 Tinnitus	1	220	Risk Ratio (M-H, Fixed, 95% CI)	0.4 [0.13, 1.24]
12 Other adverse events: Cardio-respiratory	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 Palpitations	3	1175	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.45, 0.82]
12.2 Cough	1	1148	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.54, 1.19]
12.3 Dyspnoea	1	220	Risk Ratio (M-H, Fixed, 95% CI)	0.3 [0.08, 1.06]
12.4 Prolonged QT interval (reported as adverse events)	1	1148	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.72, 2.24]
12.5 Prolonged QT interval (Bazett's correction)	1	1148	Risk Ratio (M-H, Fixed, 95% CI)	2.05 [1.20, 3.49]
12.6 Prolonged QT interval (Fridericia's correction)	1	1148	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.52, 1.52]
13 Other adverse events: Musculoskeletal/ dermatological	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 Arthralgia	1	1148	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.60, 1.65]
13.2 Myalgia	1	1148	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.63, 1.70]
13.3 Urticaria	2	719	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.15, 2.35]
13.4 Pruritis	2	872	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.26, 1.60]
13.5 Rash	1	220	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.09]
14 Sensitivity analysis: Total failure Day 63 PCR-unadjusted	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
14.1 Total failure (*P. falciparum*) Day 63 PCR-unadjusted	4	1627	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.52, 1.70]
14.2 Total failure Day 63 PCR-unadjusted (losses to follow-up included as failures)	4	1801	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.65, 1.38]
14.3 Total failure Day 63 PCR-unadjusted (losses to follow-up included as successes)	4	1801	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.52, 1.68]
15 Sensitivity analysis: Total failure Day 63 PCR-adjusted	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
15.1 Total failure (*P. falciparum*) Day 63 PCR-adjusted	4	1497	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.17, 1.83]
15.2 Total failure Day 63 PCR-adjusted (indeterminate PCR included as failures)	4	1508	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.32, 1.39]
15.3 Total failure Day 63 PCR-adjusted (new infections included as successes)	4	1627	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.34, 1.35]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.4 Total failure Day 63 PCR-adjusted (losses to follow-up included as failures)	4	1801	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.67, 1.30]
15.5 Total failure Day 63 PCR-adjusted (losses to follow-up included as successes)	4	1801	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.34, 1.33]

Comparison 2.   Dihydroartemisinin-piperaquine dose analysis: 3 dose versus 4 dose regimen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total failure PCR-unadjusted	1	318	Risk Ratio (M-H, Fixed, 95% CI)	1.72 [0.84, 3.53]
1.1 Day 63	1	318	Risk Ratio (M-H, Fixed, 95% CI)	1.72 [0.84, 3.53]
2 Total failure PCR-adjusted	1	292	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.05, 6.09]
2.1 Day 63	1	292	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.05, 6.09]

Comparison 3.   Dihydroartemisinin-piperaquine dose analysis (versus Artesunate plus mefloquine)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total failure Day 28 PCR-unadjusted	8	3644	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.25, 2.41]
1.1 DHA-P 4 doses	4	1075	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.10, 3.14]
1.2 DHA-P 3 doses	5	2569	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.19, 5.07]
2 Total failure Day 28 PCR-adjusted	8	3633	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.15, 1.65]
2.1 DHA-P 4 doses	4	1067	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.10, 6.11]
2.2 DHA-P 3 doses	5	2566	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.08, 1.94]
3 Total failure Day 42 PCR-unadjusted	7	3578	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.51, 1.31]
3.1 DHA-P 4 doses	3	957	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.50, 1.28]
3.2 DHA-P 3 doses	5	2621	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.40, 1.99]
4 Total failure Day 42 PCR-adjusted	6	3046	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.20, 1.18]
4.1 DHA-P 4 doses	3	903	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.14, 2.82]
4.2 DHA-P 3 doses	4	2143	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.12, 1.48]
5 Total failure Day 63 PCR-unadjusted	6	3317	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.62, 1.40]
5.1 DHA-P 4 doses	3	1019	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.59, 1.10]
5.2 DHA-P 3 doses	4	2298	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.52, 2.90]
6 Total failure Day 63 PCR-adjusted	6	3072	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.28, 1.15]
6.1 DHA-P 4 doses	3	908	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.17, 1.04]
6.2 DHA-P 3 doses	4	2164	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.26, 2.77]

Comparison 4.   Dihydroartemisinin-piperaquine versus Artemether-lumefantrine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total failure (*P. falciparum*) Day 28 PCR-unadjusted	13		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Africa	9	6200	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.30, 0.39]
1.2 Asia and Oceania	4	1143	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.64, 1.47]
2 Total failure (*P. falciparum*) Day 28 PCR-adjusted	12		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Africa	9	5417	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.29, 0.62]
2.2 Asia and Oceania	3	925	Risk Ratio (M-H, Fixed, 95% CI)	2.01 [0.81, 5.03]
3 Total failure (*P. falciparum*) Day 42 PCR-unadjusted	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Africa	7	3301	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.53, 0.67]
3.2 Asia and Oceania	2	572	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.65, 1.17]
4 Total failure (*P. falciparum*) Day 42 PCR-adjusted	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Africa	7	2559	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.41, 0.81]
4.2 Asia and Oceania	2	468	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [0.75, 3.83]
5 Total failure (*P. falciparum*) Day 63 PCR-unadjusted	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Africa	2	3200	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.65, 0.78]
5.2 Asia	1	323	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.47, 1.88]
6 Total failure (*P. falciparum*) Day 63 PCR-adjusted	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Africa	2	2097	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.50, 1.04]
6.2 Asia	1	298	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.14, 7.01]
7 Gametocyte development (in those negative at baseline)	6		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8 Gametocyte carriage	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Gametocyte carriage day 1 to 14	4	1537	Risk Ratio (M-H, Fixed, 95% CI)	4.32 [1.48, 12.63]
8.2 Gametocyte carriage day 15 to 28	4	1516	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.06, 0.72]
8.3 Gametocyte carriage day 29 to 42	2	650	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.13, 0.61]
9 Anaemia	8		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 Mean haemoglobin (g/dL) at baseline	8	6599	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.09, 0.01]
9.2 Mean haemoglobin (g/dL) at day 28	1	134	Mean Difference (IV, Fixed, 95% CI)	0.36 [-0.03, 0.75]
9.3 Mean haemoglobin (g/dL) at day 42	1	375	Mean Difference (IV, Fixed, 95% CI)	0.30 [-0.02, 0.62]
9.4 Mean change in haemoglobin (g/dL) from baseline to day 28	2	2185	Mean Difference (IV, Fixed, 95% CI)	0.19 [0.03, 0.34]
9.5 Mean change in haemoglobin (g/dL) from baseline to day 42	2	835	Mean Difference (IV, Fixed, 95% CI)	0.26 [0.00, 0.51]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10 Serious adverse events (including deaths)	9	7246	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [0.93, 2.68]
11 Other adverse events: Gastrointestinal	12		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 Early vomiting	4	2969	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [1.00, 2.83]
11.2 Vomiting	9	6761	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.89, 1.20]
11.3 Nausea	2	547	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.36, 3.76]
11.4 Diarrhoea	7	4889	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.81, 1.09]
11.5 Abdominal pain	5	911	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.65, 1.08]
11.6 Anorexia	5	3834	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.80, 1.08]
12 Other adverse events: Neuro-psychiatric	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 Headache	2	309	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.90, 1.63]
12.2 Sleeplessness	2	547	Risk Ratio (M-H, Fixed, 95% CI)	2.07 [0.69, 6.16]
12.3 Dizziness	2	547	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.67, 4.15]
12.4 Sleepiness	1	384	Risk Ratio (M-H, Fixed, 95% CI)	2.85 [0.12, 69.49]
12.5 Weakness	5	1812	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.89, 1.27]
13 Other adverse events: Cardio-respiratory	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 Cough	5	4342	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.95, 1.09]
13.2 Coryza	2	832	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.89, 1.07]
13.3 Prolonged QTc interval (reported as adverse events)	1	1548	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.51, 1.90]
13.4 Prolonged QTc interval (Bazett's correction)	1	1548	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.91, 1.92]
13.5 Prolonged QTc interval (Fridericia's correction)	1	1548	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.09, 10.81]
14 Other adverse events: Musculoskeletal/ dermatological	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 Pruritis	5	2033	Risk Ratio (M-H, Fixed, 95% CI)	1.74 [1.03, 2.92]
14.2 Face oedema	1	384	Risk Ratio (M-H, Fixed, 95% CI)	2.85 [0.12, 69.49]

Comparison 5. Dihydroartemisinin-piperaquine versus Artesunate plus amodiaquine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total failure (*P. falciparum*) Day 28 PCR-unadjusted	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Africa	2	2800	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.41, 0.59]
1.2 Asia	2	482	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.18, 0.77]
2 Total failure (*P. falciparum*) Day 28 PCR-adjusted	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Africa	2	2486	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.42, 1.06]
2.2 Asia	2	466	Risk Ratio (M-H, Fixed, 95% CI)	0.08 [0.01, 0.40]
3 Total failure (*P. falciparum*) Day 42 PCR-unadjusted	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Asia	1	152	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.10, 0.72]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Total failure (*P. falciparum*) Day 42 PCR-adjusted	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Asia	1	141	Risk Ratio (M-H, Fixed, 95% CI)	0.10 [0.01, 0.81]
5 Total failure (*P. falciparum*) Day 63 PCR-unadjusted	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Africa	1	2292	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.86, 1.07]
5.2 Asia	1	304	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.27, 0.89]
6 Total failure (*P. falciparum*) Day 63 PCR-adjusted	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Africa	1	1506	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [0.85, 3.83]
6.2 Asia	1	278	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.03, 0.59]
7 Serious adverse events (including deaths)	2	2805	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.19, 0.87]
8 Other adverse events: Gastrointestinal	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Early vomiting	2	650	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.44, 1.56]
8.2 Vomiting	1	2471	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.62, 1.01]
8.3 Nausea	1	316	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.62, 1.61]
8.4 Diarrhoea	2	2787	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.83, 1.27]
8.5 Abdominal pain	1	316	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.51, 1.65]
8.6 Anorexia	2	2787	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.72, 1.13]
9 Other adverse events: Neuro-psychiatric	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Headache	1	316	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.14, 6.75]
9.2 Sleeplessness	1	316	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.44, 1.41]
10 Other adverse events: Cardio-respiratory	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Cough	1	2471	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.91, 1.15]
10.2 Palpitations	1	316	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.58, 1.35]

Comparison 6. Dihydroartemisinin-piperaquine versus Artesunate plus sulfadoxine-pyrimethamine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total failure (*P. falciparum*) Day 28 PCR-unadjusted	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Oceania	1	223	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.62, 1.64]
2 Total failure (*P. falciparum*) Day 28 PCR-adjusted	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Oceania	1	195	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.46, 2.22]
3 Total failure (*P. falciparum*) Day 42 PCR-unadjusted	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Oceania	1	215	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.74, 1.45]
4 Total failure (*P. falciparum*) Day 42 PCR-adjusted	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Oceania	1	161	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.39, 1.51]

Analysis 1.1.   Comparison I Dihydroartemisinin-piperaquine versus Artesunate plus mefloquine, Outcome I Total failure (P. falciparum) Day 28 PCR-unadjusted.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: I Dihydroartemisinin-piperaquine versus Artesunate plus mefloquine

Outcome: I Total failure (*P. falciparum*) Day 28 PCR-unadjusted

Study or subgroup	DHA-P n/N	AS+MQ n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
I Asia				
Tran 2004 VNM	0/166	0/77		0.0 [0.0, 0.0]
Janssens 2007 KHM	2/195	2/207		1.06 [0.15, 7.46]
Ashley 2004a THA	1/59	0/59		3.00 [0.12, 72.18]
Smithuis 2006 MMR	6/319	0/316		12.88 [0.73, 227.64]
Ashley 2005 THA	5/318	13/157		0.19 [0.07, 0.52]
Tangpukdee 2005 THA	1/107	0/54		1.53 [0.06, 36.89]
Valecha 2010 AS	6/667	17/336		0.18 [0.07, 0.45]
Smithuis 2010 MMR	5/154	2/296		4.81 [0.94, 24.48]
Subtotal (95% CI)	**1985**	**1502**		**1.02 [0.28, 3.72]**

Total events: 26 (DHA-P), 34 (AS+MQ)

Heterogeneity: Tau^2 = I.99; Chi^2 = 23.4I, df = 6 (P = 0.00067); I^2 =74%

Test for overall effect: Z = 0.02 (P = 0.98)

```
          0.005   0.1     I      10     200
        Favours DHA-P        Favours AS+MQ
```
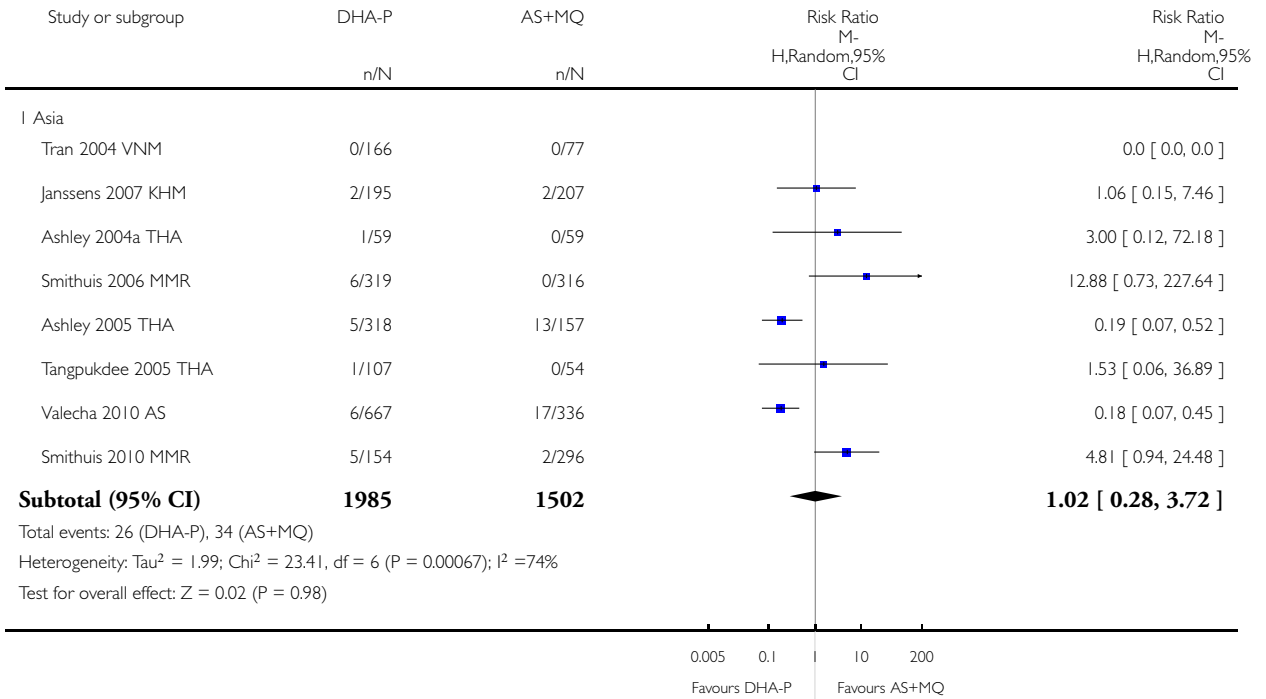
Analysis 1.2.   Comparison 1 Dihydroartemisinin-piperaquine versus Artesunate plus mefloquine, Outcome 2 Total failure (P. falciparum) Day 28 PCR-adjusted.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 1 Dihydroartemisinin-piperaquine versus Artesunate plus mefloquine

Outcome: 2 Total failure (*P. falciparum*) Day 28 PCR-adjusted

Study or subgroup	DHA-P n/N	AS+MQ n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Asia				
Tran 2004 VNM	0/166	0/77		0.0 [0.0, 0.0]
Ashley 2004a THA	1/59	0/59		3.00 [0.12, 72.18]
Janssens 2007 KHM	2/195	1/206		2.11 [0.19, 23.11]
Smithuis 2006 MMR	2/315	0/316		5.02 [0.24, 104.06]
Tangpukdee 2005 THA	1/107	0/54		1.53 [0.06, 36.89]
Ashley 2005 THA	2/315	7/151		0.14 [0.03, 0.65]
Valecha 2010 AS	1/667	8/336		0.06 [0.01, 0.50]
Smithuis 2010 MMR	0/149	1/310		0.69 [0.03, 16.86]
Subtotal (95% CI)	**1973**	**1509**		**0.41 [0.21, 0.80]**

Total events: 9 (DHA-P), 17 (AS+MQ)

Heterogeneity: Chi² = 11.72, df = 6 (P = 0.07); I² =49%

Test for overall effect: Z = 2.60 (P = 0.0094)

0.002   0.1   1   10   500

Favours DHA-P   Favours AS+MQ

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 1 Dihydroartemisinin-piperaquine versus Artesunate plus mefloquine

Outcome: 3 Total failure (*P. falciparum*) Day 42 PCR-unadjusted

Study or subgroup	DHA-P	AS+MQ	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
	n/N	n/N			
1 Asia					
Tran 2004 VNM	16/166	7/77		15.5 %	1.06 [0.45, 2.47]
Janssens 2007 KHM	9/195	9/207		14.7 %	1.06 [0.43, 2.62]
Mayxay 2006 LAO	4/106	5/108		9.9 %	0.82 [0.23, 2.95]
Smithuis 2006 MMR	6/319	1/316		4.8 %	5.94 [0.72, 49.09]
Ashley 2005 THA	16/318	19/157		19.1 %	0.42 [0.22, 0.79]
Valecha 2010 AS	39/667	34/336		22.7 %	0.58 [0.37, 0.90]
Smithuis 2010 MMR	8/150	7/299		13.3 %	2.28 [0.84, 6.16]
Subtotal (95% CI)	**1921**	**1500**		**100.0 %**	**0.90 [0.54, 1.50]**

Total events: 98 (DHA-P), 82 (AS+MQ)

Heterogeneity: Tau^2 = 0.24; Chi^2 = 14.44, df = 6 (P = 0.03); I^2 =58%

Test for overall effect: Z = 0.39 (P = 0.70)

```
         0.01   0.1    1    10   100
       Favours DHA-P        Favours AS+MQ
```

Analysis 1.4. Comparison 1 Dihydroartemisinin-piperaquine versus Artesunate plus mefloquine, Outcome 4 Total failure (P. falciparum) Day 42 PCR-adjusted.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 1 Dihydroartemisinin-piperaquine versus Artesunate plus mefloquine

Outcome: 4 Total failure (*P. falciparum*) Day 42 PCR-adjusted

Study or subgroup	DHA-P n/N	AS+MQ n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Asia					
Tran 2004 VNM	2/152	1/71		5.2 %	0.93 [0.09, 10.13]
Janssens 2007 KHM	3/189	2/200		7.4 %	1.59 [0.27, 9.39]
Mayxay 2006 LAO	1/103	1/104		3.8 %	1.01 [0.06, 15.93]
Smithuis 2006 MMR	2/315	0/315		1.9 %	5.00 [0.24, 103.73]
Ashley 2005 THA	2/304	7/145		36.1 %	0.14 [0.03, 0.65]
Valecha 2010 AS	5/667	9/336		45.6 %	0.28 [0.09, 0.83]
Subtotal (95% CI)	**1730**	**1171**		**100.0 %**	**0.48 [0.26, 0.88]**
Total events: 15 (DHA-P), 20 (AS+MQ)					
Heterogeneity: Chi² = 8.06, df = 5 (P = 0.15); I² =38%					
Test for overall effect: Z = 2.36 (P = 0.018)					

```
        0.002   0.1    1    10    500
        Favours DHA-P      Favours AS+MQ
```

Analysis 1.5. Comparison 1 Dihydroartemisinin-piperaquine versus Artesunate plus mefloquine, Outcome 5 Total failure (P. falciparum) Day 63 PCR-unadjusted.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 1 Dihydroartemisinin-piperaquine versus Artesunate plus mefloquine

Outcome: 5 Total failure (*P. falciparum*) Day 63 PCR-unadjusted

Study or subgroup	DHA-P n/N	AS+MQ n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Asia					
Janssens 2007 KHM	18/195	22/207		12.9 %	0.87 [0.48, 1.57]
Ashley 2004b THA	26/154	29/151		17.7 %	0.88 [0.54, 1.42]
Ashley 2005 THA	29/318	27/157		21.8 %	0.53 [0.33, 0.86]
Valecha 2010 AS	86/718	53/358		42.7 %	0.81 [0.59, 1.11]
Smithuis 2010 MMR	14/152	12/305		4.8 %	2.34 [1.11, 4.94]
Subtotal (95% CI)	**1537**	**1178**		**100.0 %**	**0.84 [0.69, 1.03]**
Total events: 173 (DHA-P), 143 (AS+MQ)					
Heterogeneity: Chi² = 10.77, df = 4 (P = 0.03); I² =63%					
Test for overall effect: Z = 1.64 (P = 0.10)					
2 South America					
Grande 2007 PER	12/219	2/226		100.0 %	6.19 [1.40, 27.35]
Subtotal (95% CI)	**219**	**226**		**100.0 %**	**6.19 [1.40, 27.35]**
Total events: 12 (DHA-P), 2 (AS+MQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.41 (P = 0.016)					

0.01   0.1   1   10   100

Favours DHA-P   Favours AS+MQ

Analysis 1.6. Comparison 1 Dihydroartemisinin-piperaquine versus Artesunate plus mefloquine, Outcome 6 Total failure (P. falciparum) Day 63 PCR-adjusted.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 1 Dihydroartemisinin-piperaquine versus Artesunate plus mefloquine

Outcome: 6 Total failure (*P. falciparum*) Day 63 PCR-adjusted

Study or subgroup	DHA-P n/N	AS+MQ n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Asia					
Janssens 2007 KHM	4/181	5/190		12.8 %	0.84 [0.23, 3.08]
Ashley 2004b THA	3/131	9/131		23.7 %	0.33 [0.09, 1.20]
Ashley 2005 THA	3/292	7/137		25.1 %	0.20 [0.05, 0.77]
Valecha 2010 AS	11/667	10/336		35.0 %	0.55 [0.24, 1.29]
Smithuis 2010 MMR	2/140	2/295		3.4 %	2.11 [0.30, 14.80]
Subtotal (95% CI)	**1411**	**1089**		**100.0 %**	**0.50 [0.30, 0.84]**
Total events: 23 (DHA-P), 33 (AS+MQ)					
Heterogeneity: Chi² = 4.92, df = 4 (P = 0.30); I² =19%					
Test for overall effect: Z = 2.61 (P = 0.0092)					
2 South America					
Grande 2007 PER	4/211	0/224		100.0 %	9.55 [0.52, 176.35]
Subtotal (95% CI)	**211**	**224**		**100.0 %**	**9.55 [0.52, 176.35]**
Total events: 4 (DHA-P), 0 (AS+MQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.52 (P = 0.13)					

0.005   0.1   1   10   200

Favours DHA-P   Favours AS+MQ

Analysis 1.7.   Comparison 1 Dihydroartemisinin-piperaquine versus Artesunate plus mefloquine, Outcome 7 Gametocyte carriage.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 1 Dihydroartemisinin-piperaquine versus Artesunate plus mefloquine

Outcome: 7 Gametocyte carriage

Study or subgroup	DHA-P	AS+MQ	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
	n/N	n/N		
1 Gametocyte carriage day 0				
Smithuis 2006 MMR	137/327	103/325		1.32 [1.08, 1.62]
Grande 2007 PER	35/262	43/260		0.81 [0.54, 1.22]
Valecha 2010 AS	0/767	0/381		0.0 [0.0, 0.0]
Subtotal (95% CI)	**1356**	**966**		**1.07 [0.66, 1.73]**
Total events: 172 (DHA-P), 146 (AS+MQ)				
Heterogeneity: Tau^2 = 0.10; Chi^2 = 4.48, df = 1 (P = 0.03); I^2 =78%				
Test for overall effect: Z = 0.27 (P = 0.79)				
2 Gametocyte carriage day 7				
Smithuis 2006 MMR	118/322	58/318		2.01 [1.53, 2.64]
Grande 2007 PER	17/256	9/256		1.89 [0.86, 4.16]
Valecha 2010 AS	59/749	15/369		1.94 [1.11, 3.37]
Subtotal (95% CI)	**1327**	**943**		**1.99 [1.57, 2.51]**
Total events: 194 (DHA-P), 82 (AS+MQ)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.03, df = 2 (P = 0.98); I^2 =0.0%				
Test for overall effect: Z = 5.74 (P < 0.00001)				
3 Gametocyte carriage day 14				
Smithuis 2006 MMR	84/318	17/318		4.94 [3.00, 8.13]
Grande 2007 PER	10/253	1/253		10.00 [1.29, 77.54]
Valecha 2010 AS	30/742	3/365		4.92 [1.51, 16.01]
Subtotal (95% CI)	**1313**	**936**		**5.11 [3.26, 7.99]**
Total events: 124 (DHA-P), 21 (AS+MQ)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.44, df = 2 (P = 0.80); I^2 =0.0%				
Test for overall effect: Z = 7.14 (P < 0.00001)				
4 Gametocyte carriage day 21				
Smithuis 2006 MMR	26/316	0/310		52.00 [3.18, 849.49]
Grande 2007 PER	1/247	1/250		1.01 [0.06, 16.09]
Valecha 2010 AS	16/733	0/362		16.32 [0.98, 271.26]
Subtotal (95% CI)	**1296**	**922**		**9.44 [0.80, 110.80]**

```
        0.001 0.01  0.1   1   10  100 1000
        Favours DHA-P      Favours AS+MQ
```

(*Continued* . . .)

| Study or subgroup | DHA-P | AS+MQ | Risk Ratio M-H,Random,95% CI | Risk Ratio M-H,Random,95% CI |
> |---|---|---|---|---|
> | | n/N | n/N | | |

Total events: 43 (DHA-P), 1 (AS+MQ)

Heterogeneity: Tau² = 2.71; Chi² = 4.68, df = 2 (P = 0.10); I² =57%

Test for overall effect: Z = 1.79 (P = 0.074)

5 Gametocyte carriage day 28

Smithuis 2006 MMR	6/318	0/314		12.84 [0.73, 226.91]
Grande 2007 PER	3/243	0/249		7.17 [0.37, 138.12]
Valecha 2010 AS	9/722	0/353		9.30 [0.54, 159.38]
Subtotal (95% CI)	**1283**	**916**		**9.55 [1.80, 50.61]**

Total events: 18 (DHA-P), 0 (AS+MQ)

Heterogeneity: Tau² = 0.0; Chi² = 0.08, df = 2 (P = 0.96); I² =0.0%

Test for overall effect: Z = 2.65 (P = 0.0080)

```
      0.001 0.01 0.1   1   10  100 1000
        Favours DHA-P      Favours AS+MQ
```

Analysis 1.8. Comparison 1 Dihydroartemisinin-piperaquine versus Artesunate plus mefloquine, Outcome 8 Gametocyte development (in those negative at baseline).

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 1 Dihydroartemisinin-piperaquine versus Artesunate plus mefloquine

Outcome: 8 Gametocyte development (in those negative at baseline)

Study or subgroup	DHA-P	AS+MQ	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
Ashley 2004b THA	3/168	2/163		37.4 %	1.46 [0.25, 8.60]
Ashley 2005 THA	9/310	1/153		24.6 %	4.44 [0.57, 34.74]
Grande 2007 PER	8/227	2/213		38.0 %	3.75 [0.81, 17.48]
Total (95% CI)	**705**	**529**		**100.0 %**	**3.06 [1.13, 8.33]**

Total events: 20 (DHA-P), 5 (AS+MQ)

Heterogeneity: Chi² = 0.87, df = 2 (P = 0.65); I² =0.0%

Test for overall effect: Z = 2.19 (P = 0.028)

Test for subgroup differences: Not applicable

```
      0.05   0.2   1   5   20
       Favours DHA-P   Favours AS+MQ
```
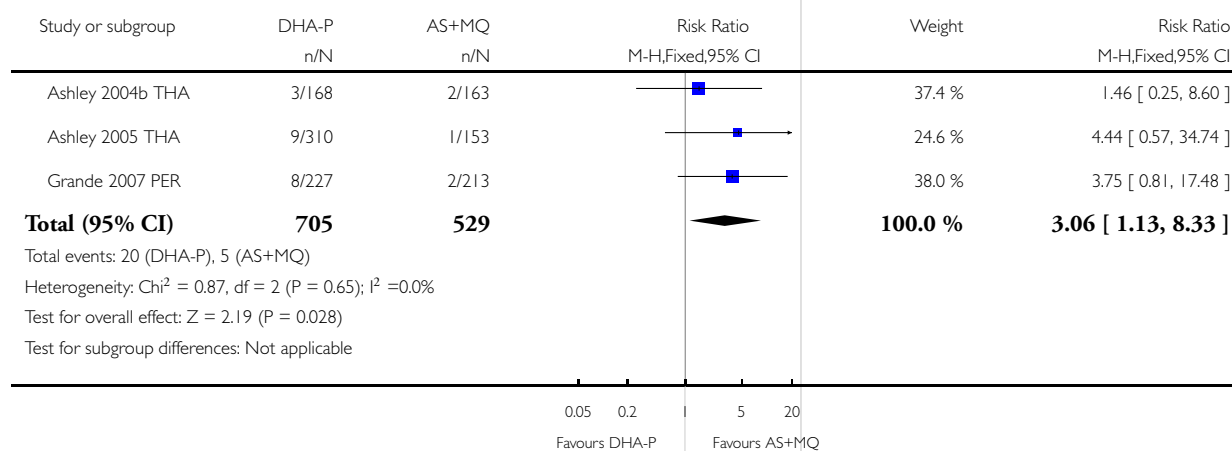
Analysis 1.9.   Comparison 1 Dihydroartemisinin-piperaquine versus Artesunate plus mefloquine, Outcome 9 Serious adverse events (including deaths).

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 1 Dihydroartemisinin-piperaquine versus Artesunate plus mefloquine

Outcome: 9 Serious adverse events (including deaths)

Study or subgroup	DHA-P n/N	AS+MQ n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Janssens 2007 KHM (1)	0/228	0/236		0.0 [0.0, 0.0]
Ashley 2004b THA (2)	1/179	0/176		2.95 [0.12, 71.93]
Ashley 2004a THA (3)	0/67	0/67		0.0 [0.0, 0.0]
Mayxay 2006 LAO (4)	0/110	1/110		0.33 [0.01, 8.09]
Ashley 2005 THA (5)	11/333	4/166		1.37 [0.44, 4.24]
Grande 2007 PER (6)	0/262	3/260		0.14 [0.01, 2.73]
Tangpukdee 2005 THA	0/120	0/60		0.0 [0.0, 0.0]
Valecha 2010 AS (7)	12/767	3/381		1.99 [0.56, 7.00]
Total (95% CI)	**2066**	**1456**		**1.20 [0.59, 2.42]**

Total events: 24 (DHA-P), 11 (AS+MQ)

Heterogeneity: Chi² = 3.60, df = 4 (P = 0.46); I² =0.0%

Test for overall effect: Z = 0.50 (P = 0.62)

Test for subgroup differences: Not applicable

0.001 0.01 0.1   1   10 100 1000

Favours DHA-P   Favours AS+MQ

all deemed related to drug: 1 anaemia, 1 convulsion, 1 encephalitis)
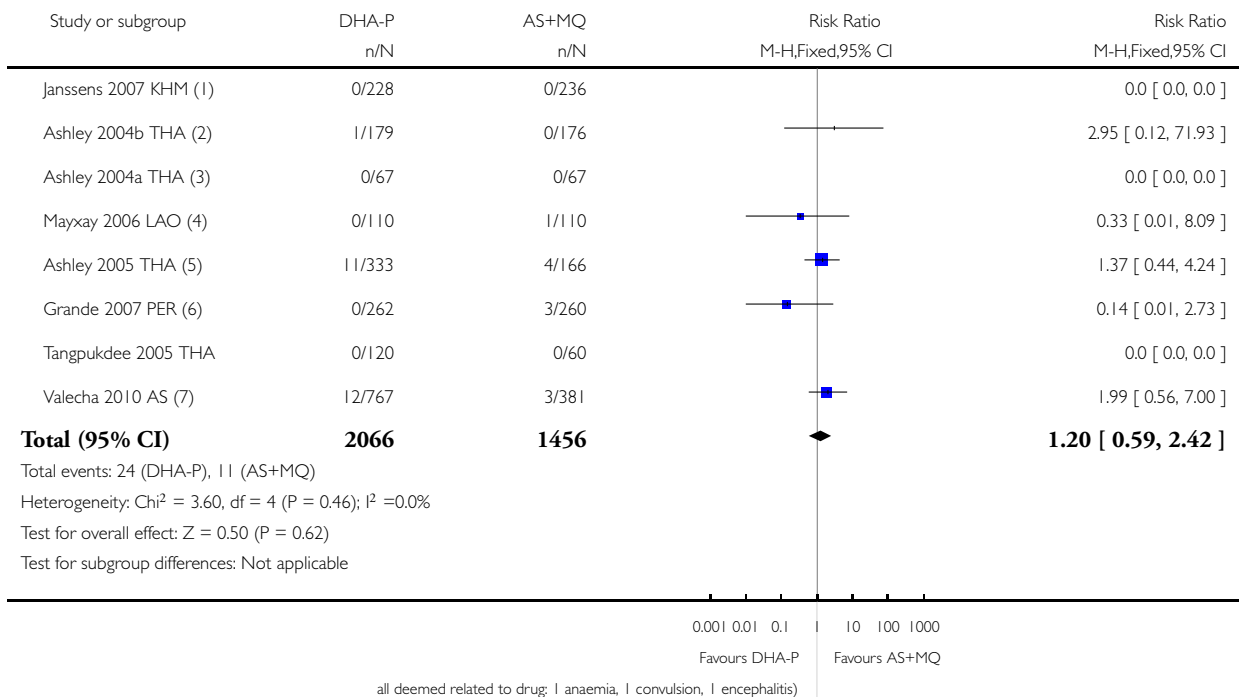
(1) Janssens 2007 KHM: No serious adverse events reported

(2) Ashley 2004b THA: One death occurred following DHA-P. No Other serious adverse events reported.

