Artemisinin-naphthoquine for treating uncomplicated *Plasmodium falciparum* malaria (Review)

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[Intervention Review]

Artemisinin-naphthoquine for treating uncomplicated *Plasmodium falciparum* malaria

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ABSTRACT

Background

The World Health Organization (WHO) recommends artemisinin-based combination therapy (ACT) for treating people with *Plasmodium falciparum* malaria. Five combinations are currently recommended, all administered over three days. Artemisinin-naphthoquine is a new combination developed in China, which is being marketed as a one-day treatment. Although shorter treatment courses may improve adherence, the WHO recommends at least three days of the short-acting artemisinin component to eliminate 90% *P. falciparum* parasites in the bloodstream, before leaving the longer-acting partner drug to clear the remaining parasites.

Objectives

To evaluate the efficacy and safety of the artemisinin-naphthoquine combination for treating adults and children with uncomplicated *P. falciparum* malaria.

Search methods

We searched the Cochrane Infectious Diseases Group Specialized Register; Cochrane Central Register of Controlled Trials (CENTRAL) published in *The Cochrane Library*; MEDLINE; EMBASE; and LILACS up to January 2015. We also searched the *meta*Register of Controlled Trials (*m*RCT) using 'malaria' and 'arte* OR dihydroarte*' as search terms.

Selection criteria

Randomized controlled trials comparing artemisinin-naphthoquine combinations with established WHO-recommended ACTs for the treatment of adults and children with uncomplicated malaria due to *P. falciparum*.

Data collection and analysis

Two review 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.

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Main results

Four trials, enrolling 740 adults and children, met the inclusion criteria. Artemisinin-naphthoquine was administered as a single dose (two trials), as two doses given eight hours apart (one trial), and once daily for three days (one trial), and compared to three-day regimens of established ACTs. Three additional small pharmaceutical company trials have been carried out. We have requested the data but have not received a response from the company.

Artemisinin-naphthoquine versus artemether-lumefantrine

In three small trials from Benin, Côte d'Ivoire, and Papua New Guinea, both combinations had a very low incidence of treatment failure at Day 28, and there were no differences demonstrated in PCR-unadjusted, or PCR-adjusted treatment failure (three trials, 487 participants, *low quality evidence*). Only the single study from Papua New Guinea followed participants up to Day 42, and the number of treatment failures remained very low with both combinations (one trial, 186 participants, *very low quality evidence*).

Artemisinin-naphthoquine versus dihydroartemisinin-piperaquine

In a single small trial from Indonesia, treatment failure at Day 28 and Day 42 was very low in both groups with no differences demonstrated (one trial, 144 participants, *very low quality evidence*).

Authors' conclusions

The results of these few trials of artemisinin-naphthoquine are promising, but further trials from multiple settings are required to reliably demonstrate the relative efficacy and safety compared to established ACTs. Future trials should be adequately powered to demonstrate non-inferiority, and regimens incorporating three days of the artemisinin component are probably preferable to the one-day regimens.

PLAIN LANGUAGE SUMMARY

Artemisinin-naphthoquine for treating uncomplicated *Plasmodium falciparum* malaria

This Cochrane Review summarises trials evaluating the effects of artemisinin-naphthoquine compared to other artemisinin-based combination therapies (ACTs) recommended by the World Health Organization (WHO) for treating adults and children with uncomplicated *P. falciparum* malaria. After searching for relevant trials up to January 2015, we included four randomized controlled trials, enrolling 740 adults and children.

What is uncomplicated malaria and how might artemisinin-naphthoquine 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.

The WHO recommends ACT for treating people with *P. falciparum* malaria. Five combinations are currently recommended, all administered over three days. Artemisinin-naphthoquine is a new combination developed in China, which is being marketed and evaluated as one-day or three-day regimens.

What the research says

Artemisinin-naphthoquine versus artemether-lumefantrine

In three small trials from Benin, Côte d'Ivoire, and Papua New Guinea, both artemisinin-naphthoquine and AL had a very low incidence of treatment failure at Day 28 (*low quality evidence*), and in the trial from Papua New Guinea it remained low in both groups at Day 42 (*very low quality evidence*).

Artemisinin-naphthoquine versus dihydroartemisinin-piperaquine

In a single small study from Indonesia, treatment failure at Day 28 and Day 42 was very low with both artemisinin-naphthoquine and DHA-P (*very low quality evidence*).

Conclusions

The results of these few trials of artemisinin-naphthoquine are promising, but larger trials from multiple settings are required to be confident that artemisinin-naphthoquine is as effective and well tolerated as other antimalarials.

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SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Artemisinin-naphthoquine versus AL for treating uncomplicated *P. falciparum* malaria

Patient or population: Adults and children with uncomplicated *P. falciparum* malaria
Settings: Malaria endemic settings
Intervention: Artemisinin-naphthoquine (ART-NQ) (one or three-day course)
Comparison: Artemether-lumefantrine (AL) (three-day course)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	AL	ART-NQ			
Treatment failure at day 28	PCR-unadjusted		RR 1.02 (0.24 to 4.37)	487 (3 trials)	⊕⊕◯◯ low[1,2,3,4]
	1 per 100	1 per 100 (0 to 4)			
	PCR-adjusted		RR 1.03 (0.15 to 7.07)	485 (3 trials)	⊕⊕◯◯ low[1,2,3,4]
	0 per 100	0 per 100 (0 to 0)			
Treatment failure at day 42	PCR-unadjusted		RR 0.09 (0.00 to 1.59)	186 (1 trial)	⊕◯◯◯ very low[5,6,7]
	5 per 100	0 per 100 (0 to 8)			
	PCR-adjusted		RR 0.33 (0.01 to 7.91)	186 (1 trial)	⊕◯◯◯ very low[5,6,7]
	1 per 100	0 per 100 (0 to 8)			

The basis for the **assumed risk** is the mean control group risk across included studies. 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: Two studies adequately concealed allocation to be at low risk of selection bias. In the other study the process of randomization and allocation concealment was unclear.
[2] No serious inconsistency: Statistical heterogeneity was low.
[3] Downgraded by 1 for serious indirectness: Three studies have now evaluated this comparison, but only one used a three-day regimen as recommended by the WHO. The three studies are from Benin, Côte d'Ivoire, and Papua New Guinea, and the level of treatment failure with both artemisinin-naphthoquine and AL was very low, lower than seen in many trials of AL. Further studies from additional settings are required before this result can be generalized to elsewhere.
[4] Downgraded by 1 for serious imprecision: to demonstrate non-inferiority at 95% efficacy requires a sample size of 472. These trials are individually significantly underpowered, and the number of events is too low to have full confidence in this result.
[5] No serious risk of bias: This study adequately concealed allocation to be at low risk of selection bias.
[6] Downgraded by 1 for serious indirectness: This single study is from Papua New Guinea. Further studies from additional settings are required before this result can be generalized to elsewhere.
[7] Downgraded by 2 for very serious imprecision: This trial is significantly underpowered to demonstrate non-inferiority.

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BACKGROUND

Description of the condition

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

Uncomplicated malaria is the mild form of the disease, characterised by fever with or without associated headache, tiredness, muscle pains, abdominal pains, rigors, and nausea and vomiting (WHO 2010a). If left untreated, uncomplicated malaria can rapidly develop into severe, life threatening forms of the disease, particularly in those without acquired immunity. Effective immunity generally requires repeated infections over five to 10 years, and is reduced during pregnancy. Consequently, in highly endemic settings, as seen in many areas of rural sub-Saharan Africa, young children and pregnant women are most at risk, while in settings with low or seasonal transmission, all age groups can be equally at risk (WHO 2010a).

P. falciparum has now developed resistance in many parts of the world to most antimalarial drugs used as monotherapy (White 2004; WHO 2010b). Consequently, the World Health Organization (WHO) now recommends that *P. falciparum* malaria is always treated with a combination of two drugs that act at different biochemical sites within the parasite (WHO 2010a). If a parasite mutation producing drug resistance arises spontaneously during treatment, the parasite should then be killed by the partner drug, reducing or delaying the development of resistance, and increasing the useful lifetime of the individual drugs (White 1996; White 1999).

Description of the intervention

Five artemisinin-based combination therapies (ACTs) are recommended for the first-line treatment of uncomplicated malaria; artemether-lumefantrine (AL), artesunate plus amodiaquine (AS+AQ), artesunate plus mefloquine (AS+MQ), artesunate plus sulphadoxine-pyrimethamine (AS+SP), and dihydroartemisinin-piperaquine (DHA-P) (WHO 2010a). The artemisinin components (artemether, artesunate, and dihydroartemisinin) are highly effective schizonticides, and over three days of treatment rapidly eliminate up to 90% of the blood stage asexual forms of *P. falciparum*. The partner drugs are longer acting and are used to clear any residual infection (WHO 2010a). The combinations with very long half-lives (AS+MQ and DHA-P), can provide a period of post-treatment prophylaxis which may last for up to six weeks (Sinclair 2009).

Artemisinin-naphthoquine is a new ACT developed by the Academy of Military Medical Sciences Research Institute for Microbial Epidemics in China (Wang 2004). Contrary to the WHO recommendation for three-days of the artemisinin-derivative (WHO 2010a), this combination is being promoted for use as either a single dose or two dose regimen administered over 24 hours (Hombhanje 2010). The rationale provided for the shortened regimen is to improve compliance with treatment.

Naphthoquine is a tetra-aminoquinoline that was developed in China in the late 1980s. Whilst it was used as monotherapy within China, it has never been widely used in other countries (Hombhanje 2010). It is reported to be well absorbed orally, with high bioavailability, and is excreted mainly via the kidneys (Wang 2004). Several pharmacokinetic studies are available but with conflicting estimates of the elimination half-life (Liu 2012). Early reports were of a half-life of two to three days (Wang 2004), but subsequent published studies found a mean half-life of 10.6 days in healthy adult Chinese volunteers (Qu 2010), and 22.8 days in children aged five to 12 years with malaria (Batty 2012). For comparison, the elimination half-lives of lumefantrine and mefloquine in people with uncomplicated malaria are around three days, and 14 days respectively (Ezzet 2000; Karbwang 1990; WHO 2010a).

Artemisinin is a naturally occurring antimalarial compound which can be extracted from the plant *Artemisia annua*. Since its discovery in the 1970s, product development has concentrated on its semi-synthetic derivatives (artesunate, artemether, dihydroartemisinin) due to the poor water solubility of artemisinin (Pawluk 2013; Woodrow 2005). Once absorbed, these derivatives are rapidly converted to the active metabolite dihydroartemisinin. Parasites resistant to the artemisinin derivatives were first reported in Cambodia in 2007 (Noedl 2008), and confirmed in Cambodia in 2008 (Dondorp 2009), and in Thailand in 2012 (Phyo 2012; WHO 2011).

Assessment of antimalarial drug efficacy

The WHO recommends that new antimalarials should have a treatment failure rate of less than 5%, and failure rates with existing first-line antimalarials higher than 10% should trigger a change in treatment policy (WHO 2010a).

The late reappearance of *P. falciparum* parasites in the blood can be due to failure of the drug to completely clear the original parasite infection (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 (Cattamanchi 2003; White 2002; WHO 2008).

The WHO recommends a minimum follow-up period of 28 days for antimalarial efficacy trials, but longer periods of follow-up may be required for antimalarials with long elimination half-lives (Bloland 2003; White 2002). This is because treatment failure due

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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 trials of mefloquine (WHO 2010a).

Why it is important to do this review

This Cochrane Review aims to systematically evaluate the available studies on the efficacy and safety of the artemisinin-naphthoquine combination for consideration by global and national policy makers.

OBJECTIVES

To evaluate the efficacy and safety of the artemisinin-naphthoquine combination for treating adults and children with uncomplicated *P. falciparum* malaria.

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.

Types of interventions

Intervention

A course of artemisinin-naphthoquine given as a single dose, or multiple doses over one, two, or three days.

Control

A three-day course of a WHO-recommended ACT.
The specific ACTs included are: DHA-P; AS+MQ; AL (six doses); AS+AQ; and AS+SP.

