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[Intervention Review]

Artemether-lumefantrine for treating uncomplicated falciparum malaria

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ABSTRACT

Background

Artemether-lumefantrine is being recommended by the World Health Organization for treating uncomplicated malaria. It is expensive. We sought evidence of its superiority over existing treatment regimens.

Objectives

To compare artemether-lumefantrine with other antimalarial drugs for treating uncomplicated falciparum malaria.

Search methods

We searched the Cochrane Infectious Diseases Group specialized trials register (May 2005), CENTRAL (*The Cochrane Library* Issue 2, 2005), MEDLINE (1966 to May 2005), EMBASE (1988 to May 2005), conference proceedings, and reference lists of articles. We contacted experts in malaria research and the pharmaceutical company that manufactures artemether-lumefantrine.

Selection criteria

Randomized and quasi-randomized trials comparing artemether-lumefantrine administered orally with standard treatment regimens (single drug or combination).

Data collection and analysis

Two reviewers independently applied inclusion criteria to potentially relevant trials, assessed trial quality, and extracted data. Parasitaemia on day 28 (day 42 for sulfadoxine-pyrimethamine and day 63 for mefloquine) was the primary outcome. Adverse event information was collected from the studies.

Main results

Six trials (1698 participants) tested a four dose regimen. Failure rates for artemether-lumefantrine tended to be higher (comparisons included sulfadoxine-pyrimethamine, halofantrine, and mefloquine; difference statistically significant for mefloquine). When compared with chloroquine, artemether-lumefantrine was better in two studies, but the failure rate for chloroquine at these sites was over 50%.

Two trials (419 participants) tested a six dose regimen against mefloquine plus artesunate. Artemether-lumefantrine was associated with higher failure rates but the studies were small.

Authors' conclusions

The four dose regimen of artemether-lumefantrine seems to be less effective than most other current antimalarial regimens. The six dose regimen is largely untested.

The authors are aware that some recently published trials may change the results of this review, and are preparing an update. These trials are referenced in 'Studies awaiting assessment'.

PLAIN LANGUAGE SUMMARY

Artemether-lumefantrine for treating uncomplicated falciparum malaria

Plain language summary pending.

BACKGROUND

MALARIA

Malaria is a major health problem in the tropics; at least 300 to 500 million people are diagnosed with the illness every year (WHO 2000a). The main cause is *Plasmodium falciparum*, one of the four species of malaria parasites found in humans. Uncomplicated malaria occurs in the majority of those affected, and is the form of the illness which presents with such symptoms as fever, headache, muscle pain (myalgia), vomiting, mild diarrhoea, anaemia, and enlarged spleen (splenomegaly). In addition, children commonly present with rapid breathing (tachypnoea), cough, and convulsions.

DRUG RESISTANCE

In the past chloroquine was the most commonly used drug for the treatment of uncomplicated malaria; however, drug resistance has reduced its effectiveness. Resistance first emerged in South East Asia and South America (White 1999a), and then spread to Africa and western Oceania. It is now common and has resulted in increased morbidity and mortality in endemic regions. Sulfadoxine-pyrimethamine has replaced chloroquine as first line treatment in some African countries (such as Malawi and Kenya), but resistance to this is now also emerging (WHO 2000a). Resistance to sulfadoxine-pyrimethamine is relatively common in South East Asia (WHO 2001b). In South East Asian countries, where mefloquine and quinine (in combination with doxycycline) are used, resistance and declining sensitivity to mefloquine have also been reported (WHO 2000a). The use of mefloquine is contraindicated in areas of intensive malaria transmission (eg, sub Saharan Africa) because its long half life may expose parasites to subcurative doses, which could result in the development of resistant strains (WHO 2000a).

Artemisinin drugs, including artemether and artesunate, are now used as first line treatment in some countries in South East Asia, but are recommended only as combination treatment (WHO 2000a). Such combination therapy affords rapid clinical response and higher cure rates when compared to other antimalarial combinations (White 1999a). It is also thought combination therapy may slow the parasite developing resistance to the drug (White 1999b).

ARTEMETHER-LUMEFANTRINE COMBINATION

The fixed dose combination of artemether-lumefantrine, called co-artemether, contains 20 mg of artemether and 120 mg of lumefantrine (previously called benflumetol). It was initially developed by scientists at the Academy of Military Medical Sciences in China before the pharmaceutical company, Novartis (Switzerland) became a partner and was licensed to market it as Coartem® or Riamet®. This oral preparation has been designed for use against chloroquine resistant falciparum malaria. Artemether has a rapid onset of action and is rapidly eliminated from the plasma (half life of two to three hours; Lefevre 1999). Lumefantrine is cleared more slowly and has a longer elimination half life (approximately 4.5 days; Ezzet 1998). The rationale behind this combination is that artemether initially provides rapid symptomatic relief by reducing the number of parasites present, and that lumefantrine eliminates any residual parasites. This is thought to minimize development of resistance because the malaria parasites are never exposed to artemether alone (due to its rapid elimination). Although they may be exposed to lumefantrine alone, the probability of resistance developing simultaneously to both drugs used in combination is extremely low (Boland 2000). Artemether-lumefantrine also reduces gametocyte carriage thereby reducing malaria transmission (van Vugt 1998).