(3) Ashley 2004a: No serious adverse events reported

(4) Mayxay 2006 LAO: One severe neuropsychiatric reaction in AS+MQ group

(5) Ashley 2005 THA: All serious adverse events except one case of severe vomiting after AS+MQ were judged to be unrelated or unlikely to be due to the study treatment

(6) Grande 2007 PER: Three serious drug related events with AS+MQ requiring stopping treatment (encephalopathy, anxiety and arrhythmia, palpitations and chest pain)

(7) Valecha 2010 AS: For DHA-P six SAE deemed related to drug: 2 cases of anemia, 1 viral infection, 1 Wolf-Parkinson-White synrome, 1 convulsion, 1 encephalitis), for AS+MQ three SAE,

Analysis 1.10. Comparison 1 Dihydroartemisinin-piperaquine versus Artesunate plus mefloquine, Outcome 10 Other adverse events: Gastrointestinal.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 1 Dihydroartemisinin-piperaquine versus Artesunate plus mefloquine

Outcome: 10 Other adverse events: Gastrointestinal

Study or subgroup	DHA-P n/N	AS+MQ n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Early vomiting				
Ashley 2004a THA (1)	0/67	0/67		0.0 [0.0, 0.0]
Ashley 2004b THA (2)	9/179	5/177		1.78 [0.61, 5.21]
Ashley 2005 THA (3)	8/333	6/166		0.66 [0.23, 1.88]
Grande 2007 PER (4)	10/262	11/260		0.90 [0.39, 2.09]
Janssens 2007 KHM (5)	56/228	67/236		0.87 [0.64, 1.17]
Smithuis 2006 MMR (6)	8/156	10/162		0.83 [0.34, 2.05]
Smithuis 2010 MMR (7)	10/161	25/330		0.82 [0.40, 1.67]
Tangpukdee 2005 THA (8)	0/120	0/60		0.0 [0.0, 0.0]
Valecha 2010 AS (9)	4/769	0/381		4.46 [0.24, 82.72]
Subtotal (95% CI)	**2275**	**1839**		**0.91 [0.71, 1.15]**

Total events: 105 (DHA-P), 124 (AS+MQ)
Heterogeneity: Chi^2 = 3.21, df = 6 (P = 0.78); I^2 =0.0%
Test for overall effect: Z = 0.81 (P = 0.42)

0.005 0.1 1 10 200

Favours DHA-P   Favours AS+MQ

(*Continued* . . .)

Study or subgroup	DHA-P n/N	AS+MQ n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
2 Nausea				
Ashley 2004b THA	16/179	26/176		0.61 [0.34, 1.09]
Ashley 2005 THA	37/333	22/166		0.84 [0.51, 1.37]
Grande 2007 PER	126/262	156/260		0.80 [0.68, 0.94]
Janssens 2007 KHM	15/228	29/236		0.54 [0.29, 0.97]
Mayxay 2006 LAO	6/110	24/110		0.25 [0.11, 0.59]
Smithuis 2006 MMR	39/327	65/325		0.60 [0.41, 0.86]
Smithuis 2010 MMR	28/161	63/330		0.91 [0.61, 1.36]
Tangpukdee 2005 THA	5/120	4/60		0.63 [0.17, 2.24]
Valecha 2010 AS	22/767	26/381		0.42 [0.24, 0.73]
Subtotal (95% CI)	**2487**	**2044**		**0.68 [0.60, 0.78]**

Total events: 294 (DHA-P), 415 (AS+MQ)
Heterogeneity: Chi² = 15.98, df = 8 (P = 0.04); I² =50%
Test for overall effect: Z = 5.85 (P < 0.00001)

Study or subgroup	DHA-P n/N	AS+MQ n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
3 Vomiting				
Ashley 2004b THA	8/179	14/176		0.56 [0.24, 1.31]
Ashley 2005 THA	23/333	18/166		0.64 [0.35, 1.15]
Grande 2007 PER	53/262	73/260		0.72 [0.53, 0.98]
Mayxay 2006 LAO	3/110	11/110		0.27 [0.08, 0.95]
Valecha 2010 AS	19/767	24/381		0.39 [0.22, 0.71]
Subtotal (95% CI)	**1651**	**1093**		**0.59 [0.47, 0.75]**

Total events: 106 (DHA-P), 140 (AS+MQ)
Heterogeneity: Chi² = 4.95, df = 4 (P = 0.29); I² =19%
Test for overall effect: Z = 4.39 (P = 0.000011)

Study or subgroup	DHA-P n/N	AS+MQ n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
4 Anorexia				
Grande 2007 PER	111/262	112/260		0.98 [0.81, 1.20]
Janssens 2007 KHM	15/228	26/236		0.60 [0.32, 1.10]
Mayxay 2006 LAO	10/110	17/110		0.59 [0.28, 1.23]
Smithuis 2006 MMR	10/327	19/325		0.52 [0.25, 1.11]
Smithuis 2010 MMR	22/161	46/330		0.98 [0.61, 1.57]
Valecha 2010 AS	38/767	21/381		0.90 [0.54, 1.51]
Subtotal (95% CI)	**1855**	**1642**		**0.86 [0.73, 1.02]**

Total events: 206 (DHA-P), 241 (AS+MQ)
Heterogeneity: Chi² = 6.12, df = 5 (P = 0.29); I² =18%
Test for overall effect: Z = 1.77 (P = 0.076)

5 Diarrhoea

0.005   0.1   1   10   200

Favours DHA-P   Favours AS+MQ

(*Continued* . . .)

Study or subgroup	DHA-P n/N	AS+MQ n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Ashley 2004b THA	12/179	8/176		1.47 [0.62, 3.52]
Ashley 2005 THA	33/333	8/166		2.06 [0.97, 4.35]
Mayxay 2006 LAO	8/110	9/110		0.89 [0.36, 2.22]
Smithuis 2006 MMR	11/327	9/325		1.21 [0.51, 2.89]
Smithuis 2010 MMR	20/161	27/330		1.52 [0.88, 2.62]
Subtotal (95% CI)	**1110**	**1107**		**1.46 [1.05, 2.04]**

Total events: 84 (DHA-P), 61 (AS+MQ)
Heterogeneity: Chi² = 2.13, df = 4 (P = 0.71); I² =0.0%
Test for overall effect: Z = 2.24 (P = 0.025)
6 Abdominal pain

Study or subgroup	DHA-P n/N	AS+MQ n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Ashley 2004b THA	22/179	8/176		2.70 [1.24, 5.91]
Ashley 2005 THA	28/333	13/166		1.07 [0.57, 2.02]
Grande 2007 PER	73/262	79/260		0.92 [0.70, 1.20]
Mayxay 2006 LAO	12/110	18/110		0.67 [0.34, 1.32]
Smithuis 2006 MMR	3/327	0/325		6.96 [0.36, 134.16]
Smithuis 2010 MMR	19/161	49/330		0.79 [0.48, 1.30]
Valecha 2010 AS	40/767	20/381		0.99 [0.59, 1.68]
Subtotal (95% CI)	**2139**	**1748**		**0.99 [0.82, 1.20]**

Total events: 197 (DHA-P), 187 (AS+MQ)
Heterogeneity: Chi² = 10.45, df = 6 (P = 0.11); I² =43%
Test for overall effect: Z = 0.08 (P = 0.94)
Test for subgroup differences: Chi² = 31.62, df = 5 (P = 0.00), I² =84%

```
         0.005   0.1    1    10   200
        Favours DHA-P       Favours AS+MQ
```

(1) Ashley 2004a: 'Early vomiting'

(2) Ashley 2004b: Vomiting of drug dose

(3) Ashley 2005: Vomiting of drug dose

(4) Grande 2007: Vomiting within 1 hour of dose

(5) Janssens 2007: Vomiting on day 0

(6) Smithius 2006: Vomiting within 1 hour of dose

(7) Smithius: Vomiting in first 24 hours

(8) Tangpukdee 2005: Vomiting due to study drug

(9) Valecha 2010: Excluded due to persistent vomiting

Analysis 1.11. Comparison 1 Dihydroartemisinin-piperaquine versus Artesunate plus mefloquine, Outcome 11 Other adverse events: Neuro-psychiatric.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 1 Dihydroartemisinin-piperaquine versus Artesunate plus mefloquine

Outcome: 11 Other adverse events: Neuro-psychiatric

Study or subgroup	DHA-P n/N	AS+MQ n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Headache					
Mayxay 2006 LAO	11/110	30/110		22.1 %	0.37 [0.19, 0.69]
Smithuis 2010 MMR	2/161	0/330		0.2 %	10.22 [0.49, 211.56]
Tangpukdee 2005 THA	4/120	2/60		2.0 %	1.00 [0.19, 5.31]
Valecha 2010 AS	138/767	77/381		75.7 %	0.89 [0.69, 1.14]
Subtotal (95% CI)	**1158**	**881**		**100.0 %**	**0.80 [0.64, 1.00]**
Total events: 155 (DHA-P), 109 (AS+MQ)					
Heterogeneity: Chi² = 9.22, df = 3 (P = 0.03); I² =67%					
Test for overall effect: Z = 1.94 (P = 0.052)					
2 Dizziness					
Ashley 2004b THA	25/179	34/176		5.1 %	0.72 [0.45, 1.16]
Ashley 2005 THA	37/333	28/166		5.5 %	0.66 [0.42, 1.04]
Grande 2007 PER	185/262	218/260		32.3 %	0.84 [0.77, 0.93]
Janssens 2007 KHM	9/228	26/236		3.8 %	0.36 [0.17, 0.75]
Mayxay 2006 LAO	12/110	39/110		5.8 %	0.31 [0.17, 0.56]
Smithuis 2006 MMR	104/327	144/325		21.3 %	0.72 [0.59, 0.88]
Smithuis 2010 MMR	87/161	215/330		20.8 %	0.83 [0.70, 0.98]
Tangpukdee 2005 THA	4/120	3/60		0.6 %	0.67 [0.15, 2.88]
Valecha 2010 AS	11/767	24/381		4.7 %	0.23 [0.11, 0.46]
Subtotal (95% CI)	**2487**	**2044**		**100.0 %**	**0.72 [0.66, 0.78]**
Total events: 474 (DHA-P), 731 (AS+MQ)					
Heterogeneity: Chi² = 35.76, df = 8 (P = 0.00002); I² =78%					
Test for overall effect: Z = 7.94 (P < 0.00001)					
3 Sleeplessness					
Ashley 2004b THA	15/179	28/176		10.9 %	0.53 [0.29, 0.95]
Ashley 2005 THA	42/333	26/166		13.4 %	0.81 [0.51, 1.27]
Grande 2007 PER	27/262	98/260		37.9 %	0.27 [0.19, 0.40]
Janssens 2007 KHM	16/228	36/236		13.6 %	0.46 [0.26, 0.81]

0.005   0.1   1   10   200

Favours DHA-P   Favours AS+MQ

(*Continued* . . .)

Study or subgroup	DHA-P n/N	AS+MQ n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Mayxay 2006 LAO	17/110	31/110		11.9 %	0.55 [0.32, 0.93]
Smithuis 2010 MMR	18/161	49/330		12.4 %	0.75 [0.45, 1.25]
Subtotal (95% CI)	**1273**	**1278**		**100.0 %**	**0.49 [0.40, 0.60]**

Total events: 135 (DHA-P), 268 (AS+MQ)

Heterogeneity: Chi² = 16.29, df = 5 (P = 0.01); I² =69%

Test for overall effect: Z = 7.13 (P < 0.00001)

4 Fatigue

Mayxay 2006 LAO	13/110	28/110		82.3 %	0.46 [0.25, 0.85]
Smithuis 2006 MMR	1/327	6/325		17.7 %	0.17 [0.02, 1.37]
Subtotal (95% CI)	**437**	**435**		**100.0 %**	**0.41 [0.23, 0.73]**

Total events: 14 (DHA-P), 34 (AS+MQ)

Heterogeneity: Chi² = 0.87, df = 1 (P = 0.35); I² =0.0%

Test for overall effect: Z = 3.01 (P = 0.0026)

5 Nightmares

Mayxay 2006 LAO	1/110	11/110		100.0 %	0.09 [0.01, 0.69]
Subtotal (95% CI)	**110**	**110**		**100.0 %**	**0.09 [0.01, 0.69]**

Total events: 1 (DHA-P), 11 (AS+MQ)

Heterogeneity: not applicable

Test for overall effect: Z = 2.32 (P = 0.021)

6 Anxiety

Grande 2007 PER	3/262	29/260		100.0 %	0.10 [0.03, 0.33]
Subtotal (95% CI)	**262**	**260**		**100.0 %**	**0.10 [0.03, 0.33]**

Total events: 3 (DHA-P), 29 (AS+MQ)

Heterogeneity: not applicable

Test for overall effect: Z = 3.79 (P = 0.00015)

7 Blurred vision

Janssens 2007 KHM	10/228	21/236		100.0 %	0.49 [0.24, 1.02]
Subtotal (95% CI)	**228**	**236**		**100.0 %**	**0.49 [0.24, 1.02]**

Total events: 10 (DHA-P), 21 (AS+MQ)

Heterogeneity: not applicable

Test for overall effect: Z = 1.90 (P = 0.058)

8 Tinnitus

Mayxay 2006 LAO	4/110	10/110		100.0 %	0.40 [0.13, 1.24]
Subtotal (95% CI)	**110**	**110**		**100.0 %**	**0.40 [0.13, 1.24]**

Total events: 4 (DHA-P), 10 (AS+MQ)

Heterogeneity: not applicable

Test for overall effect: Z = 1.59 (P = 0.11)

Test for subgroup differences: Chi² = 32.52, df = 7 (P = 0.00), I² =78%

```
         0.005   0.1    1    10   200
         Favours DHA-P      Favours AS+MQ
```

Analysis 1.12.   Comparison I Dihydroartemisinin-piperaquine versus Artesunate plus mefloquine, Outcome 12 Other adverse events: Cardio-respiratory.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: I Dihydroartemisinin-piperaquine versus Artesunate plus mefloquine

Outcome: 12 Other adverse events: Cardio-respiratory

Study or subgroup	DHA-P n/N	AS+MQ n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
I Palpitations					
Janssens 2007 KHM	9/228	23/236		23.2 %	0.41 [0.19, 0.86]
Mayxay 2006 LAO	7/110	23/110		23.6 %	0.30 [0.14, 0.68]
Smithuis 2010 MMR	32/161	79/330		53.2 %	0.83 [0.58, 1.20]
Subtotal (95% CI)	**499**	**676**		**100.0 %**	**0.61 [0.45, 0.82]**
Total events: 48 (DHA-P), 125 (AS+MQ)					
Heterogeneity: Chi² = 6.78, df = 2 (P = 0.03); I² =71%					
Test for overall effect: Z = 3.26 (P = 0.0011)					
2 Cough					
Valecha 2010 AS	60/767	37/381		100.0 %	0.81 [0.54, 1.19]
Subtotal (95% CI)	**767**	**381**		**100.0 %**	**0.81 [0.54, 1.19]**
Total events: 60 (DHA-P), 37 (AS+MQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.08 (P = 0.28)					
3 Dyspnoea					
Mayxay 2006 LAO	3/110	10/110		100.0 %	0.30 [0.08, 1.06]
Subtotal (95% CI)	**110**	**110**		**100.0 %**	**0.30 [0.08, 1.06]**
Total events: 3 (DHA-P), 10 (AS+MQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.87 (P = 0.062)					
4 Prolonged QT interval (reported as adverse events)					
Valecha 2010 AS (1)	41/767	16/381		100.0 %	1.27 [0.72, 2.24]
Subtotal (95% CI)	**767**	**381**		**100.0 %**	**1.27 [0.72, 2.24]**
Total events: 41 (DHA-P), 16 (AS+MQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.84 (P = 0.40)					
5 Prolonged QT interval (Bazett's correction)					
Valecha 2010 AS	66/767	16/381		100.0 %	2.05 [1.20, 3.49]
Subtotal (95% CI)	**767**	**381**		**100.0 %**	**2.05 [1.20, 3.49]**
Total events: 66 (DHA-P), 16 (AS+MQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.64 (P = 0.0082)					

0.05   0.2   I   5   20

Favours DHA-P   Favours AS+MQ

(*Continued* . . .)

Study or subgroup	DHA-P	AS+MQ	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI

6 Prolonged QT interval (Fridericia's correction)

| Valecha 2010 AS | 36/767 | 20/381 | | 100.0 % | 0.89 [0.52, 1.52] |
| **Subtotal (95% CI)** | **767** | **381** | | **100.0 %** | **0.89 [0.52, 1.52]** |

Total events: 36 (DHA-P), 20 (AS+MQ)

Heterogeneity: not applicable

Test for overall effect: Z = 0.41 (P = 0.68)

Test for subgroup differences: Chi^2 = 20.02, df = 5 (P = 0.00), I^2 =75%

```
        0.05   0.2    1    5    20
        Favours DHA-P    Favours AS+MQ
```

(1) Defined as >450 ms in children and adult men and > 470 ms in adult women on day 2.

Analysis 1.13. Comparison 1 Dihydroartemisinin-piperaquine versus Artesunate plus mefloquine, Outcome 13 Other adverse events: Musculoskeletal/dermatological.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 1 Dihydroartemisinin-piperaquine versus Artesunate plus mefloquine

Outcome: 13 Other adverse events: Musculoskeletal/dermatological

Study or subgroup	DHA-P	AS+MQ	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI

1 Arthralgia

| Valecha 2010 AS | 42/767 | 21/381 | | 100.0 % | 0.99 [0.60, 1.65] |
| **Subtotal (95% CI)** | **767** | **381** | | **100.0 %** | **0.99 [0.60, 1.65]** |

Total events: 42 (DHA-P), 21 (AS+MQ)

Heterogeneity: not applicable

Test for overall effect: Z = 0.03 (P = 0.98)

2 Myalgia

| Valecha 2010 AS | 46/767 | 22/381 | | 100.0 % | 1.04 [0.63, 1.70] |
| **Subtotal (95% CI)** | **767** | **381** | | **100.0 %** | **1.04 [0.63, 1.70]** |

Total events: 46 (DHA-P), 22 (AS+MQ)

Heterogeneity: not applicable

Test for overall effect: Z = 0.15 (P = 0.88)

3 Urticaria

```
        0.002   0.1    1    10    500
        Favours DHA-P    Favours AS+MQ
```

(*Continued* . . .)

Study or subgroup	DHA-P	AS+MQ	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
Ashley 2005 THA	3/333	0/166		11.8 %	3.50 [0.18, 67.36]
Mayxay 2006 LAO	1/110	5/110		88.2 %	0.20 [0.02, 1.68]
Subtotal (95% CI)	**443**	**276**		**100.0 %**	**0.59 [0.15, 2.35]**

Total events: 4 (DHA-P), 5 (AS+MQ)

Heterogeneity: Chi² = 2.38, df = 1 (P = 0.12); I² =58%

Test for overall effect: Z = 0.75 (P = 0.45)

4 Pruritis

Mayxay 2006 LAO	4/110	11/110		95.6 %	0.36 [0.12, 1.11]
Smithuis 2006 MMR	3/327	0/325		4.4 %	6.96 [0.36, 134.16]
Subtotal (95% CI)	**437**	**435**		**100.0 %**	**0.65 [0.26, 1.60]**

Total events: 7 (DHA-P), 11 (AS+MQ)

Heterogeneity: Chi² = 3.51, df = 1 (P = 0.06); I² =72%

Test for overall effect: Z = 0.93 (P = 0.35)

5 Rash

Mayxay 2006 LAO	0/110	1/110		100.0 %	0.33 [0.01, 8.09]
Subtotal (95% CI)	**110**	**110**		**100.0 %**	**0.33 [0.01, 8.09]**

Total events: 0 (DHA-P), 1 (AS+MQ)

Heterogeneity: not applicable

Test for overall effect: Z = 0.68 (P = 0.50)

Test for subgroup differences: Chi² = 1.67, df = 4 (P = 0.80), I² =0.0%

```
          0.002    0.1    1    10    500
         Favours DHA-P        Favours AS+MQ
```

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 1 Dihydroartemisinin-piperaquine versus Artesunate plus mefloquine

Outcome: 14 Sensitivity analysis: Total failure Day 63 PCR-unadjusted

Study or subgroup	DHA-P	AS+MQ	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
	n/N	n/N			
1 Total failure (*P. falciparum*) Day 63 PCR-unadjusted					
Ashley 2004b THA	26/154	29/151		30.6 %	0.88 [0.54, 1.42]
Janssens 2007 KHM	18/195	22/207		27.7 %	0.87 [0.48, 1.57]
Ashley 2005 THA	29/318	27/157		30.4 %	0.53 [0.33, 0.86]
Grande 2007 PER	12/219	2/226		11.3 %	6.19 [1.40, 27.35]
Subtotal (95% CI)	**886**	**741**		**100.0 %**	**0.94 [0.52, 1.70]**
Total events: 85 (DHA-P), 80 (AS+MQ)					
Heterogeneity: Tau² = 0.24; Chi² = 10.50, df = 3 (P = 0.01); I² =71%					
Test for overall effect: Z = 0.21 (P = 0.83)					
2 Total failure Day 63 PCR-unadjusted (losses to follow-up included as failures)					
Ashley 2004b THA	51/179	54/176		27.4 %	0.93 [0.67, 1.28]
Janssens 2007 KHM	38/215	45/230		25.0 %	0.90 [0.61, 1.33]
Ashley 2005 THA	43/332	36/166		24.6 %	0.60 [0.40, 0.89]
Grande 2007 PER	45/252	27/251		23.1 %	1.66 [1.06, 2.59]
Subtotal (95% CI)	**978**	**823**		**100.0 %**	**0.95 [0.65, 1.38]**
Total events: 177 (DHA-P), 162 (AS+MQ)					
Heterogeneity: Tau² = 0.11; Chi² = 11.26, df = 3 (P = 0.01); I² =73%					
Test for overall effect: Z = 0.29 (P = 0.77)					
3 Total failure Day 63 PCR-unadjusted (losses to follow-up included as successes)					
Ashley 2004b THA	26/179	29/176		30.6 %	0.88 [0.54, 1.43]
Janssens 2007 KHM	18/215	22/230		27.7 %	0.88 [0.48, 1.59]
Ashley 2005 THA	29/332	27/166		30.5 %	0.54 [0.33, 0.88]
Grande 2007 PER	12/252	2/251		11.1 %	5.98 [1.35, 26.43]
Subtotal (95% CI)	**978**	**823**		**100.0 %**	**0.94 [0.52, 1.68]**
Total events: 85 (DHA-P), 80 (AS+MQ)					
Heterogeneity: Tau² = 0.23; Chi² = 10.06, df = 3 (P = 0.02); I² =70%					
Test for overall effect: Z = 0.22 (P = 0.82)					

```
        0.05   0.2    1    5    20
        Favours DHA-P      Favours AS+MQ
```

Analysis 1.15. Comparison 1 Dihydroartemisinin-piperaquine versus Artesunate plus mefloquine, Outcome 15 Sensitivity analysis: Total failure Day 63 PCR-adjusted.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 1 Dihydroartemisinin-piperaquine versus Artesunate plus mefloquine

Outcome: 15 Sensitivity analysis: Total failure Day 63 PCR-adjusted

Study or subgroup	DHA-P n/N	AS+MQ n/N	Risk Ratio M- H,Random,95% CI	Weight	Risk Ratio M- H,Random,95% CI
1 Total failure (*P. falciparum*) Day 63 PCR-adjusted					
Ashley 2004b THA	3/131	9/131		29.7 %	0.33 [0.09, 1.20]
Janssens 2007 KHM	4/181	5/190		29.5 %	0.84 [0.23, 3.08]
Ashley 2005 THA	3/292	7/137		28.8 %	0.20 [0.05, 0.77]
Grande 2007 PER	4/211	0/224		12.0 %	9.55 [0.52, 176.35]
Subtotal (95% CI)	**815**	**682**		**100.0 %**	**0.57 [0.17, 1.83]**
Total events: 14 (DHA-P), 21 (AS+MQ)					
Heterogeneity: Tau² = 0.78; Chi² = 6.94, df = 3 (P = 0.07); I² =57%					
Test for overall effect: Z = 0.95 (P = 0.34)					
2 Total failure Day 63 PCR-adjusted (indeterminate PCR included as failures)					
Ashley 2004b THA	7/135	10/132		35.1 %	0.68 [0.27, 1.74]
Janssens 2007 KHM	4/181	6/191		24.2 %	0.70 [0.20, 2.45]
Ashley 2005 THA	6/295	8/138		30.9 %	0.35 [0.12, 0.99]
Grande 2007 PER	4/211	1/225		9.8 %	4.27 [0.48, 37.86]
Subtotal (95% CI)	**822**	**686**		**100.0 %**	**0.67 [0.32, 1.39]**
Total events: 21 (DHA-P), 25 (AS+MQ)					
Heterogeneity: Tau² = 0.17; Chi² = 4.28, df = 3 (P = 0.23); I² =30%					
Test for overall effect: Z = 1.08 (P = 0.28)					
3 Total failure Day 63 PCR-adjusted (new infections included as successes)					
Ashley 2004b THA	7/154	10/151		35.8 %	0.69 [0.27, 1.76]
Janssens 2007 KHM	4/195	6/207		23.8 %	0.71 [0.20, 2.47]
Ashley 2005 THA	6/318	8/157		31.1 %	0.37 [0.13, 1.05]
Grande 2007 PER	4/219	1/226		9.3 %	4.13 [0.47, 36.64]
Subtotal (95% CI)	**886**	**741**		**100.0 %**	**0.67 [0.34, 1.35]**
Total events: 21 (DHA-P), 25 (AS+MQ)					
Heterogeneity: Tau² = 0.12; Chi² = 3.96, df = 3 (P = 0.27); I² =24%					
Test for overall effect: Z = 1.11 (P = 0.27)					
4 Total failure Day 63 PCR-adjusted (losses to follow-up included as failures)					
Ashley 2004b THA	32/179	35/176		29.3 %	0.90 [0.58, 1.38]

0.001 0.01 0.1 1 10 100 1000

Favours DHA-P   Favours AS+MQ

(*Continued* . . .)

Study or subgroup	DHA-P	AS+MQ	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
	n/N	n/N			
Janssens 2007 KHM	24/215	29/230		24.6 %	0.89 [0.53, 1.47]
Ashley 2005 THA	20/332	17/166		19.2 %	0.59 [0.32, 1.09]
Grande 2007 PER	37/252	26/251		26.9 %	1.42 [0.89, 2.27]
Subtotal (95% CI)	**978**	**823**		**100.0 %**	**0.93 [0.67, 1.30]**

Total events: 113 (DHA-P), 107 (AS+MQ)

Heterogeneity: Tau^2 = 0.05; Chi^2 = 5.22, df = 3 (P = 0.16); I^2 =43%

Test for overall effect: Z = 0.41 (P = 0.68)

5 Total failure Day 63 PCR-adjusted (losses to follow-up included as successes)

Ashley 2004b THA	7/179	10/176		36.1 %	0.69 [0.27, 1.77]
Janssens 2007 KHM	4/215	6/230		23.6 %	0.71 [0.20, 2.49]
Ashley 2005 THA	6/332	8/166		31.3 %	0.38 [0.13, 1.06]
Grande 2007 PER	4/252	1/251		9.0 %	3.98 [0.45, 35.40]
Subtotal (95% CI)	**978**	**823**		**100.0 %**	**0.67 [0.34, 1.33]**

Total events: 21 (DHA-P), 25 (AS+MQ)

Heterogeneity: Tau^2 = 0.10; Chi^2 = 3.80, df = 3 (P = 0.28); I^2 =21%

Test for overall effect: Z = 1.14 (P = 0.25)

```
0.001 0.01  0.1   1   10  100 1000
```

Favours DHA-P   Favours AS+MQ

Analysis 2.1.   Comparison 2 Dihydroartemisinin-piperaquine dose analysis: 3 dose versus 4 dose regimen, Outcome 1 Total failure PCR-unadjusted.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 2 Dihydroartemisinin-piperaquine dose analysis: 3 dose versus 4 dose regimen

Outcome: 1 Total failure PCR-unadjusted

Study or subgroup	DHA-P (4 doses) n/N	DHA-P (3 doses) n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Day 63					
Ashley 2005 THA	18/155	11/163		100.0 %	1.72 [0.84, 3.53]
Total (95% CI)	**155**	**163**		**100.0 %**	**1.72 [0.84, 3.53]**
Total events: 18 (DHA-P (4 doses)), 11 (DHA-P (3 doses))					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.48 (P = 0.14)					
Test for subgroup differences: Not applicable					

```
            0.01    0.1    1    10    100
      Favours DHA-P (4 doses)    Favours DHA-P (3 doses)
```
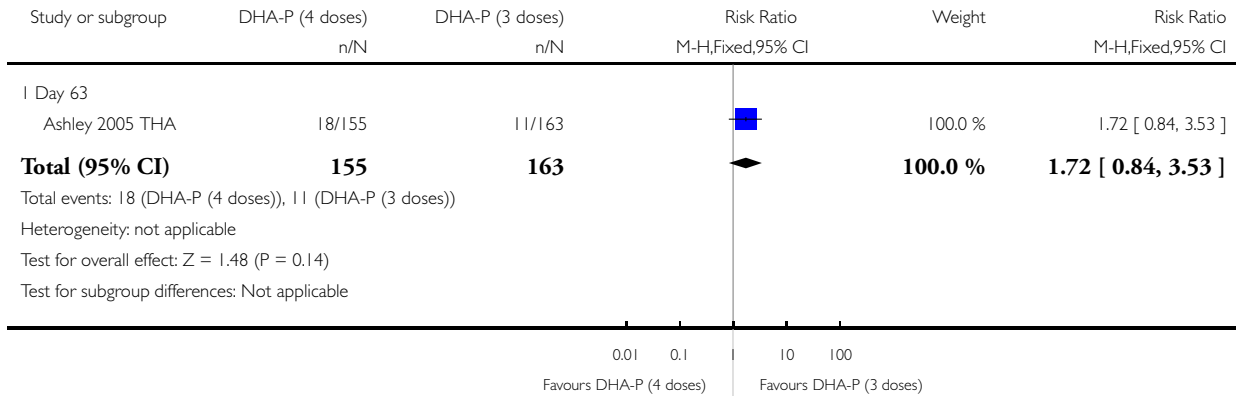
Analysis 2.2.   Comparison 2 Dihydroartemisinin-piperaquine dose analysis: 3 dose versus 4 dose regimen, Outcome 2 Total failure PCR-adjusted.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 2 Dihydroartemisinin-piperaquine dose analysis: 3 dose versus 4 dose regimen

Outcome: 2 Total failure PCR-adjusted

Study or subgroup	DHA-P (4 doses) n/N	DHA-P (3 doses) n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Day 63					
Ashley 2005 THA	1/138	2/154		100.0 %	0.56 [0.05, 6.09]
Total (95% CI)	**138**	**154**		**100.0 %**	**0.56 [0.05, 6.09]**
Total events: 1 (DHA-P (4 doses)), 2 (DHA-P (3 doses))					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.48 (P = 0.63)					
Test for subgroup differences: Not applicable					

```
            0.01    0.1    1    10    100
      Favours DHA-P (4 doses)    Favours DHA-P (3 doses)
```
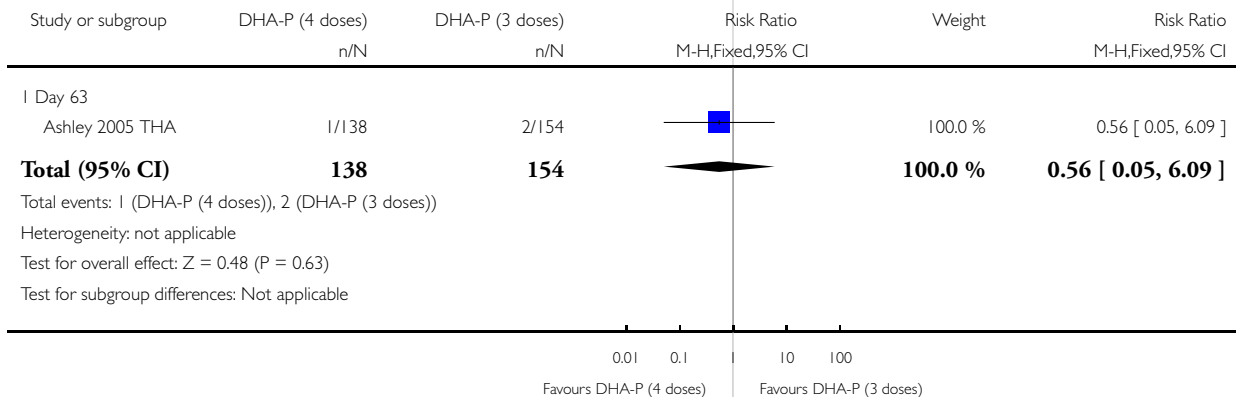
Analysis 3.1. Comparison 3 Dihydroartemisinin-piperaquine dose analysis (versus Artesunate plus mefloquine), Outcome 1 Total failure Day 28 PCR-unadjusted.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 3 Dihydroartemisinin-piperaquine dose analysis (versus Artesunate plus mefloquine)

Outcome: 1 Total failure Day 28 PCR-unadjusted

Study or subgroup	DHA-P n/N	ASMQ n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 DHA-P 4 doses				
Ashley 2004a THA	1/59	0/59		3.00 [0.12, 72.18]
Ashley 2005 THA	2/155	13/157		0.16 [0.04, 0.68]
Janssens 2007 KHM	2/195	2/207		1.06 [0.15, 7.46]
Tran 2004 VNM	0/166	0/77		0.0 [0.0, 0.0]
Subtotal (95% CI)	**575**	**500**		**0.56 [0.10, 3.14]**
Total events: 5 (DHA-P), 15 (ASMQ)				
Heterogeneity: Tau² = 1.18; Chi² = 4.12, df = 2 (P = 0.13); I² =52%				
Test for overall effect: Z = 0.66 (P = 0.51)				
2 DHA-P 3 doses				
Ashley 2005 THA	3/163	13/157		0.22 [0.06, 0.77]
Smithuis 2006 MMR	6/319	0/316		12.88 [0.73, 227.64]
Smithuis 2010 MMR	5/154	2/296		4.81 [0.94, 24.48]
Tangpukdee 2005 THA	1/107	0/54		1.53 [0.06, 36.89]
Valecha 2010 AS	6/667	17/336		0.18 [0.07, 0.45]
Subtotal (95% CI)	**1410**	**1159**		**0.98 [0.19, 5.07]**
Total events: 21 (DHA-P), 32 (ASMQ)				
Heterogeneity: Tau² = 2.52; Chi² = 19.65, df = 4 (P = 0.00059); I² =80%				
Test for overall effect: Z = 0.02 (P = 0.98)				
Total (95% CI)	**1985**	**1659**		**0.78 [0.25, 2.41]**
Total events: 26 (DHA-P), 47 (ASMQ)				
Heterogeneity: Tau² = 1.68; Chi² = 23.45, df = 7 (P = 0.001); I² =70%				
Test for overall effect: Z = 0.44 (P = 0.66)				
Test for subgroup differences: Chi² = 0.21, df = 1 (P = 0.64), I² =0.0%				

```
        0.005   0.1    1    10   200
      Favours DHA-P      Favours ASMQ
```