Types of outcome measures

Primary outcomes

Treatment failure at Days 28, 42, and 63; PCR-adjusted and PCR-unadjusted.

Secondary outcomes

- Fever clearance.
- Parasite clearance.
- Gametocyte carriage at Day 7 or 14 (preference for Day 14 in data analysis).
- 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 13 January 2015 using the search terms detailed in Appendix 1: Cochrane Infectious Diseases Group Specialized Register; Cochrane Central Register of Controlled Trials (CENTRAL) published in *The Cochrane Library*; MEDLINE; EMBASE; and LILACS.

Searching other resources

We contacted the manufacturer of artemisinin-naphthoquine in October 2013 requesting further unpublished data.
We also checked the reference lists of all trials identified by the database search.

Data collection and analysis

Selection of studies

Rachel Isba (RI) and Babalwa Zani (BZ) independently reviewed the results of the literature search and obtained full-text copies

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of all potentially relevant trials. We checked each trial report for evidence of multiple publications from the same data set. RI and BZ then independently assessed each trial for inclusion in this review using an eligibility form based on the inclusion criteria. We resolved any disagreements through discussion or, where necessary, by consultation with DS. If clarification was necessary, we attempted to contact the trial authors for further information.

Data extraction and management

Two review authors (RI and BZ) independently extracted data using a pre-tested data extraction form. We extracted data on trial characteristics including methods, participants, interventions, and outcomes as well as data on dose and drug ratios of the combinations.

We extracted the number of participants randomized and the number analysed in each treatment group for each outcome. We calculated and report the loss to follow-up in each group.

For dichotomous outcomes, we recorded the number of participants experiencing the event and the number of participants in each treatment group. For continuous outcomes, we extracted the arithmetic means and standard deviations for each treatment group together with the numbers of participants in each group. If the data were reported using geometric means, we recorded this information and extracted standard deviations on the log scale. If medians were reported we extracted medians and ranges.

Primary outcome

Our primary analysis drew on the WHO 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 sensitivity analysis 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 1).

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

PCR-adjusted total failure (*P. falciparum*) was calculated as the sum of early treatment failures plus late treatment failures due to PCR-confirmed recrudescence. We treated participants with indeterminate PCR results, missing PCR results, or PCR-confirmed new infections as involuntary withdrawals and excluded them from the calculation. The denominator excludes 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.

These primary outcomes relate solely to failure due to *P. falciparum*. For both PCR-unadjusted and PCR-adjusted total failure, participants infected with *P. vivax* during follow-up were retained in the calculation if they were treated with chloroquine and continued in follow-up. As long as they did not go on to develop *P. falciparum* parasitaemia they were classified as treatment successes. We excluded from the calculation those participants who were infected with *P. vivax* and were removed from the trial's follow-up at the time of *P. vivax* parasitaemia.

Assessment of risk of bias in included studies

Two review authors (RI and BZ) independently assessed the risk of bias for each trial using The Cochrane Collaboration's tool for assessing the 'Risk of bias' (Higgins 2011). We resolved any differences of opinion through discussion with a third review author. 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 report the methods used. For blinding, we describe who was blinded and the blinding method. For incomplete outcome data, we report the percentage and proportion lost to follow-up. For selective outcome reporting, we state any discrepancies between the methods used and the results, in terms of the outcomes measured or the outcomes reported. For other biases, we describe any other trial features that we think could affect the trial result (for example, if the trial was stopped early).

We then categorized our judgements as 'low', 'high', or 'unclear' risk of bias, and used this information to guide our interpretation of the presented data. Where our judgement 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). Dichotomous data were combined and presented using risk ratios. For continuous data summarized by arithmetic means and standard

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deviations, we combined data using mean differences. Risk ratios and mean differences are accompanied by 95% CIs.

Unit of analysis issues

We did not encounter any unit of analysis issues.

Dealing with missing data

When trial reports were insufficient, unclear, or missing, we attempted to contact the trial authors for additional information.

Assessment of heterogeneity

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

Assessment of reporting biases

We planned to assess the possibility of publication bias by examining funnel plots for asymmetry, but there were too few trials to make this meaningful.

Data synthesis

We gave the included trials identity codes which include the three-letter international country code, and listed the trials in forest plots in chronological order (by the final date of enrolment).
Treatments were compared directly using pair-wise comparisons. For outcomes that were measured at different time points, we stratified the analysis by the time point.
We performed meta-analysis where appropriate after assessment and investigation of heterogeneity. In the first instance we used a fixed-effect model, and used 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 for each outcome measure using the GRADE approach. The quality rating across studies has four levels: high, moderate, low, or very low. Randomized trials are initially categorized as high quality but downgraded after assessment of five criteria: risk of bias, consistency, directness, imprecision, and publication bias (Guyatt 2008).

Subgroup analysis and investigation of heterogeneity

We planned to investigate potential sources of heterogeneity through a series of analyses subgrouping 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). However, there were too few trials to make this meaningful.

Sensitivity analysis

We conducted a series of sensitivity analyses to investigate the robustness of the methodology used in the primary analysis. We aimed to restore the integrity of the randomization process by adding excluded groups back into the analysis in a stepwise fashion (see Table 1 for details).

RESULTS

Description of studies

Results of the search

We identified 15 articles as potentially relevant to this Cochrane Review. Four RCTs met our inclusion criteria and we excluded 11 articles (see Figure 1).

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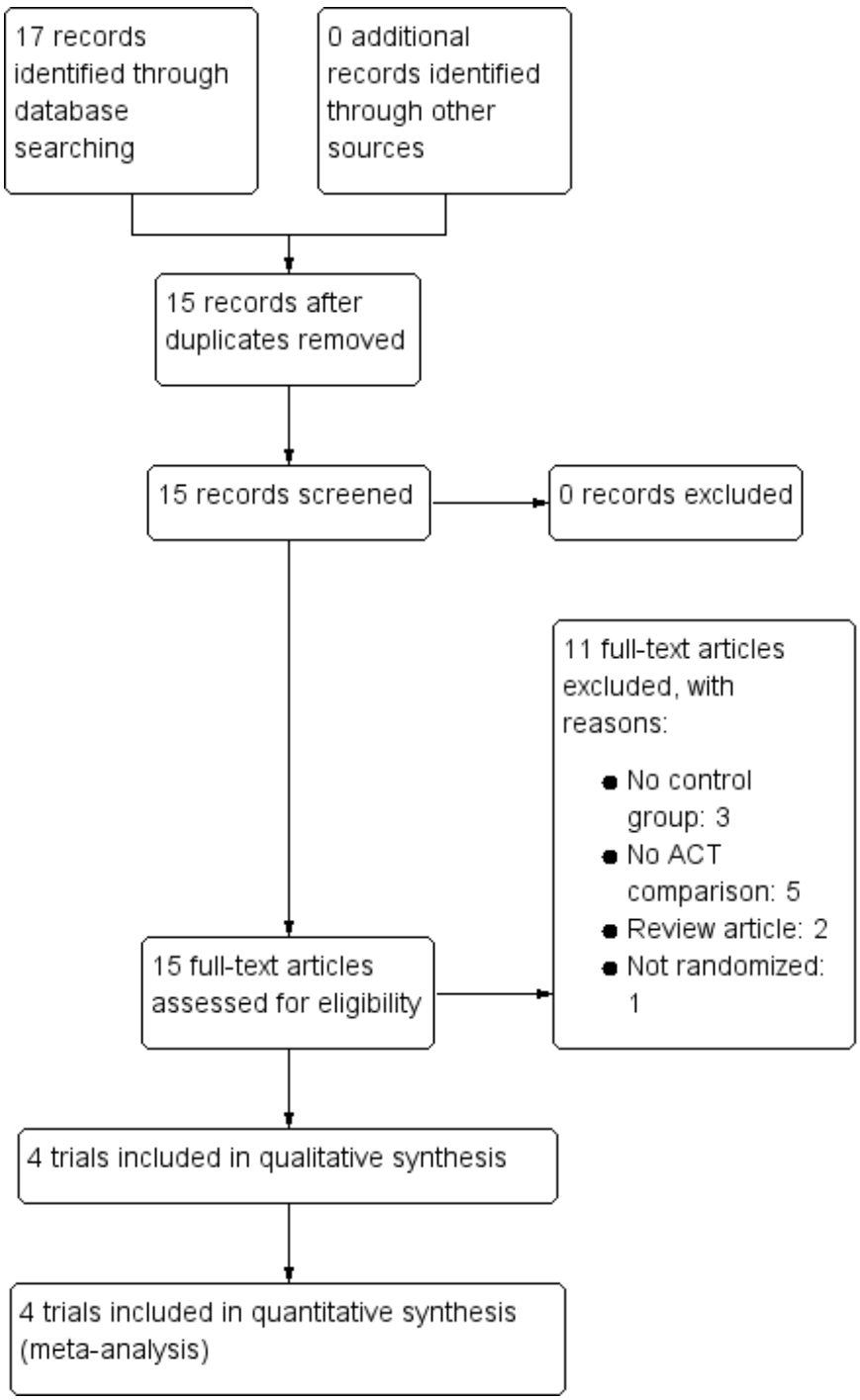
Figure 1. Study flow diagram.



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Included studies

The four trials randomized 740 participants with uncomplicated *P. falciparum* malaria. Two trials (Laman 2014 PNG; Tjitra 2012 IDN) also included participants with *P. vivax* malaria or mixed infections but we excluded these participants from this review.

The trials were conducted in Benin, Côte d'Ivoire, Papua New Guinea, and Indonesia. The trial sites in Benin and Côte d'Ivoire are described as having high transmission intensity and high levels of resistance to chloroquine and SP (Kinde-Gazard 2012 BEN; Toure 2009 CIV). In Indonesia, there were multiple trial sites which are likely to have covered variable levels of transmission (although this was not explicitly stated), and Indonesia has reported resistance to chloroquine, quinine, and SP (Tjitra 2012 IDN). Endemicity and resistance are not described in the study from Papua New Guinea (Laman 2014 PNG).

Kinde-Gazard 2012 BEN recruited participants older than six months, Toure 2009 CIV recruited children aged six months to 15 years, Laman 2014 PNG recruited children aged 6 months to five years, and Tjitra 2012 IDN only recruited adults.

Three trials compared artemisinin-naphthoquine with a three-day course of AL, but each trial used a different regimen of artemisinin-naphthoquine: Kinde-Gazard 2012 BEN gave a single dose, Toure 2009 CIV gave two doses eight hours apart, and Laman 2014 PNG gave a daily dose for three days. It is unclear whether the total dose is comparable across these three trials. Tjitra 2012 IDN compared a single dose of artemisinin-naphthoquine with a three day course of DHA-P.

Kinde-Gazard 2012 BEN and Toure 2009 CIV only report the primary outcome at Day 28 post-treatment, while Laman 2014 PNG and Tjitra 2012 IDN report both Day 28 and Day 42.

Excluded studies

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

Risk of bias in included studies

We summarised the 'Risk of bias' assessments in Figure 2 and the reasons for these judgements in the 'Characteristics of included studies' table.