Artemether-lumefantrine is recommended as first line therapy in areas of chloroquine resistance or areas of multiple drug resistance (resistance to more than one antimalarial) (Novartis 1999). A course of Co-artem ®/Riamet ® consists of either four or six doses. The drug manufacturers recommend the four dose regimen over 48 hours in semi-immune patients in areas where resistance to other antimalarials has developed. The six dose regimen over three days is recommended in areas with multiple drug resistance or for nonimmune travellers.

There has been some concern about the possible risk of neurotoxicity with artemisinin derivatives, which arose from animal studies using high doses of lipid soluble preparations given intramuscularly (WHO 1999). Lumefantrine could also have adverse cardiac effects due to its similar structure to halofantrine (Bindschedler 2000). These potential adverse effects have to be considered when assessing the toxicity of the drug combination.

A recent addition to the Essential Drugs List, Coartem ® is being promoted in Africa as a replacement treatment for chloroquine by the World Health Organization (WHO). WHO have commended the company for providing the drug at discounted prices for developing countries in malaria endemic areas, stating that “Coartem ® demonstrates cure rates above 95%, even in areas of multi-drug resistance” (WHO 2001a).

This review aims to summarize the existing evidence of how well artemether-lumefantrine performs in comparison to other regimens for treating uncomplicated falciparum malaria. We focus on the comparison with mefloquine, sulfadoxine-pyrimethamine, and chloroquine as single agent therapies, as artemether-lumefantrine is a potential substitute for these compounds (though mefloquine is not recommended in areas of high malaria transmission because of its long residual half life and the inherent risk of the rapid development of resistance).

For our endpoint, we use the standard 28 day parasitaemia (parasites present) as the primary outcome. In areas where malaria transmission is intense, parasitaemia at day 28 could also be due to reinfection, so we also examine the polymerase chain reaction (PCR) which is thought to distinguish between a new infection and recurrence of malaria due to drug resistance.

Over the last year, recommendations for artemether-lumefantrine are for the six dose regimen, with acknowledgement that the four dose regimen is associated with treatment failures (Nosten 2003). We have therefore restructured the review around these dose comparisons.

OBJECTIVES

To compare artemether-lumefantrine with other antimalarial treatments for treating uncomplicated falciparum malaria.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized and quasi-randomized controlled trials.

Types of participants

Adults and children with acute uncomplicated malaria with confirmed asexual *Plasmodium falciparum* parasitaemia. Uncomplicated falciparum malaria is defined as the absence of prostration (extreme physical weakness), impaired consciousness, multiple convulsions, severe anaemia, respiratory distress, acidosis (accumulation of acid in blood and body tissues), shock, renal failure, abnormal bleeding, jaundice, haemoglobinuria (haemoglobin in urine), and hypoglycaemia (low blood sugar) (WHO 2000b). *Plasmodium falciparum* parasitaemia is confirmed from blood slides.

Types of interventions

Intervention: Artemether-lumefantrine administered orally.

Control: Standard treatment regimens for uncomplicated falciparum malaria. Standard treatment regimens may be either a single drug or a combination.

Types of outcome measures

PRIMARY

Parasitaemia (parasites present) on day 28 (day 42 for sulfadoxine-pyrimethamine and day 63 for mefloquine).

SECONDARY

Parasitaemia (parasites present) on day 7 and 14.

Plasmodium falciparum parasitaemia on day 28, corrected by polymerase chain reaction to exclude new infections.

Fever clearance time (time between commencing treatment and the temperature returning back to normal and remaining normal for > 48 hours).

Parasite clearance time (this includes PCT; time between commencing treatment and the first negative blood test when negativity persists for >48 hours), PCT 50 (time taken for parasites to be reduced to 50% of first test value), and PCT 90 (time taken for parasites to be reduced to 10% of first test value).

Gametocyte carriage on days 14 and 28.

Gametocyte clearance time (if present in the blood initially, time taken for gametocytes to disappear after commencing treatment).

ADVERSE EVENTS

Adverse events during treatment that are:

(1) fatal;

- (2) life threatening;
- (3) require hospitalization;
- (4) result in the discontinuation of treatment.

Search methods for identification of studies

We formulated a comprehensive and exhaustive search strategy in an attempt to identify all relevant studies regardless of language or publication status (published, unpublished, in press, and in progress).