Analysis 3.2. Comparison 3 Dihydroartemisinin-piperaquine dose analysis (versus Artesunate plus mefloquine), Outcome 2 Total failure Day 28 PCR-adjusted.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 3 Dihydroartemisinin-piperaquine dose analysis (versus Artesunate plus mefloquine)

Outcome: 2 Total failure Day 28 PCR-adjusted

Study or subgroup	DHA-P n/N	ASMQ n/N	Risk Ratio M- H,Random,95% CI	Risk Ratio M- H,Random,95% CI
1 DHA-P 4 doses				
Ashley 2004a THA	1/59	0/59		3.00 [0.12, 72.18]
Ashley 2005 THA	1/154	7/151		0.14 [0.02, 1.12]
Janssens 2007 KHM	2/195	1/206		2.11 [0.19, 23.11]
Tran 2004 VNM	0/166	0/77		0.0 [0.0, 0.0]
Subtotal (95% CI)	**574**	**493**		**0.79 [0.10, 6.11]**
Total events: 4 (DHA-P), 8 (ASMQ)				
Heterogeneity: Tau² = 1.62; Chi² = 3.99, df = 2 (P = 0.14); I² =50%				
Test for overall effect: Z = 0.22 (P = 0.82)				
2 DHA-P 3 doses				
Ashley 2005 THA	1/161	7/151		0.13 [0.02, 1.08]
Smithuis 2006 MMR	2/315	0/316		5.02 [0.24, 104.06]
Smithuis 2010 MMR	0/149	1/310		0.69 [0.03, 16.86]
Tangpukdee 2005 THA	1/107	0/54		1.53 [0.06, 36.89]
Valecha 2010 AS	1/667	8/336		0.06 [0.01, 0.50]
Subtotal (95% CI)	**1399**	**1167**		**0.39 [0.08, 1.94]**
Total events: 5 (DHA-P), 16 (ASMQ)				
Heterogeneity: Tau² = 1.48; Chi² = 7.33, df = 4 (P = 0.12); I² =45%				
Test for overall effect: Z = 1.14 (P = 0.25)				
Total (95% CI)	**1973**	**1660**		**0.50 [0.15, 1.65]**
Total events: 9 (DHA-P), 24 (ASMQ)				
Heterogeneity: Tau² = 1.20; Chi² = 12.01, df = 7 (P = 0.10); I² =42%				
Test for overall effect: Z = 1.13 (P = 0.26)				
Test for subgroup differences: Chi² = 0.28, df = 1 (P = 0.60), I² =0.0%				

```
0.002   0.1   1   10   500
Favours DHA-P   Favours ASMQ
```

Analysis 3.3. Comparison 3 Dihydroartemisinin-piperaquine dose analysis (versus Artesunate plus mefloquine), Outcome 3 Total failure Day 42 PCR-unadjusted.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 3 Dihydroartemisinin-piperaquine dose analysis (versus Artesunate plus mefloquine)

Outcome: 3 Total failure Day 42 PCR-unadjusted

Study or subgroup	DHA-P n/N	ASMQ n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 DHA-P 4 doses					
Ashley 2005 THA	10/155	19/157		15.4 %	0.53 [0.26, 1.11]
Janssens 2007 KHM	9/195	9/207		12.9 %	1.06 [0.43, 2.62]
Tran 2004 VNM	16/166	7/77		13.7 %	1.06 [0.45, 2.47]
Subtotal (95% CI)	**516**	**441**		**42.1 %**	**0.80 [0.50, 1.28]**
Total events: 35 (DHA-P), 35 (ASMQ)					
Heterogeneity: Tau² = 0.0; Chi² = 1.98, df = 2 (P = 0.37); I² =0.0%					
Test for overall effect: Z = 0.94 (P = 0.35)					
2 DHA-P 3 doses					
Ashley 2005 THA	6/163	19/157		13.1 %	0.30 [0.12, 0.74]
Mayxay 2006 LAO	4/106	5/108		8.6 %	0.82 [0.23, 2.95]
Smithuis 2006 MMR	6/319	1/316		4.1 %	5.94 [0.72, 49.09]
Smithuis 2010 MMR	8/150	7/299		11.7 %	2.28 [0.84, 6.16]
Valecha 2010 AS	39/667	34/336		20.3 %	0.58 [0.37, 0.90]
Subtotal (95% CI)	**1405**	**1216**		**57.9 %**	**0.89 [0.40, 1.99]**
Total events: 63 (DHA-P), 66 (ASMQ)					
Heterogeneity: Tau² = 0.53; Chi² = 13.49, df = 4 (P = 0.01); I² =70%					
Test for overall effect: Z = 0.28 (P = 0.78)					
Total (95% CI)	**1921**	**1657**		**100.0 %**	**0.82 [0.51, 1.31]**
Total events: 98 (DHA-P), 101 (ASMQ)					
Heterogeneity: Tau² = 0.23; Chi² = 15.74, df = 7 (P = 0.03); I² =56%					
Test for overall effect: Z = 0.82 (P = 0.41)					
Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.81), I² =0.0%					

```
        0.01   0.1    I    10   100
          Favours DHA-P      Favours ASMQ
```

Analysis 3.4. Comparison 3 Dihydroartemisinin-piperaquine dose analysis (versus Artesunate plus mefloquine), Outcome 4 Total failure Day 42 PCR-adjusted.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 3 Dihydroartemisinin-piperaquine dose analysis (versus Artesunate plus mefloquine)

Outcome: 4 Total failure Day 42 PCR-adjusted

Study or subgroup	DHA-P n/N	ASMQ n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 DHA-P 4 doses					
Ashley 2005 THA	1/146	7/145		13.4 %	0.14 [0.02, 1.14]
Janssens 2007 KHM	3/189	2/200		16.8 %	1.59 [0.27, 9.39]
Tran 2004 VNM	2/152	1/71		10.9 %	0.93 [0.09, 10.13]
Subtotal (95% CI)	**487**	**416**		**41.2 %**	**0.62 [0.14, 2.82]**
Total events: 6 (DHA-P), 10 (ASMQ)					
Heterogeneity: Tau² = 0.69; Chi² = 3.24, df = 2 (P = 0.20); I² =38%					
Test for overall effect: Z = 0.62 (P = 0.54)					
2 DHA-P 3 doses					
Ashley 2005 THA	1/158	7/145		13.4 %	0.13 [0.02, 1.05]
Mayxay 2006 LAO	1/103	1/104		8.6 %	1.01 [0.06, 15.93]
Smithuis 2006 MMR	2/315	0/315		7.3 %	5.00 [0.24, 103.73]
Valecha 2010 AS	5/667	9/336		29.4 %	0.28 [0.09, 0.83]
Subtotal (95% CI)	**1243**	**900**		**58.8 %**	**0.43 [0.12, 1.48]**
Total events: 9 (DHA-P), 17 (ASMQ)					
Heterogeneity: Tau² = 0.57; Chi² = 4.56, df = 3 (P = 0.21); I² =34%					
Test for overall effect: Z = 1.34 (P = 0.18)					
Total (95% CI)	**1730**	**1316**		**100.0 %**	**0.49 [0.20, 1.18]**
Total events: 15 (DHA-P), 27 (ASMQ)					
Heterogeneity: Tau² = 0.39; Chi² = 8.31, df = 6 (P = 0.22); I² =28%					
Test for overall effect: Z = 1.60 (P = 0.11)					
Test for subgroup differences: Chi² = 0.14, df = 1 (P = 0.71), I² =0.0%					

```
        0.002    0.1     1    10    500
      Favours DHA-P      Favours ASMQ
```

Analysis 3.5. Comparison 3 Dihydroartemisinin-piperaquine dose analysis (versus Artesunate plus mefloquine), Outcome 5 Total failure Day 63 PCR-unadjusted.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 3 Dihydroartemisinin-piperaquine dose analysis (versus Artesunate plus mefloquine)

Outcome: 5 Total failure Day 63 PCR-unadjusted

Study or subgroup	DHA-P n/N	ASMQ n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 DHA-P 4 doses					
Ashley 2004b THA	26/154	29/151		17.1 %	0.88 [0.54, 1.42]
Ashley 2005 THA	18/155	27/157		15.8 %	0.68 [0.39, 1.17]
Janssens 2007 KHM	18/195	22/207		15.2 %	0.87 [0.48, 1.57]
Subtotal (95% CI)	**504**	**515**		**48.0 %**	**0.81 [0.59, 1.10]**
Total events: 62 (DHA-P), 78 (ASMQ)					
Heterogeneity: Tau² = 0.0; Chi² = 0.58, df = 2 (P = 0.75); I² =0.0%					
Test for overall effect: Z = 1.36 (P = 0.17)					
2 DHA-P 3 doses					
Ashley 2005 THA	11/163	27/157		14.0 %	0.39 [0.20, 0.76]
Grande 2007 PER	12/219	2/226		5.6 %	6.19 [1.40, 27.35]
Smithuis 2010 MMR	14/152	12/305		12.7 %	2.34 [1.11, 4.94]
Valecha 2010 AS	86/718	53/358		19.7 %	0.81 [0.59, 1.11]
Subtotal (95% CI)	**1252**	**1046**		**52.0 %**	**1.22 [0.52, 2.90]**
Total events: 123 (DHA-P), 94 (ASMQ)					
Heterogeneity: Tau² = 0.60; Chi² = 19.24, df = 3 (P = 0.00024); I² =84%					
Test for overall effect: Z = 0.46 (P = 0.65)					
Total (95% CI)	**1756**	**1561**		**100.0 %**	**0.93 [0.62, 1.40]**
Total events: 185 (DHA-P), 172 (ASMQ)					
Heterogeneity: Tau² = 0.19; Chi² = 19.96, df = 6 (P = 0.003); I² =70%					
Test for overall effect: Z = 0.33 (P = 0.74)					
Test for subgroup differences: Chi² = 0.80, df = 1 (P = 0.37), I² =0.0%					

```
        0.01    0.1      1     10    100
        Favours DHA-P        Favours ASMQ
```

Analysis 3.6. Comparison 3 Dihydroartemisinin-piperaquine dose analysis (versus Artesunate plus mefloquine), Outcome 6 Total failure Day 63 PCR-adjusted.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 3 Dihydroartemisinin-piperaquine dose analysis (versus Artesunate plus mefloquine)

Outcome: 6 Total failure Day 63 PCR-adjusted

Study or subgroup	DHA-P	ASMQ	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
	n/N	n/N			
1 DHA-P 4 doses					
Ashley 2004b THA	3/131	9/131		17.7 %	0.33 [0.09, 1.20]
Ashley 2005 THA	1/138	7/137		9.0 %	0.14 [0.02, 1.14]
Janssens 2007 KHM	4/181	5/190		17.5 %	0.84 [0.23, 3.08]
Subtotal (95% CI)	**450**	**458**		**44.2 %**	**0.42 [0.17, 1.04]**
Total events: 8 (DHA-P), 21 (ASMQ)					
Heterogeneity: Tau^2 = 0.09; Chi^2 = 2.31, df = 2 (P = 0.31); I^2 =13%					
Test for overall effect: Z = 1.88 (P = 0.060)					
2 DHA-P 3 doses					
Ashley 2005 THA	2/154	7/137		13.9 %	0.25 [0.05, 1.20]
Grande 2007 PER	4/211	0/224		5.1 %	9.55 [0.52, 176.35]
Smithuis 2010 MMR	2/140	2/295		10.0 %	2.11 [0.30, 14.80]
Valecha 2010 AS	11/667	10/336		26.8 %	0.55 [0.24, 1.29]
Subtotal (95% CI)	**1172**	**992**		**55.8 %**	**0.85 [0.26, 2.77]**
Total events: 19 (DHA-P), 19 (ASMQ)					
Heterogeneity: Tau^2 = 0.73; Chi^2 = 6.32, df = 3 (P = 0.10); I^2 =53%					
Test for overall effect: Z = 0.27 (P = 0.79)					
Total (95% CI)	**1622**	**1450**		**100.0 %**	**0.57 [0.28, 1.15]**
Total events: 27 (DHA-P), 40 (ASMQ)					
Heterogeneity: Tau^2 = 0.29; Chi^2 = 9.09, df = 6 (P = 0.17); I^2 =34%					
Test for overall effect: Z = 1.57 (P = 0.12)					
Test for subgroup differences: Chi^2 = 0.87, df = 1 (P = 0.35), I^2 =0.0%					

0.005   0.1   1   10   200

Favours DHA-P   Favours ASMQ

Analysis 4.1. Comparison 4 Dihydroartemisinin-piperaquine versus Artemether-lumefantrine, Outcome 1 Total failure (P. falciparum) Day 28 PCR-unadjusted.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 4 Dihydroartemisinin-piperaquine versus Artemether-lumefantrine

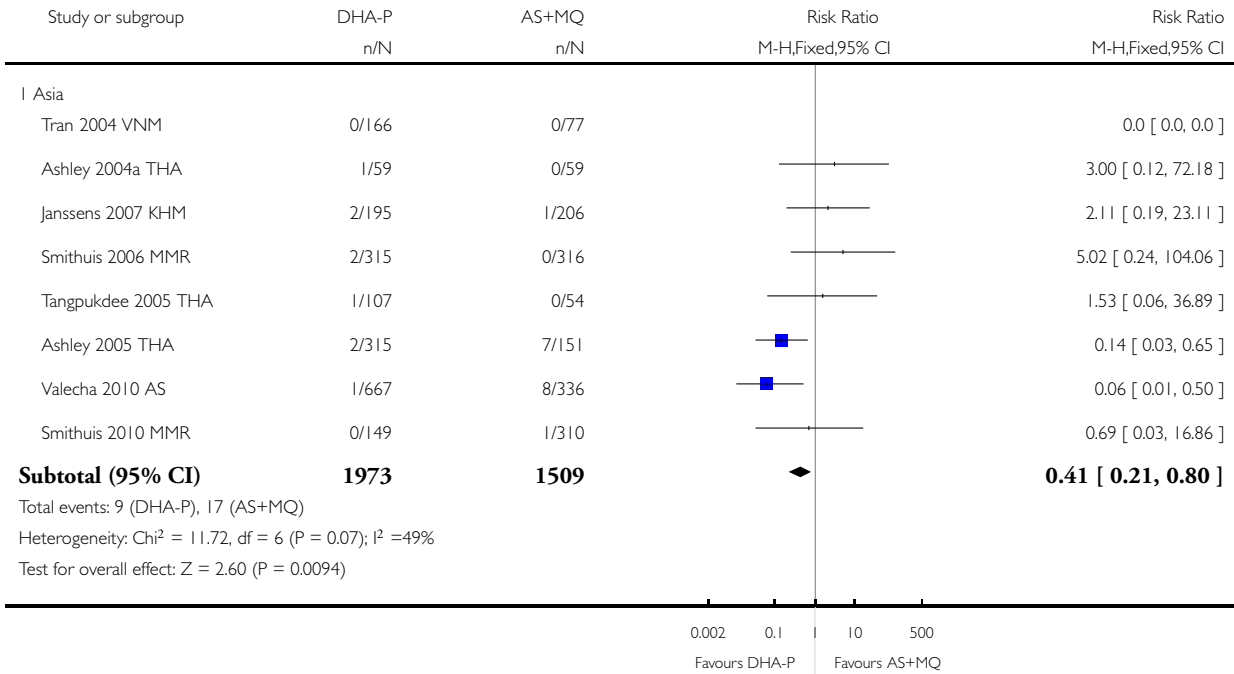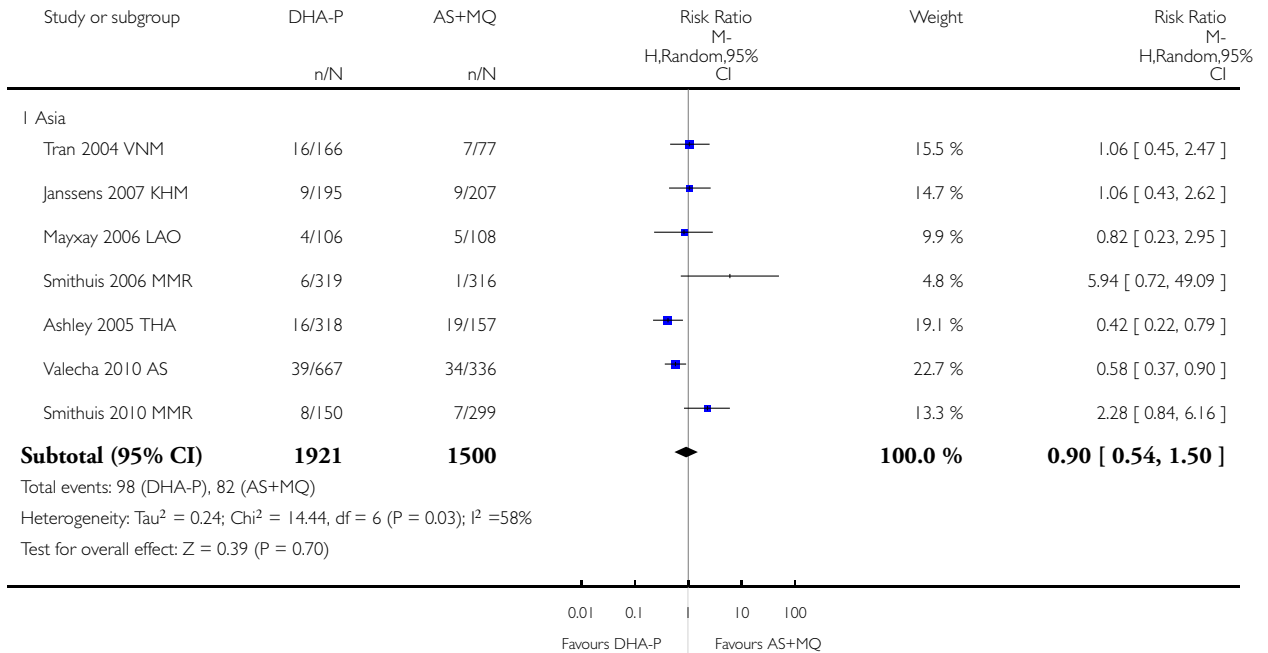Outcome: 1 Total failure (*P. falciparum*) Day 28 PCR-unadjusted

Study or subgroup	DHA-P n/N	AL6 n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Africa					
Bassat 2009 AF (1)	72/986	89/482		17.2 %	0.40 [0.30, 0.53]
Mens 2008 KEN	0/67	1/67		0.2 %	0.33 [0.01, 8.04]
Zongo 2007 BFA	4/172	36/178		5.1 %	0.11 [0.04, 0.32]
Yavo 2011 AF (2)	2/191	5/183		0.7 %	0.38 [0.08, 1.95]
Arinaitwe 2009 UGA	39/345	109/315		16.4 %	0.33 [0.23, 0.46]
Sawa 2013 KEN	0/137	10/147		1.5 %	0.05 [0.00, 0.86]
The 4ABC Study 2011 AF (3)	134/1378	334/1171		52.1 %	0.34 [0.28, 0.41]
Adam 2010 SDN	0/75	1/74		0.2 %	0.33 [0.01, 7.95]
Agarwal 2013 KEN	20/116	45/116		6.5 %	0.44 [0.28, 0.70]
Subtotal (95% CI)	**3467**	**2733**		**100.0 %**	**0.34 [0.30, 0.39]**

Total events: 271 (DHA-P), 630 (AL6)
Heterogeneity: Chi² = 8.59, df = 8 (P = 0.38); I² =7%
Test for overall effect: Z = 15.93 (P < 0.00001)

2 Asia and Oceania					
Ratcliff 2007 IDN	6/233	13/218		34.6 %	0.43 [0.17, 1.12]
Krudsood 2007 THA	1/82	0/81		1.3 %	2.96 [0.12, 71.70]
Karunajeewa 2008 PNG	25/111	20/113		51.1 %	1.27 [0.75, 2.15]
Smithuis 2010 MMR	5/154	5/151		13.0 %	0.98 [0.29, 3.32]
Subtotal (95% CI)	**580**	**563**		**100.0 %**	**0.97 [0.64, 1.47]**

Total events: 37 (DHA-P), 38 (AL6)
Heterogeneity: Chi² = 4.29, df = 3 (P = 0.23); I² =30%
Test for overall effect: Z = 0.17 (P = 0.87)
Test for subgroup differences: Chi² = 21.88, df = 1 (P = 0.00), I² =95%

```
        0.002   0.1    1    10    500
       Favours DHA-P      Favours AL6
```

(1) Bassat 2009 was conducted in Burkino Faso, Kenya, Mozambique, Uganda and Zambia

(2) Yavo 2011 was conducted in Senegal, Cote d'Ivoire and Cameroon

(3) The 4ABC study was conducted in Burkina Faso, Gabon, Nigeria, Zambia, Rwanda, Uganda and Mozambique

Analysis 4.2.   Comparison 4 Dihydroartemisinin-piperaquine versus Artemether-lumefantrine, Outcome 2 Total failure (P. falciparum) Day 28 PCR-adjusted.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 4 Dihydroartemisinin-piperaquine versus Artemether-lumefantrine

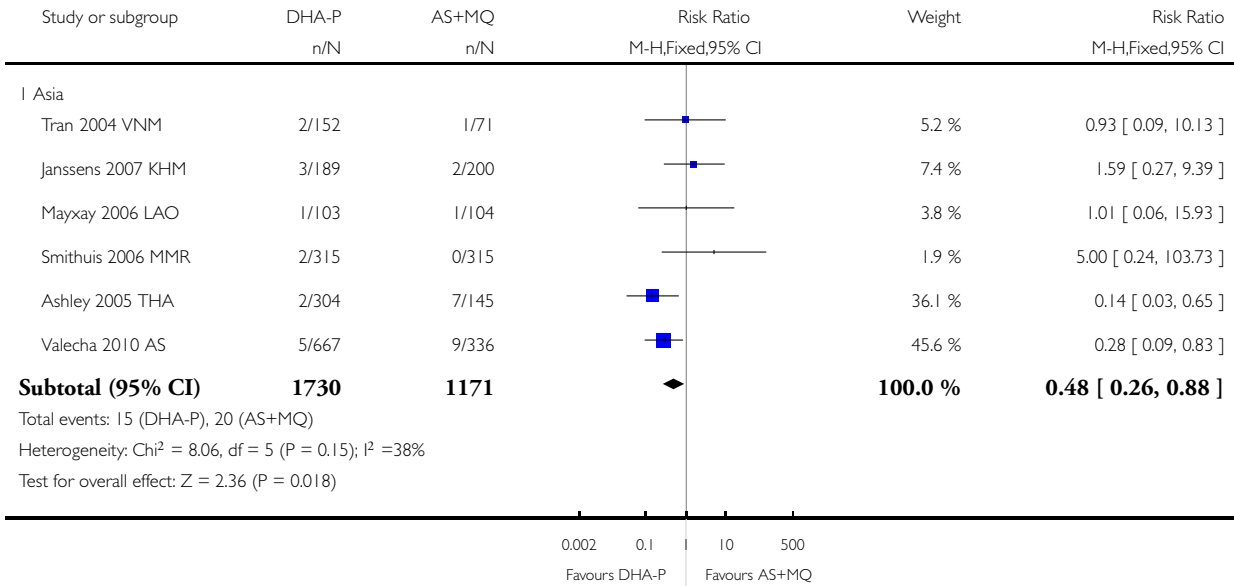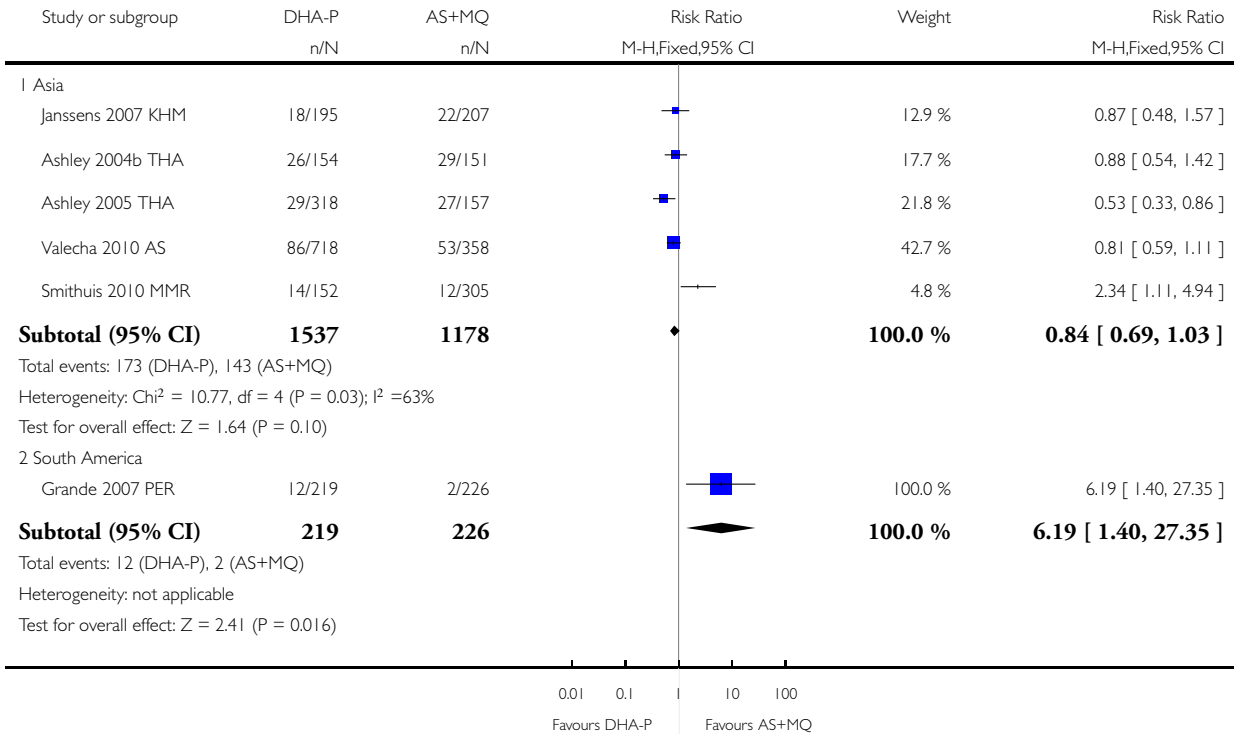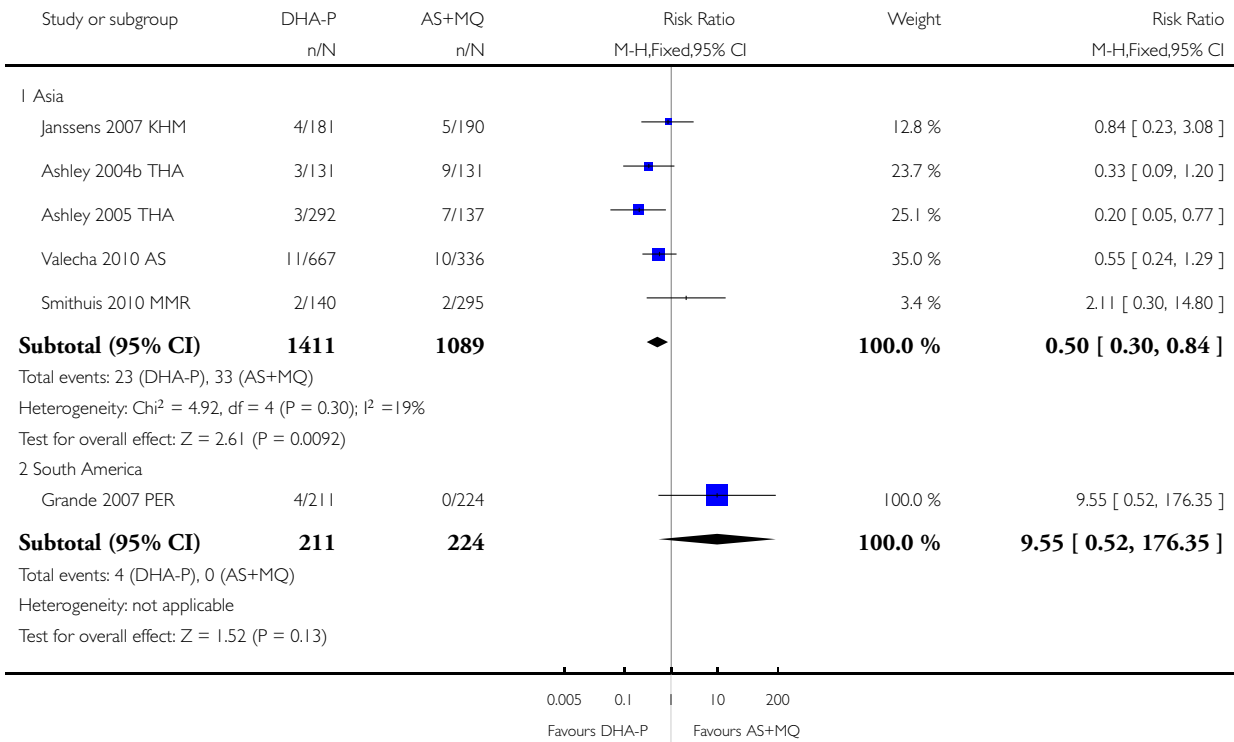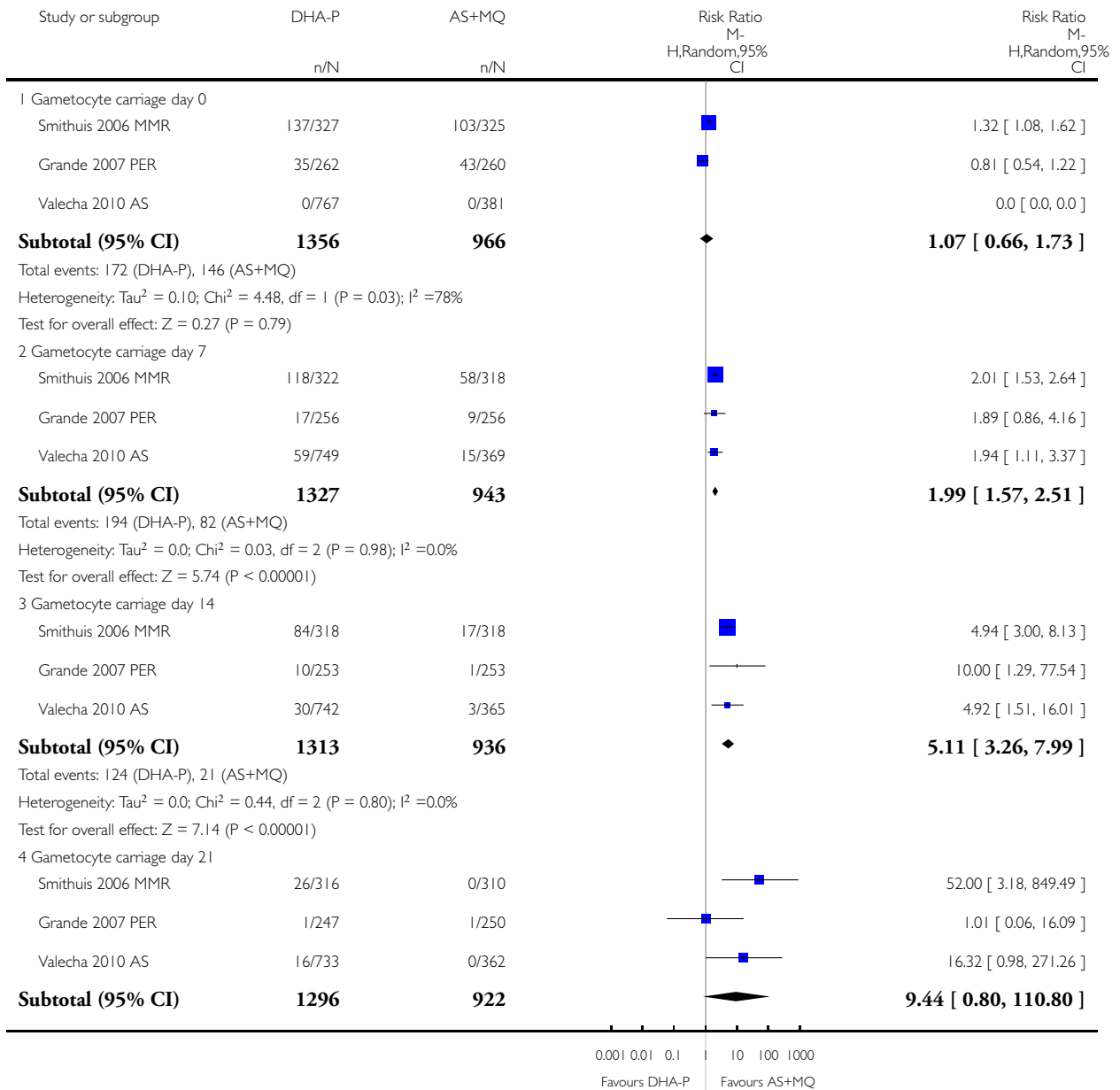Outcome: 2 Total failure (*P. falciparum*) Day 28 PCR-adjusted

Study or subgroup	DHA-P n/N	AL6 n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Africa				
Bassat 2009 AF (1)	14/937	11/400		0.54 [0.25, 1.19]
Mens 2008 KEN	0/67	0/66		0.0 [0.0, 0.0]
Zongo 2007 BFA	4/172	6/148		0.57 [0.17, 1.99]
Yavo 2011 AF (2)	1/190	2/180		0.47 [0.04, 5.18]
Arinaitwe 2009 UGA	1/307	3/208		0.23 [0.02, 2.16]
The 4ABC Study 2011 AF (3)	24/1268	41/878		0.41 [0.25, 0.67]
Sawa 2013 KEN	0/137	2/139		0.20 [0.01, 4.19]
Adam 2010 SDN	0/75	1/74		0.33 [0.01, 7.95]
Agarwal 2013 KEN	1/97	3/74		0.25 [0.03, 2.40]
Subtotal (95% CI)	**3250**	**2167**		**0.42 [0.29, 0.62]**
Total events: 45 (DHA-P), 69 (AL6)				
Heterogeneity: Chi² = 1.40, df = 7 (P = 0.99); I² =0.0%				
Test for overall effect: Z = 4.50 (P < 0.00001)				
2 Asia and Oceania				
Ratcliff 2007 IDN	2/229	2/207		0.90 [0.13, 6.36]
Karunajeewa 2008 PNG	11/97	3/96		3.63 [1.04, 12.60]
Smithuis 2010 MMR	0/149	1/147		0.33 [0.01, 8.01]
Subtotal (95% CI)	**475**	**450**		**2.01 [0.81, 5.03]**
Total events: 13 (DHA-P), 6 (AL6)				
Heterogeneity: Chi² = 2.74, df = 2 (P = 0.25); I² =27%				
Test for overall effect: Z = 1.50 (P = 0.13)				
Test for subgroup differences: Chi² = 9.54, df = 1 (P = 0.00), I² =90%				