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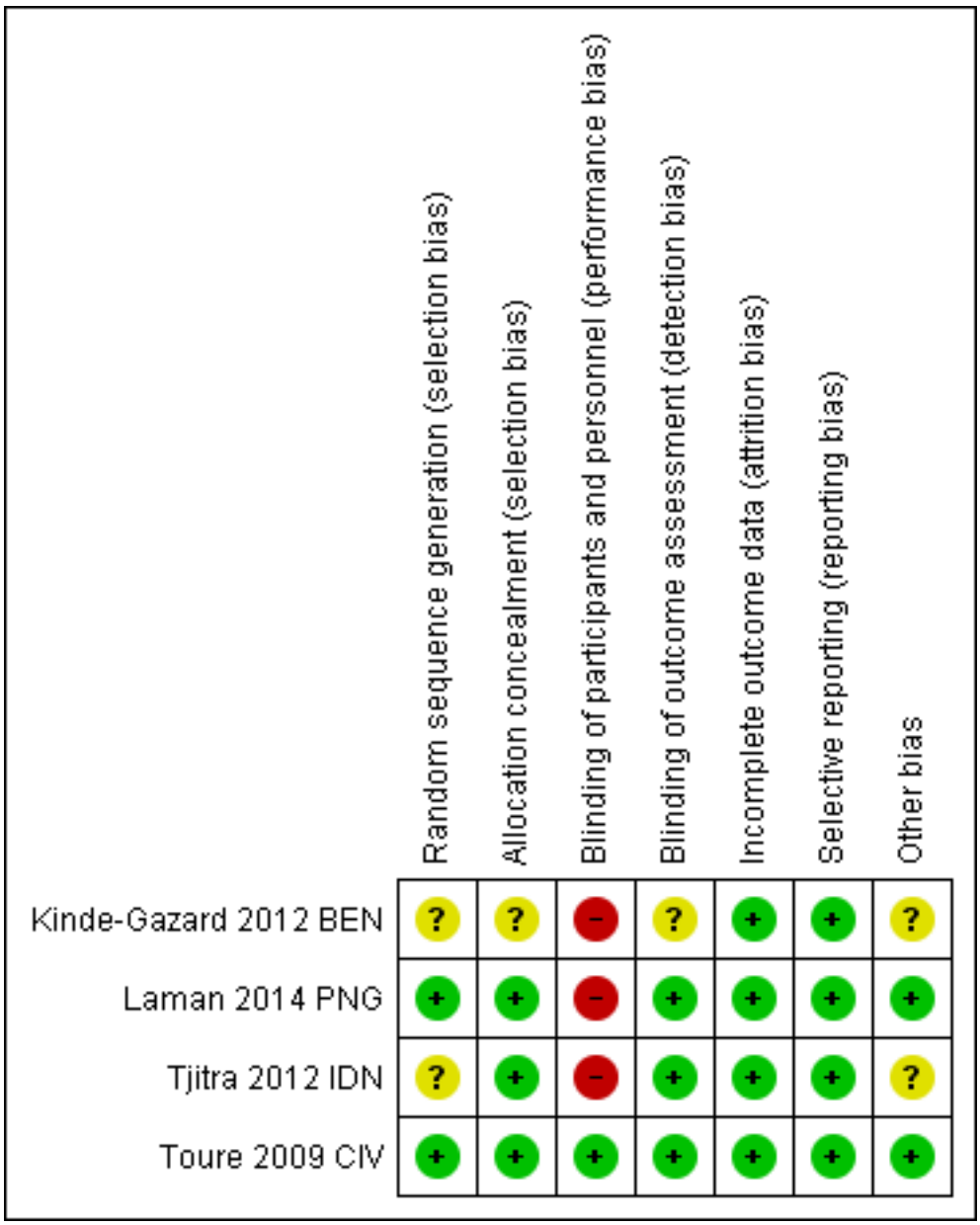
Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included trial.



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Allocation

Two trials adequately described random sequence generation and allocation concealment to be considered at low risk of selection bias (Laman 2014 PNG; Toure 2009 CIV). In the other two trials the description was unclear (Kinde-Gazard 2012 BEN; Tjitra 2012 IDN).

Blinding

Three trials adequately blinded the outcome assessors (laboratory staff and study physicians) to be at low risk of detection bias. In the remaining trial it was unclear whether outcome assessments had been adequately blinded (Kinde-Gazard 2012 BEN).

Incomplete outcome data

All four trials were judged to be of low risk for attrition bias.

Selective reporting

We found no evidence of selective reporting.

Other potential sources of bias

The drug manufacturer was involved in three trials (Kinde-Gazard 2012 BEN; Tjitra 2012 IDN; Toure 2009 CIV); however, it is clearly stated in one of these that they had no involvement in the design or analysis of the study (Toure 2009 CIV).

Effects of interventions

See: **Summary of findings for the main comparison** Artemisinin-naphthoquine versus AL for treating uncomplicated *P. falciparum* malaria; **Summary of findings 2** Artemisinin-naphthoquine versus DHA-P for treating uncomplicated *P. falciparum* malaria

Comparison 1. Artemisinin-naphthoquine versus AL

Three trials compared artemisinin-naphthoquine with AL. These trials recruited adults and children and administered artemisinin-naphthoquine as a single dose (Kinde-Gazard 2012 BEN), as two doses eight hours apart (Toure 2009 CIV), or once daily for three days (Laman 2014 PNG). It is unclear whether the total dose is comparable across these three trials.

Early clinical response to treatment

Two trials reported on fever clearance, with no significant differences between groups in the risk of remaining febrile after 24, 48, or 72 hours (two trials, 321 participants, Analysis 1.1).

All three trials reported parasite clearance, with no significant differences between groups at 24, 48 or 72 hours (three trials, 494 participants, Analysis 1.2).

Treatment failure

Across all three trials, only four participants had recurrent parasitaemia before Day 28, and only two were deemed to have a recrudescence after PCR-adjustment. Consequently, there were no statistically significant differences between groups (three trials, 487 participants, Analysis 1.3; Analysis 1.4). The trial from Papua New Guinea continued follow-up until Day 42, by which time there were five treatment failures with AL (one recrudescence and four new infections) compared to none with artemisinin-naphthoquine (one trial, 186 participants, Analysis 1.5; Analysis 1.6).

Gametocytemia

Two trials reported on gametocyte carriage (Toure 2009 CIV and Laman 2014 PNG). Gametocyte carriage was very low at baseline in both groups in the trial from Côte d'Ivoire. Gametocyte carriage was higher at baseline in the trial from Papua New Guinea and AL appeared to clear gametocytes quicker than artemisinin-naphthoquine (Day 7 gametocyte carriage: RR 2.56, 95% CI 1.42 to 4.60, one trial, 197 participants, Analysis 1.7).

Anaemia

Toure 2009 CIV reported the number of participants who were anaemic on Day 7 and found no significant difference between the two groups (one trial, 120 participants, Analysis 1.8). Laman 2014 PNG presented mean haemoglobin for both groups graphically over 42 days follow-up. There was a small reduction in mean haemoglobin in both groups during the first week which recovered over the following five weeks. There was no difference between groups at any time point other than Day 42 when mean haemoglobin was slightly lower with AL ($P < 0.001$, authors' own figures).

Adverse events

Across the three trials only one severe adverse event is described, and this was considered non-drug-related; one child given artemisinin-naphthoquine was admitted and treated for lobar pneumonia (Laman 2014 PNG; see Table 2).

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All three trials conducted some form of clinical adverse event monitoring and no differences were reported in clinical symptoms after treatment (three trials, 554 participants, Analysis 1.9).

One trial also conducted biochemical monitoring for adverse events on Days 0, 3 and 7. No clinically important differences were seen in tests of renal or liver function (Laman 2014 PNG). The same trial also conducted ECG monitoring on Day 0, 2, 3 and 7 in a non-random sample of participants. After the second dose on day two there were statistically significant differences in the QT interval with 33.3% of those treated with artemisinin-naphthoquine having a QTc > 460 msec compared with 3.7% with AL (P value not reported). Differences were not statistically significant at Day 3 or 7.

Comparison 2. Artemesinin-naphthoquine versus DHA-P

One multi-centre trial in Indonesia compared artemisinin-naphthoquine with DHA-P (Tjitra 2012 IDN). This trial recruited only adults and administered artemisinin-naphthoquine as a single dose.

Early response to treatment

There was no significant differences in fever clearance, or parasite clearance between the two groups (one trial, 149 participants, Analysis 2.1; Analysis 2.2). All blood slides were clear of parasites by Day 3.

Treatment failure

There were no PCR-unadjusted or PCR-adjusted treatment failures before Day 28 in either group (one trial, 143 participants, Analysis 2.3; Analysis 2.4). By Day 42, two participants in each group had recurrent parasitaemia, and after PCR-adjustment the participants given artemisinin-naphthoquine were deemed to have new infections, and those given DHA-P were deemed to have recrudescences (one trial, 143 participants; Analysis 2.5; Analysis 2.6).

Gametocytemia

On Day 7, there was no significant differences in gametocytaemia between the two trial arms (one trial, 150 participants, Analysis 2.7).

Anaemia

Not reported.

Adverse events

No serious adverse events were reported, and adverse events were rare with no differences detected between the two treatments (one trial, 152 participants, Analysis 2.8; see Table 2).

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ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Artemisinin-naphthoquine versus DHA-P for treating uncomplicated *P. falciparum* malaria

Patient or population: Adults and children with uncomplicated *P. falciparum* malaria
Settings: Malaria endemic settings
Intervention: Artemisinin-naphthoquine (ART-NQ) (one-day course)
Comparison: Dihydroartemisinin-piperaquine (DHA-P) (three-day course)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	DHA-P	ART-NQ			
Treatment failure at day 28	**PCR-unadjusted**		Not estimable	143 (1 trial)	⊕◯◯◯ **very low**[1,2,3]
	0 per 100	**0 per 100**			
	PCR-adjusted		Not estimable	143 (1 trial)	⊕◯◯◯ **very low**[1,2,3]
	0 per 100	**0 per 100**			
Treatment failure at day 42	**PCR-unadjusted**		**RR 0.91** (0.13 to 6.26)	143 (1 trial)	⊕◯◯◯ **very low**[1,2,3]
	3 per 100	**3 per 100** (0 to 19)			
	PCR-adjusted		**RR 0.19** (0.01 to 3.82)	141 (1 trial)	⊕◯◯◯ **very low**[1,2,3]
	3 per 100	**0 per 100** (0 to 11)			

The basis for the **assumed risk** is the mean control group risk on the included studies. 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: Although the description of the randomization procedure is vague, this trial is probably at low risk of selection bias.

[2] Downgraded by 1 for serious indirectness: This comparison has only been evaluated in a single setting. Further studies from additional settings are required before this result can be generalized to elsewhere.

[3] Downgraded by 2 for very serious imprecision: to demonstrate non-inferiority at 95% efficacy would require a sample size of 472. This trial is significantly underpowered.

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DISCUSSION

Summary of main results

In three small trials from Benin, Côte d'Ivoire, and Papua New Guinea, both artemisinin-naphthoquine and AL had a very low incidence of treatment failure at day 28 (*low quality evidence*).
In a single small study from Indonesia, treatment failure at day 28 and day 42 was very low with both artemisinin-naphthoquine and DHA-P (*very low quality evidence*).
These trials were underpowered to detect clinically important differences.

Overall completeness and applicability of evidence

To date, there are only very limited data available on either the efficacy or safety of artemisinin-naphthoquine and much larger trials, from a wider variety of epidemiological settings will be required before this combination could be recommended. It is perhaps helpful to note that DHA-P had been evaluated in 22 RCTs enrolling almost 15,000 adults and children before it was formally recommended by the WHO (Sinclair 2009), and artesunate plus pyronaridine has been evaluated in three large multicentre trials enrolling over 3000 participants but still requires further evidence of efficacy and safety to have confidence in its effects (Bukirwa 2014).
Trials of around 500 participants are required to demonstrate equivalent efficacy in a single setting (Table 3), and trials from multiple settings are required to demonstrate that the findings can be generalised to regions or continents, particularly for infectious diseases such as malaria where infection patterns and drug resistance vary widely. To rule out serious side-effects, particularly rare ones, much larger patient numbers are required and this is usually done through observational cohorts.
The trials included in this review suggest that this combination has potential, but it is unclear whether the rationale of a shortened 24 hour regimen is justified. The current WHO recommendation for three-day regimens is based on a trade-off between compliance (enhanced by shorter regimens), efficacy (enhanced by longer regimens), and the desire to reduce the risk of drug resistance developing (enhanced by combinations of two drugs acting via different mechanisms until parasitaemia is reduced to very low levels). While compliance with the three-day regimens of established ACTs has been poor in some studies, it is hard to understand why shortening the regimen to 24 hours with artemisinin-naphthoquine would be any different to ensuring very poor compliance with any other ACT. Consequently, it would probably be preferable if future studies evaluated a three-day regimen.