We used the following search terms to search all trial registers and databases: co-artemether; artemether; lumefantrine; benflumetol; CGP 56697; and malaria.

We searched the Cochrane Infectious Diseases Group specialized trials register for relevant trials up to May 2004. Full details of the Cochrane Infectious Diseases Group methods and the journals hand searched are published in *The Cochrane Library* in the section on Collaborative Review Groups.

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (Issue 2, 2005). This contains mainly reference information to randomized controlled trials and controlled clinical trials in health care.

We searched the following electronic databases in combination with the search strategy defined by the Cochrane Collaboration and detailed in the Cochrane Reviewer's Handbook (Clarke 2003):

- (1) MEDLINE (1966 to May 2005);
- (2) EMBASE (1988 to May 2005).

We searched the 'Proceedings of the 2nd European Congress on Tropical Medicine (Liverpool, UK, 14 to 18 September 1998)' and the programme from the 3rd MIM Pan-African Malaria Conference (Arusha, Tanzania, 17 to 22 November 2002) for relevant abstracts.

We contacted organizations (including the World Health Organization), individual researchers working in the field, and the pharmaceutical company, Novartis, for unpublished data, confidential reports, and raw data of published trials in 2002 and 2003.

We also checked the reference lists of existing reviews and of all trials identified by the above methods.

Data collection and analysis

Aika Omari (AO) screened the results of the search strategy to identify potentially relevant trials. AO and Carrol Preston (CP) independently assessed the eligibility of these trials for inclusion in the review using the stated inclusion criteria. Any differences in opinion between the reviewers were discussed with the third reviewer (PG).

We assessed methodological quality in terms of generation of allocation sequence, allocation concealment, blinding, and inclusion of all randomized participants in accordance with guidelines (Appendix 1, in Notes). AO and CP independently extracted data

of study characteristics including methods, participants, interventions, and outcomes, and recorded the data on standard forms. Where data from the published papers were insufficient or missing, we contacted the authors for additional information.

Where possible we extracted data to allow an intention-to-treat analysis (the analysis should include all the participants in the groups to which they were originally randomly assigned). If the number randomized and the numbers analysed were inconsistent, we calculated the percentage loss-to-follow-up. For binary outcomes, we recorded the number of participants experiencing the event in each group of the trial. For continuous outcomes, where possible, we extracted arithmetic means and standard deviations and combined means using weighted mean difference for each group. If the data were reported using geometric means we extracted standard deviations on the log scale. We extracted and reported medians and ranges.

We analysed data using Review Manager (Version 4.1). We compared outcome measures for binary data using Relative Risk, which is the risk of achieving an outcome in the artemether-lumefantrine group relative to that in the control group. As the value of the Relative Risk is constrained to lie between 0 and 1/CGER (Control Group Event Rate), large values of the Relative Risk are impossible when events are common. For this reason the primary outcome of the protocol, parasitological cure (parasite clearance) on day 28, has been reversed to consider the number of participants with remaining parasitaemia (parasites present). Reversal of this outcome enhances interpretation and allows us to contrast this result with the polymerase chain reaction (PCR) analysis.

Where it was appropriate to pool data and heterogeneity was present, we used the DerSimonian Laird random effects model. We did not intend to combine results of trials with different comparator drugs.

We intended to explore the following potential sources of heterogeneity using subgroup analyses or meta-regression:

- (1) intervention - four compared to six dose regimens;
- (2) participants - age (under five years, and over five years);
- (3) setting of trial - high transmission compared to low transmission;
- (4) presence of drug resistance to comparator drug.

After including all eligible studies in the primary analysis, we aimed to conduct sensitivity analyses according to randomization (randomized compared to quasi-randomized); blinding; allocation concealment; and intention-to-treat analysis.

In determining the effectiveness of antimalarial treatment, we intended to extract the results of analyses conducted according to the intention-to-treat principle. This approach is considered to be more pragmatic as it attempts to estimate the effectiveness of the treatment in routine practice rather than in the context of a clinical trial. To allow the intention-to-treat principle to be applied, all participants should be followed for the duration of the trial irrespective of whether or not the treatment course was completed

or other protocol deviations. Any reason for dropping out of the trial and any exclusions should be documented (WHO 1996). For day 28 parasitaemia with studies that had conducted PCR analysis, we classified the infections into: (1) recrudescence infection (matching genotypes on day 0 and day of recurrence); and (2) new infection (different genotypes on day 0 and day of recurrence); (3) missing values. We conducted an analysis of day 14 and day 28 parasitaemia corrected for PCR.

RESULTS

Description of studies

We identified 15 papers describing trials that were potentially eligible. Of these, four trials did not meet our inclusion criteria (see Characteristics of excluded studies). Results in [Hatz 98:Tanzania](#) were split across two papers; [Vugt 00:Thailand](#) also had results reported in two papers. One trial is a draft report which is not yet complete (Espino 2002). This left a total of eight included trials (See [Table 1](#)).