0.005   0.1   1   10   200

Favours DHA-P   Favours AL6
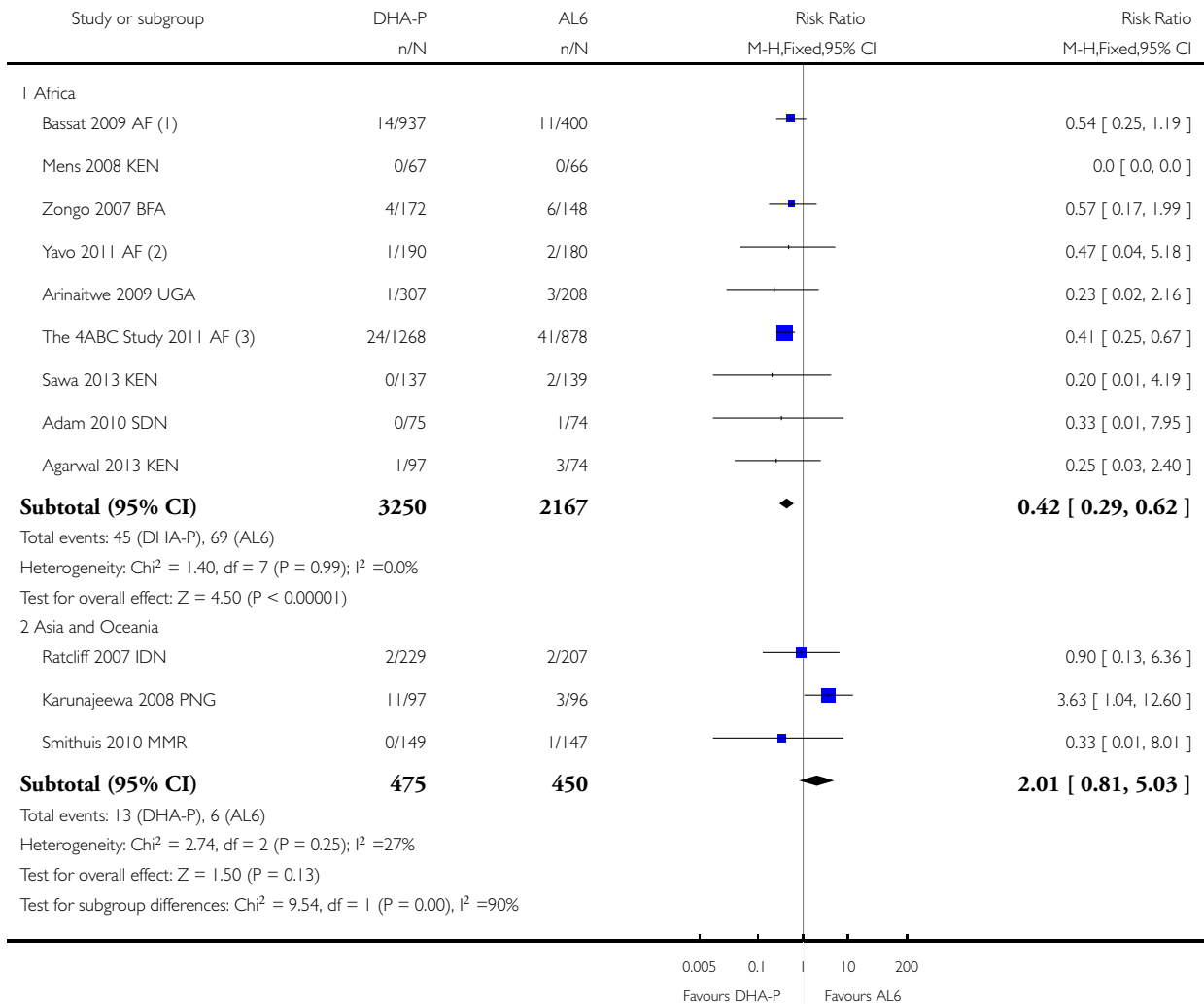
(1) Bassat 2009 was conducted in Burkino Faso, Kenya, Mozambique, Uganda and Zambia

(2) Yavo 2011 was conducted in Senegal, Cote d'Ivoire and Cameroon

(3) The 4ABC study was conducted in Burkina Faso, Gabon, Nigeria, Zambia, Rwanda, Uganda and Mozambique

Analysis 4.3. Comparison 4 Dihydroartemisinin-piperaquine versus Artemether-lumefantrine, Outcome 3 Total failure (P. falciparum) Day 42 PCR-unadjusted.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 4 Dihydroartemisinin-piperaquine versus Artemether-lumefantrine

Outcome: 3 Total failure (*P. falciparum*) Day 42 PCR-unadjusted

Study or subgroup	DHA-P n/N	AL6 n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Africa					
Kamya 2007 UGA	90/207	108/197		20.6 %	0.79 [0.65, 0.97]
Bassat 2009 AF (1)	200/973	147/467		36.9 %	0.65 [0.54, 0.78]
Zongo 2007 BFA	13/172	55/176		10.1 %	0.24 [0.14, 0.43]
Yeka 2008 UGA	21/207	46/177		9.2 %	0.39 [0.24, 0.63]
Arinaitwe 2009 UGA	16/114	33/108		6.3 %	0.46 [0.27, 0.79]
Sawa 2013 KEN	5/134	30/145		5.4 %	0.18 [0.07, 0.45]
Agarwal 2013 KEN	52/113	62/111		11.6 %	0.82 [0.64, 1.07]
Subtotal (95% CI)	**1920**	**1381**		**100.0 %**	**0.60 [0.53, 0.67]**
Total events: 397 (DHA-P), 481 (AL6)					
Heterogeneity: Chi² = 34.72, df = 6 (P<0.00001); I² =83%					
Test for overall effect: Z = 8.97 (P < 0.00001)					
2 Asia and Oceania					
Ratcliff 2007 IDN	19/195	26/161		41.8 %	0.60 [0.35, 1.05]
Karunajeewa 2008 PNG	42/107	40/109		58.2 %	1.07 [0.76, 1.50]
Subtotal (95% CI)	**302**	**270**		**100.0 %**	**0.87 [0.65, 1.17]**
Total events: 61 (DHA-P), 66 (AL6)					
Heterogeneity: Chi² = 3.07, df = 1 (P = 0.08); I² =67%					
Test for overall effect: Z = 0.90 (P = 0.37)					
Test for subgroup differences: Chi² = 5.66, df = 1 (P = 0.02), I² =82%					

```
        0.01    0.1      1      10     100
        Favours DHA-P        Favours AL6
```

(1) Bassat 2009 was conducted in Burkino Faso, Kenya, Mozambique, Uganda and Zambia

Analysis 4.4. Comparison 4 Dihydroartemisinin-piperaquine versus Artemether-lumefantrine, Outcome 4 Total failure (P. falciparum) Day 42 PCR-adjusted.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

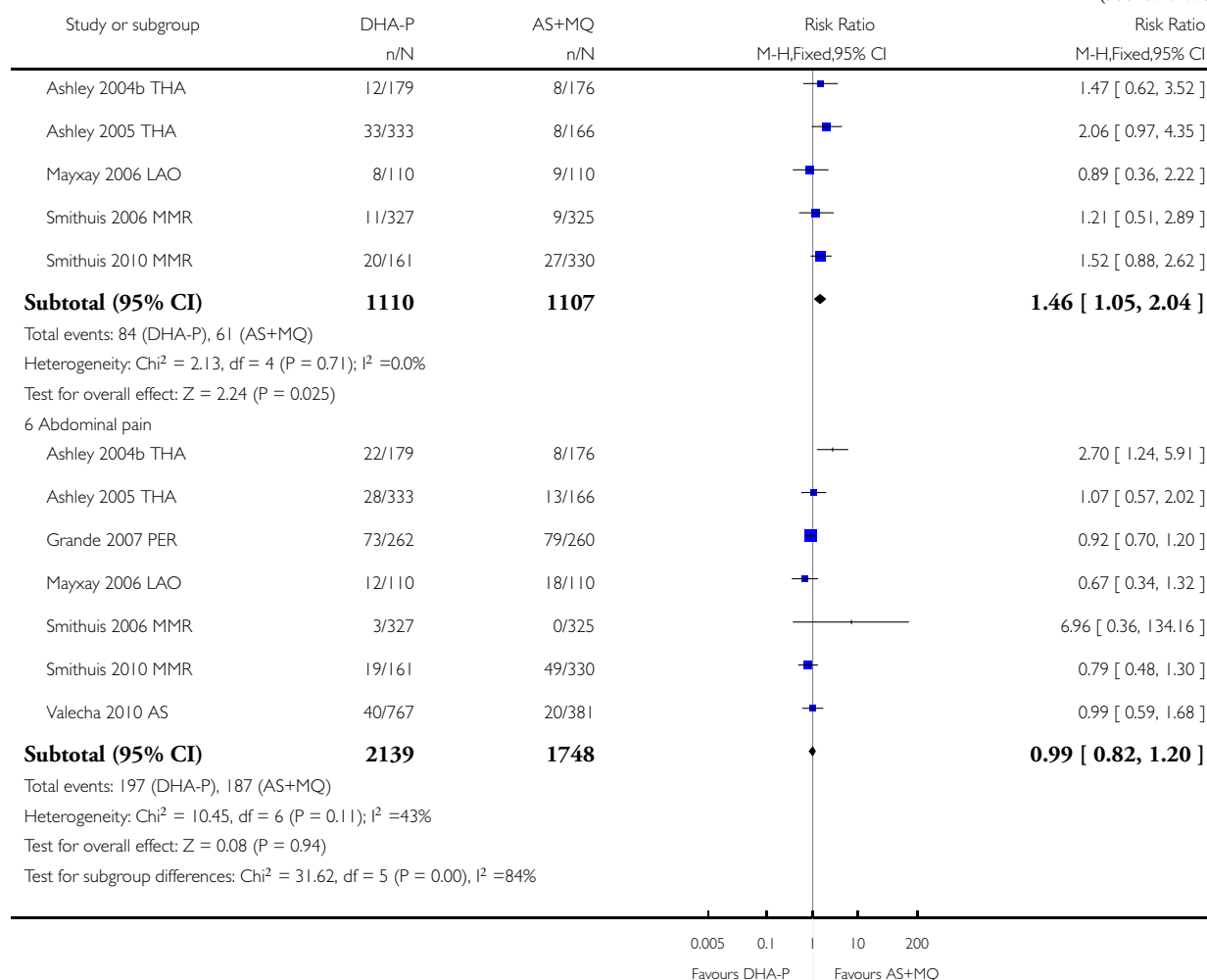Comparison: 4 Dihydroartemisinin-piperaquine versus Artemether-lumefantrine

Outcome: 4 Total failure (*P. falciparum*) Day 42 PCR-adjusted

Study or subgroup	DHA-P n/N	AL6 n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Africa				
Kamya 2007 UGA	13/130	28/117		0.42 [0.23, 0.77]
Bassat 2009 AF (1)	41/814	17/337		1.00 [0.58, 1.73]
Zongo 2007 BFA	4/163	7/128		0.45 [0.13, 1.50]
Yeka 2008 UGA	4/190	10/141		0.30 [0.10, 0.93]
Arinaitwe 2009 UGA	0/98	0/75		0.0 [0.0, 0.0]
Sawa 2013 KEN	0/129	4/119		0.10 [0.01, 1.88]
Agarwal 2013 KEN	4/65	4/53		0.82 [0.21, 3.11]
Subtotal (95% CI)	**1589**	**970**		**0.58 [0.41, 0.81]**
Total events: 66 (DHA-P), 70 (AL6)				
Heterogeneity: Chi² = 7.97, df = 5 (P = 0.16); I² =37%				
Test for overall effect: Z = 3.16 (P = 0.0016)				
2 Asia and Oceania				
Ratcliff 2007 IDN	3/179	3/138		0.77 [0.16, 3.76]
Karunajeewa 2008 PNG	12/77	5/74		2.31 [0.85, 6.23]
Subtotal (95% CI)	**256**	**212**		**1.69 [0.75, 3.83]**
Total events: 15 (DHA-P), 8 (AL6)				
Heterogeneity: Chi² = 1.32, df = 1 (P = 0.25); I² =24%				
Test for overall effect: Z = 1.26 (P = 0.21)				
Test for subgroup differences: Chi² = 5.68, df = 1 (P = 0.02), I² =82%				

0.005   0.1   1   10   200

Favours DHA-P   Favours AL6
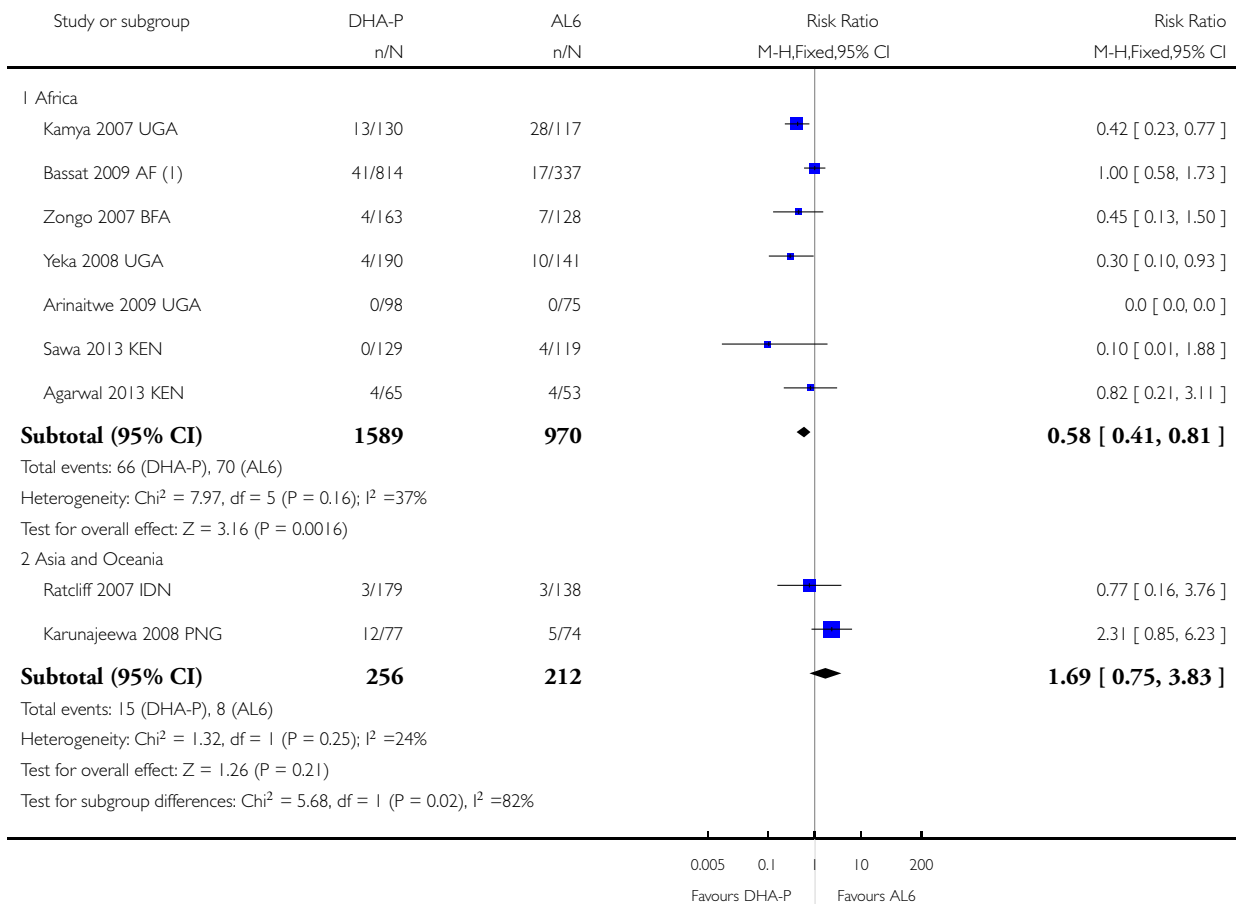
(1) Bassat 2009 was conducted in Burkino Faso, Kenya, Mozambique, Uganda and Zambia

Analysis 4.5. Comparison 4 Dihydroartemisinin-piperaquine versus Artemether-lumefantrine, Outcome 5 Total failure (P. falciparum) Day 63 PCR-unadjusted.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 4 Dihydroartemisinin-piperaquine versus Artemether-lumefantrine

Outcome: 5 Total failure (*P. falciparum*) Day 63 PCR-unadjusted

Study or subgroup	DHA-P n/N	AL6 n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Africa					
Arinaitwe 2009 UGA	46/351	110/320		16.2 %	0.38 [0.28, 0.52]
The 4ABC Study 2011 AF (1)	503/1369	550/1160		83.8 %	0.77 [0.71, 0.85]
Subtotal (95% CI)	**1720**	**1480**		**100.0 %**	**0.71 [0.65, 0.78]**
Total events: 549 (DHA-P), 660 (AL6)					
Heterogeneity: Chi² = 18.97, df = 1 (P = 0.00001); I² =95%					
Test for overall effect: Z = 7.54 (P < 0.00001)					
2 Asia					
Smithuis 2010 MMR	14/161	15/162		100.0 %	0.94 [0.47, 1.88]
Subtotal (95% CI)	**161**	**162**		**100.0 %**	**0.94 [0.47, 1.88]**
Total events: 14 (DHA-P), 15 (AL6)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.18 (P = 0.86)					
Test for subgroup differences: Chi² = 0.61, df = 1 (P = 0.44), I² =0.0%					

```
        0.05   0.2    1    5    20
        Favours DHA-P      Favours AL6
```

(1) The 4ABC study was conducted in Burkina Faso, Gabon, Nigeria, Zambia, Rwanda, Uganda and Mozambique

Analysis 4.6.   Comparison 4 Dihydroartemisinin-piperaquine versus Artemether-lumefantrine, Outcome 6 Total failure (P. falciparum) Day 63 PCR-adjusted.
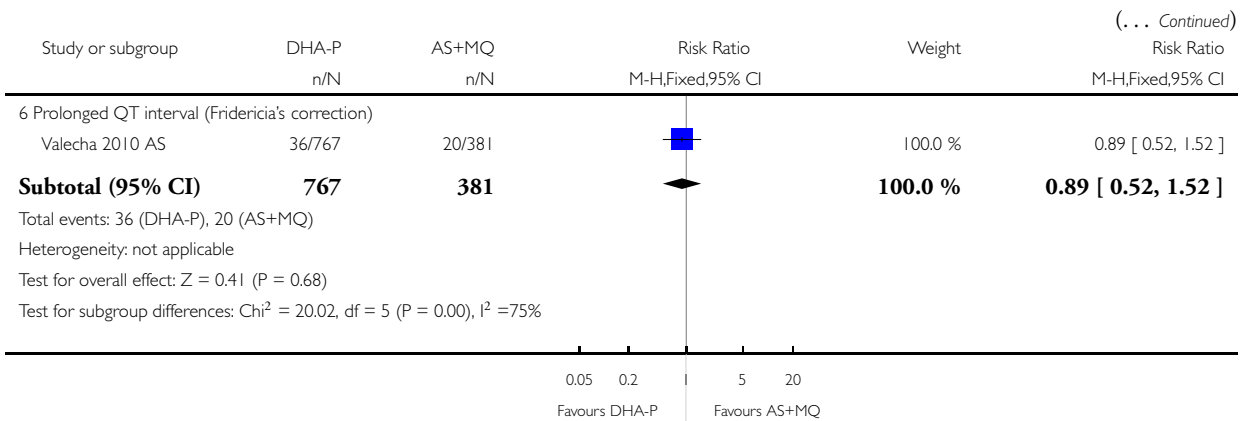
Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 4 Dihydroartemisinin-piperaquine versus Artemether-lumefantrine

Outcome: 6 Total failure (*P. falciparum*) Day 63 PCR-adjusted

Study or subgroup	DHA-P n/N	AL6 n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Africa					
Arinaitwe 2009 UGA	8/313	4/214		7.7 %	1.37 [0.42, 4.48]
The 4ABC Study 2011 AF (1)	45/911	49/659		92.3 %	0.66 [0.45, 0.98]
Subtotal (95% CI)	**1224**	**873**		**100.0 %**	**0.72 [0.50, 1.04]**
Total events: 53 (DHA-P), 53 (AL6)					
Heterogeneity: Chi² = 1.28, df = 1 (P = 0.26); I² =22%					
Test for overall effect: Z = 1.75 (P = 0.080)					
2 Asia					
Smithuis 2010 MMR	2/149	2/149		100.0 %	1.00 [0.14, 7.01]
Subtotal (95% CI)	**149**	**149**		**100.0 %**	**1.00 [0.14, 7.01]**
Total events: 2 (DHA-P), 2 (AL6)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
Test for subgroup differences: Chi² = 0.11, df = 1 (P = 0.74), I² =0.0%					

```
           0.01    0.1     1      10    100

         Favours DHA-P        Favours AL6
```
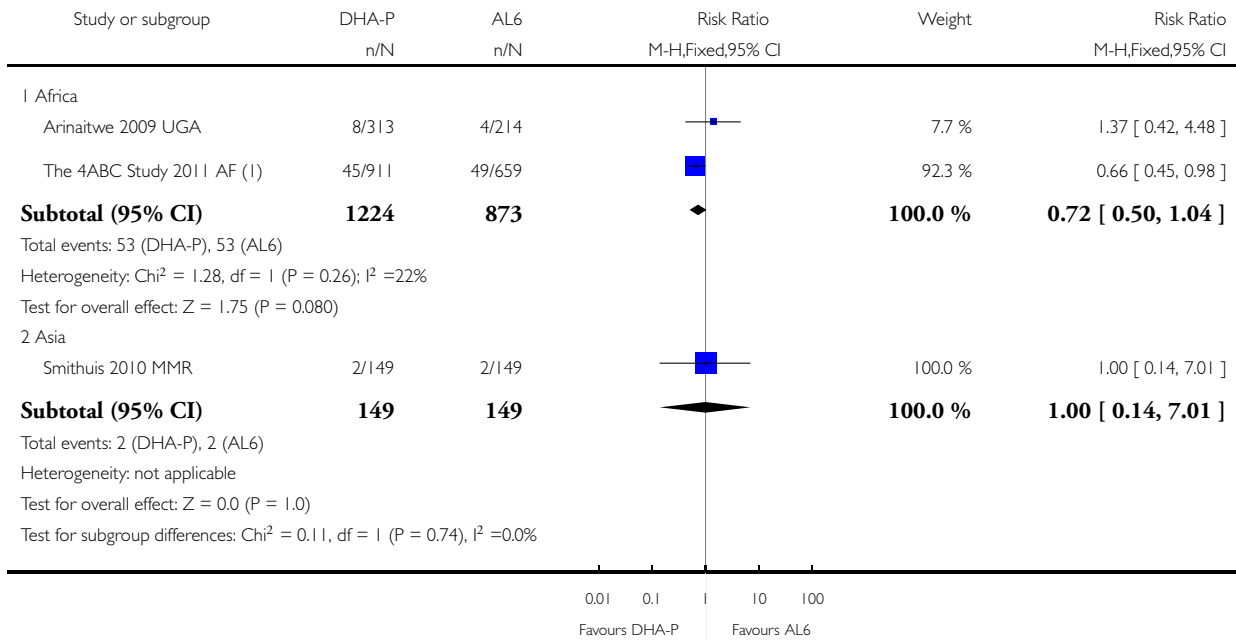
(1) The 4ABC study was conducted in Burkina Faso, Gabon, Nigeria, Zambia, Rwanda, Uganda and Mozambique

Analysis 4.7.   Comparison 4 Dihydroartemisinin-piperaquine versus Artemether-lumefantrine, Outcome 7 Gametocyte development (in those negative at baseline).

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 4 Dihydroartemisinin-piperaquine versus Artemether-lumefantrine

Outcome: 7 Gametocyte development (in those negative at baseline)

Study or subgroup	DHA-P	AL6	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
	n/N	n/N		
Kamya 2007 UGA	9/170	18/156		0.46 [0.21, 0.99]
Zongo 2007 BFA	7/184	3/188		2.38 [0.63, 9.08]
Yeka 2008 UGA	9/201	21/179		0.38 [0.18, 0.81]
Mens 2008 KEN	10/64	3/61		3.18 [0.92, 11.00]
Arinaitwe 2009 UGA	9/321	1/294		8.24 [1.05, 64.67]
Adam 2010 SDN	0/76	0/74		0.0 [0.0, 0.0]

```
          0.02  0.1       1      10   50
        Favours DHA-P      Favours AL6
```
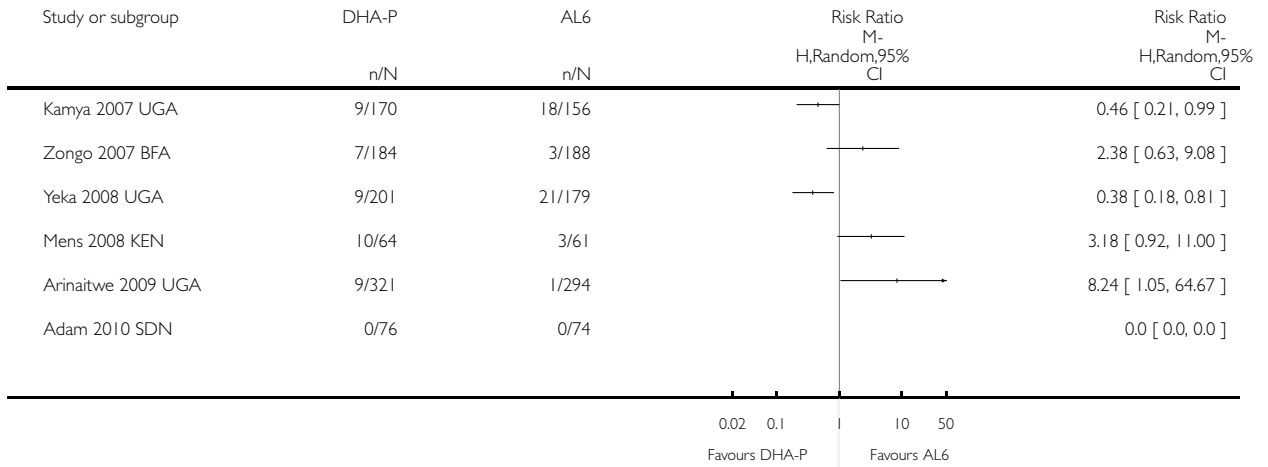
Analysis 4.8. Comparison 4 Dihydroartemisinin-piperaquine versus Artemether-lumefantrine, Outcome 8 Gametocyte carriage.
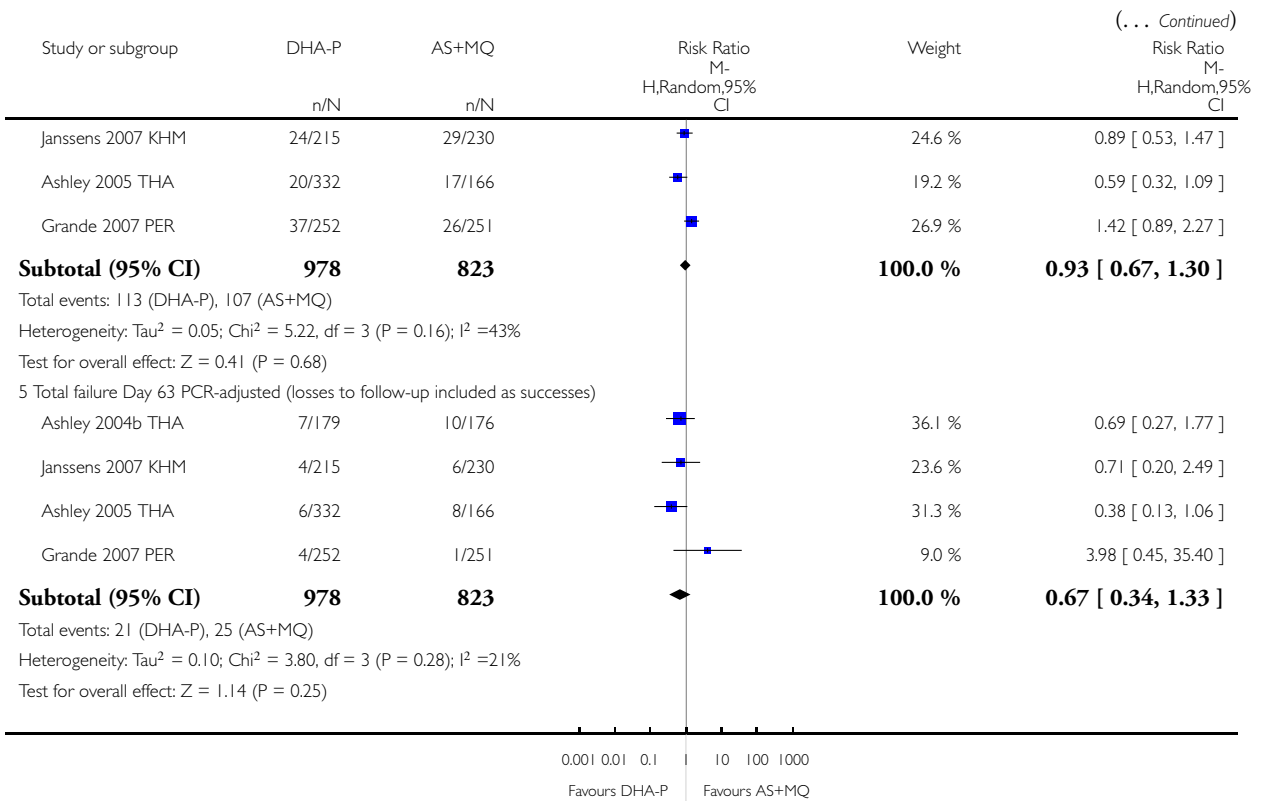
Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 4 Dihydroartemisinin-piperaquine versus Artemether-lumefantrine

Outcome: 8 Gametocyte carriage

Study or subgroup	DHA-P n/N	AL6 n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Gametocyte carriage day 1 to 14				
Kamya 2007 UGA	5/170	2/156		2.29 [0.45, 11.65]
Yeka 2008 UGA	4/201	1/179		3.56 [0.40, 31.58]
Arinaitwe 2009 UGA	10/351	1/320		9.12 [1.17, 70.82]
Adam 2010 SDN	0/80	0/80		0.0 [0.0, 0.0]
Subtotal (95% CI)	**802**	**735**		**4.32 [1.48, 12.63]**
Total events: 19 (DHA-P), 4 (AL6)				
Heterogeneity: Chi² = 1.12, df = 2 (P = 0.57); I² =0.0%				
Test for overall effect: Z = 2.67 (P = 0.0075)				
2 Gametocyte carriage day 15 to 28				
Kamya 2007 UGA	0/168	5/150		0.08 [0.00, 1.46]
Yeka 2008 UGA	1/200	7/178		0.13 [0.02, 1.02]
Arinaitwe 2009 UGA	1/351	0/320		2.74 [0.11, 66.92]
Adam 2010 SDN	0/75	0/74		0.0 [0.0, 0.0]
Subtotal (95% CI)	**794**	**722**		**0.21 [0.06, 0.72]**
Total events: 2 (DHA-P), 12 (AL6)				
Heterogeneity: Chi² = 3.12, df = 2 (P = 0.21); I² =36%				
Test for overall effect: Z = 2.47 (P = 0.013)				
3 Gametocyte carriage day 29 to 42				
Kamya 2007 UGA	4/159	11/123		0.28 [0.09, 0.86]
Yeka 2008 UGA	4/194	13/174		0.28 [0.09, 0.83]
Subtotal (95% CI)	**353**	**297**		**0.28 [0.13, 0.61]**
Total events: 8 (DHA-P), 24 (AL6)				
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.98); I² =0.0%				
Test for overall effect: Z = 3.19 (P = 0.0014)				

```
         0.005   0.1    1    10   200

         Favours DHA-P      Favours AL6
```

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 4 Dihydroartemisinin-piperaquine versus Artemether-lumefantrine

Outcome: 9 Anaemia

Study or subgroup	DHA-P N	Mean(SD)	AL6 N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Mean haemoglobin (g/dL) at baseline							
Bassat 2009 AF	1038	89.23 (18.15)	510	90.59 (18.2)		0.1 %	-1.36 [-3.29, 0.57]
Kamya 2007 UGA	211	9.5 (1.9)	210	9.7 (1.8)		1.8 %	-0.20 [-0.55, 0.15]
Yeka 2008 UGA	215	9.9 (2.1)	199	9.9 (1.9)		1.5 %	0.0 [-0.39, 0.39]
Zongo 2007 BFA	187	10.1 (2.4)	188	10.2 (2)		1.1 %	-0.10 [-0.55, 0.35]
Mens 2008 KEN	73	6.33 (1.29)	73	6.28 (1.27)		1.3 %	0.05 [-0.37, 0.47]
Arinaitwe 2009 UGA	351	9.9 (1.5)	320	9.8 (1.5)		4.4 %	0.10 [-0.13, 0.33]
The 4ABC Study 2011 AF	1475	9.4 (1.5)	1226	9.2 (1.5)		17.4 %	0.20 [0.09, 0.31]
Smithuis 2010 MMR	161	11.3 (0.24)	162	11.4 (0.27)		72.4 %	-0.10 [-0.16, -0.04]
Subtotal (95% CI)	**3711**		**2888**			**100.0 %**	**-0.04 [-0.09, 0.01]**
Heterogeneity: Chi² = 25.93, df = 7 (P = 0.00052); I² =73%							
Test for overall effect: Z = 1.58 (P = 0.11)							
2 Mean haemoglobin (g/dL) at day 28							
Mens 2008 KEN	67	7.15 (1.07)	67	6.79 (1.24)		100.0 %	0.36 [-0.03, 0.75]
Subtotal (95% CI)	**67**		**67**			**100.0 %**	**0.36 [-0.03, 0.75]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.80 (P = 0.072)							
3 Mean haemoglobin (g/dL) at day 42							
Zongo 2007 BFA	187	11.6 (1.6)	188	11.3 (1.6)		100.0 %	0.30 [-0.02, 0.62]
Subtotal (95% CI)	**187**		**188**			**100.0 %**	**0.30 [-0.02, 0.62]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.82 (P = 0.069)							
4 Mean change in haemoglobin (g/dL) from baseline to day 28							
Bassat 2009 AF	1020	1.7 (1.82)	494	1.43 (1.85)		60.9 %	0.27 [0.07, 0.47]
Arinaitwe 2009 UGA	351	0.62 (1.68)	320	0.56 (1.58)		39.1 %	0.06 [-0.19, 0.31]
Subtotal (95% CI)	**1371**		**814**			**100.0 %**	**0.19 [0.03, 0.34]**
Heterogeneity: Chi² = 1.69, df = 1 (P = 0.19); I² =41%							
Test for overall effect: Z = 2.39 (P = 0.017)							
5 Mean change in haemoglobin (g/dL) from baseline to day 42							

-2   -1   0   1   2

Favours AL6   Favours DHA-P

(*Continued* . . .)