Quality of the evidence

We assessed the quality of the evidence in this review using the GRADE approach and presented the evidence in two 'Summary of findings' tables for efficacy (Summary of findings for the main comparison; Summary of findings 2). We judge the evidence to be of low or very low quality meaning that we have little confidence in the findings of no statistically significant difference between the tested ACTs. We downgraded the evidence by one level for serious indirectness as artemisinin-naphthoquine has only been evaluated in a limited number of settings and the findings are not easily generalized, and by one or two levels for serious imprecision as the trials are severely underpowered to detect differences.

Potential biases in the review process

None identified.

Agreements and disagreements with other studies or reviews

We found two review articles authored by representatives of the pharmaceutical developers (Hombhanje 2010; Wang 2004). Both are narrative overviews rather than systematic reviews. Hombhanje 2010 includes the data from the three trials included here plus some additional data from three unpublished trials. We have contacted the pharmaceutical company requesting access to these data but have not yet received it. Should these become available, we will include them in the future updates of this review. Hombhanje 2010 concludes that "ARCO® demonstrated high level of efficaciousness and safety" but notes that further research is still necessary. We are more conservative in our conclusions, and feel that neither the efficacy nor the safety has yet been reliably established.

AUTHORS' CONCLUSIONS

Implications for practice

The results of these few trials of artemisinin-naphthoquine are promising, but further trials from multiple settings are required to reliably demonstrate the relative efficacy and safety compared to established ACTs.

Implications for research

Future trials should be adequately powered to demonstrate non-inferiority, and regimens incorporating three days of the artemisinin component are probably preferable to the one-day regimens.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

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

Kinde-Gazard 2012 BEN

Methods	Trial design: RCT Follow-up: Patients were hospitalized for the first three days, and monitored clinically and biochemically. Following discharge patients were seen on Day 7, 14, 21, and 28 with a malaria blood film at each visit Adverse event monitoring: A symptom questionnaire, biochemistry (U and E, LFT), and haematology were conducted at each visit
Participants	Number: 174 participants randomized Inclusion criteria: Age 6 months to 15 years, clinical signs of uncomplicated malaria, temp > 37.5°C or history of fever in the last 24 hours, asexual *P. falciparum* density > 2000/μL, able to take oral medication, informed consent Exclusion criteria: Signs of severe malaria, known hypersensitivity to study medications, treatment with antimalarials within the past 7 days, positive pregnancy test In addition the trial authors state that they planned to exclude the following groups from the study: severe toxicity, abnormal biochemical tests, unsatisfactory therapeutic response. However, no participants appear to have been excluded for these reasons
Interventions	1. Artemesinin-naphthoquine 125 mg/50 mg, fixed-dose combination (Arco, Kunming Pharmaceutical Corporation, China): • weight < 10 kg 1 tablet, single dose • weight 10 to 15 kg 2 tablets, single dose • weight 16 to 25 kg 4 tablets, single dose • weight 26 to 35 kg 6 tablets, single dose • weight > 35 kg 8 tablets, single dose 2. AL 20 mg/120 mg, fixed-dose combination (Coartem, Novartis SA, Switzerland): • weight < 15 kg 1 tablet, twice a day for 3 days • weight 15 to 24 kg 2 tablets, twice a day for 3 days • weight 25 to 35 kg 3 tablets, twice a day for 3 days • weight > 35 kg 4 tablets, twice a day for 3 days
Outcomes	1. PCR-adjusted and PCR-unadjusted treatment failure at Day 28 2. Haemoglobin 3. Adverse event 4. Fever clearance 5. Parasite clearance
Notes	Country: Benin Setting: Hospital Transmission: High Resistance: Chloroquine and SP Dates: July to Oct 2008 and May to Sept 2009 Funding: None stated, however the randomization procedure was done by the manufacturer of artemisinin-naphthoquine

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Kinde-Gazard 2012 BEN (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"According to a randomization method".
Allocation concealment (selection bias)	Unclear risk	None described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Described as "single blind", however as the drug regimens differed significantly blinding of patients and personnel is unlikely
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up reported.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Unclear risk	Funding is unclear, but the pharmaceutical company appear to be involved

Laman 2014 PNG

Methods	Trial design: open-label, randomized controlled trial Follow-up: Standardized assessment including axillary temp and blood film on Days 1, 2, 3, 7, 14, 28 and 42 Adverse event monitoring: Standardized assessment at each visit plus blood tests for full blood count, hepatorenal function, and an electrocardiogram on Days 0, 3 and 7. An additional electrocardiogram was performed 4 hours after Day 2 dose in those treated with ART-NQ and in a convenience sample of 30 people treated with artemether-lumefantrine
Participants	Number: 198 participants with *P. falciparum* randomized. Inclusion criteria: Age 6 months to 5 years, axillary temp > 37.5°C or history of fever in the last 24 hours, asexual *P. falciparum* density > 1000/μL, or *P. vivax* > 250/μL. Exclusion criteria: Signs of severe malaria, taken study drug in the previous 14 days, known allergy to study medications, evidence of other infection or co-morbidity
Interventions	1. Artemesinin-naphthoquine; fixed-dose combination (Kunming Pharmaceutical Corporation, China): • Artemisinin 20 mg/kg plus naphthoquine 8 mg/kg daily for 3 days • Dosed as 1 to 4 whole tablets per dose as per manufacturers instructions 2. AL: fixed-dose combination (Novartis Pharma, Switzerland): • Artemether 1.7 mg/kg plus lumefantrine 10 mg/kg, twice daily for three days

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	• Dosed as 1 to 3 whole tablets per dose (plus 250 mL of milk) as per manufacturer's instructions. Direct observation of morning AL dose only
Outcomes	1. PCR-adjusted and PCR-unadjusted treatment failure at day 28 and day 42 2. Fever clearance 3. Parasite clearance 4. Gametocyte carriage 5. Haematological and biochemical adverse events 6. Clinical adverse events
Notes	Country: Papua New Guinea Setting: Health centres Transmission: Not described Resistance: Not described Dates: March 2011 to April 2013 Funding: National Health and Medical Research Council, Australian Award PhD Scholarship, Esso-Highlands PNGIMR scholarship

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Computer-generated block randomization".
Allocation concealment (selection bias)	Low risk	"Allocated treatments were concealed in sealed numbered envelopes that were opened in sequence by study medical or nursing staff, and the specified treatment was administered."
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Treatments were not blinded, primarily because the endpoints were based on objective clinical and parasitologic criteria"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All blood films were reexamined independently by two skilled microscopists who were blind to allocated treatment."
Incomplete outcome data (attrition bias) All outcomes	Low risk	At day 28: 2/98 (2%) were lost to follow-up with artemisinin-naphthoquine versus 6/100 (6%) with artemether-lumefantrine At day 42: 4/98 (4%) were lost to follow-up with artemisinin-naphthoquine versus 8/100 (8%) with artemether-lumefantrine
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.

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Laman 2014 PNG (*Continued*)

Other bias	Low risk	"The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript."

Tjitra 2012 IDN

Methods	Trial design: A phase III, randomized, open label, multi-centre, comparative study Follow-up: Limited physical exam on Days 1-2, 3, 7, 14, 12, 28, 35, and 42 and if clinically indicated. ECG 2 to 4 hours after drug administration and on follow-up Days 7, 28, and 42. Thick and thin smears eight hourly in Days 0 to 2, then Days 3, 7, 14, 21, 28, 35, and 42. Haematology and blood chemistry at Days 3, 7, and 28. Blood spot for PCR at Day 42 or failure. Urinalysis on Day 3. HCG for women on Days 0 and 28 Adverse event monitoring: "adverse events collected each time" and "Safety was assessed through direct questioning, physical examinations, ECG abnormalities (prolongation QT-interval), and significant change from baseline clinical laboratory parameters [17]. Adverse events were followed up until the event had resolved."
Participants	Number: 401 randomized (153 *P. falciparum* only, 90 mixed, 158 *P. vivax* only). Inclusion criteria: adult, absence of severe malnutrition, axillary temperature > 37.5°C or a history of fever within the preceding 24 hours, asexual *P. falciparum* density 1000 to 200,000/μL, *P. vivax* and other malaria density $\geq$ 250/μL, able to take oral treatment, informed consent, uncomplicated *P. falciparum* or *P. vivax* mono-infection, or mixed infection. Exclusion criteria: severe vomiting, history or evidence of 'clinically systematic significant disorders', other febrile conditions, hypersensitivity or adverse reactions to antimalarials, history of use of any other antimalarial agent within four weeks of the start of the trial and confirmed by urine test, and pregnancy or lactating
Interventions	1. Artemesinin-naphthoquine, fixed-dose combination, 250 mg/100 mg tablets (Arco, Kunming Pharmaceutical Corporation, China): • 4 tablets as a single dose 2. DHA-P, fixed-dose combination, 40 mg/320 mg tablets (Duo-Cotecxin: Holey-Cotec Pharmaceutical Co. Ltd, China): • Daily doses of dihydroartemisinin 2 to 4 mg/kg and piperaquine 16 to 32 mg/kg • weight $\leq$ 60 kg 3 tablets each day for 3 days • weight > 60 kg 4 tablets each day for 3 days All doses supervised.
Outcomes	1. ACPR at Day 42, PCR-adjusted and PCR-unadjusted 2. Gametocyte carriage 3. Adverse events 4. Fever clearance 5. Parasite clearance
Notes	Country: Indonesia Setting: Three Armed Forces hospitals in Jayapura (Marthen Indeys/Army, Soedibjo Sardadi/Navy, and Bhayangkara/Police Hospitals) and one public hospital in Maumere

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Tjitra 2012 IDN (*Continued*)

	(St. Gabriel Hospital) Transmission: Not reported Resistance: Widely reported resistance of *P. falciparum* to chloroquine, sulphadoxine-pyrimethamine, and quinine Dates: 2007 to 2008 Funding: Kunming Pharmaceutical Corporation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Eligible subjects were blindly, randomly assigned equally to one of the two treatment groups using sealed envelopes"
Allocation concealment (selection bias)	Low risk	"Eligible subjects were blindly, randomly assigned equally to one of the two treatment groups using sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Trial described as "open label".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Microscopy results were blind cross-checked by certified microscopists"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low losses to follow-up in both groups (3.5% AS-N versus 5% DHA-P)
Selective reporting (reporting bias)	Low risk	All listed outcomes reported.
Other bias	Unclear risk	"We also thank to Kunming Pharmaceutical Corporation for funding the artemisinin-naphthoquine trial." The role of the pharmaceutical company in the design, conduct, and interpretation of the trial is unclear