Study or subgroup	DHA-P		AL6		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Kamya 2007 UGA	211	1.9 (1.8)	210	1.5 (1.8)		53.3 %	0.40 [0.06, 0.74]
Yeka 2008 UGA	215	1.75 (1.8)	199	1.66 (2)		46.7 %	0.09 [-0.28, 0.46]
Subtotal (95% CI)	**426**		**409**			**100.0 %**	**0.26 [0.00, 0.51]**

Heterogeneity: Chi² = 1.46, df = 1 (P = 0.23); I² =31%

Test for overall effect: Z = 1.99 (P = 0.046)

```
        -2    -1    0    1    2
      Favours AL6      Favours DHA-P
```

Analysis 4.10. Comparison 4 Dihydroartemisinin-piperaquine versus Artemether-lumefantrine, Outcome 10 Serious adverse events (including deaths).

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 4 Dihydroartemisinin-piperaquine versus Artemether-lumefantrine

Outcome: 10 Serious adverse events (including deaths)

Study or subgroup	DHA-P	AL6	Risk Ratio	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI	M-H,Fixed,95% CI
Ratcliff 2007 IDN	1/379	2/375		0.49 [0.05, 5.43]
Kamya 2007 UGA	4/211	2/210		1.99 [0.37, 10.75]
Bassat 2009 AF	18/1038	5/510		1.77 [0.66, 4.74]
Zongo 2007 BFA	0/187	0/188		0.0 [0.0, 0.0]
Yeka 2008 UGA	5/215	2/199		2.31 [0.45, 11.79]
Mens 2008 KEN	1/73	0/73		3.00 [0.12, 72.45]
Arinaitwe 2009 UGA	3/351	1/320		2.74 [0.29, 26.16]
The 4ABC Study 2011 AF	10/1468	6/1225		1.39 [0.51, 3.82]
Agarwal 2013 KEN	1/113	2/111		0.49 [0.05, 5.34]
Total (95% CI)	**4035**	**3211**		**1.58 [0.93, 2.68]**

Total events: 43 (DHA-P), 20 (AL6)

Heterogeneity: Chi² = 2.60, df = 7 (P = 0.92); I² =0.0%

Test for overall effect: Z = 1.68 (P = 0.093)

Test for subgroup differences: Not applicable

```
      0.01   0.1    1    10   100
      Favours DHA-P      Favours AL6
```

Analysis 4.11. Comparison 4 Dihydroartemisinin-piperaquine versus Artemether-lumefantrine, Outcome 11 Other adverse events: Gastrointestinal.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 4 Dihydroartemisinin-piperaquine versus Artemether-lumefantrine

Outcome: 11 Other adverse events: Gastrointestinal

Study or subgroup	DHA-P n/N	AL6 n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Early vomiting					
Ratcliff 2007 IDN (1)	11/379	10/375		42.9 %	1.09 [0.47, 2.53]
Bassat 2009 AF (2)	22/1038	4/510		22.9 %	2.70 [0.94, 7.80]
Zongo 2007 BFA (3)	7/196	3/197		12.8 %	2.35 [0.62, 8.94]
Agarwal 2013 KEN (4)	7/137	5/137		21.4 %	1.40 [0.46, 4.30]
Subtotal (95% CI)	**1750**	**1219**		**100.0 %**	**1.69 [1.00, 2.83]**
Total events: 47 (DHA-P), 22 (AL6)					
Heterogeneity: Chi² = 2.13, df = 3 (P = 0.55); I² =0.0%					
Test for overall effect: Z = 1.98 (P = 0.048)					
2 Vomiting					
Krudsood 2007 THA	4/82	0/82		0.2 %	9.00 [0.49, 164.53]
Bassat 2009 AF	71/1038	35/510		16.1 %	1.00 [0.67, 1.47]
Kamya 2007 UGA	65/210	65/211		22.2 %	1.00 [0.75, 1.34]
Mens 2008 KEN	11/73	9/73		3.1 %	1.22 [0.54, 2.77]
Yeka 2008 UGA	35/213	35/198		12.4 %	0.93 [0.61, 1.42]
Yavo 2011 AF	4/197	0/187		0.2 %	8.55 [0.46, 157.64]
Arinaitwe 2009 UGA	23/351	20/320		7.2 %	1.05 [0.59, 1.87]
The 4ABC Study 2011 AF	123/1468	102/1225		38.1 %	1.01 [0.78, 1.29]
Smithuis 2010 MMR	2/161	2/162		0.7 %	1.01 [0.14, 7.06]
Subtotal (95% CI)	**3793**	**2968**		**100.0 %**	**1.03 [0.89, 1.20]**
Total events: 338 (DHA-P), 268 (AL6)					
Heterogeneity: Chi² = 4.65, df = 8 (P = 0.79); I² =0.0%					
Test for overall effect: Z = 0.41 (P = 0.68)					

```
            0.005   0.1    1    10   200
          Favours DHA-P      Favours AL6
```

(*Continued* . . .)

Study or subgroup	DHA-P n/N	AL6 n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
3 Nausea					
Krudsood 2007 THA	4/82	3/81		59.5 %	1.32 [0.30, 5.70]
Yavo 2011 AF	2/197	2/187		40.5 %	0.95 [0.14, 6.67]
Subtotal (95% CI)	**279**	**268**		**100.0 %**	**1.17 [0.36, 3.76]**
Total events: 6 (DHA-P), 5 (AL6)					
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² =0.0%					
Test for overall effect: Z = 0.26 (P = 0.79)					
4 Diarrhoea					
Krudsood 2007 THA	3/82	1/81		0.3 %	2.96 [0.31, 27.90]
Kamya 2007 UGA	19/210	25/211		8.2 %	0.76 [0.43, 1.34]
Mens 2008 KEN	9/73	7/73		2.3 %	1.29 [0.51, 3.27]
Yeka 2008 UGA	26/213	23/198		7.9 %	1.05 [0.62, 1.78]
Arinaitwe 2009 UGA	79/351	86/320		29.6 %	0.84 [0.64, 1.09]
Yavo 2011 AF	4/197	2/187		0.7 %	1.90 [0.35, 10.24]
The 4ABC Study 2011 AF	166/1468	142/1225		51.0 %	0.98 [0.79, 1.20]
Subtotal (95% CI)	**2594**	**2295**		**100.0 %**	**0.94 [0.81, 1.09]**
Total events: 306 (DHA-P), 286 (AL6)					
Heterogeneity: Chi² = 3.65, df = 6 (P = 0.72); I² =0.0%					
Test for overall effect: Z = 0.77 (P = 0.44)					
5 Abdominal pain					
Kamya 2007 UGA	20/45	19/36		24.2 %	0.84 [0.54, 1.32]
Krudsood 2007 THA	8/82	5/81		5.8 %	1.58 [0.54, 4.63]
Mens 2008 KEN	23/73	26/73		29.8 %	0.88 [0.56, 1.40]
Yeka 2008 UGA	17/74	24/63		29.7 %	0.60 [0.36, 1.02]
Yavo 2011 AF	9/197	9/187		10.6 %	0.95 [0.39, 2.34]
Subtotal (95% CI)	**471**	**440**		**100.0 %**	**0.84 [0.65, 1.08]**
Total events: 77 (DHA-P), 83 (AL6)					
Heterogeneity: Chi² = 2.99, df = 4 (P = 0.56); I² =0.0%					
Test for overall effect: Z = 1.35 (P = 0.18)					
6 Anorexia					
Krudsood 2007 THA	4/82	4/81		1.4 %	0.99 [0.26, 3.82]
Kamya 2007 UGA	91/210	90/211		31.3 %	1.02 [0.82, 1.27]
Mens 2008 KEN	8/73	10/73		3.5 %	0.80 [0.33, 1.91]
Yeka 2008 UGA	47/213	49/198		17.7 %	0.89 [0.63, 1.27]
The 4ABC Study 2011 AF	130/1468	121/1225		46.0 %	0.90 [0.71, 1.13]
Subtotal (95% CI)	**2046**	**1788**		**100.0 %**	**0.93 [0.80, 1.08]**
Total events: 280 (DHA-P), 274 (AL6)					

0.005 0.1 1 10 200

Favours DHA-P   Favours AL6

(Continued . . .)

Study or subgroup	DHA-P	AL6	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI

Heterogeneity: Chi² = 0.89, df = 4 (P = 0.93); I² =0.0%

Test for overall effect: Z = 0.96 (P = 0.34)

Test for subgroup differences: Chi² = 6.80, df = 5 (P = 0.24), I² =27%

```
         0.005   0.1      1     10    200
            Favours DHA-P    Favours AL6
```

(1) Ratcliff 2007: Vomiting within the first hour after drug administration.

(2) Bassat 2009: Excluded due to persistent vomiting on day 0

(3) Zongo 2007b: Repeated vomiting on day 0.

(4) Agarwal 2013 KEN: Vomiting the first dose.

Analysis 4.12. Comparison 4 Dihydroartemisinin-piperaquine versus Artemether-lumefantrine, Outcome 12 Other adverse events: Neuro-psychiatric.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 4 Dihydroartemisinin-piperaquine versus Artemether-lumefantrine

Outcome: 12 Other adverse events: Neuro-psychiatric
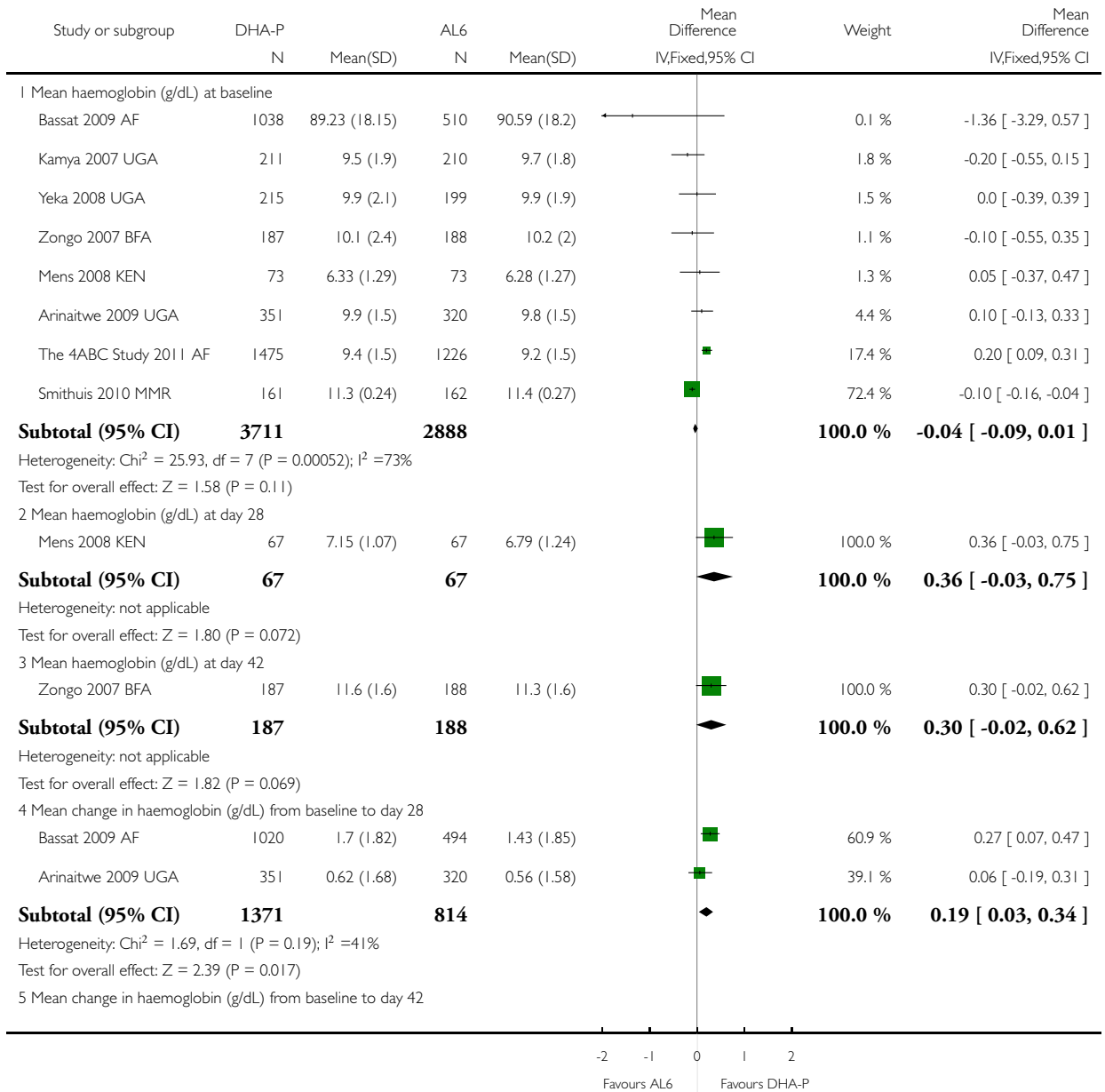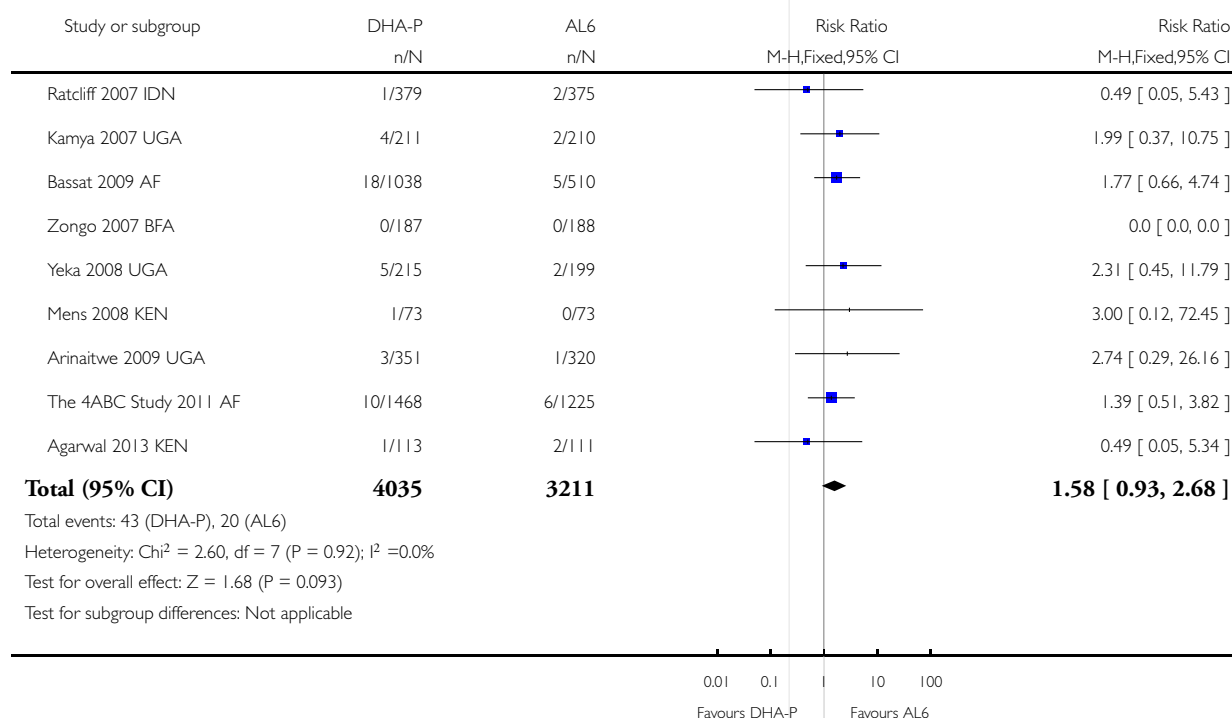
Study or subgroup	DHA-P	AL6	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
1 Headache					
Krudsood 2007 THA	8/82	5/81		12.0 %	1.58 [0.54, 4.63]
Mens 2008 KEN	43/73	37/73		88.0 %	1.16 [0.86, 1.56]
Subtotal (95% CI)	**155**	**154**		**100.0 %**	**1.21 [0.90, 1.63]**
Total events: 51 (DHA-P), 42 (AL6)					
Heterogeneity: Chi² = 0.31, df = 1 (P = 0.58); I² =0.0%					
Test for overall effect: Z = 1.28 (P = 0.20)					
2 Sleeplessness					
Krudsood 2007 THA	9/82	3/81		66.2 %	2.96 [0.83, 10.55]
Yavo 2011 AF	0/197	1/187		33.8 %	0.32 [0.01, 7.72]
Subtotal (95% CI)	**279**	**268**		**100.0 %**	**2.07 [0.69, 6.16]**
Total events: 9 (DHA-P), 4 (AL6)					

```
         0.005   0.1      1     10    200
            Favours DHA-P    Favours AL6
```

(*Continued* ...)

Study or subgroup	DHA-P n/N	AL6 n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heterogeneity: Chi² = 1.63, df = 1 (P = 0.20); I² =39%					
Test for overall effect: Z = 1.31 (P = 0.19)					
3 Dizziness					
Krudsood 2007 THA	7/82	5/81		71.0 %	1.38 [0.46, 4.18]
Yavo 2011 AF	5/197	2/187		29.0 %	2.37 [0.47, 12.08]
Subtotal (95% CI)	**279**	**268**		**100.0 %**	**1.67 [0.67, 4.15]**
Total events: 12 (DHA-P), 7 (AL6)					
Heterogeneity: Chi² = 0.29, df = 1 (P = 0.59); I² =0.0%					
Test for overall effect: Z = 1.11 (P = 0.27)					
4 Sleepiness					
Yavo 2011 AF	1/197	0/187		100.0 %	2.85 [0.12, 69.49]
Subtotal (95% CI)	**197**	**187**		**100.0 %**	**2.85 [0.12, 69.49]**
Total events: 1 (DHA-P), 0 (AL6)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.64 (P = 0.52)					
5 Weakness					
Kamya 2007 UGA	103/210	85/211		56.4 %	1.22 [0.98, 1.51]
Krudsood 2007 THA	9/82	7/81		4.7 %	1.27 [0.50, 3.25]
Yeka 2008 UGA	28/213	27/198		18.6 %	0.96 [0.59, 1.58]
Mens 2008 KEN	19/73	30/73		20.0 %	0.63 [0.39, 1.02]
Arinaitwe 2009 UGA	1/351	0/320		0.3 %	2.74 [0.11, 66.92]
Subtotal (95% CI)	**929**	**883**		**100.0 %**	**1.06 [0.89, 1.27]**
Total events: 160 (DHA-P), 149 (AL6)					
Heterogeneity: Chi² = 6.75, df = 4 (P = 0.15); I² =41%					
Test for overall effect: Z = 0.65 (P = 0.52)					
Test for subgroup differences: Chi² = 2.89, df = 4 (P = 0.58), I² =0.0%					

```
        0.005   0.1    1    10    200
      Favours DHA-P       Favours AL6
```
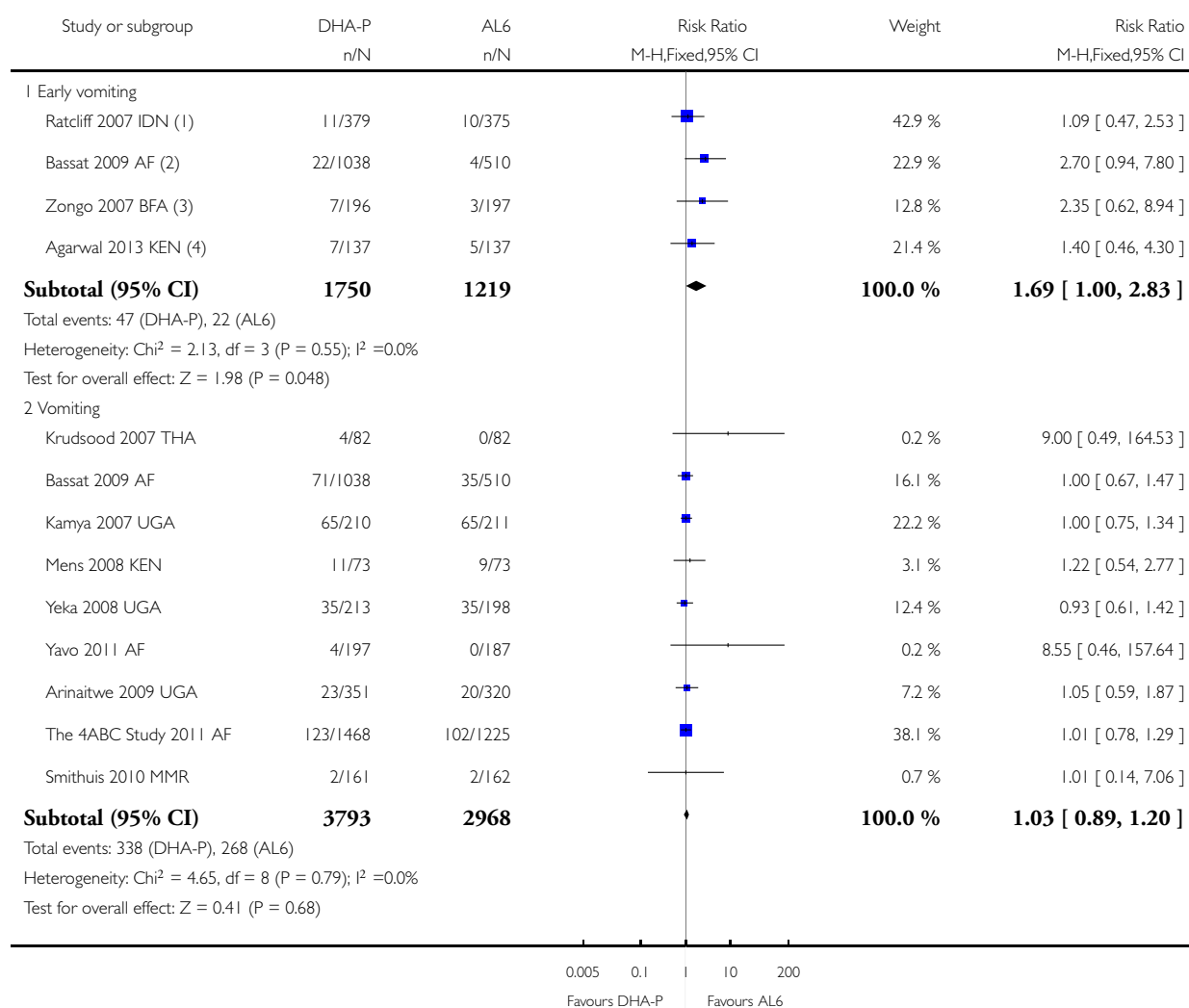
Analysis 4.13. Comparison 4 Dihydroartemisinin-piperaquine versus Artemether-lumefantrine, Outcome 13 Other adverse events: Cardio-respiratory.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria
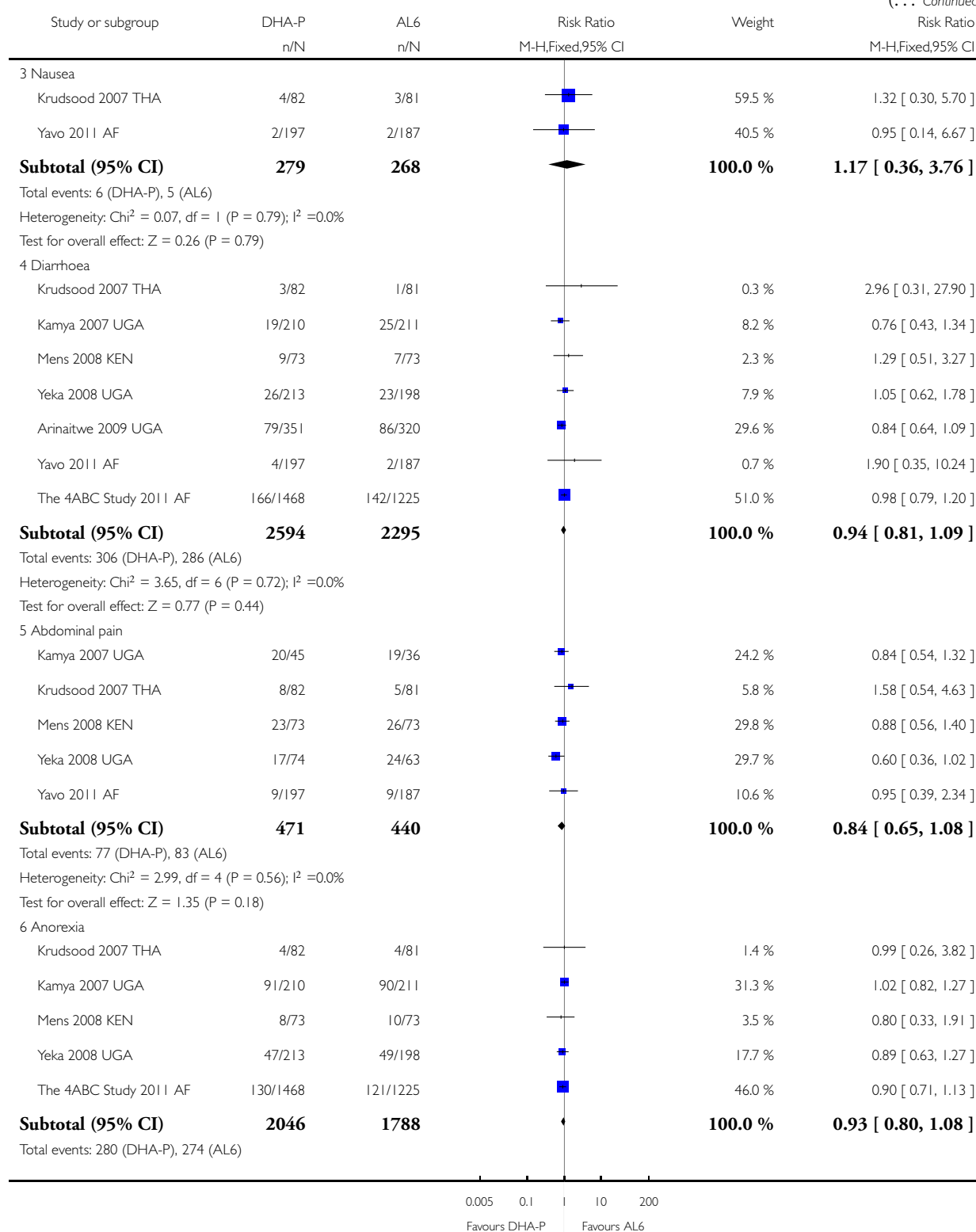
Comparison: 4 Dihydroartemisinin-piperaquine versus Artemether-lumefantrine
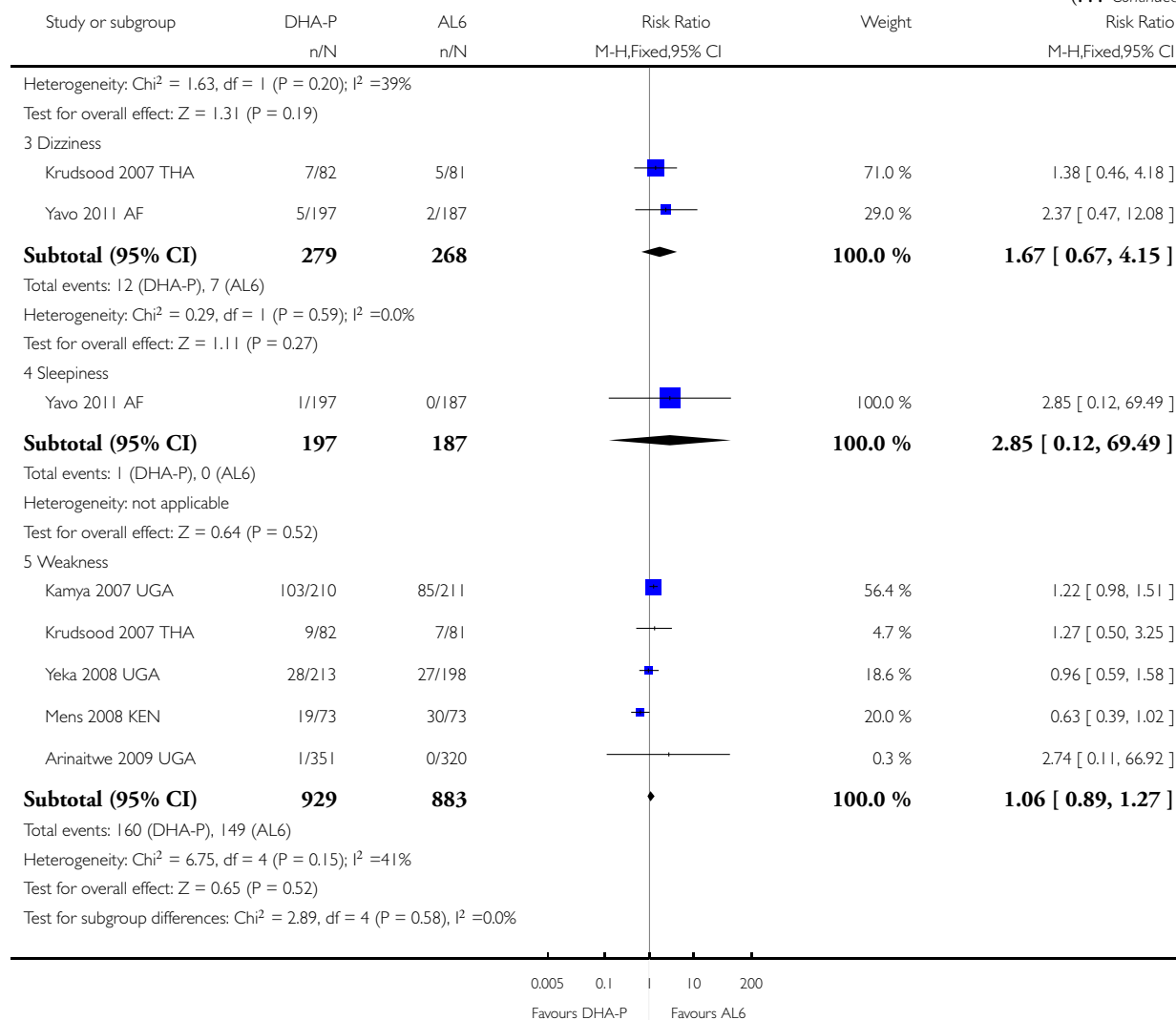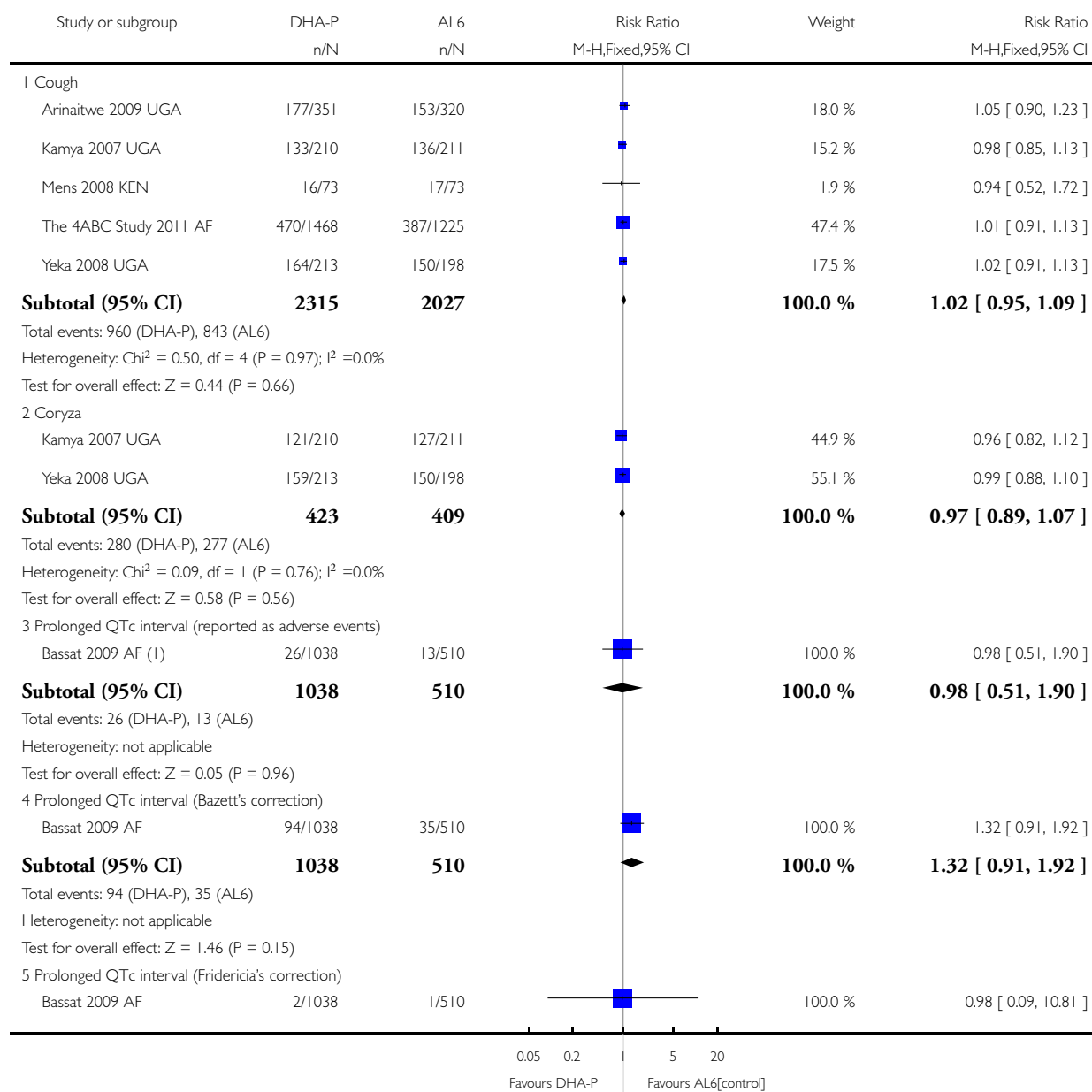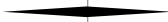
Outcome: 13 Other adverse events: Cardio-respiratory

Study or subgroup	DHA-P n/N	AL6 n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Cough					
Arinaitwe 2009 UGA	177/351	153/320		18.0 %	1.05 [0.90, 1.23]
Kamya 2007 UGA	133/210	136/211		15.2 %	0.98 [0.85, 1.13]
Mens 2008 KEN	16/73	17/73		1.9 %	0.94 [0.52, 1.72]
The 4ABC Study 2011 AF	470/1468	387/1225		47.4 %	1.01 [0.91, 1.13]
Yeka 2008 UGA	164/213	150/198		17.5 %	1.02 [0.91, 1.13]
Subtotal (95% CI)	**2315**	**2027**		**100.0 %**	**1.02 [0.95, 1.09]**
Total events: 960 (DHA-P), 843 (AL6)					
Heterogeneity: Chi² = 0.50, df = 4 (P = 0.97); I² =0.0%					
Test for overall effect: Z = 0.44 (P = 0.66)					
2 Coryza					
Kamya 2007 UGA	121/210	127/211		44.9 %	0.96 [0.82, 1.12]
Yeka 2008 UGA	159/213	150/198		55.1 %	0.99 [0.88, 1.10]
Subtotal (95% CI)	**423**	**409**		**100.0 %**	**0.97 [0.89, 1.07]**
Total events: 280 (DHA-P), 277 (AL6)					
Heterogeneity: Chi² = 0.09, df = 1 (P = 0.76); I² =0.0%					
Test for overall effect: Z = 0.58 (P = 0.56)					
3 Prolonged QTc interval (reported as adverse events)					
Bassat 2009 AF (1)	26/1038	13/510		100.0 %	0.98 [0.51, 1.90]
Subtotal (95% CI)	**1038**	**510**		**100.0 %**	**0.98 [0.51, 1.90]**
Total events: 26 (DHA-P), 13 (AL6)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.05 (P = 0.96)					
4 Prolonged QTc interval (Bazett's correction)					
Bassat 2009 AF	94/1038	35/510		100.0 %	1.32 [0.91, 1.92]
Subtotal (95% CI)	**1038**	**510**		**100.0 %**	**1.32 [0.91, 1.92]**
Total events: 94 (DHA-P), 35 (AL6)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.46 (P = 0.15)					
5 Prolonged QTc interval (Fridericia's correction)					
Bassat 2009 AF	2/1038	1/510		100.0 %	0.98 [0.09, 10.81]

0.05 0.2 1 5 20

Favours DHA-P   Favours AL6[control]

(Continued . . .)