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Toure 2009 CIV

Methods	Trial design: randomized single-blinded clinical trial Follow-up: on Days 1, 2, 3, 7, 14, 21, and 28 (or any other day if they felt ill). Follow-up evaluation was history and examination. Day 7 follow-up included full blood count and liver profile. Blood spots collected for PCR on day of failure Adverse event monitoring: "All observed adverse events were monitored actively and passively from the time the participant has taken one dose of study treatment through last visit, and were recorded on the Case Report Form (CRF) according to Good Clinical Practice (GCP) and ICH guidelines."
Participants	Number: 125 randomized Inclusion criteria: ≥ six months old, *P. falciparum* monoinfection with parasitaemia level of 2000 to 200,000 asexual parasites/μL, axillary temperature > 37.5°C or a history of fever within the preceding 24 hours, no history of serious side effects to study medications, no evidence of concomitant febrile illness, provision of written informed consent by the participant or parent/guardian Exclusion criteria: symptoms or signs of severe malaria, or both, any "danger sign" (persistent vomiting; inability to sit, stand, drink or breast feed), recent history of convulsions or lethargy, or both, or otherwise impaired consciousness, haemoglobin concentration ≤ 6 mg/dL, serious underlying disease, or known allergy to the study drugs "Participants were also excluded after randomization, if they repeatedly vomited their first dose of study medications." "Participants were excluded after enrolment if any of the following occurred: (1) use of antimalarial drugs outside of the study protocol; (2) parasitaemia in the presence of a concomitant febrile illness; (3) withdrawal of consent; (4) loss to follow-up, (5) protocol violation, or (6) death due to a non-malaria illness."
Interventions	1. Artemesinin-naphthoquine, 125 mg/50 mg fixed-dose combination at 0, 8 hours (Arco, Kunming Pharmaceutical Corporation, China): • weight 6 to 10 kg ½ crushed tablet, 2 doses • weight 10 to 15 kg 1 crushed tablet, 2 doses • weight 15 to 25 kg 2 crushed tablets, 2 doses • weight 25 to 35 kg 3 tablets, 2 doses • weight ≥ 35 kg 4 tablets, 2 doses 2. AL fixed-dose combination (Coartem, Novartis SA, Switzerland): • weight 5 to 15 kg 1 crushed tablet, twice a day for 3 days • weight 15 to 25 kg 2 crushed tablets, twice a day for 3 days • weight 25 to 35 kg 3 tablets, twice a day for 3 days • weight ≥ 35 kg 4 tablets, twice a day for 3 days Morning doses supervised and evening doses taken at home. "The empty sachets were returned to study site as evidence of taking the drug"
Outcomes	1. PCR-adjusted and PCR-unadjusted treatment failure at day 28 2. Gametocyte carriage 3. Adverse events 4. Fever clearance 5. Parasite clearance
Notes	Country: Côte d'Ivoire Setting: Primary care centre in Anonkoua-kouté (crowded sub-urban area) Transmission: "extremely high transmission intensity" and "holoendemic"

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	Resistance: "*Plasmodium falciparum* resistance to affordable anti-malarial drugs (chloroquine and sulphadoxine-pyrimethamine) has reached high levels" Dates: November 2006 to January 2007 Funding: Institut Pasteur, Kunming Pharmaecutical Corporation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Participants recruited into the study were allocated to two treatment groups using a computer generated random list based on a simple random selection procedure without the use of blocking or stratification 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 clinical investigators assigned treatment numbers sequentially and a third party investigator who is an appropriately qualified member of the study site, allocated treatment by opening the envelope corresponding to the treatment number. The randomization codes were secured in a locked cabinet accessible only by the third party. Participants were enrolled by the study physicians, and treatments were assigned and administered by the third party."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Participants were not informed of their treatment regimen." Comment: As the regimens are different and no placebos were used participants were essentially unblinded to treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Only the third party was aware of treatment assignments. All other study personnel, including the study physicians and laboratory personnel involved in assessing outcomes, were blinded to the treatment assignments."
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant from each group didn't complete the study: 1 from AN lost to follow-up and 1 from AL excluded

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Toure 2009 CIV (*Continued*)

Selective reporting (reporting bias)	Low risk	All listed outcomes reported.
Other bias	Low risk	No other sources of bias identified. "Artemisinin/naphthoquine and Artemether/lumefantrine were provided free of charge respectively by Kunming Pharmaceutical Corp. and Novartis S A. The funders had no involvement in the study design, data collection and its analysis and interpretation, in the writing of paper or in decision to submit it for publication"

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

Study	Reason for exclusion
Batty 2012	Study 1 - no control group. Study 2 - not a relevant comparison. This study is a pharmacokinetic study comparing a single dose of AS-N with two doses of AS-N given 24 hours apart
Benjamin 2012	Not a relevant comparison: this study compares a single dose of AS-N given with water versus a single dose of AS-N given with milk versus two doses of AS-N
Guo 2003	Not a relevant comparison: this study compares naphthoquine monotherapy with artesunate monotherapy or mefloquine monotherapy
Hombhanje 2009	Not a relevant comparison: this study compares a single dose of ART-NQ with a three day course of chloroquine plus sulphadoxine-pyrimethamine
Liu 2012	A review article: discusses a pharmacokinetic study (Batty 2012).
Lui 2013	Not a relevant comparison: this study compares a three day course of ART-NQ with CQ plus primaquine for treating *P. vivax*.
Meremikwu 2012	Not a relevant comparison: this study compares a single dose of ART-NQ versus a high single dose of ART-NQ versus two dose of ART-NQ
Tun 2009	No control group: a single arm trial of a single dose ART-NQ in adults with uncomplicated *P. falciparum* malaria.
Wang 2002	No control group: single-arm trial of dihydroartemisinin combined with naphthoquine
Wang 2003	Not randomized.
Wang 2004	A review article.

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DATA AND ANALYSES

Comparison 1. Artemisinin-naphthoquine versus AL

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fever clearance	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Fever on day 1	2	321	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.48, 1.29]
1.2 Fever on day 2	2	319	Risk Ratio (M-H, Fixed, 95% CI)	2.73 [0.89, 8.43]
1.3 Fever on day 3	2	320	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.39, 3.52]
2 Parasite clearance	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Parasitaemia on day 1	3	494	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.86, 1.19]
2.2 Parasitaemia on day 2	3	494	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.43, 1.80]
2.3 Parasitaemia on day 3	3	494	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.18, 21.70]
3 PCR-unadjusted treatment failure at day 28	3	487	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.24, 4.37]
4 PCR-adjusted treatment failure at day 28	3	485	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.15, 7.07]
5 PCR-unadjusted treatment failure at day 42	1	186	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.00, 1.59]
6 PCR-adjusted treatment failure at day 42	1	186	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.91]
7 Gametocyte carriage	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 At baseline	2	321	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.87, 1.80]
7.2 At day 7	2	320	Risk Ratio (M-H, Fixed, 95% CI)	2.56 [1.42, 4.60]
7.3 At day 14	1	197	Risk Ratio (M-H, Fixed, 95% CI)	13.13 [1.75, 98.47]
8 Anaemia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.1 At baseline	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 On day 7	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Adverse events	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Vomiting	2	380	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.39, 2.64]
9.2 Diarrhoea	2	380	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.30, 2.54]
9.3 Nausea	2	297	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.40, 2.25]
9.4 Abdominal pain	3	554	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.73, 2.45]
9.5 Anorexia	1	123	Risk Ratio (M-H, Fixed, 95% CI)	2.95 [0.32, 27.60]
9.6 Dizziness	1	123	Risk Ratio (M-H, Fixed, 95% CI)	1.97 [0.18, 21.14]
9.7 Headaches	1	257	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.61, 2.92]
9.8 Asthenia	1	123	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.06, 15.38]
9.9 Trouble sleeping	1	257	Risk Ratio (M-H, Fixed, 95% CI)	2.05 [0.19, 22.30]
9.10 Cough	1	257	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.81, 1.84]
9.11 Difficulty breathing	1	257	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.06, 16.19]
9.12 Pruritus	2	297	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [0.29, 7.34]
9.13 Skin rash	1	257	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.26, 4.00]

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Comparison 2. Artemisinin-naphthoquine versus DHA-P

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fever clearance	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Fever on day 2	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Fever on day 3	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Parasite clearance	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Parasitaemia on day 1	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Parasitaemia on day 2	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Parasitaemia on day 3	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 PCR-unadjusted treatment failure at day 28	1	143	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 PCR-adjusted treatment failure at day 28	1	143	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 PCR-unadjusted treatment failure at day 42	1	143	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.13, 6.26]
6 PCR-adjusted treatment failure at day 42	1	141	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.01, 3.82]
7 Gametocyte carriage	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.1 At baseline	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 At day 7	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Vomiting	1	152	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Diarrhoea	1	152	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.3 Nausea	1	152	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.4 Anorexia	1	152	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.5 Dizziness	1	152	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.6 Asthenia	1	152	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.7 Abdominal pain	1	152	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.8 Pruritus	1	152	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.9 Cough	1	152	Risk Ratio (M-H, Fixed, 95% CI)	1.85 [0.17, 19.95]

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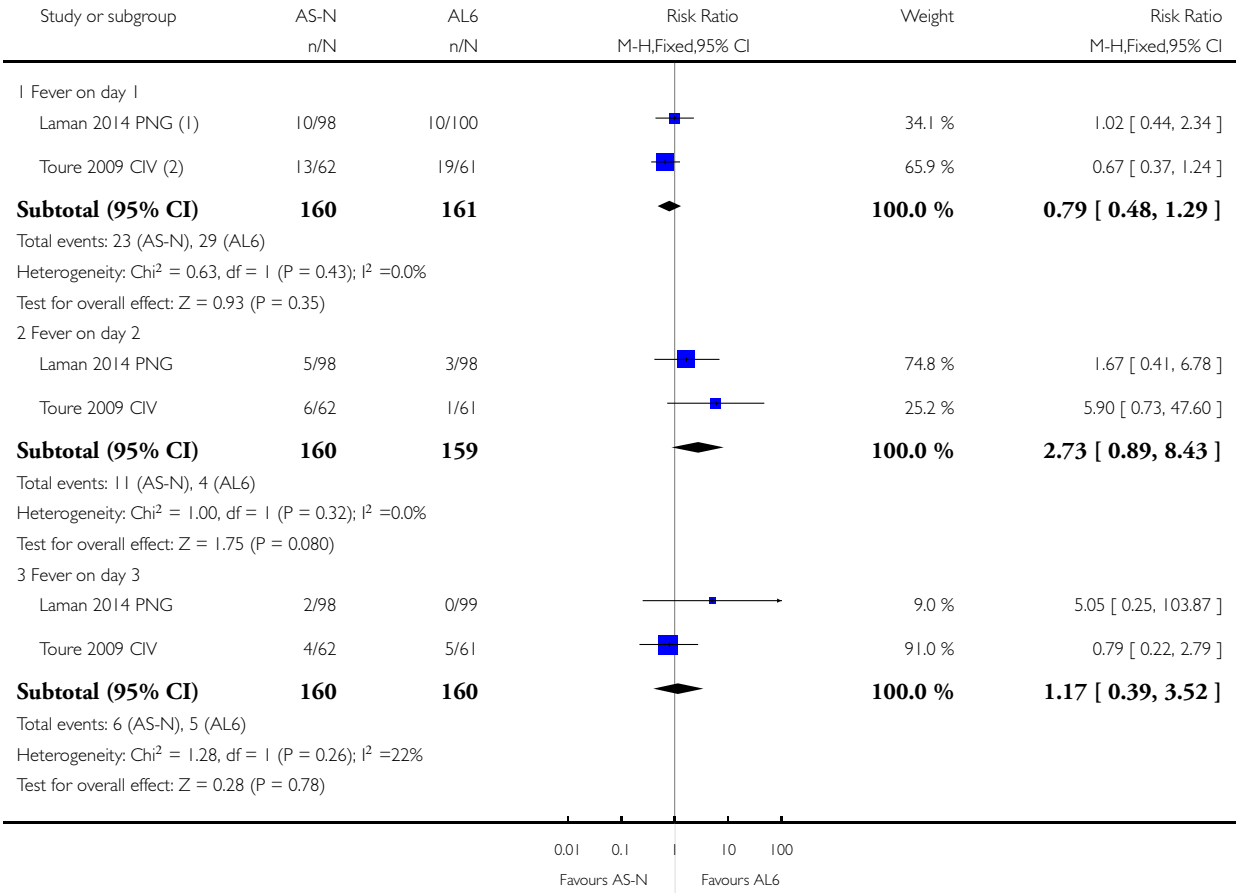
Analysis 1.1. Comparison 1 Artemisinin-naphthoquine versus AL, Outcome 1 Fever clearance.

Review: Artemisinin-naphthoquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 1 Artemisinin-naphthoquine versus AL

Outcome: 1 Fever clearance



(1) Laman 2014: Artemisinin-naphthoquine once daily for three days versus Artemether-lumefantrine twice daily for three days

(2) Toure 2009: Two doses of Artemisinin-Naphthoquine given on the same day vs Artemether-lumefantrine twice daily for three days

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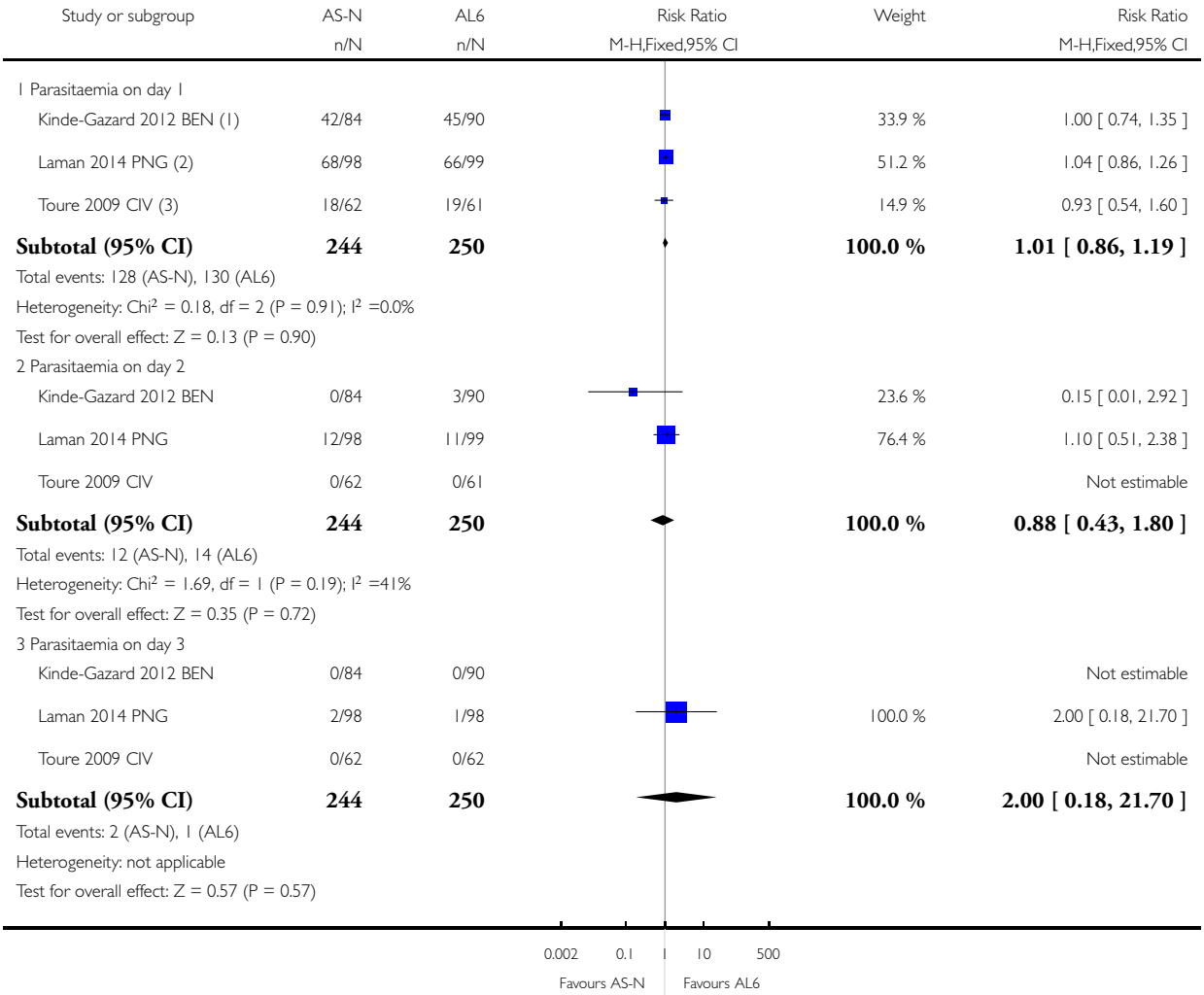
Analysis 1.2. Comparison 1 Artemisinin-naphthoquine versus AL, Outcome 2 Parasite clearance.

Review: Artemisinin-naphthoquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 1 Artemisinin-naphthoquine versus AL

Outcome: 2 Parasite clearance



(1) Kinde-Gazard 2012: A single dose of Artemisinin-Naphthoquine vs Artemether-lumefantrine twice daily for three days

(2) Laman 2014: Artemisinin-naphthoquine once daily for three days versus Artemether-lumefantrine twice daily for three days

(3) Toure 2009: Two doses of Artemisinin-Naphthoquine given on the same day vs Artemether-lumefantrine twice daily for three days

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Analysis 1.3. Comparison 1 Artemisinin-naphthoquine versus AL, Outcome 3 PCR-unadjusted treatment failure at day 28.

Review: Artemisinin-naphthoquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 1 Artemisinin-naphthoquine versus AL

Outcome: 3 PCR-unadjusted treatment failure at day 28

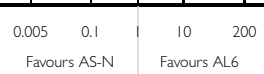
Study or subgroup	AS-N n/N	AL6 n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kinde-Gazard 2012 BEN (1)	2/84	0/90		13.8 %	5.35 [0.26, 109.90]
Laman 2014 PNG (2)	0/96	1/94		43.2 %	0.33 [0.01, 7.91]
Toure 2009 CIV (3)	0/62	1/61		43.1 %	0.33 [0.01, 7.90]
Total (95% CI)	**242**	**245**		**100.0 %**	**1.02 [0.24, 4.37]**

Total events: 2 (AS-N), 2 (AL6)

Heterogeneity: $Chi^2 = 2.13$, df = 2 (P = 0.34); $I^2 = 6\%$

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

Test for subgroup differences: Not applicable



(1) Kinde-Gazard 2012: A single dose of Artemisinin-Naphthoquine vs Artemether-lumefantrine twice daily for three days

(2) Laman 2014: Artemisinin-naphthoquine once daily for three days versus Artemether-lumefantrine twice daily for three days

(3) Toure 2009: Two doses of Artemisinin-Naphthoquine given on the same day vs Artemether-lumefantrine twice daily for three days

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Analysis 1.4. Comparison 1 Artemisinin-naphthoquine versus AL, Outcome 4 PCR-adjusted treatment failure at day 28.

Review: Artemisinin-naphthoquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 1 Artemisinin-naphthoquine versus AL

Outcome: 4 PCR-adjusted treatment failure at day 28

Study or subgroup	AS-N n/N	AL6 n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kinde-Gazard 2012 BEN (1)	1/83	0/90		24.1 %	3.25 [0.13, 78.69]
Laman 2014 PNG (2)	0/96	1/94		75.9 %	0.33 [0.01, 7.91]
Toure 2009 CIV (3)	0/62	0/60			Not estimable
Total (95% CI)	**241**	**244**		**100.0 %**	**1.03 [0.15, 7.07]**

Total events: 1 (AS-N), 1 (AL6)

Heterogeneity: Chi^2 = 1.00, df = 1 (P = 0.32); I^2 =0.0%

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

Test for subgroup differences: Not applicable

(1) Kinde-Gazard 2012: A single dose of Artemisinin-Naphthoquine vs Artemether-lumefantrine twice daily for three days

(2) Laman 2014: Artemisinin-naphthoquine once daily for three days versus Artemether-lumefantrine twice daily for three days

(3) Toure 2009: Two doses of Artemisinin-Naphthoquine given on the same day vs Artemether-lumefantrine twice daily for three days

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Analysis 1.5. Comparison 1 Artemisinin-naphthoquine versus AL, Outcome 5 PCR-unadjusted treatment failure at day 42.

Review: Artemisinin-naphthoquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 1 Artemisinin-naphthoquine versus AL

Outcome: 5 PCR-unadjusted treatment failure at day 42

Study or subgroup	AS-N n/N	AL6 n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Laman 2014 PNG (1)	0/94	5/92		100.0 %	0.09 [0.00, 1.59]
Total (95% CI)	**94**	**92**		**100.0 %**	**0.09 [0.00, 1.59]**
Total events: 0 (AS-N), 5 (AL6)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.65 (P = 0.10)					
Test for subgroup differences: Not applicable					

(1) Laman 2014: Artemisinin-naphthoquine once daily for three days versus Artemether-lumefantrine twice daily for three days

Analysis 1.6. Comparison 1 Artemisinin-naphthoquine versus AL, Outcome 6 PCR-adjusted treatment failure at day 42.

Review: Artemisinin-naphthoquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 1 Artemisinin-naphthoquine versus AL

Outcome: 6 PCR-adjusted treatment failure at day 42

Study or subgroup	AS-N n/N	AL6 n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Laman 2014 PNG (1)	0/94	1/92		100.0 %	0.33 [0.01, 7.91]
Total (95% CI)	**94**	**92**		**100.0 %**	**0.33 [0.01, 7.91]**
Total events: 0 (AS-N), 1 (AL6)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.69 (P = 0.49)					
Test for subgroup differences: Not applicable					

(1) Laman 2014: Artemisinin-naphthoquine once daily for three days versus Artemether-lumefantrine twice daily for three days

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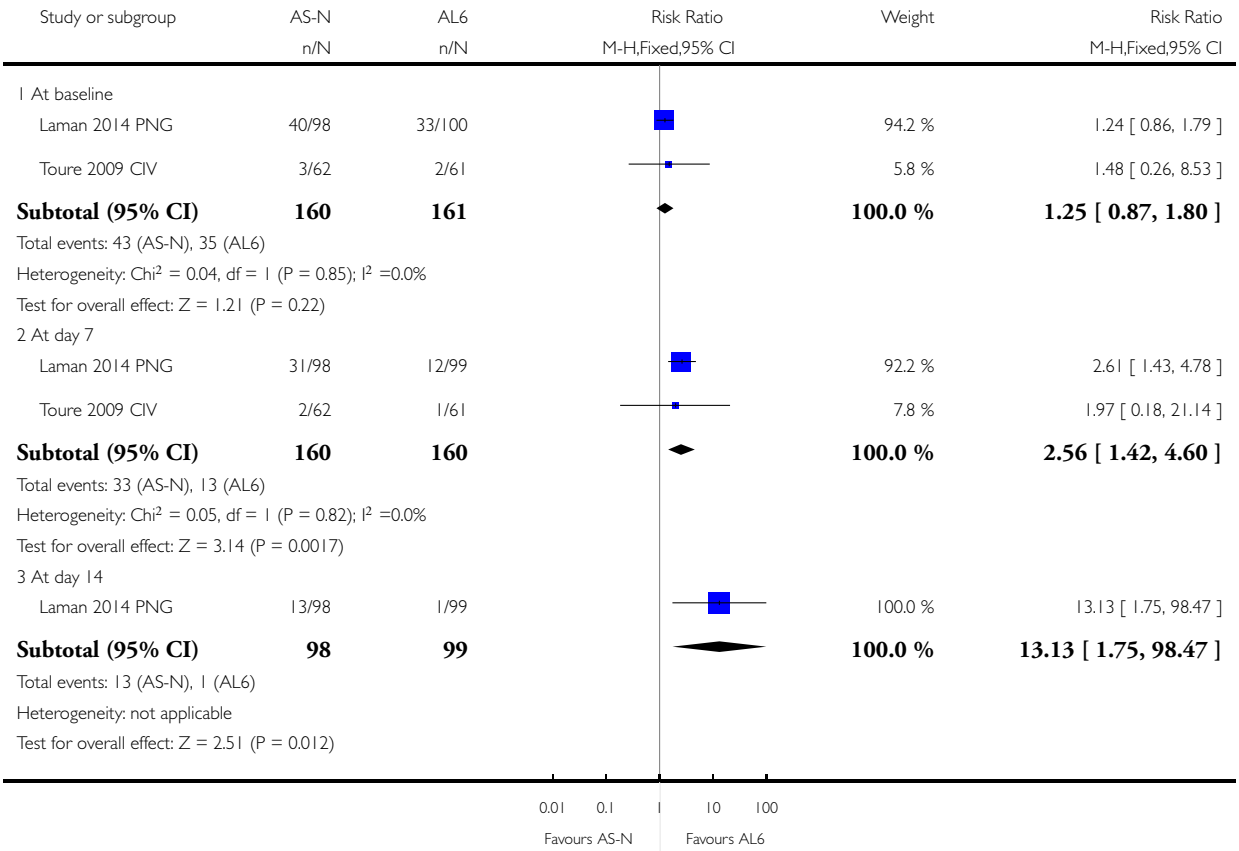
Analysis 1.7. Comparison 1 Artemisinin-naphthoquine versus AL, Outcome 7 Gametocyte carriage.