Study or subgroup	DHA-P	AL6	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
Subtotal (95% CI)	**1038**	**510**		**100.0 %**	**0.98 [0.09, 10.81]**

Total events: 2 (DHA-P), 1 (AL6)

Heterogeneity: not applicable

Test for overall effect: Z = 0.01 (P = 0.99)

Test for subgroup differences: Chi² = 2.60, df = 4 (P = 0.63), I² =0.0%

0.05 0.2 1 5 20

Favours DHA-P   Favours AL6[control]

(1) Defined as QTc > 450 ms on day 2.

Analysis 4.14.   Comparison 4 Dihydroartemisinin-piperaquine versus Artemether-lumefantrine, Outcome 14 Other adverse events: Musculoskeletal/dermatological.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 4 Dihydroartemisinin-piperaquine versus Artemether-lumefantrine

Outcome: 14 Other adverse events: Musculoskeletal/dermatological

Study or subgroup	DHA-P	AL6	Risk Ratio	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI	M-H,Fixed,95% CI
1 Pruritis				
Arinaitwe 2009 UGA	0/351	0/320		0.0 [0.0, 0.0]
Kamya 2007 UGA	22/210	14/211		1.58 [0.83, 3.00]
Mens 2008 KEN	4/73	3/73		1.33 [0.31, 5.75]
Yavo 2011 AF	3/197	1/187		2.85 [0.30, 27.14]
Yeka 2008 UGA	8/213	3/198		2.48 [0.67, 9.21]
Subtotal (95% CI)	**1044**	**989**		**1.74 [1.03, 2.92]**
Total events: 37 (DHA-P), 21 (AL6)				
Heterogeneity: Chi² = 0.68, df = 3 (P = 0.88); I² =0.0%				
Test for overall effect: Z = 2.08 (P = 0.037)				
2 Face oedema				
Yavo 2011 AF	1/197	0/187		2.85 [0.12, 69.49]
Subtotal (95% CI)	**197**	**187**		**2.85 [0.12, 69.49]**
Total events: 1 (DHA-P), 0 (AL6)				

0.01 0.1 1 10 100

Favours DHA-P   Favours AL6

(*Continued* ...)

Study or subgroup	DHA-P	AL6	Risk Ratio	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI	M-H,Fixed,95% CI

Heterogeneity: not applicable

Test for overall effect: Z = 0.64 (P = 0.52)

Test for subgroup differences: Chi² = 0.09, df = 1 (P = 0.76), I² =0.0%

```
            0.01   0.1    1    10   100
              Favours DHA-P    Favours AL6
```

Analysis 5.1.   Comparison 5 Dihydroartemisinin-piperaquine versus Artesunate plus amodiaquine, Outcome 1 Total failure (P. falciparum) Day 28 PCR-unadjusted.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 5 Dihydroartemisinin-piperaquine versus Artesunate plus amodiaquine

Outcome: 1 Total failure (*P. falciparum*) Day 28 PCR-unadjusted

Study or subgroup	DHA-P	AS+AQ	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
1 Africa					
Karema 2006 RWA	24/250	45/251		16.6 %	0.54 [0.34, 0.85]
The 4ABC Study 2011 AF	134/1371	189/928		83.4 %	0.48 [0.39, 0.59]
Subtotal (95% CI)	**1621**	**1179**		**100.0 %**	**0.49 [0.41, 0.59]**

Total events: 158 (DHA-P), 234 (AS+AQ)

Heterogeneity: Chi² = 0.18, df = 1 (P = 0.67); I² =0.0%

Test for overall effect: Z = 7.47 (P < 0.00001)

2 Asia					
Hasugian 2007 IDN	5/94	9/84		37.0 %	0.50 [0.17, 1.42]
Smithuis 2010 MMR	5/154	16/150		63.0 %	0.30 [0.11, 0.81]
Subtotal (95% CI)	**248**	**234**		**100.0 %**	**0.38 [0.18, 0.77]**

Total events: 10 (DHA-P), 25 (AS+AQ)

Heterogeneity: Chi² = 0.45, df = 1 (P = 0.50); I² =0.0%

Test for overall effect: Z = 2.69 (P = 0.0071)

Test for subgroup differences: Chi² = 0.49, df = 1 (P = 0.48), I² =0.0%

```
            0.01   0.1    1    10   100
              Favours DHA-P    Favours AS+AQ
```

Analysis 5.2. Comparison 5 Dihydroartemisinin-piperaquine versus Artesunate plus amodiaquine, Outcome 2 Total failure (P. falciparum) Day 28 PCR-adjusted.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 5 Dihydroartemisinin-piperaquine versus Artesunate plus amodiaquine

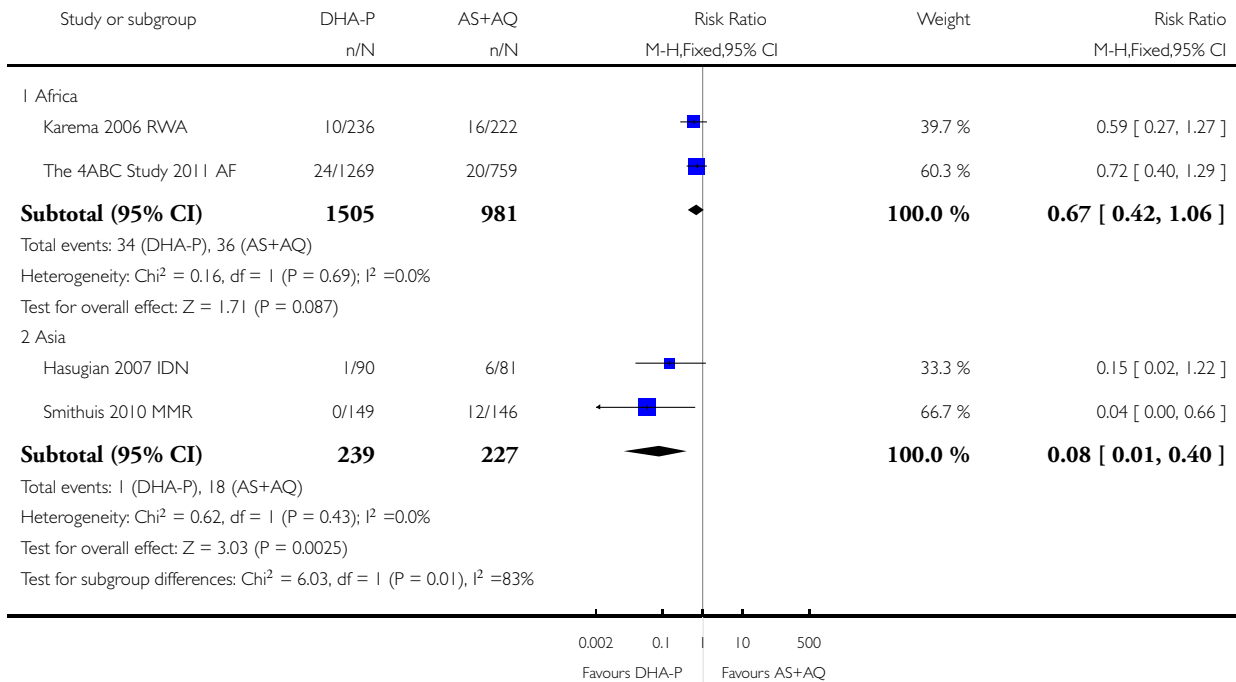Outcome: 2 Total failure (*P. falciparum*) Day 28 PCR-adjusted

Study or subgroup	DHA-P n/N	AS+AQ n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Africa					
Karema 2006 RWA	10/236	16/222		39.7 %	0.59 [0.27, 1.27]
The 4ABC Study 2011 AF	24/1269	20/759		60.3 %	0.72 [0.40, 1.29]
Subtotal (95% CI)	**1505**	**981**		**100.0 %**	**0.67 [0.42, 1.06]**
Total events: 34 (DHA-P), 36 (AS+AQ)					
Heterogeneity: Chi² = 0.16, df = 1 (P = 0.69); I² =0.0%					
Test for overall effect: Z = 1.71 (P = 0.087)					
2 Asia					
Hasugian 2007 IDN	1/90	6/81		33.3 %	0.15 [0.02, 1.22]
Smithuis 2010 MMR	0/149	12/146		66.7 %	0.04 [0.00, 0.66]
Subtotal (95% CI)	**239**	**227**		**100.0 %**	**0.08 [0.01, 0.40]**
Total events: 1 (DHA-P), 18 (AS+AQ)					
Heterogeneity: Chi² = 0.62, df = 1 (P = 0.43); I² =0.0%					
Test for overall effect: Z = 3.03 (P = 0.0025)					
Test for subgroup differences: Chi² = 6.03, df = 1 (P = 0.01), I² =83%					

0.002   0.1   1   10   500

Favours DHA-P   Favours AS+AQ

Analysis 5.3. Comparison 5 Dihydroartemisinin-piperaquine versus Artesunate plus amodiaquine, Outcome 3 Total failure (P. falciparum) Day 42 PCR-unadjusted.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 5 Dihydroartemisinin-piperaquine versus Artesunate plus amodiaquine

Outcome: 3 Total failure (*P. falciparum*) Day 42 PCR-unadjusted

Study or subgroup	DHA-P n/N	AS+AQ n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Asia					
Hasugian 2007 IDN	5/86	14/66		100.0 %	0.27 [0.10, 0.72]
Subtotal (95% CI)	**86**	**66**		**100.0 %**	**0.27 [0.10, 0.72]**
Total events: 5 (DHA-P), 14 (AS+AQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.62 (P = 0.0089)					
Test for subgroup differences: Not applicable					

0.01 0.1 1 10 100

Favours DHA-P   Favours AS+AQ

Analysis 5.4. Comparison 5 Dihydroartemisinin-piperaquine versus Artesunate plus amodiaquine, Outcome 4 Total failure (P. falciparum) Day 42 PCR-adjusted.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 5 Dihydroartemisinin-piperaquine versus Artesunate plus amodiaquine

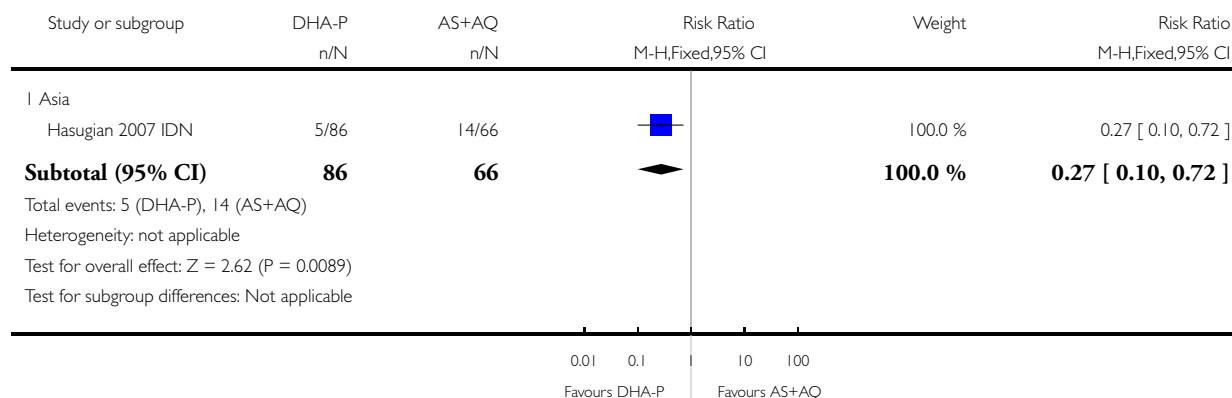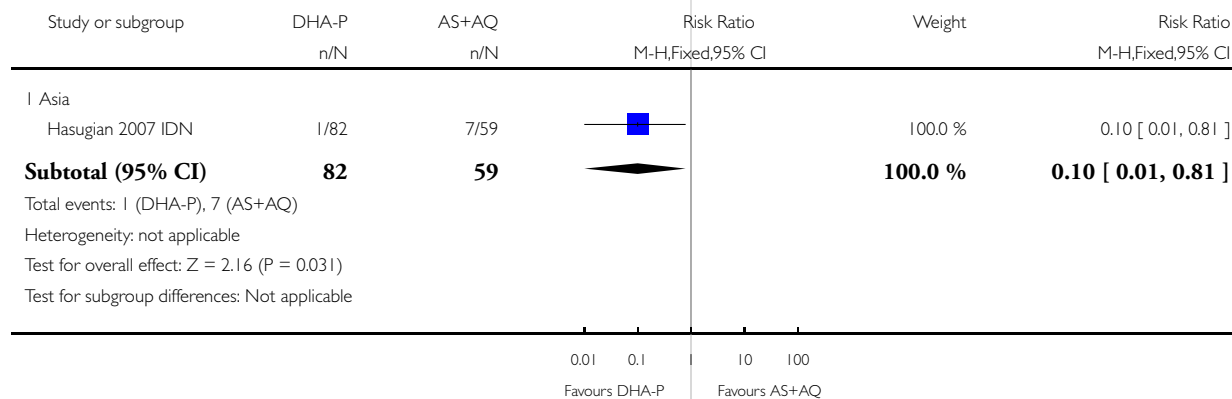Outcome: 4 Total failure (*P. falciparum*) Day 42 PCR-adjusted

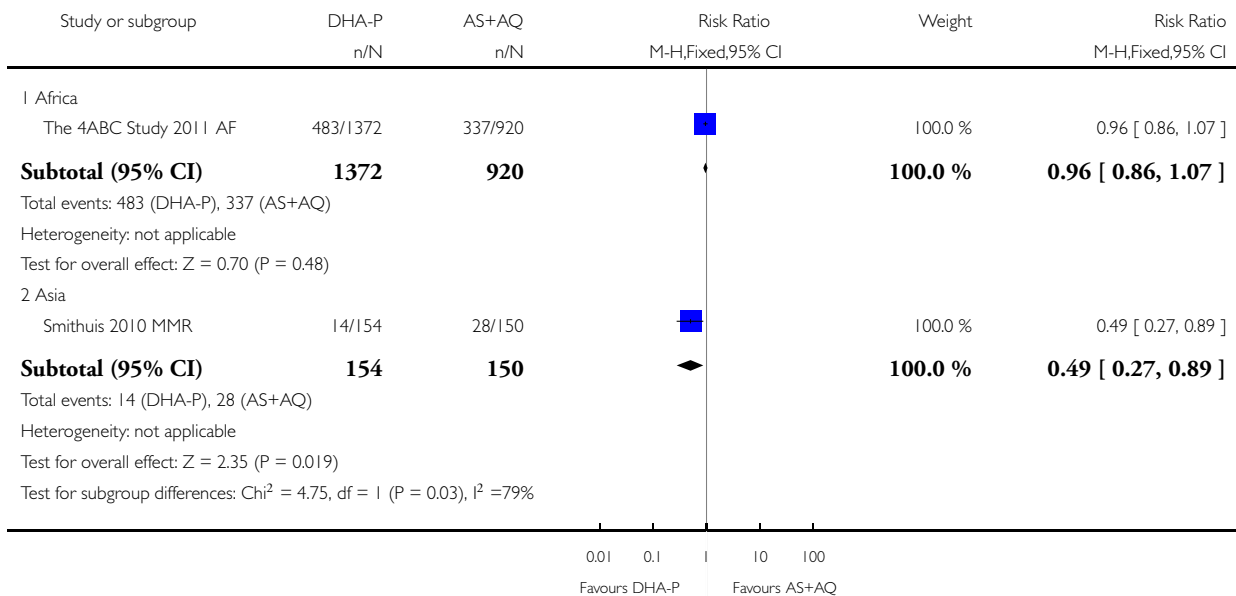| Study or subgroup	DHA-P n/N	AS+AQ n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Asia					
Hasugian 2007 IDN	1/82	7/59		100.0 %	0.10 [0.01, 0.81]
Subtotal (95% CI)	**82**	**59**		**100.0 %**	**0.10 [0.01, 0.81]**
Total events: 1 (DHA-P), 7 (AS+AQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.16 (P = 0.031)					
Test for subgroup differences: Not applicable					

0.01 0.1 1 10 100

Favours DHA-P   Favours AS+AQ

Analysis 5.5. Comparison 5 Dihydroartemisinin-piperaquine versus Artesunate plus amodiaquine, Outcome 5 Total failure (P. falciparum) Day 63 PCR-unadjusted.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 5 Dihydroartemisinin-piperaquine versus Artesunate plus amodiaquine

Outcome: 5 Total failure (*P. falciparum*) Day 63 PCR-unadjusted

Study or subgroup	DHA-P n/N	AS+AQ n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Africa					
The 4ABC Study 2011 AF	483/1372	337/920	■	100.0 %	0.96 [0.86, 1.07]
Subtotal (95% CI)	**1372**	**920**	◆	**100.0 %**	**0.96 [0.86, 1.07]**
Total events: 483 (DHA-P), 337 (AS+AQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.70 (P = 0.48)					
2 Asia					
Smithuis 2010 MMR	14/154	28/150	■	100.0 %	0.49 [0.27, 0.89]
Subtotal (95% CI)	**154**	**150**	◆	**100.0 %**	**0.49 [0.27, 0.89]**
Total events: 14 (DHA-P), 28 (AS+AQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.35 (P = 0.019)					
Test for subgroup differences: Chi² = 4.75, df = 1 (P = 0.03), I² =79%					

```
        0.01   0.1    1    10   100
        Favours DHA-P    Favours AS+AQ
```

Analysis 5.6. Comparison 5 Dihydroartemisinin-piperaquine versus Artesunate plus amodiaquine, Outcome 6 Total failure (P. falciparum) Day 63 PCR-adjusted.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 5 Dihydroartemisinin-piperaquine versus Artesunate plus amodiaquine

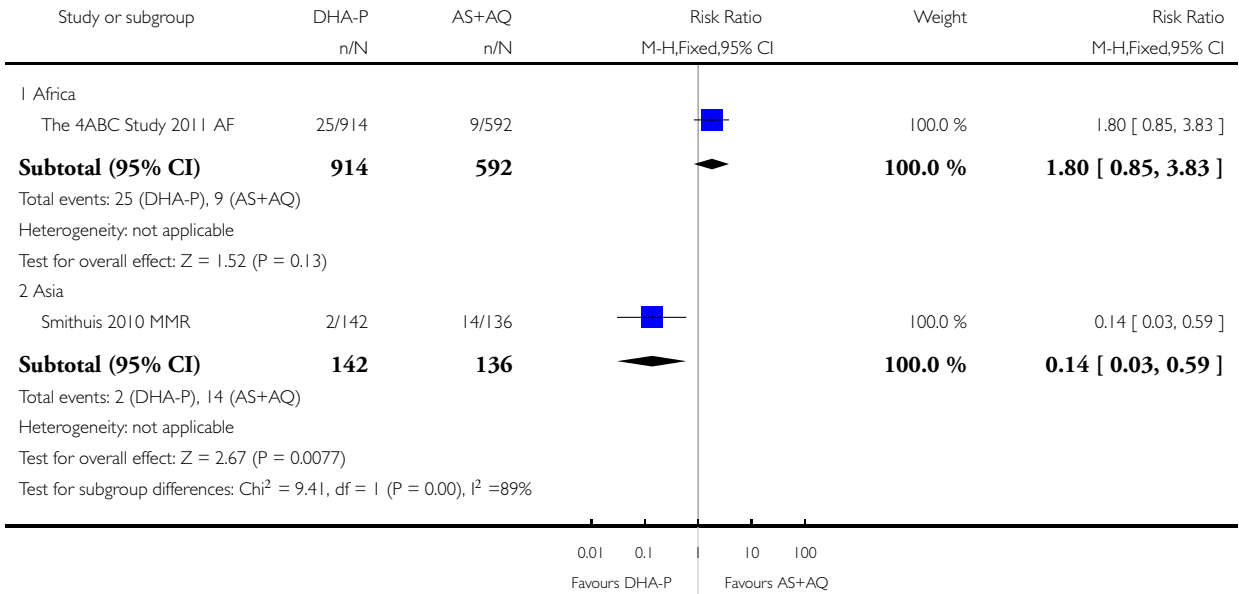Outcome: 6 Total failure (*P. falciparum*) Day 63 PCR-adjusted

Study or subgroup	DHA-P n/N	AS+AQ n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Africa					
The 4ABC Study 2011 AF	25/914	9/592		100.0 %	1.80 [0.85, 3.83]
Subtotal (95% CI)	**914**	**592**		**100.0 %**	**1.80 [0.85, 3.83]**
Total events: 25 (DHA-P), 9 (AS+AQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.52 (P = 0.13)					
2 Asia					
Smithuis 2010 MMR	2/142	14/136		100.0 %	0.14 [0.03, 0.59]
Subtotal (95% CI)	**142**	**136**		**100.0 %**	**0.14 [0.03, 0.59]**
Total events: 2 (DHA-P), 14 (AS+AQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.67 (P = 0.0077)					
Test for subgroup differences: Chi² = 9.41, df = 1 (P = 0.00), I² =89%					

```
          0.01   0.1    1    10   100
         Favours DHA-P      Favours AS+AQ
```
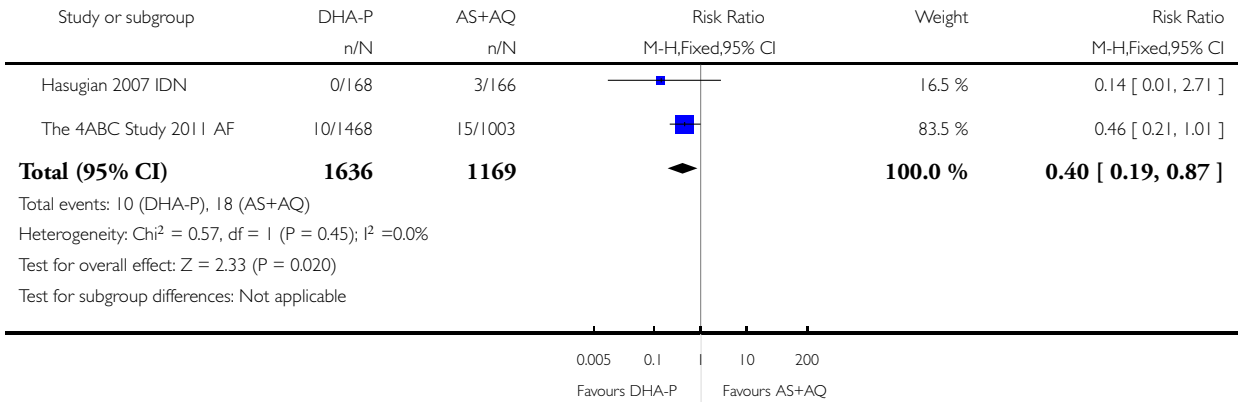
Analysis 5.7. Comparison 5 Dihydroartemisinin-piperaquine versus Artesunate plus amodiaquine, Outcome 7 Serious adverse events (including deaths).

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 5 Dihydroartemisinin-piperaquine versus Artesunate plus amodiaquine

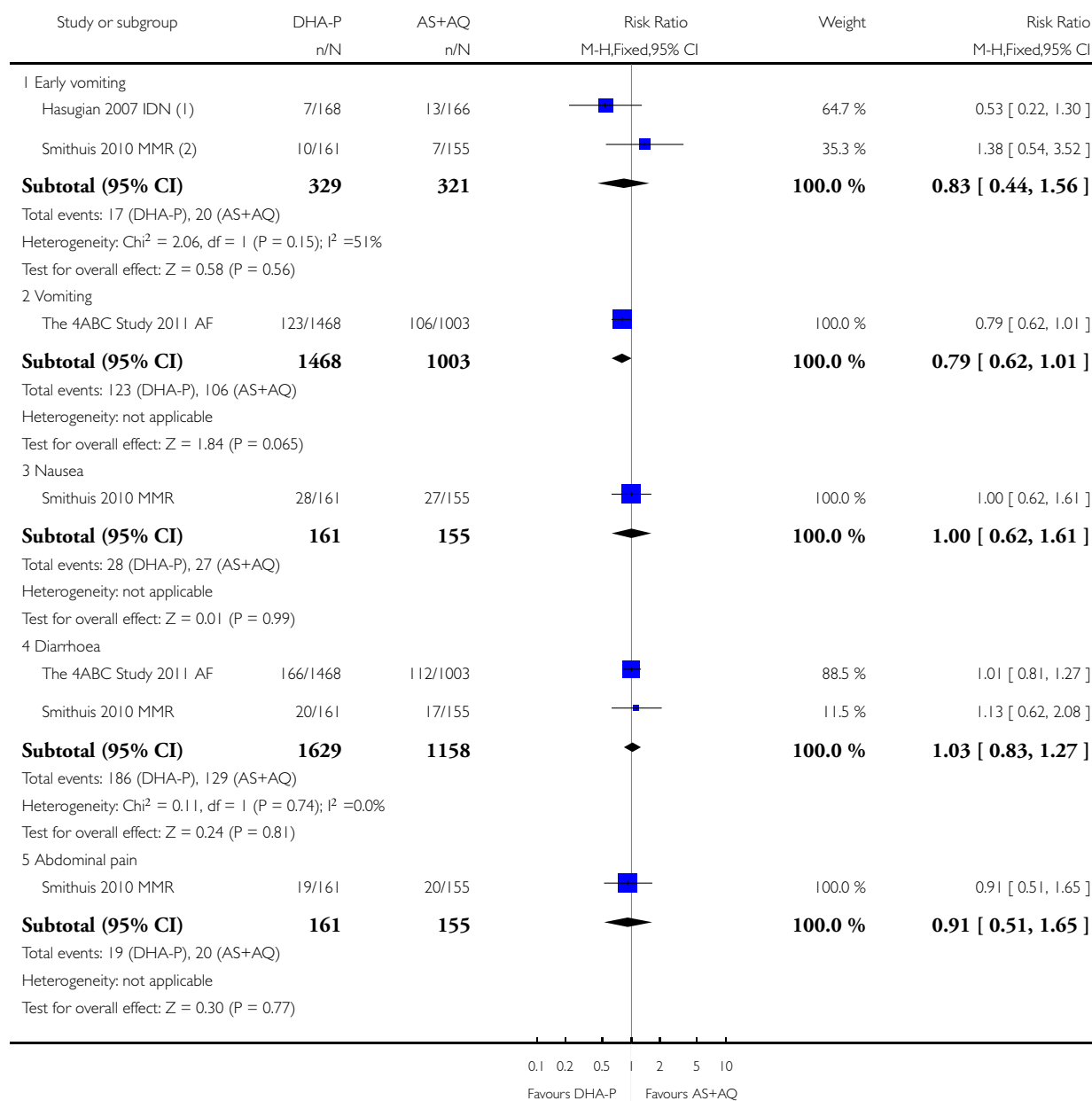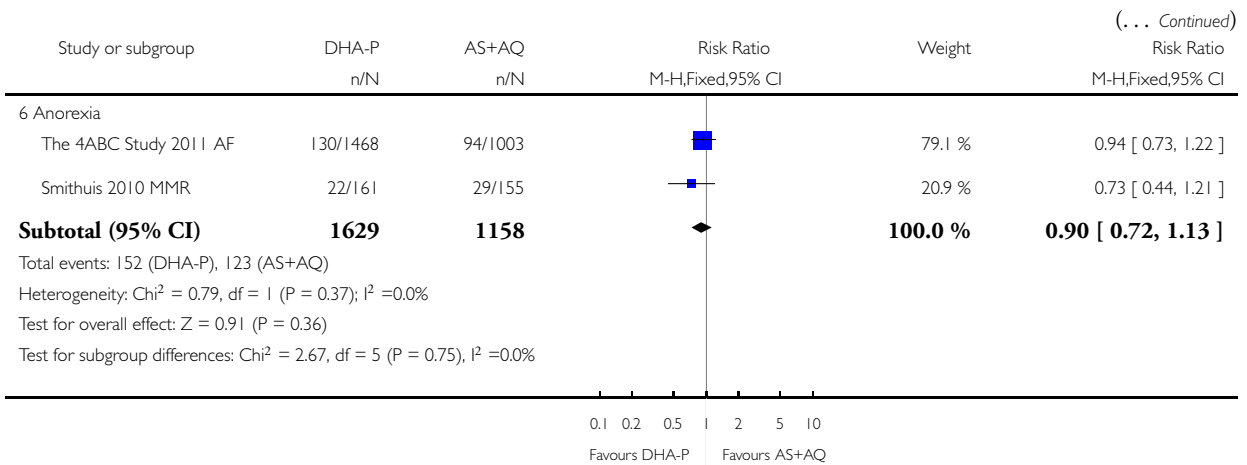Outcome: 7 Serious adverse events (including deaths)

Study or subgroup	DHA-P n/N	AS+AQ n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hasugian 2007 IDN	0/168	3/166		16.5 %	0.14 [0.01, 2.71]
The 4ABC Study 2011 AF	10/1468	15/1003		83.5 %	0.46 [0.21, 1.01]
Total (95% CI)	**1636**	**1169**		**100.0 %**	**0.40 [0.19, 0.87]**

Total events: 10 (DHA-P), 18 (AS+AQ)

Heterogeneity: Chi² = 0.57, df = 1 (P = 0.45); I² =0.0%

Test for overall effect: Z = 2.33 (P = 0.020)

Test for subgroup differences: Not applicable

```
        0.005   0.1    1    10    200
        Favours DHA-P      Favours AS+AQ
```
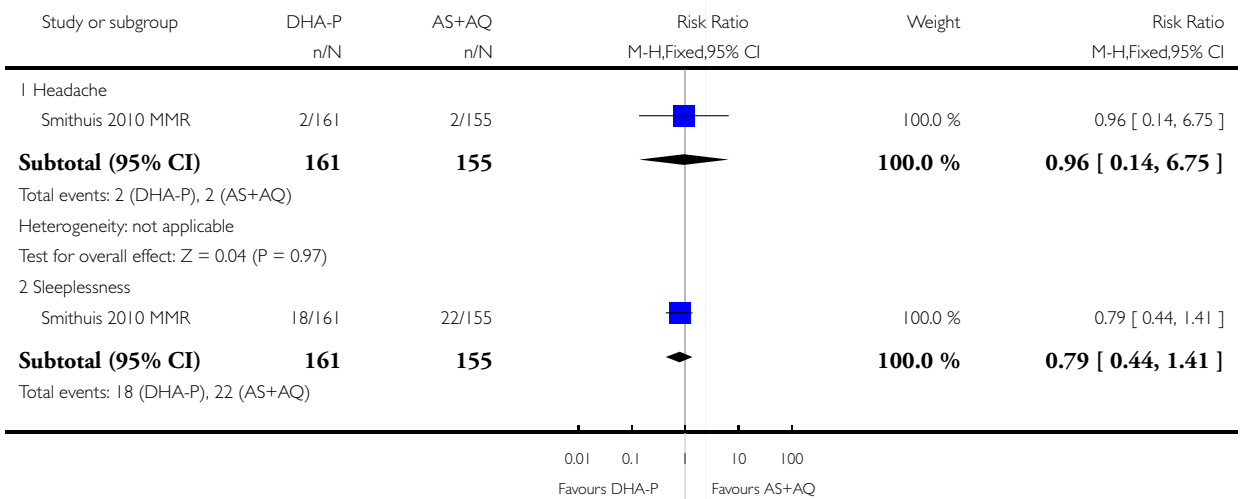
Analysis 5.8.   Comparison 5 Dihydroartemisinin-piperaquine versus Artesunate plus amodiaquine, Outcome 8 Other adverse events: Gastrointestinal.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 5 Dihydroartemisinin-piperaquine versus Artesunate plus amodiaquine