Review: Artemisinin-naphthoquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 1 Artemisinin-naphthoquine versus AL

Outcome: 7 Gametocyte carriage



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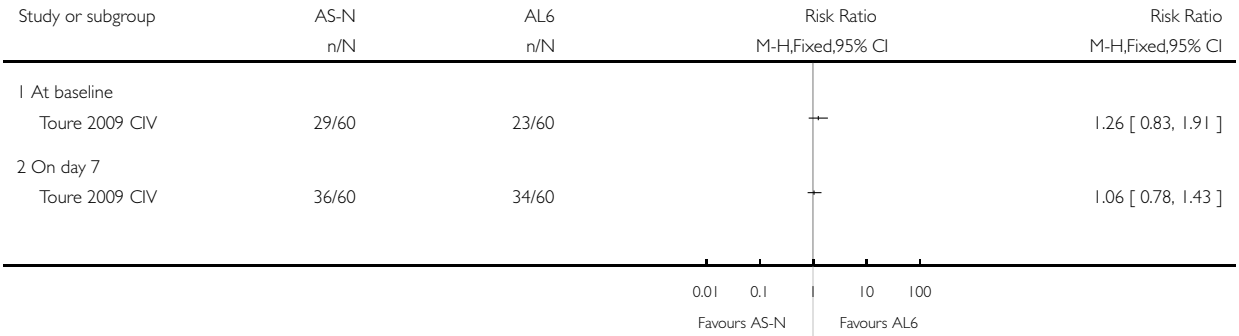
Analysis 1.8. Comparison 1 Artemisinin-naphthoquine versus AL, Outcome 8 Anaemia.

Review: Artemisinin-naphthoquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 1 Artemisinin-naphthoquine versus AL

Outcome: 8 Anaemia

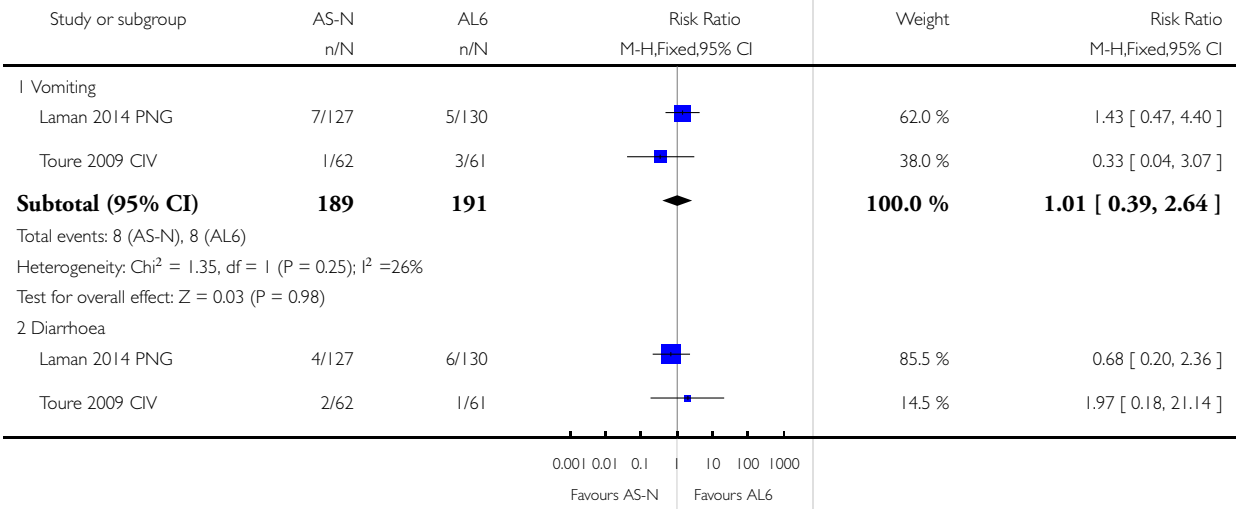


Analysis 1.9. Comparison 1 Artemisinin-naphthoquine versus AL, Outcome 9 Adverse events.

Review: Artemisinin-naphthoquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 1 Artemisinin-naphthoquine versus AL

Outcome: 9 Adverse events



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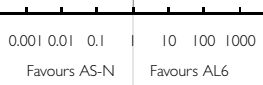
Study or subgroup	AS-N n/N	AL6 n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**189**	**191**		**100.0 %**	**0.87 [0.30, 2.54]**
Total events: 6 (AS-N), 7 (AL6)					
Heterogeneity: Chi² = 0.60, df = 1 (P = 0.44); I² =0.0%					
Test for overall effect: Z = 0.26 (P = 0.80)					
3 Nausea					
Kinde-Gazard 2012 BEN	8/84	7/90		69.1 %	1.22 [0.46, 3.23]
Toure 2009 CIV	1/62	3/61		30.9 %	0.33 [0.04, 3.07]
Subtotal (95% CI)	**146**	**151**		**100.0 %**	**0.95 [0.40, 2.25]**
Total events: 9 (AS-N), 10 (AL6)					
Heterogeneity: Chi² = 1.13, df = 1 (P = 0.29); I² =12%					
Test for overall effect: Z = 0.12 (P = 0.90)					
4 Abdominal pain					
Kinde-Gazard 2012 BEN	6/84	5/90		28.9 %	1.29 [0.41, 4.06]
Laman 2014 PNG	15/127	10/130		59.1 %	1.54 [0.72, 3.29]
Toure 2009 CIV	1/62	2/61		12.1 %	0.49 [0.05, 5.29]
Subtotal (95% CI)	**273**	**281**		**100.0 %**	**1.34 [0.73, 2.45]**
Total events: 22 (AS-N), 17 (AL6)					
Heterogeneity: Chi² = 0.81, df = 2 (P = 0.67); I² =0.0%					
Test for overall effect: Z = 0.94 (P = 0.35)					
5 Anorexia					
Toure 2009 CIV	3/62	1/61		100.0 %	2.95 [0.32, 27.60]
Subtotal (95% CI)	**62**	**61**		**100.0 %**	**2.95 [0.32, 27.60]**
Total events: 3 (AS-N), 1 (AL6)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.95 (P = 0.34)					
6 Dizziness					
Toure 2009 CIV	2/62	1/61		100.0 %	1.97 [0.18, 21.14]
Subtotal (95% CI)	**62**	**61**		**100.0 %**	**1.97 [0.18, 21.14]**
Total events: 2 (AS-N), 1 (AL6)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.56 (P = 0.58)					
7 Headaches					
Laman 2014 PNG	13/127	10/130		100.0 %	1.33 [0.61, 2.92]
Subtotal (95% CI)	**127**	**130**		**100.0 %**	**1.33 [0.61, 2.92]**
Total events: 13 (AS-N), 10 (AL6)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.71 (P = 0.48)					
8 Asthenia					
Toure 2009 CIV	1/62	1/61		100.0 %	0.98 [0.06, 15.38]
Subtotal (95% CI)	**62**	**61**		**100.0 %**	**0.98 [0.06, 15.38]**
Total events: 1 (AS-N), 1 (AL6)					



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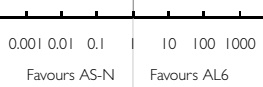
Study or subgroup	AS-N n/N	AL6 n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heterogeneity: not applicable					
Test for overall effect: Z = 0.01 (P = 0.99)					
9 Trouble sleeping					
Laman 2014 PNG	2/127	1/130		100.0 %	2.05 [0.19, 22.30]
Subtotal (95% CI)	**127**	**130**		**100.0 %**	**2.05 [0.19, 22.30]**
Total events: 2 (AS-N), 1 (AL6)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.59 (P = 0.56)					
10 Cough					
Laman 2014 PNG	37/127	31/130		100.0 %	1.22 [0.81, 1.84]
Subtotal (95% CI)	**127**	**130**		**100.0 %**	**1.22 [0.81, 1.84]**
Total events: 37 (AS-N), 31 (AL6)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.96 (P = 0.34)					
11 Difficulty breathing					
Laman 2014 PNG	1/127	1/130		100.0 %	1.02 [0.06, 16.19]
Subtotal (95% CI)	**127**	**130**		**100.0 %**	**1.02 [0.06, 16.19]**
Total events: 1 (AS-N), 1 (AL6)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.02 (P = 0.99)					
12 Pruritus					
Kinde-Gazard 2012 BEN	2/84	2/90		79.3 %	1.07 [0.15, 7.44]
Toure 2009 CIV	1/62	0/61		20.7 %	2.95 [0.12, 71.09]
Subtotal (95% CI)	**146**	**151**		**100.0 %**	**1.46 [0.29, 7.34]**
Total events: 3 (AS-N), 2 (AL6)					
Heterogeneity: Chi^2 = 0.29, df = 1 (P = 0.59); I^2 =0.0%					
Test for overall effect: Z = 0.46 (P = 0.65)					
13 Skin rash					
Laman 2014 PNG	4/127	4/130		100.0 %	1.02 [0.26, 4.00]
Subtotal (95% CI)	**127**	**130**		**100.0 %**	**1.02 [0.26, 4.00]**
Total events: 4 (AS-N), 4 (AL6)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.03 (P = 0.97)					
Test for subgroup differences: Chi^2 = 2.07, df = 12 (P = 1.00), I^2 =0.0%					



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Analysis 2.1. Comparison 2 Artemisinin-naphthoquine versus DHA-P, Outcome 1 Fever clearance.

Review: Artemisinin-naphthoquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 2 Artemisinin-naphthoquine versus DHA-P

Outcome: 1 Fever clearance

Study or subgroup	AS-N n/N	DHA-P n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Fever on day 2				
Tjitra 2012 IDN	0/67	0/61		Not estimable
2 Fever on day 3				
Tjitra 2012 IDN	0/56	1/50		0.30 [0.01, 7.16]

Analysis 2.2. Comparison 2 Artemisinin-naphthoquine versus DHA-P, Outcome 2 Parasite clearance.

Review: Artemisinin-naphthoquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 2 Artemisinin-naphthoquine versus DHA-P

Outcome: 2 Parasite clearance

Study or subgroup	AS-N n/N	DHA-P n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Parasitaemia on day 1				
Tjitra 2012 IDN	43/77	39/72		1.03 [0.77, 1.38]
2 Parasitaemia on day 2				
Tjitra 2012 IDN	3/78	0/70		6.29 [0.33, 119.69]
3 Parasitaemia on day 3				
Tjitra 2012 IDN	0/76	0/68		Not estimable

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Analysis 2.3. Comparison 2 Artemisinin-naphthoquine versus DHA-P, Outcome 3 PCR-unadjusted treatment failure at day 28.

Review: Artemisinin-naphthoquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 2 Artemisinin-naphthoquine versus DHA-P

Outcome: 3 PCR-unadjusted treatment failure at day 28

Study or subgroup	AS-N n/N	DHA-P n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Tjitra 2012 IDN	0/75	0/68			Not estimable
Total (95% CI)	**75**	**68**			**Not estimable**
Total events: 0 (AS-N), 0 (DHA-P)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					

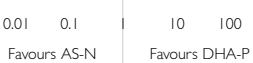
Analysis 2.4. Comparison 2 Artemisinin-naphthoquine versus DHA-P, Outcome 4 PCR-adjusted treatment failure at day 28.

Review: Artemisinin-naphthoquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 2 Artemisinin-naphthoquine versus DHA-P

Outcome: 4 PCR-adjusted treatment failure at day 28

Study or subgroup	AS-N n/N	DHA-P n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Tjitra 2012 IDN	0/75	0/68			Not estimable
Total (95% CI)	**75**	**68**			**Not estimable**
Total events: 0 (AS-N), 0 (DHA-P)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					



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Analysis 2.5. Comparison 2 Artemisinin-naphthoquine versus DHA-P, Outcome 5 PCR-unadjusted treatment failure at day 42.

Review: Artemisinin-naphthoquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 2 Artemisinin-naphthoquine versus DHA-P

Outcome: 5 PCR-unadjusted treatment failure at day 42

Study or subgroup	AS-N n/N	DHA-P n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Tjitra 2012 IDN	2/75	2/68		100.0 %	0.91 [0.13, 6.26]
Total (95% CI)	**75**	**68**		**100.0 %**	**0.91 [0.13, 6.26]**

Total events: 2 (AS-N), 2 (DHA-P)
Heterogeneity: not applicable
Test for overall effect: Z = 0.10 (P = 0.92)
Test for subgroup differences: Not applicable

Analysis 2.6. Comparison 2 Artemisinin-naphthoquine versus DHA-P, Outcome 6 PCR-adjusted treatment failure at day 42.

Review: Artemisinin-naphthoquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 2 Artemisinin-naphthoquine versus DHA-P

Outcome: 6 PCR-adjusted treatment failure at day 42

Study or subgroup	AS-N n/N	DHA-P n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Tjitra 2012 IDN	0/73	2/68		100.0 %	0.19 [0.01, 3.82]
Total (95% CI)	**73**	**68**		**100.0 %**	**0.19 [0.01, 3.82]**

Total events: 0 (AS-N), 2 (DHA-P)
Heterogeneity: not applicable
Test for overall effect: Z = 1.09 (P = 0.28)
Test for subgroup differences: Not applicable

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Analysis 2.7. Comparison 2 Artemisinin-naphthoquine versus DHA-P, Outcome 7 Gametocyte carriage.

Review: Artemisinin-naphthoquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 2 Artemisinin-naphthoquine versus DHA-P

Outcome: 7 Gametocyte carriage

Study or subgroup	AS-N n/N	DHA-P n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 At baseline				
Tjitra 2012 IDN	21/79	18/74		1.09 [0.63, 1.88]
2 At day 7				
Tjitra 2012 IDN	9/78	6/72		1.38 [0.52, 3.70]

Analysis 2.8. Comparison 2 Artemisinin-naphthoquine versus DHA-P, Outcome 8 Adverse events.

Review: Artemisinin-naphthoquine for treating uncomplicated *Plasmodium falciparum* malaria

Comparison: 2 Artemisinin-naphthoquine versus DHA-P

Outcome: 8 Adverse events

Study or subgroup	AS-N n/N	DHA-P n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Vomiting					
Tjitra 2012 IDN	0/79	0/73			Not estimable
Subtotal (95% CI)	**79**	**73**			**Not estimable**
Total events: 0 (AS-N), 0 (DHA-P)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Diarrhoea					
Tjitra 2012 IDN	0/79	0/73			Not estimable
Subtotal (95% CI)	**79**	**73**			**Not estimable**
Total events: 0 (AS-N), 0 (DHA-P)					
Heterogeneity: not applicable					

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Study or subgroup	AS-N n/N	DHA-P n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Test for overall effect: not applicable					
3 Nausea					
Tjitra 2012 IDN	0/79	0/73			Not estimable
Subtotal (95% CI)	**79**	**73**			**Not estimable**
Total events: 0 (AS-N), 0 (DHA-P)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
4 Anorexia					
Tjitra 2012 IDN	0/79	0/73			Not estimable
Subtotal (95% CI)	**79**	**73**			**Not estimable**
Total events: 0 (AS-N), 0 (DHA-P)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
5 Dizziness					
Tjitra 2012 IDN	0/79	0/73			Not estimable
Subtotal (95% CI)	**79**	**73**			**Not estimable**
Total events: 0 (AS-N), 0 (DHA-P)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
6 Asthenia					
Tjitra 2012 IDN	0/79	0/73			Not estimable
Subtotal (95% CI)	**79**	**73**			**Not estimable**
Total events: 0 (AS-N), 0 (DHA-P)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
7 Abdominal pain					
Tjitra 2012 IDN	0/79	0/73			Not estimable
Subtotal (95% CI)	**79**	**73**			**Not estimable**
Total events: 0 (AS-N), 0 (DHA-P)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
8 Pruritus					
Tjitra 2012 IDN	0/79	0/73			Not estimable
Subtotal (95% CI)	**79**	**73**			**Not estimable**
Total events: 0 (AS-N), 0 (DHA-P)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
9 Cough					
Tjitra 2012 IDN	2/79	1/73		100.0 %	1.85 [0.17, 19.95]
Subtotal (95% CI)	**79**	**73**		**100.0 %**	**1.85 [0.17, 19.95]**
Total events: 2 (AS-N), 1 (DHA-P)					
Heterogeneity: not applicable					

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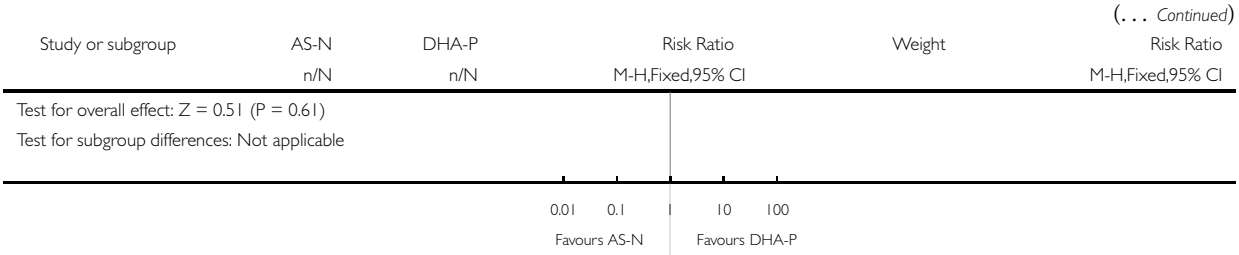

ADDITIONAL TABLES

Table 1. Primary outcome measure (Total failure)

Analysis	Participants	PCR[b]-unadjusted		PCR-adjusted	
		Numerator	**Denominator**	**Numerator**	**Denominator**
Primary analysis[a]	Exclusions after enrolment	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

[a] Note: participants who were found to not satisfy the inclusion criteria after randomization are removed from all calculations.
[b] PCR: polymerase chain reaction.
[c] 'Excluded' means removed from the calculation.
[d] To re-classify all indeterminate or missing PCR results as treatment failures in the PCR-adjusted analysis.

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[e] To re-classify all PCR-confirmed new infections as treatment successes in the PCR-adjusted analysis. (This analysis may overestimate efficacy as PCR is not wholly reliable and some recrudescences may be falsely classified as new infections. Also some participants may have gone on to develop a recrudescence after the new infection.)
[f] To re-classify all exclusions after enrolment (losses to follow-up, withdrawn consent, other antimalarial use, or failure to complete treatment) as treatment failures. For PCR-unadjusted total failure this represents a true worse-case scenario.
[g] To re-classify all exclusions after enrolment (losses to follow-up, withdrawn consent, other antimalarial use, or failure to complete treatment) as treatment successes.

Table 2. Serious adverse events

Comparison	Trial ID	Description of severe adverse events provided by publication
ART-NQ versus AL	Kinde-Gazard 2012 BEN	Not mentioned.
	Toure 2009 CIV	"No severe alterations in renal, haematologic or hepatic function were observed with any of the drug combinations under study." Other adverse events are described as mild.
	Laman 2014 PNG	"The only severe adverse event was considered non-drug related. A 48 month old child allocated to artemisinin-naphthoquine was hospitalized and treated successfully for lobar pneumonia."
ART-NQ versus DHA-P	Tjitra 2012 IDN	"There were no serious adverse events reported in malaria subjects treated with ART-NQ and DHA-P during the study"

Table 3. Optimal information size calculations

Outcome	Hypothesis	Example	Power	α error	Proportion in control group	Proportion in intervention group	Maximum risk difference	Total sample size
PCR-adjusted treatment failure	Superiority	Assuming a 10% failure rate with the old drug and that a new drug should be at least 95% effective	80%	5%	0.10	0.05	-	864
	Non-inferiority	Assuming that both drugs are 95% effective and that there is no more than a 5%	80%	5%	0.05	0.05	0.05	472

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Table 3. Optimal information size calculations (*Continued*)

		difference in efficacy						

We performed calculations with http://www.sealedenvelope.com

APPENDICES

Appendix 1. Detailed search strategy

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	EMBASE[b]	LILACS
1	malaria	Malaria ti, ab, Mesh	Malaria ti, ab, Mesh	Malaria ti, ab, Emtree	malaria
2	arte*	arte* ti, ab	arte* ti, ab	arte*	Arte$
3	dihydroarte*	dihydroarte* ti, ab	dihydroarte* ti, ab	dihydroarte*	Dihydroarte$
4	Coartem*	Coartem* ti, ab	Coartem* ti, ab	Coartem$	Coartem$
5	lumefantrine	Lumefantrine ti, ab	Lumefantrine ti, ab	lumefantrine	lumefantrine
6	2 or 3 or 4 or 5	2 or 3 or 4 or 5	2 or 3 or 4 or 5	2 or 3 or 4 or 5	2 or 3 or 4 or 5
7	Naphthoquin*	Naphthoquin* ti, ab	Naphthoquin* ti, ab	Naphthoquin* ti, ab	Naphthoquin$
8	1 and 6 and 7	Naphtho-quinones[Mesh]	Naphtho-quinones[Mesh]	Naphthoquinone [Emtree]	1 and 6 and 7
9		7 or 8	7 or 8	7 or 8	
10		1 and 6 and 9	1 and 6 and 9	1 and 6 and 9	

[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 2011).

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Appendix 2. Adverse event monitoring

Trial ID	Sample Size	Blinding	Clinical symptoms monitoring	Biochemistry	Haematological	Electrocardiogram
Laman 2014 PNG	198	Open label	Standardized assessment on days 1, 2, 3, 7, 14, 28 and 42.	Hepatorenal function on days 0, 3 and 7.	Full blood count, on days 0, 3 and 7.	Electrocardiogram on days 0, 3 and 7. An additional electrocardiogram was performed 4 hours after day 2 dose in those treated with ART-NQ and in a convenience sample of 30 people treated with artemether-lumefantrine
Tjitra 2012 IDN	243	Open label	Limited physical exam on days 1 to 2, 3, 7, 14, 12, 28, 35, and 42 and if clinically indicated	Blood chemistry at days 3, 7, and 28.	Haematology at days 3, 7, and 28.	ECG 2 to 4 hours after drug administration and on follow-up days 7, 28, and 42
Kinde-Gazard 2012 BEN	174	Single	Patients were hospitalized for the first three days, and monitored clinically; following discharge patients were seen on days 7, 14, 21, 28 and a symptom questionnaire was conducted at each visit	Biochemistry (U and E, LFT) whilst patients were hospitalized for the first three days; then following discharge on days 7, 14, 21, 28	Haematology whilst patients were hospitalized for the first three days; then following discharge on days 7, 14, 21, 28	-
Toure 2009 CIV	125	Single	Follow-up: on days 1, 2, 3, 7, 14, 21, and 28 (or any other day if they felt ill). Follow-up evaluation was history and examination. "All observed adverse events were monitored actively and passively from	Day 7 follow-up included liver profile.	Day 7 follow-up included liver profile.	-

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			the time the participant has taken one dose of study treatment through last visit, and were recorded on the Case Report Form (CRF) according to Good Clinical Practice (GCP) and ICH guidelines."			

CONTRIBUTIONS OF AUTHORS

DS and BZ contributed to the development of the standard protocol as used in Sinclair 2009. BZ drafted the background. RI and MG reviewed the reference list, extracted data, and entered it into Review Manager (RevMan). RI, MG, and DS conducted the analyses, constructed 'Summary of findings' tables, and evaluated the quality of evidence using the GRADE approach. RI wrote the first draft and all authors reviewed and contributed to the final draft.

DECLARATIONS OF INTEREST

The review authors have no conflicting interests.

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK.

External sources

- Department for International Development (DFID), UK.

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