Outcome: 8 Other adverse events: Gastrointestinal
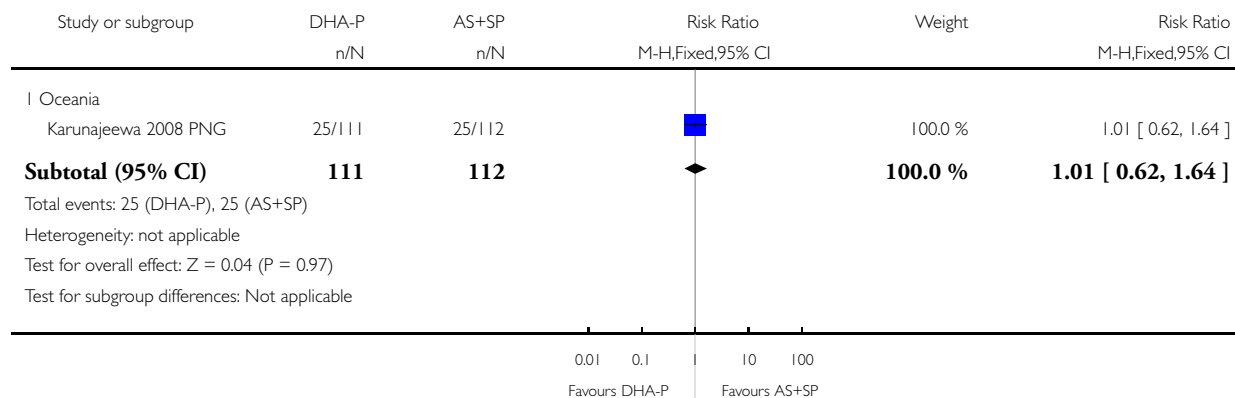
Study or subgroup	DHA-P n/N	AS+AQ n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Early vomiting					
Hasugian 2007 IDN (1)	7/168	13/166		64.7 %	0.53 [0.22, 1.30]
Smithuis 2010 MMR (2)	10/161	7/155		35.3 %	1.38 [0.54, 3.52]
Subtotal (95% CI)	**329**	**321**		**100.0 %**	**0.83 [0.44, 1.56]**
Total events: 17 (DHA-P), 20 (AS+AQ)					
Heterogeneity: Chi² = 2.06, df = 1 (P = 0.15); I² =51%					
Test for overall effect: Z = 0.58 (P = 0.56)					
2 Vomiting					
The 4ABC Study 2011 AF	123/1468	106/1003		100.0 %	0.79 [0.62, 1.01]
Subtotal (95% CI)	**1468**	**1003**		**100.0 %**	**0.79 [0.62, 1.01]**
Total events: 123 (DHA-P), 106 (AS+AQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.84 (P = 0.065)					
3 Nausea					
Smithuis 2010 MMR	28/161	27/155		100.0 %	1.00 [0.62, 1.61]
Subtotal (95% CI)	**161**	**155**		**100.0 %**	**1.00 [0.62, 1.61]**
Total events: 28 (DHA-P), 27 (AS+AQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.01 (P = 0.99)					
4 Diarrhoea					
The 4ABC Study 2011 AF	166/1468	112/1003		88.5 %	1.01 [0.81, 1.27]
Smithuis 2010 MMR	20/161	17/155		11.5 %	1.13 [0.62, 2.08]
Subtotal (95% CI)	**1629**	**1158**		**100.0 %**	**1.03 [0.83, 1.27]**
Total events: 186 (DHA-P), 129 (AS+AQ)					
Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² =0.0%					
Test for overall effect: Z = 0.24 (P = 0.81)					
5 Abdominal pain					
Smithuis 2010 MMR	19/161	20/155		100.0 %	0.91 [0.51, 1.65]
Subtotal (95% CI)	**161**	**155**		**100.0 %**	**0.91 [0.51, 1.65]**
Total events: 19 (DHA-P), 20 (AS+AQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.30 (P = 0.77)					

0.1 0.2 0.5 1 2 5 10

Favours DHA-P   Favours AS+AQ

Study or subgroup	DHA-P	AS+AQ	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
6 Anorexia					
The 4ABC Study 2011 AF	130/1468	94/1003		79.1 %	0.94 [0.73, 1.22]
Smithuis 2010 MMR	22/161	29/155		20.9 %	0.73 [0.44, 1.21]
Subtotal (95% CI)	**1629**	**1158**		**100.0 %**	**0.90 [0.72, 1.13]**

Total events: 152 (DHA-P), 123 (AS+AQ)

Heterogeneity: Chi² = 0.79, df = 1 (P = 0.37); I² =0.0%

Test for overall effect: Z = 0.91 (P = 0.36)

Test for subgroup differences: Chi² = 2.67, df = 5 (P = 0.75), I² =0.0%

0.1 0.2 0.5 1 2 5 10

Favours DHA-P   Favours AS+AQ

(1) Vomited at least one dose of medication

(2) Vomiting in first 24h

Analysis 5.9. Comparison 5 Dihydroartemisinin-piperaquine versus Artesunate plus amodiaquine, Outcome 9 Other adverse events: Neuro-psychiatric.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 5 Dihydroartemisinin-piperaquine versus Artesunate plus amodiaquine

Outcome: 9 Other adverse events: Neuro-psychiatric

Study or subgroup	DHA-P	AS+AQ	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
1 Headache					
Smithuis 2010 MMR	2/161	2/155		100.0 %	0.96 [0.14, 6.75]
Subtotal (95% CI)	**161**	**155**		**100.0 %**	**0.96 [0.14, 6.75]**
Total events: 2 (DHA-P), 2 (AS+AQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.04 (P = 0.97)					
2 Sleeplessness					
Smithuis 2010 MMR	18/161	22/155		100.0 %	0.79 [0.44, 1.41]
Subtotal (95% CI)	**161**	**155**		**100.0 %**	**0.79 [0.44, 1.41]**

Total events: 18 (DHA-P), 22 (AS+AQ)

0.01 0.1 1 10 100

Favours DHA-P   Favours AS+AQ

(*Continued* . . .)

Study or subgroup	DHA-P	AS+AQ	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI

Heterogeneity: not applicable

Test for overall effect: Z = 0.80 (P = 0.42)

Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.85), I² =0.0%

```
        0.01   0.1    1    10   100
        Favours DHA-P      Favours AS+AQ
```

Analysis 5.10. Comparison 5 Dihydroartemisinin-piperaquine versus Artesunate plus amodiaquine, Outcome 10 Other adverse events: Cardio-respiratory.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 5 Dihydroartemisinin-piperaquine versus Artesunate plus amodiaquine

Outcome: 10 Other adverse events: Cardio-respiratory

Study or subgroup	DHA-P	AS+AQ	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
1 Cough					
The 4ABC Study 2011 AF	470/1468	314/1003		100.0 %	1.02 [0.91, 1.15]
Subtotal (95% CI)	**1468**	**1003**		**100.0 %**	**1.02 [0.91, 1.15]**
Total events: 470 (DHA-P), 314 (AS+AQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.37 (P = 0.71)					
2 Palpitations					
Smithuis 2010 MMR	32/161	35/155		100.0 %	0.88 [0.58, 1.35]
Subtotal (95% CI)	**161**	**155**		**100.0 %**	**0.88 [0.58, 1.35]**
Total events: 32 (DHA-P), 35 (AS+AQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.59 (P = 0.56)					
Test for subgroup differences: Chi² = 0.44, df = 1 (P = 0.51), I² =0.0%					

```
        0.01   0.1    1    10   100
        Favours DHA-P      Favours AS+AQ
```

Analysis 6.1.   Comparison 6 Dihydroartemisinin-piperaquine versus Artesunate plus sulfadoxine-pyrimethamine, Outcome 1 Total failure (P. falciparum) Day 28 PCR-unadjusted.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 6 Dihydroartemisinin-piperaquine versus Artesunate plus sulfadoxine-pyrimethamine

Outcome: 1 Total failure (*P. falciparum*) Day 28 PCR-unadjusted

Study or subgroup	DHA-P n/N	AS+SP n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Oceania					
Karunajeewa 2008 PNG	25/111	25/112		100.0 %	1.01 [0.62, 1.64]
Subtotal (95% CI)	**111**	**112**		**100.0 %**	**1.01 [0.62, 1.64]**
Total events: 25 (DHA-P), 25 (AS+SP)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.04 (P = 0.97)					
Test for subgroup differences: Not applicable					

```
                      0.01    0.1    1    10    100
                     Favours DHA-P      Favours AS+SP
```

Analysis 6.2.   Comparison 6 Dihydroartemisinin-piperaquine versus Artesunate plus sulfadoxine-pyrimethamine, Outcome 2 Total failure (P. falciparum) Day 28 PCR-adjusted.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 6 Dihydroartemisinin-piperaquine versus Artesunate plus sulfadoxine-pyrimethamine

Outcome: 2 Total failure (*P. falciparum*) Day 28 PCR-adjusted

Study or subgroup	DHA-P n/N	AS+SP n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Oceania					
Karunajeewa 2008 PNG	11/97	11/98		100.0 %	1.01 [0.46, 2.22]
Subtotal (95% CI)	**97**	**98**		**100.0 %**	**1.01 [0.46, 2.22]**
Total events: 11 (DHA-P), 11 (AS+SP)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.03 (P = 0.98)					

```
                      0.01    0.1    1    10    100
                     Favours DHA-P      Favours AS+SP
```
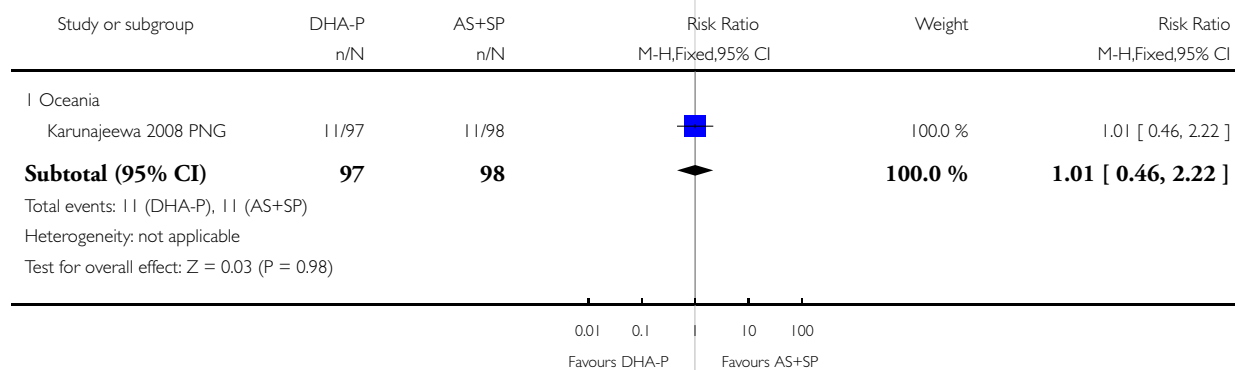
Analysis 6.3.   Comparison 6 Dihydroartemisinin-piperaquine versus Artesunate plus sulfadoxine-pyrimethamine, Outcome 3 Total failure (P. falciparum) Day 42 PCR-unadjusted.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 6 Dihydroartemisinin-piperaquine versus Artesunate plus sulfadoxine-pyrimethamine

Outcome: 3 Total failure (*P. falciparum*) Day 42 PCR-unadjusted

Study or subgroup	DHA-P n/N	AS+SP n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Oceania					
Karunajeewa 2008 PNG	42/107	41/108	■	100.0 %	1.03 [0.74, 1.45]
Subtotal (95% CI)	**107**	**108**	◆	**100.0 %**	**1.03 [0.74, 1.45]**
Total events: 42 (DHA-P), 41 (AS+SP)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.19 (P = 0.85)					

```
          0.01   0.1    1    10   100
        Favours DHA-P      Favours AS+SP
```
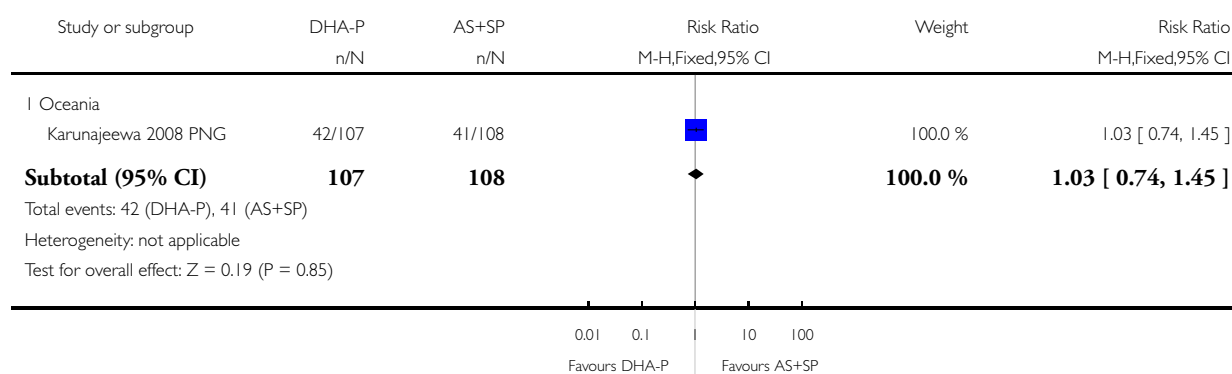
Analysis 6.4. Comparison 6 Dihydroartemisinin-piperaquine versus Artesunate plus sulfadoxine-pyrimethamine, Outcome 4 Total failure (P. falciparum) Day 42 PCR-adjusted.

Review: Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 6 Dihydroartemisinin-piperaquine versus Artesunate plus sulfadoxine-pyrimethamine

Outcome: 4 Total failure (*P. falciparum*) Day 42 PCR-adjusted

Study or subgroup	DHA-P n/N	AS+SP n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Oceania					
Karunajeewa 2008 PNG	12/77	17/84		100.0 %	0.77 [0.39, 1.51]
Subtotal (95% CI)	**77**	**84**		**100.0 %**	**0.77 [0.39, 1.51]**

Total events: 12 (DHA-P), 17 (AS+SP)

Heterogeneity: not applicable

Test for overall effect: Z = 0.76 (P = 0.45)

```
        0.01    0.1    I    I0   100
      Favours DHA-P        Favours AS+SP
```
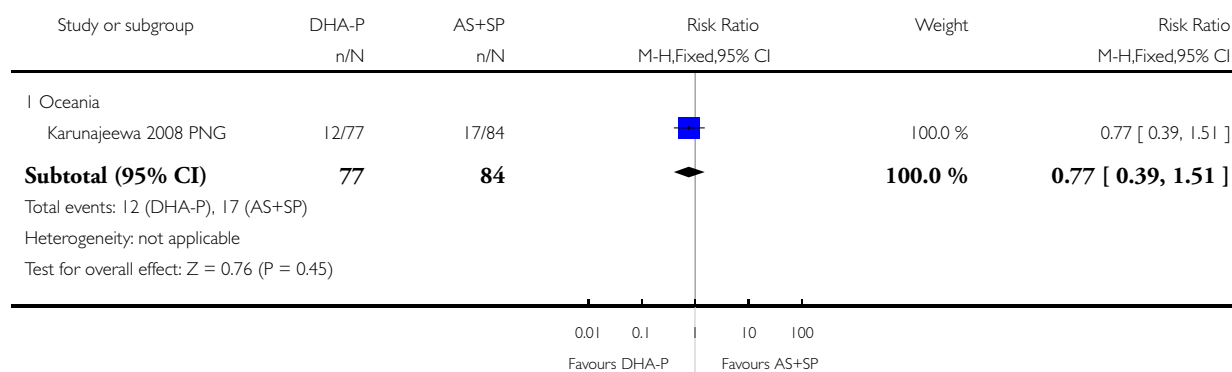
ADDITIONAL TABLES

Table 1. Detailed search strategy

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	EMBASE[b]	LILACS[b]
1	malaria	malaria	malaria	malaria	malaria
2	arte*	arte*	arte*	arte*	arte*
3	dihydroarte*	dihydroarte*	dihydroarte*	dihydroarte*	dihydroarte*
4	amodiaq*	amodiaq*	amodiaq*	amodiaq$	amodiaq$
5	lumefantrine	lumefantrine	lumefantrine	lumefantrine	lumefantrine
6	Coartem*	Coartem*	Coartem*	Coartem$	Coartem$
7	mefloquine	mefloquine	mefloquine	mefloquine	mefloquine
8	2 or 3	2 or 3	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	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	1 and 8 and 9	1 and 8 and 9

Table 1. Detailed search strategy (*Continued*)

| 11 | - | - | Limit 10 to humans | Limit 10 to human | - |

[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 2008); upper case: MeSH or EMTREE heading; lower case: free text term.

Table 2. Primary outcome measure (Total failure)

Analysis	Participants	PCR[b]-unadjusted		PCR-adjusted	
		Numerator	Denominator	Numerator	Denominator
Primary analysis	Exclusions after enrolment[a]	Excluded[c]	Excluded	Excluded	Excluded
	Missing or indeterminate PCR	Included as failures	Included	Excluded	Excluded
	New infections	Included as failures	Included	Excluded	Excluded
Sensitivity analysis 1 [d]	As 'Primary analysis' except: missing or indeterminate PCR	-	-	Included as failures	Included
Sensitivity analysis 2 [e]	As 'Sensitivity analysis 1' except: new infections	-	-	Included as successes	Included
Sensitivity analysis 3 [f]	As 'Sensitivity analysis 2' except: exclusions after enrolment	Included as failures	Included	Included as failures	Included
Sensitivity analysis 4 [g]	As 'Sensitivity analysis 2' except: exclusions after enrolment	Included as successes	Included	Included as successes	Included

Table 3. DHA-P versus AS+MQ: Additional secondary outcomes data

Outcome	Study ID	Measure	DHA-P	AS+MQ	P value	Comment
Gametocyte carriage	Grande 2007 PER	Person gametocytemia weeks per 1000 person weeks	32.5	24.9	0.31	
	Mayxay 2006 LAO	Proportion with gametocytes at any timepoint after treatment (on or after day 7)	9/110	3/110	0.07	
		Person gametocytemia weeks per 1000 person weeks	-	-	> 0.05	Mean across all groups was 0.10 (95% CI 0. 03 to 0.20). No difference between groups (published data)
	Smithuis 2006 MMR	Gametocyte incidence at day 7	18/188	5/218	0.01	
		Gametocyte incidence at day 14	3/168	1/212	0.12	
		Person gametocytemia weeks per 1000 person weeks	-	-	0.03	Gametocyte carriage in DHA-P group was higher than in AS+MQ group (published data). Figures not given
	Smithuis 2010 MMR	Person gametocytemia weeks per 1000 person	112.8	29.5	Not stated	Data presented are for fixed-dose AS+MQ combination.

		weeks				
	Valecha 2010 AS	Person game-tocytemia weeks per 1000 person weeks	20.2 (130/6420)	7.4 (23/3108)	0.01	Published data in paper presented as "person ga-metocytemia weeks per 100 person weeks"
Anaemia	Ashley 2004b THA	Median decrease in HCT by day 7	6.3%	9.4%	0.21	"Mean decrease in HCT up to day 7 then recovery in all groups"
	Ashley 2005 THA	Absolute changes in HCT	-	-	-	"Mean decrease in HCT up to day 7 then recovery in all groups"
	Janssens 2007 KHM	Mean HCT at day 63	40.0 % (3.7)	40.2% (3.8)	Not stated	"Patients in both treatment groups showed similar haemato-logical recovery during the 63-day follow-up period".
	Mayxay 2006 LAO	Mean HCT days 7 to 42	Not stated	Not stated	> 0.05	"the mean hematocrit af-ter treatment did not sig-nificantly differ between groups"
	Smithuis 2006 MMR	Mean haemoglo-bin at day 28	10.4 g/dL	10.5 g/dL	0.65	Data presented are for supervised treatment groups.
		Pro-portion anaemic (Hb < 10 g/dL) on day 28	56/152	59/156	0.85	Data presented are for supervised treatment groups.
	Smithuis 2010 MMR	Mean increase in haemoglobin	Not stated	Not stated	> 0.05	"The mean increase of haemoglobin was simi-lar among the treatment groups"
	Valecha 2010 AS	Mean increase in Hb from day 0 to day 63 in g/dL	1.28 ± 2.22	1.42 ± 2.12	0.30	

Hb - Haemoglobin

HCT - Haematocrit

Table 4. DHA-P versus AS+MQ/AL6: QTc measurements

Study ID	No. of participants	Day	Outcome	Correction method	DHA-P (%)	AS+MQ (%)	P value
Valecha 2010 AS	1150	At baseline	Border-line QTc (431 to 450ms)	QTcB	16.6	12.1	0.066
				QTcF	2.9	1.6	>0.05
		Day 2	Border-line QTc (431 to 450ms)	QTcB	21.4	16.3	0.043
				QTcF	13.0	5.3	<0.001
			Pro-longed QTc (> 450ms)	QTcB	8.6	4.2	0.007
				QTcF	4.7	5.3	< 0.001[1]
			QTc increase > 60 ms	QTcB	0.9	0.8	> 0.05
				QTcF	4.6	2.9	< 0.001
		Day 7	No differences between groups		N/R	N/R	> 0.05

					DHA-P (%)	AL6 (%)	P value
Bassat 2009 AF	1553	At baseline	Border-line QTc (431-450ms)		N/R	N/R	
		Day 2	Border-line QTc (431-450ms)	QTcB	29.1	19.8	< 0.001
				QTcF	1.0	1.2	0.76
			Pro-longed QTc (> 450ms)	QTcB	9.1	6.9	0.15[2]
				QTcF	0.2	0.2	0.99[2]
			QTc > 500 ms	QTcB	0.19	0.39	> 0.05
				QTcF	N/R	N/R	
			QTc increase > 60 ms	QTcB	2.7	2.0	> 0.05
				QTcF	N/R	N/R	
		Day 7	No differences between		N/R	N/R	> 0.05

Table 4. DHA-P versus AS+MQ/AL6: QTc measurements *(Continued)*

			groups				

[1] In this analysis the direction of effect is reversed. These figures have been confirmed as correct by the study authors.

[2] Figures not presented in paper: Taken from Analysis 4.13.

N/R - Not reported

QTcB - QT interval corrected for rate and gender using Bazett's method.

QTcF - Qt interval corrected for rate and gender using Fridericia's method.

Table 5. DHA-P versus AS+MQ: Biochemical monitoring and adverse events

Study ID	No. of participants	Tests	Days tested	Days reported	Days tested adequate to detect adverse events?	For adequate testing, was reporting complete?	Results as presented in the paper
Ashley 2004a THA	134	U&E, LFTs	Days 0 and 7	None	Adequate[1]	Incomplete[2]	"No biochemical evidence of toxicity was observed".
Grande 2007 PER	522	U&E, LFTs	Days 0 and 7	None	Adequate[1]	Incomplete[2]	"No patient had abnormal liver and renal function test results of clinical significance, both at entry and at day 7"
Tran 2004 VNM	243	LFTs	Days 3,7,28	None	Adequate[1]	Incomplete[2]	"There were no significant differences between the three groups in the results of liver function tests done on all patients on days 3, 7, and 28"
Valecha 2010 AS	1150	Not clearly stated	Days 0, 28, 63	None	Inadequate[3]	Incomplete[2]	"Other than elevated liver parameters, as might be expected in

Table 5. DHA-P versus AS+MQ: Biochemical monitoring and adverse events *(Continued)*

						this population, there were no relevant changes in biochemistry parameters".'

[1] Judged as adequate given that no clinically important abnormalities were seen at day 7. Longer follow-up is therefore probably unnecessary.

[2] Judged as incomplete as data were not presented. Only a text summary was given.

[3] Judged as inadequate as biochemical abnormalities are likely to occur earlier than day 28.

LFT = Liver Function Tests

U&E = Urea and electrolytes

Table 6. DHA-P versus AS+MQ dosing regimens

Study ID	Year of study	Age limits	DHA-P	AS+MQ
Ashley 2004a THA	2003	> 14 yrs	6 mg/kg DHA + 48 mg/kg P in 4 divided doses at 0, 8, 24, and 48 hrs	4 mg/kg AS once daily for 3 days + 8 mg/kg MQ once daily for 3 days
Ashley 2004b THA	2003	1 to 65 yrs	6 mg/kg DHA + 48 mg/kg P in 4 divided doses at 0, 8, 24, and 48 hrs	4 mg/kg AS once daily for 3 days + 8 mg/kg MQ once daily for 3 days
Ashley 2005 THA	2005	1 to 65 yrs	6.4 mg/kg DHA and 51.2 mg/kg P in 4 divided doses at 0, 8, 24, and 48 hrs or 3 divided doses at 0, 24, and 48 hrs	4 mg/kg AS once daily for 3 days + 8 mg/kg MQ once daily for 3 days
Grande 2007 PER	2005	5 to 60 yrs	Total dose: 6.3 mg/kg DHA and 50.4 mg/kg PQP in 3 divided doses, given once daily for 3 days	4 mg/kg AS once daily for 3 days + 8 mg/kg MQ once daily for 3 days
Janssens 2007 KHM	2003	> 1 yr	**Adult total dose**: 6 mg/kg DHA and + 48 mg/kg P in 4 divided doses at 0, 8, 24, and 48 hrs **Children total dose**: 6.4 mg/kg DHA + 51.2 mg/kg P in 4 divided doses at 0, 8, 24, and 48 hrs	**Adults**: 100 mg AS plus 500 mg MQ twice daily on day 0, 200 mg AS once daily on days 1 and 2 **Children**: 4 mg/kg AS once daily for 3 days + 25 mg/kg MQ in 2 equal doses on day 0

Table 6. DHA-P versus AS+MQ dosing regimens *(Continued)*

Mayxay 2006 LAO	2004	> 1 yr	6.3 mg/kg DHA + 50.4 mg/kg P in 3 divided doses, once daily for 3 days	4 mg/kg AS once daily for 3 days + 15 mg MQ base/kg on day 1 and 10 mg base/kg on day 2
Smithuis 2006 MMR	2004	> 1 yr	6.3 mg/kg DHA + 50.4 mg/kg P in 3 divided doses, once daily for 3 days	4 mg/kg AS once daily for 3 days. 25 mg MQ base/kg as a single dose on day 0.
Smithuis 2010 MMR	2009	> 1 yr	2.5 mg/kg DHA + 20 mg/kg P daily, given once daily for 3 days	**Fixed combination**: 4 mg/kg AS + 8.8 mg/kg MQ daily, once daily for 3 days. **Loose combination**: 4 mg/kg AS once daily for 3 days + 25 mg base/kg MQ as a single dose on day 0
Tangpukdee 2005 THA	Not stated	> 14 yrs	6 mg/kg DHA + 45 mg/kg P in 3 divided doses, given once daily for 3 days	4 mg/kg AS once daily for 3 days + 8 mg/kg MQ once daily for 3 days
Tran 2004 VNM	2002	> 2 yrs	40 mg/320 mg tablets **Adults**: 2 tablets at 0, 6, 24, and 48 hrs **Children < 15 yrs**: 1 tablet at 0, 6, 24, and 48 hrs	4 mg/kg AS once daily for 3 days + 25 mg base/kg MQ as 2 divided doses 6 hrs apart on day 3
Valecha 2010 AS	2007	3m to 65 yrs (≥18 yrs in India)	DHA: 2.25 mg/kg DHA + 18 mg/kg P daily dose for 3 days	4mg/kg AS once daily for 3 days + MQ none on day 0, then 15 mg/kg once on day 1 and 10 mg/kg once on day 2

Table 7. DHA-P versus AL6: Additional secondary outcomes data

Outcome	Trial ID	Measure	DHA-P	AL6	P value	Comment
Gametocyte carriage	Bassat 2009 AF	Person gametocytemia weeks per 1000 person weeks	43.97	21.43	0.005	
	Smithuis 2010 MMR	Person gametocytemia weeks per 1000 person weeks	112.8	58.2	Not stated	

Ratcliff 2007 IDN	Person game-tocytemia weeks per 1000 person weeks	-	-	Not significant	Figures not given.
Karunajeewa 2008 PNG	Post-treatment gametocytemia	-	-	No difference	Figures not given.
Mens 2008 KEN	Final mean Hb level (mmol/L)	7.15 ± 1.07	6.79 ± 1.24	Not significant	
Arinaitwe 2009 UGA	Mean Hb recovery (g/dL)	0.62 ± 1.68	0.56 ± 1.58	0.41	
Agarwal 2013 KEN	Mean Hb increase from baseline in patients not re-infected	11.6 g/dL	9.8 g/dL	Not stated	P value for difference in mean Hb increase in re-infected patients and those not re-infected is given as 0.9
	Mean Hb increase from baseline in re-infected patients	11.1 g/dL	9.9 g/dL	Not stated	

Hb - Haemoglobin

Table 8.   DHA-P versus AL6: Biochemical monitoring and adverse events

Trial ID	No. of participants	Tests	Days tested	Days reported	Days tested adequate to detect adverse events?	For adequate testing, was reporting complete?	Results as presented in the paper
Bassat 2009 AF	1553	LFTs and renal function	Days 3, 28, and 42	None	Adequate[1]	Incomplete [2]	"...altered liver enzymes (ALT)... was similar between the two treatment groups"
The 4ABC Study 2011 AF	2701	LFT and renal function	Days 7 and 28	Days 7 and 28	Adequate[1]	Complete[3]	"The median levels of alanine aminotransferase and cre-

Table 8. DHA-P versus AL6: Biochemical monitoring and adverse events   (*Continued*)

							atinine before treatment, as well as the proportion of patients with values above the normal range (both clinically and non-clinically significant, the latter not shown), were similar between the four study arms, and this did not change during the follow-ups at day 7 and 28"
Yavo 2011 AF	384	LFTs	Days 0 and 4	Baseline and day 4	Adequate[1]	Complete[3]	"In DP group from the beginning of the treatment to day 4, there was a decrease of the mean of AST and a small increase of ALT mean, while in the AL group, AST and ALT means increased. However, these variations were not significantly different. The decrease of the mean of creatinin from the beginning

Table 8. DHA-P versus AL6: Biochemical monitoring and adverse events *(Continued)*

							of the treatment to day 4 was not significant in the DP group but was significant in the AL group. In the two groups, the bilirubin decrease was significant"

[1] Adequate given that no clinically important abnormalities were seen.

[2] Incomplete as trial authors did not present data and only gave a text summary.

[3] Complete as trial authors presented data for the two days tested.

Table 9. DHA-P versus AS+AQ: Additional secondary outcomes data

Outcome	Trial ID	Measure	DHA-P	AS+AQ	P value	Comment
Gametocyte carriage	Karema 2006 RWA	Gametocyte prevalence	-	-	Not significant	Figures not given.
		Mean PCV at day 14	33.4 ± 3.6	34.0 ± 3.7	0.08	
	Hasugian 2007 IDN	Proportion of patients with anaemia at day 7	-	-	0.02	"Although there was no significant difference in haemoglobin levels between treatment groups at the time of admission, the rates of anemia at days 7 and 28 were significantly higher in AS+AQ recipients"
		Proportion of patients with anaemia at day 28	-	-	0.006	
	Smithuis 2010 MMR	Mean increase in haemoglobin	Not stated	Not stated	> 0.05	"The mean increase of haemoglobin was similar among the treatment groups"

Hb - Haemoglobin

PCV - Packed cell volume

Neutropenia - neutrophil count < 1000/μL

Table 10. DHA-P versus AS+AQ: Biochemical monitoring and adverse events

Study ID	No. of participnts	Tests	Days tested	Days reported	Days tested adequate?	For adequate testing, was reporting complete?	Results as presented in the paper
Karema 2006 RWA	762	LFTs at one site only	Days 0 and 14	None	Adequate[1]	Incomplete [2]	"No hepatotoxicity was observed, although analyses were performed at one site only (data not shown)"
The 4ABC Study 2011 AF	2701	LFT and renal function	Days 7 and 28	Days 7 and 28	Adequate[1]	Complete[3]	"The median levels of alanine aminotransferase and creatinine before treatment, as well as the proportion of patients with values above the normal range (both clinically and non-clinically significant, the latter not shown), were similar between the four study arms, and this did not change during the follow-ups at day 7 and 28"

[1] Adequate given that no clinically important abnormalities were seen.
[2] Incomplete as trial authors did not present data and only gave a text summary.
[3] Complete as trial authors presented data for the two days tested.

Table 11. Dihydroartemisinin-piperaquine compared to Artemether-lumefantrine for uncomplicated *P. falciparum* malaria in Asia and Oceania

Dihydroartemisinin-piperaquine compared to Artemether-lumefantrine for uncomplicated *P. falciparum malaria in Asia*

Patient or population: Patients with uncomplicated *P. falciparum* malaria
Settings: Asia and Oceania
Intervention: Dihydroartemisinin-piperaquine (DHA-P)
Comparison: Artemether-lumefantrine (AL6)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	**Corresponding risk**			
	AL6	**DHA-P**			
Treatment failure Day 28	**PCR-unadjusted**		**RR 0.97** (0.64 to 1.47)	1143 (4 trials)	⊕⊕⊕◯ **moderate**[1,2,3,4]
	7 per 100	**7 per 100** (4 to 10)			
	PCR-adjusted		**RR 2.01** (0.81 to 5.03)	925 (3 trials)	⊕⊕⊕◯ **moderate**[1,2,3,4]
	1 per 100	**3 per 100** (1 to 7)			
Treatment failure Day 63	**PCR-unadjusted**		**RR 0.94** (0.47 to 1.88)	323 (1 trial)	⊕⊕◯◯ **low**[4,5,6,7]
	9 per 100	**8 per 100** (4 to 17)			
	PCR-adjusted		**RR 1.00** (0.14 to 7.01)	298 (1 trial)	⊕⊕◯◯ **low**[4,5,6,7]
	1 per 100	**1 per 100** (0 to 7)			

*The basis for the **assumed risk** (for example, the median control group risk across trials) is provided in footnotes. The **corresponding risk** (and its 95% CI) 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.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] No serious risk of bias: Trials are generally at low or unclear risk of bias. Exclusion of trials as high risk of selection bias or detection bias did not change the result.

[2] No serious inconsistency: Statistical heterogeneity was low.

[3] No serious indirectness: The trials were conducted in adults and children in Indonesia, Thailand, Papua New Guinea, and Myanmar.

[4] Downgraded by 1 for serious imprecision: The 95% CI is wide and includes appreciable differences between drugs.

[5] No serious risk of bias: This single trial is generally at low risk of bias.

[6] Downgraded by 1 for serious indirectness: This single trial is from Myanmar. The results may not be easily generalized to elsewhere.

[7] Two trials from Indonesia and Papua New Guinea reported outcomes at Day 42. At this timepoint there was no difference in PCR unadjusted or PCR adjusted treatment failure (two trials, 572 participants, *low quality evidence*).

Table 12. Dihydroartemisinin-piperaquine compared to Artesunate plus mefloquine for treating uncomplicated *P. falciparum* malaria in Asia

Dihydroartemisinin-piperaquine compared to Artesunate plus mefloquine for treating uncomplicated *P. falciparum malaria in Asia*					
Patient or population: Patients with treating uncomplicated *P. falciparum* malaria **Settings:** Endemic settings in Asia **Intervention:** Dihydroartemisinin-piperaquine (DHA-P) **Comparison:** Artesunate plus mefloquine (AS+MQ)					
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of participants (trials)**	**Quality of the evidence (GRADE)**
	Assumed risk	**Corresponding risk**			
	AS+MQ	**DHA-P**			
Treatment failure Day 28	PCR-unadjusted		**RR 1.02** (0.28 to 3.72)	3487 (8 trials)	⊕⊕⊕⊕ **high**[1,2,3,4]
	2 per 100	2 per 100 (1 to 8)			
	PCR-adjusted		**RR 0.41** (0.21 to 0.8)	3467 (8 trials)	⊕⊕⊕⊕ **high**[1,2,3,5]
	1 per 100	0 per 100 (0 to 1)			
Treatment failure Day 63	PCR-unadjusted		**RR 0.84** (0.69 to 1.03)	2715 (5 trials)	⊕⊕⊕◯ **moderate**[1,6,7,8]
	12 per 100	10 per 100 (8 to 13)			
	PCR-adjusted		**RR 0.5** (0.3 to 0.84)	2500 (5 trials)	⊕⊕⊕⊕ **high**[1,7,8,9]
	3 per 100	2 per 100 (1 to 3)			

*The basis for the **assumed risk** (for example, the median control group risk across trials) is provided in footnotes. The **corresponding risk** (and its 95% CI) 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.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1] No serious risk of bias: Trials are generally at low risk of selection bias and detection bias. Exclusion of trials as high or unclear risk of bias did not change the result.

[2] No serious inconsistency: Six trials found very few recurrent parasitaemia in both groups. Two trials primarily conducted in Thailand in areas with multi-drug resistance found an increased risk of recurrent parasitaemia with AS+MQ.

[3] No serious indirectness: The trials were conducted in adults and children in Vietnam, Thailand, Cambodia, Myanmar, India, and Laos.

[4] No serious imprecision: The overall result is of no significant difference between treatments. However, where there is *P. falciparum* resistance to mefloquine, DHA-P may be superior.

[5] No serious imprecision: The overall result is of a statistically significant benefit with DHA-P although this benefit may only be present where there is resistance to mefloquine.

[6] Downgraded by one for serious inconsistency: Of the five trials, one from Thailand in 2005 found a statistically significant benefit with DHA-P, one from Myanmar in 2009 found a benefit with DHA-P, and three found no difference.

[7] No serious indirectness: The trials were conducted in adults and children in Thailand, Cambodia, Myanmar, India, and Laos.

[8] No serious imprecision: The overall result is of no significant difference between treatments. Although some trials found statistically significant differences, these may not be clinically important.

[9] No serious inconsistency: There is a small amount of variability between trials, with only one trial showing a statistically significant benefit with DHA-P.

Table 13. Dihydroartemisinin-piperaquine compared to Artesunate plus mefloquine for uncomplicated *P. falciparum* malaria in South America

Dihydroartemisinin-piperaquine compared to Artesunate plus mefloquine for uncomplicated *P. falciparum malaria in South America*					
Patient or population: Patients with uncomplicated *P. falciparum* malaria **Settings:** Endemic settings in South America **Intervention:** Dihydroartemisinin-piperaquine (DHA-P) **Comparison:** Artesunate plus mefloquine (AS+MQ)					
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of participants (trials)**	**Quality of the evidence (GRADE)**
	Assumed risk	**Corresponding risk**			

	AS+MQ	DHA-P			
Treatment failure Day 28	**PCR-unadjusted**		-	Data unavailable	-
	-	-			
	PCR-adjusted		-	Data unavailable	-
	-	-			
Treatment failure Day 63	**PCR-unadjusted**		**RR 6.19** (1.4 to 27.35)	445 (1 trial)	⊕⊕◯◯ **low**[1,2,3]
	1 per 100	**6 per 100** (1 to 24)			
	PCR-adjusted		**RR 9.55** (0.52 to 176.35)	435 (1 trial)	⊕⊕◯◯ **low**[1,2,4]
	0 per 100	**0 per 100** (0 to 0)			

*The basis for the **assumed risk** (for example, the median control group risk across trials) is provided in footnotes. The **corresponding risk** (and its 95% CI) 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.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] No serious risk of bias: This trial is at low risk of selection bias and unclear risk of detection bias.
[2] Downgraded by 1 for serious indirectness: This findings of this single trial are not easily generalized to other South American countries.
[3] Downgraded by 1 for serious imprecision: Although this result reached statistical significance the number of events is very low, and there is a high possibility that this is a chance finding.
[4] Downgraded by 1 for serious imprecision: There were too few events in this single trial to confidently exclude important effects.

Table 14. Dihydroartemisinin-piperaquine compared to Artesunate plus amodiaquine for uncomplicated *P. falciparum* malaria in Africa

Dihydroartemisinin-piperaquine compared to Artesunate plus amodiaquine for uncomplicated *P. falciparum malaria in Africa*

Patient or population: Patients with uncomplicated *P. falciparum* malaria
Settings: Africa
Intervention: Dihydroartemisinin-piperaquine (DHA-P)

Comparison: Artesunate plus amodiaquine (AS+AQ)				
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of participants (trials)**	**Quality of the evidence (GRADE)**
	Assumed risk	**Corresponding risk**			
	AS+AQ	**DHA-P**			
Treatment failure Day 28	PCR-unadjusted		RR 0.49 (0.41 to 0.59)	2800 (2 trials)	⊕⊕⊕⊕ **high**[1,2,3,4]
	20 per 100	10 per 100 (8 to 12)			
	PCR-adjusted		RR 0.67 (0.42 to 1.06)	2486 (2 trials)	⊕⊕⊕◯ **moderate**[1,2,3,5]
	4 per 100	2 per 100 (2 to 4)			
Treatment failure Day 63	PCR-unadjusted		RR 0.96 (0.86 to 1.07)	2292 (1 trial)	⊕⊕⊕◯ **moderate**[3,6,7,8]
	37 per 100	35 per 100 (32 to 39)			
	PCR-adjusted		RR 1.8 (0.85 to 3.83)	1506 (1 trial)	⊕⊕⊕◯ **moderate**[3,6,7,8]
	2 per 100	3 per 100 (1 to 6)			

*The basis for the **assumed risk** (for example, the median control group risk across trials) is provided in footnotes. The **corresponding risk** (and its 95% CI) 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.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] No serious risk of bias: Trials are generally at low risk of bias. Exclusion of trials as high or unclear risk of selection bias or detection bias did not change the result.
[2] No serious inconsistency: The trials had similar results and statistical heterogeneity was low.
[3] No serious indirectness: The trials were conducted in children in different transmission settings in Burkina Faso, Gabon, Nigeria, Rwanda, Uganda, Zambia, and Mozambique.
[4] No serious imprecision: Both limits of the 95% CI imply appreciable benefit.
[5] Downgraded by 1 for serious imprecision: The findings did not reach statistical significance.

6 No serious risk of bias: This finding is only reported in one trial which was at low risk of bias.
7 Downgraded by 1 for serious imprecision: There 95% CI are wide and include what might be important differences.
8 No data were presented for day 42.

Table 15. Dihydroartemisinin-piperaquine compared to Artesunate plus amodiaquine for treating uncomplicated *P. falciparum* malaria in Asia

Dihydroartemisinin-piperaquine compared to Artesunate plus amodiaquine for treating uncomplicated *P. falciparum malaria* in Asia

Patient or population: Patients with treating uncomplicated *P. falciparum* malaria
Settings: Asia
Intervention: Dihydroartemisinin-piperaquine (DHA-P)
Comparison: Artesunate plus amodiaquine (AS+AQ)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	**Corresponding risk**			
	AS+AQ	**DHA-P**			
Treatment failure Day 28	**PCR-unadjusted**		**RR 0.38** (0.18 to 0.77)	482 (2 trials)	⊕⊕⊕◯ **moderate**[1,2,3,4]
	11 per 100	4 per 100 (2 to 8)			
	PCR-adjusted		**RR 0.08** (0.01 to 0.4)	466 (2 trials)	⊕⊕⊕◯ **moderate**[1,2,3,4]
	8 per 100	1 per 100 (0 to 3)			
Treatment failure Day 63	**PCR-unadjusted**		**RR 0.49** (0.27 to 0.89)	304 (1 trial)	⊕⊕◯◯ **low**[4,5,6,7]
	19 per 100	9 per 100 (5 to 17)			
	PCR-adjusted		**RR 0.14** (0.03 to 0.59)	278 (1 trial)	⊕⊕◯◯ **low**[4,5,6,7]
	10 per 100	1 per 100 (0 to 6)			

*The basis for the **assumed risk** (for example, the median control group risk across trials) is provided in footnotes. The **corresponding risk** (and its 95% CI) 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.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change

the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1] No serious risk of bias: Trials are generally at low risk of bias. Exclusion of trials as high or unclear risk of selection bias or detection bias did not change the result.

[2] No serious inconsistency: The trials all had similar results and statistical heterogeneity was low.

[3] No serious indirectness: The trials were conducted in adults and children in Indonesia and Myanmar.

[4] Downgraded by 1 for serious imprecision: Although this result reached statistical significance there are limited data, with few events. Larger trials are needed to have full confidence in this result.

[5] No serious risk of bias: This finding is only reported in one trial which was generally at low risk of bias.

[6] Downgraded by 1 for serious indirectness: This trial was from a single setting in Myanmar, and may not be easily generalized to elsewhere.

[7] One trial from Indonesia conducted in 2007 presented day 42 outcomes and at this timepoint there was still an advantage on PCR-unadjusted treatment failure with DHA-P (RR 0.27, 95% CI 0.10 to 0.72, one trial, 152 participants, *moderate quality evidence*), and PCR-adjusted treatment failure (RR 0.10, 95% CI 0.01 to 0.81, one trial, 141 participants, *moderate quality evidence*).

APPENDICES

Appendix 1. Adverse event monitoring

DHA-P versus Artesunate plus mefloquine						
Trial ID	**Sample Size**	**Blinding**	**Clinical symptoms monitoring**	**Biochemistry**	**Haematological**	**ECG**
Ashley 2004a THA	134	Open label	Inpatient monitoring until day 28	U&E, LFT on days 0 and 7	FBC on days 0 and 7	None
Ashley 2004b THA	356	Open label	Daily review until parasites cleared then weekly until day 63	U&E, LFT on days 0 and 7 (DHA-P group only)	FBC on days 0 and 7 (DHA-P group only)	Days 0 and 7 (DHA-P group only)
Ashley 2005 THA	499	Open label	Clinical examination and symptom enquiry daily until parasites cleared then weekly until	None	Haematocrit daily until parasites cleared then weekly until day 63	None

			day 63			
Grande 2007 PER	522	Open label	Clinical assessment daily until day 3 then weekly until day 63	U&E, LFT on days 0 and 7,	FBC, PCV days 0 and 7, PCV days 14 and 63	None
Janssens 2007 KHM	464	Open label	Clinical examination and symptom questionnaire days 0, 1, 2, and 3	None	None	None
Mayxay 2006 LAO	220	Open label	Daily review until parasites cleared then weekly until day 42	None	None	None
Smithuis 2006 MMR	652	Open label	Symptom questionnaire at days 0, 1, 2, 3, and 7	None	None	None
Smithuis 2010 MMR	491	Open label	Review weekly for 9 weeks	None	None	None
Tangpukdee 2005 THA	180	Open label	Inpatient monitoring until day 28. Assessed using non-suggestive questioning	None	None	None
Tran 2004 VNM	243	Open label	Review at days 0, 2, and 7	LFTs on days 3, 7 and 28	None	None
Valecha 2010 AS	1150	Open label	Clinical review until parasites cleared then weekly until day 63	Blood and urine samples 0, 28, 63 and on the day of any recurrent parasitaemia	None	Days 0, 2, 7, 28, 63 and on the day of any recurrent parasitaemia

DHA-P versus Artemether-lumefantrine

Trial ID	Sample Size	Blinding	Clinical symptoms monitoring	Biochemistry	Haematological	ECG

Adam 2010 SDN	160	Open label	Review at days 1, 2, 3, 7, 14, 21, and 28.	None	None	None
Agarwal 2013 KEN	274	Open label	Clinical assessment on days 1, 2, 3, 7, 14, 21, 28, 35, and 42 after enrolment or at any day if ill	None	None	None
Arinaitwe 2009 UGA	671 treated episodes	Open label	Review at days 0, 2, 3, 7, 14, 21, 28 after each episode for 1 year	None	None	None
Bassat 2009 AF	1548	Open label	In-patient review throughout the dosing period then weekly till day 42	LFT and renal function at days 3, 28, and 42 and at clinician's request	FBC at days 3, 28 and 42	12-lead ECG at days 0, 2, and 7
Kamya 2007 UGA	421	Double blind	Clinical assessment daily till day 3 then weekly until day 42	None	None	None
Karunajeewa 2008 PNG	250	Open label	Clinical assessment on days 0, 1, 2, 3, 7, 14, 28, and 42.	None	None	None
Krudsood 2007 THA	191	Open label	In-patient review daily until day 28.	None	None	None
Mens 2008 KEN	146	Open label	Review on days 0, 1, 2, 3, 7, 14, and 28.	None	None	None
Ratcliff 2007 IDN	774	Open label	Review and symptom questionnaire daily until fever and parasites cleared then weekly until day 42	None	None	None

Sawa 2013 KEN	298	Single blind	Clinical examination on days 1, 2, 3, 7, 14, 28, and 42.	None	None	None
The 4ABC Study 2011 AF	2,701	Single blind	Clinical assessment on days 1, 2, 3, 7, 14, 21, and 28.	LFT and renal function at days 7 and 28	FBC at days 3, 7, 14, and 28	None
Yavo 2011 AF	384	Open label	Clinical assessment on days 1, 2, 3, 4, 7, 14, 21, and 28.	LFT at baseline and day 4	None	None
Yeka 2008 UGA	414	Single blind	Review daily till day 3 then weekly until day 42.	None	None	None
Zongo 2007 BFA	375	Open label	Assessment daily until day 3 then weekly until day 42.	None	None	None

DHA-P versus Artemether plus amodiaquine

Trial ID	Sample Size	Blinding	Clinical symptoms monitoring	Biochemistry	Haematological	ECG
Hasugian 2007 IDN	334	Open label	Clinical assessment daily until afebrile then weekly until day 42	None	None	None
Karema 2006 RWA	504	Open label	Clinical assessment on days 0, 1, 2, 3, 7, 14, 21, and 28.	Differential WBC count (and LFT at one site only) at days 0 and 14	None	None
Smithuis 2010 MMR	316	Open label	Review weekly for 9 weeks.	None	None	None
The 4ABC Study 2011 AF	2477	Single blind	Clinical assessment on days 1, 2, 3, 7, 14, 21,	Liver and renal function tests at days 7 and	FBC at days 3, 7, 14, and 28	None

			and 28.	28		

DHA-P versus artesunate plus sulfadoxine-pyrimethamine

Trial ID	Sample Size	Blinding	Clinical symptoms monitoring	Biochemistry	Haematological	ECG
Karunajeewa 2008 PNG	245	Open label	Clinical assessment on days 0, 1, 2, 3, 7, 14, 28, and 42	None	None	None

Appendix 2. Serious adverse event descriptions

DHA-P versus Artesunate plus mefloquine

Trial ID	Number of participants	Blinding	Comment
Ashley 2004a THA	134	Open label	No serious adverse events observed.
Ashley 2004b THA	356	Open label	No serious adverse events observed.
Ashley 2005 THA	499	Open label	4/166 serious events with AS+MQ (death, severe anaemia, febrile convulsion, coagulopathy) and 11/333 with DHA-P (2 deaths, bacterial sepsis, febrile convulsion, leptospirosis, haematemesis, nephritic syndrome, severe anaemia, respiratory infection, epigastric pain, and vomiting)
Grande 2007 PER	522	Open label	3 serious drug related events with AS+MQ requiring stopping treatment (encephalopathy, anxiety and arrhythmia, palpitations, and chest pain)
Janssens 2007 KHM	464	Open label	No serious adverse events observed.
Mayxay 2006 LAO	220	Open label	One neuropsychiatric reaction in AS+MQ group.
Smithuis 2006 MMR	652	Open label	No serious adverse events reported in the first 7 days.
Smithuis 2010 MMR	491	Open label	Not reported.
Tangpukdee 2005 THA	180	Open label	No serious adverse events observed.

Tran 2004 VNM	243	Open label	12 events (10 vomiting, 2 dizziness) described as significant in AS+MQ group and none with DHA-P (P = 0.002)
Valecha 2010 AS	1150	Open label	12/767 events described as serious in DHA-P group (6 deemed related to drug: 2 cases of anaemia, 1 viral infection, 1 Wolf-Parkinson-White syndrome, 1 convulsion, 1 encephalitis), 3/381 in AS+MQ group (all deemed related to drug: 1 anaemia, 1 convulsion, 1 encephalitis)

DHA-P versus Artemether-lumefantrine

Trial ID	Number of participants	Blinding	Comment
Adam 2010 SDN	160	Open label	All AE described as mild.
Agarwal 2013 KEN	274	Open label	1/137 with DHA-P, 2/137 with AL (all severe malaria and attributed to new infections)
Arinaitwe 2009 UGA	671 treated episodes	Open label	3/320 with DHA-P, 1/351 with AL6 (all due to development of severe anaemia)
Bassat 2009 AF	1548	Open label	18/1038 with DHA-P and 5/510 with AL6 (P = 0.2490. One death occurred in each group but the other SAEs are not described
Kamya 2007 UGA	421	Double blind	4/211 with DHA-P, 2/210 with AL, all judged to be unrelated to study meds (3 febrile convulsions, otitis media, asthma attack, pyomyositis)
Karunajeewa 2008 PNG	250	Open label	*Overall comment*: No treatment withdrawals were attributable to adverse events related to a study drug
Krudsood 2007 THA	191	Open label	*Overall comment*: No significant differences are noted between the treatments
Mens 2008 KEN	146	Open label	One patient treated with DHA-P died on day 14. Assessed as unrelated to treatment
Ratcliff 2007 IDN	774	Open label	One death 60 days after treatment. Cause not known.
Sawa 2013 KEN	298	Single blind	*Overall comment*: No adverse events reported.

The 4ABC Study 2011 AF	2701	Single blind	10/1468 with DHA-P compared to 6/1225 with AL6. The only ones described are one death due to diarrhoeal disease in the DHA-P group and three deaths in the AL group (two severe malaria and one unknown cause). None were related to treatment
Yavo 2011 AF	384	Open label	None reported.
Yeka 2008 UGA	414	Single blind	2/215 with AL, 5/199 with DHA-P, all judged unrelated to study meds (2 convulsions, 2 pyomyositis, vomiting, severe anaemia, dehydration)
Zongo 2007 BFA	375	Open label	None observed.
Bassat 2009 AF	1548	Open label	No difference in QT prolongation.

DHA-P versus Artesunate plus amodiaquine

Trial ID	Number of participants	Blinding	Comment
Hasugian 2007 IDN	334	Open label	3 with AS+AQ (2 vomiting, 1 ataxia), none with DHA-P.
Karema 2006 RWA	504	Open label	Not reported (one seizure with AS+AQ).
Smithuis 2010 MMR	316	Open label	Not reported.
The 4ABC Study 2011 AF	2477	Single Blind	Occurence more frequent in AS+AQ group (15/1003 in the AS+AQ group versus 10/1468 in the DHA-P group). The only ones described are one severe malaria case in AS+AQ group and one death due to diarrhoeal disease in DHA-P group

DHA-P versus artesunate plus sulfadoxine-pyrimethamine

Trial ID	Number of participants	Blinding	Comment
Karunajeewa 2008 PNG	245	Open label	*Overall comment*: No treatment withdrawals were attributable to adverse events related to a study drug

Footnotes

AE = adverse event; AL6 = artemether-lumefantrine; AQ = amodiaquine; AS = artesunate; DHA-P = dihydroartemisinin-piperaquine; ECG: electrocardiogram; MQ = mefloquine; QT = interval between the Q and T waves of an ECG; SAE = serious adverse event; SP = sulfadoxine-pyrimethamine.

Appendix 3. Adverse events GRADE tables

Dihydroartemisinin-piperaquine compared to Artesunate plus mefloquine for treating uncomplicated *P. falciparum malaria*

Patient or population: Patients with uncomplicated *P. falciparum* malaria
Settings: Malaria endemic areas
Intervention: Dihydroartemisinin-piperaquine (DHA-P)
Comparison: Artesunate plus mefloquine (AS+MQ)

Outcomes		Number of participants having adverse events (95% CI)		No of participants (trials)	Quality of the evidence (GRADE)
		AS+MQ	**DHA-P**		
Serious adverse events (including deaths)		8 per 1000	9 per 1000 (4 to 18)	3522 (8 trials)	moderate[1,2,3,4]
Gastroenterological	**Early vomiting**	7 per 100	6 per 100 (5 to 8)	4114 (9 trials)	moderate[2,3,5,6]
	Nausea	20 per 100	14 per 100 (12 to 16)	4531 (9 trials)	moderate[3,5,7,8]
	Vomiting	13 per 100	8 per 100 (6 to 10)	2744 (5 trials)	moderate[3,5,7,8]
	Anorexia	15 per 100	13 per 100 (11 to 15)	3497 (6 trials)	low[3,5,7,9]
	Diarrhoea	6 per 100	8 per 100 (6 to 11)	2217 (5 trials)	moderate[3,5,7,8]
	Abdominal pain	11 per 100	11 per 100 (9 to 13)	3887 (7 trials)	moderate[3,5,7,10]
Neuro-psychiatric	**Headache**	12 per 100	10 per 100 (8 to 12)	2039 (4 trials)	low[3,5,8,11]
	Dizziness	36 per 100	26 per 100 (24 to 28)	4531 (9 trials)	moderate[3,5,7,8]
	Sleeplessness	21 per 100	10 per 100 (8 to 13)	2551 (6 trials)	moderate[3,5,7,8]

	Fatigue	**8 per 100**	**3 per 100** (2 to 6)	872 (2 trials)	**low**[5,7,12]
	Nightmares	**10 per 100**	**1 per 100** (0 to 7)	220 (1 trial)	**low**[5,12]
	Anxiety	**11 per 100**	**1 per 100** (0 to 4)	522 (1 trial)	**low**[5,12]
	Blurred vision	**9 per 100**	**4 per 100** (2 to 9)	464 (1 trial)	**low**[5,12]
	Tinnitus	**9 per 100**	**4 per 100** (1 to 11)	220 (1 trial)	**low**[5,12]
Cardio-respiratory	**Palpitations**	**18 per 100**	**11 per 100** (8 to 15)	1175 (3 trials)	**moderate**[3,5,7,8]
	Cough	**10 per 100**	**8 per 100** (5 12)	1148 (1 trial)	**low**[5,9]
	Dyspnoea	**9 per 100**	**3 per 100** (1 to 10)	220 (1 trial)	**low**[5,13]
	Prolonged QT interval (adverse event)	**4 per 100**	**5 per 100** (3 to 9)	1148 (1 trial)	**low**[9,14,15]
	Prolonged QT interval (Bazett's correction)	**4 per 100**	**9 per 100** (5 to 15)	1148 (1 trial)	**low**[5,9,15]
	Prolonged QT interval (Fridericia's correction)	**5 per 100**	**4 per 100** (3 to 8)	1148 (1 trial)	**low**[5,9,15]
Musculoskeletal/ dermatological	**Arthralgia**	**6 per 100**	**5 per 100** (3 to 9)	1148 (1 trial)	**moderate**[5,10,14]
	Myalgia	**6 per 100**	**6 per 100** (4 to 10)	1148 (1 trial)	**moderate**[5,10,14]
	Urticaria	**2 per 100**	**1 per 100** (0 to 4)	719 (2 trials)	**low**[5,13]
	Pruritis	**3 per 100**	**2 per 100** (1 to 4)	872 (2 trials)	**low**[5,13]

	Rash	1 per 100	0 per 100 (0 to 7)	220 (1 trial)	low[5,13]

The **assumed risk** of adverse events in the AS+MQ group is an average risk across trials. The **corresponding risk** with DHA-P (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] No serious risk of bias: Only eight of the 11 trials made any comment on serious adverse events. None of these eight trials were blinded.

[2] No serious inconsistency: None of the eight trials found statistically significant differences.

[3] No serious indirectness: These trials recruited both adults and children, and were conducted in Asia and South America.

[4] Downgraded by 1 for imprecision: These trials do not exclude the possibility of rare but clinically important adverse effects.

[5] Downgraded by 1 for serious risk of bias: All trials were open label.

[6] No serious imprecision: The 95% CI around the absolute effect is narrow and excludes clinically important differences.

[7] No serious inconsistency: This finding was consistent across trials with no significant statistical heterogeneity.

[8] No serious imprecision: The result is statistically significant and the meta-analysis is adequately powered to detect this effect.

[9] Downgraded by 1 for serious imprecision: This result does not reach statistical significance.

[10] No serious imprecision: The finding is of no difference between treatments and the sample size is adequately powered to detect differences if they existed.

[11] Downgraded by 1 for serious inconsistency: There is moderate heterogeneity between trials.

[12] Downgraded by 1 for serious indirectness: Only two trials have assessed this outcome.

[13] Downgraded by 1 for imprecision: Limited data available and the result is not statistically significant.

[14] Downgraded by 1 for serious risk of bias: This trial is unblinded. Only a few of the recorded prolonged QT intervals were registered as adverse events which removed the statistical significance. The reasons for this are unclear.

[15] No serious indirectness: This single large trial was conducted in adults and children in Thailand, Laos, and India

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Dihydroartemisinin-piperaquine compared to Artemether-lumefantrine for uncomplicated *P. falciparum malaria*

Patient or population: Patients with uncomplicated *P. falciparum* malaria
Settings: Malaria endemic areas
Intervention: Dihydroartemisinin-piperaquine (DHA-P)
Comparison: Artemether-lumefantrine (AL6)

Outcomes		Number of participants having adverse events (95% CI)		No of participants (trials)	Quality of the evidence (GRADE)
		AL6	DHA-P		

Serious adverse events (including deaths)		**6 per 1000**	**10 per 1000** (6 to 17)	7022 (8 trials)	**moderate**[1,2,3,4]
Gastroenterological	**Early vomiting**	**2 per 100**	**3 per 100** (2 to 5)	2695 (3 trials)	**moderate**[2,3,5,6]
	Vomiting	**9 per 100**	**9 per 100** (8 to 11)	6761 (9 trials)	**moderate**[2,3,5,6]
	Nausea	**2 per 100**	**2 per 100** (1 to 7)	547 (2 trials)	**low**[2,3,5,7]
	Diarrhoea	**12 per 100**	**12 per 100** (10 to 14)	4889 (7 trials)	**moderate**[2,3,5,6]
	Abdominal pain	**19 per 100**	**16 per 100** (12 to 20)	911 (5 trials)	**low**[2,3,5,8]
	Anorexia	**15 per 100**	**14 per 100** (12 to 17)	3834 (5 trials)	**moderate**[2,3,5,6]
Neuro-psychiatric	**Headache**	**27 per 100**	**33 per 100** (25 to 44)	309 (2 trials)	**low**[2,3,5,8]
	Sleeplessness	**1 per 100**	**3 per 100** (1 to 9)	547 (2 trials)	**low**[2,3,5,7]
	Dizziness	**3 per 100**	**4 per 100** (2 to 11)	547 (2 trials)	**low**[3,5,7]
	Sleepiness	**0 per 100**	**0 per 100** (0 to 0)	384 (1 trial)	**low**[2,3,5,7]
	Weakness	**17 per 100**	**18 per 100** (15 to 21)	1812 (5 trials)	**moderate**[2,3,5,6]
Cardio-respiratory	**Cough**	**42 per 100**	**42 per 100** (40 to 45)	4342 (5 trials)	**moderate**[2,3,5,6]
	Coryza	**68 per 100**	**66 per 100** (60 to 72)	832 (2 trials)	**low**[1,2,3,8]
	Prolonged QT interval (adverse event)	**3 per 100**	**2 per 100** (1 to 5)	1548 (1 trial)	**low**[8,10,11]
	Prolonged QT interval (Bazett's correction)	**7 per 100**	**9 per 100** (6 to 11)	1548 (1 trial)	**low**[5,8,11]

(Continued)

	Prolonged QT interval (Fridericia's correction)	0 per 100	0 per 100 (0 to 2)	1548 (1 trial)	low[5,8,11]
Musculoskeletal/ dermatological	Pruritis	2 per 100	4 per 100 (2 to 6)	2033 (5 trials)	moderate[2,3,5,6]
	Facial oedema	0 per 100	0 per 100 (0 to 0)	384 (1 trial)	low[2,3,5,7]

*The basis for the **assumed risk** (for example, the median control group risk across trials) is provided in footnotes. The **corresponding risk** (and its 95% CI) 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.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] No serious risk of bias: All but one of the trials are open label. However, we did not down grade for this outcome.
[2] No serious inconsistency: The finding is consistent across all trials. Statistical heterogeneity is low.
[3] No serious indirectness: Trials were mainly conducted in children in Africa, with few trials in Asia or in adults.
[4] Downgraded by 1 for serious imprecision: No statistically significant difference was detected between treatments. However the current sample size does not exclude the possibility of rare but clinically important differences.
[5] Downgraded by 1 for risk of bias: The majority of trials are open label.
[6] No serious imprecision: The finding is of no effect and the CIs around the absolute effect excludes clinically important differences.
[7] Downgraded by 1 for serious imprecision: There are limited data
[8] Downgraded by 1 for serious imprecision: The result does not reach statistical significance.
[9] No serious imprecision: The total number of participants is high and findings are precise.
[10] Downgraded by 1 for serious risk of bias: This trial is unblinded. Only a few of the recorded prolonged QT intervals were registered as adverse events which removed the statistical significance. The reasons for this are unclear.
[11] No serious indirectness: This single trial was conducted in children in Uganda, Kenya, Mozambique, Zambia, and Burkina Faso

Dihydroartemisinin-piperaquine compared to Artesunate plus amodiaquine for uncomplicated P. falciparum malaria

Patient or population: Patients with uncomplicated *P. falciparum* malaria
Settings: Malaria endemic areas
Intervention: Dihydroartemisinin-piperaquine (DHA-P)
Comparison: Artesunate plus amodiaquine (AS+AQ)

Outcomes		Number of participants having adverse events (95% CI)		No of participants (trials)	Quality of the evidence (GRADE)
		AS+AQ	DHA-P		
Serious adverse events (including deaths)		2 per 100	1 per 100 (0 to 1)	2805 (2 trials)	moderate[1,2,3,4]
Gastrointestinal	Early vomiting	6 per 100	5 per 100 (3 to 10)	650 (2 trials)	low[3,5,6,7]
	Vomiting	11 per 100	8 per 100 (7 to 11)	2471 (1 trial)	moderate[7,8,9,10]
	Nausea	17 per 100	17 per 100 (11 to 28)	316 (1 trial)	moderate[5,9,11,12]
	Diarrhoea	11 per 100	11 per 100 (9 to 14)	2787 (2 trials)	moderate[2,3,12,13]
	Abdominal pain	13 per 100	12 per 100 (7 to 21)	316 (1 trial)	low[5,7,9,11]
	Anorexia	11 per 100	10 per 100 (8 to 12)	2787 (2 trials)	low[2,3,7,13]
Neuro-psychiatric	Headache	1 per 100	1 per 100 (0 to 9)	316 (1 trial)	low[5,9,11,14]
	Sleeplessness	14 per 100	11 per 100 (6 to 20)	316 (1 trial)	low[5,7,9,11]
Cardio-respiratory	Cough	31 per 100	32 per 100 (28 to 36)	2471 (1 trial)	moderate[7,8,9,10]
	Palpitations	23 per 100	20 per 100 (13 to 30)	316 (1 trial)	low[5,7,9,11]

*The basis for the **assumed risk** (for example, the median control group risk across trials) is provided in footnotes. The **corresponding risk** (and its 95% CI) 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.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1] No serious risk of bias: Only one of the two trials was blinded. However, we did not downgrade for this outcome.

[2] No serious inconsistency: The finding is consistent across all trials. Statistical heterogeneity is low.

[3] No serious indirectness: Trials were mainly conducted in children in Africa and Asia, with few Asian adults.

[4] Downgraded by 1 for serious imprecision: The number of events is low despite the findings reaching statistical significance and the total number of participants being high.

[5] Downgraded by 1 for risk of bias: The trial that reported this finding was open-label

[6] No serious inconsistency: The finding is consistent across all trials. Statistical heterogeneity can be explained by difference in definition of early vomiting.

[7] Downgraded by 1 for serious imprecision: The result does not reach statistical significance.

[8] No serious risk of bias: The trial that reported this outcome had low risk of bias for blinding of adverse events.

[9] No serious inconsistency: This outcome was only reported in one trial.

[10] No serious indirectness: This trial was mainly conducted in children in Africa.

[11] No serious indirectness: The trial was mainly conducted in children and adults in Asia.

[12] No serious imprecision: The finding is of no effect but the CIs around the absolute effect excludes clinically important differences.

[13] Downgraded by 1 for risk of bias: Only one trial was blinded for adverse events.

[14] Downgraded by 1 for serious imprecision: There are limited data and the 95% CI is wide

CONTRIBUTIONS OF AUTHORS

DS, BZ, SD, and PO developed the protocol as used in Sinclair 2009. For this update, BZ and MG reviewed the reference list, extracted data, and entered it into Review Manager (RevMan). BZ, MG, and DS conducted the analyses, constructed summary of findings tables, and evaluated the quality of evidence using the GRADE approach. All authors reviewed and edited the final draft.

DECLARATIONS OF INTEREST

None known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review was originally incorporated in a larger review of ACTs (Sinclair 2009). In this review we have included additional appraisal and GRADE assessments of adverse effects.