In addition, we identified four unpublished citations to potentially relevant trials from the Co-artem®/Riamet® monograph (Novartis 1999). We contacted Novartis in 2002 and 2003 and are still waiting for information to assess the trials for inclusion into the review.

Five trials reported that they were sponsored by Novartis ([Vugt 98:Thailand](#); [Seidlein 98:Gambia](#); [Looareesuwan 99:Thai](#); [Vugt 00:Thailand](#); [Lefevre 01:Thailand](#)). There was no mention of funding in three trials ([Hatz 98:Tanzania](#); [Agtmael 99:Europe](#); [Kshirsagar 00:India](#)).

In one trial with chloroquine as the comparator, the trial was stopped early because the overall cure rate with chloroquine decreased to 50%, due to a higher degree of chloroquine resistance present than expected ([Kshirsagar 00:India](#)). However, it was not clear from the study that this was the result of a formal pre-planned stopping rule.

LOCATION AND PARTICIPANTS ([Table 1](#))

Two studies were conducted in Africa (Gambia, Tanzania), one in Asia (India), one in Europe (travellers from the Tropics returning to France and the Netherlands), and four in South East Asia (Thailand). Two studies included children aged one to five years ([Hatz 98:Tanzania](#); [Seidlein 98:Gambia](#)), two included both adults and children ([Vugt 98:Thailand](#); [Vugt 00:Thailand](#)), and four studies included participants over 13 years of age ([Looareesuwan 99:Thai](#); [Agtmael 99:Europe](#); [Kshirsagar 00:India](#); [Lefevre 01:Thailand](#)).

INTERVENTION

Two studies compared the experimental drug with chloroquine ([Hatz 98:Tanzania](#); [Kshirsagar 00:India](#)); other comparisons consisted of only one study each: sulfadoxine-pyrimethamine

([Seidlein 98:Gambia](#)); mefloquine ([Looareesuwan 99:Thai](#)); and halofantrine ([Agtmael 99:Europe](#)). Mefloquine plus artesunate was the comparator in three studies ([Vugt 98:Thailand](#); [Vugt 00:Thailand](#); [Lefevre 01:Thailand](#)).

DOSE AND REGIMEN

Seven studies used the four dose regimen over 48 hours: three in chloroquine resistant areas ([Hatz 98:Tanzania](#); [Seidlein 98:Gambia](#); [Kshirsagar 00:India](#)); two in multiple drug resistant areas ([Looareesuwan 99:Thai](#); [Vugt 98:Thailand](#)); and one in travellers returning from the tropics ([Agtmael 99:Europe](#)). Children received between 4 and 10.6 mg/kg of artemether and between 24 and 64 mg/kg of lumefantrine; adults received 320 mg of artemether and 1920 mg of lumefantrine.

Two studies conducted in multiple drug resistant areas used a regimen of six doses over 72 hours ([Vugt 00:Thailand](#); [Lefevre 01:Thailand](#)). Children received between 3.8 and 16 mg/kg of artemether and between 48 and 96 mg/kg of lumefantrine; adults received 480 mg of artemether and 2280 mg of lumefantrine.

RESISTANCE

Multiple drug resistance was reported in the four trials conducted in Thailand; one trial specified resistance to chloroquine, mefloquine, amodiaquine, and sulfadoxine-pyrimethamine ([Looareesuwan 99:Thai](#)). Chloroquine resistance was reported in the Tanzanian study in Ifakara where 20% of *Plasmodium falciparum* strains were resistant in 1988 ([Hatz 98:Tanzania](#)). In the Indian study ([Kshirsagar 00:India](#)) in Mumbai, a high chloroquine failure led to the premature termination of the trial. The Gambian study was conducted in an area of chloroquine resistance and less than 5% of the *P. falciparum* strains were resistant to sulfadoxine-pyrimethamine ([Seidlein 98:Gambia](#)).

OUTCOMES ([Table 2](#))

Parasitaemia (parasites present) on day 28 was the most frequently reported outcome (six of the eight studies). Parasitaemia on day 63 was reported in one trial ([Vugt 98:Thailand](#)). Studies also reported the failure rate at other time points (days 4, 7, 14, and 15). Fever clearance was reported in five studies. Time to parasite clearance was reported in six studies: two studies reported it as a time to event analysis ([Looareesuwan 99:Thai](#); [Agtmael 99:Europe](#)); the other studies calculated the time to clearance on those participants in which the event occurred. Gametocyte carriage was reported in seven studies and gametocyte clearance in three studies. Polymerase chain reaction (PCR) analysis was reported in six studies and eight studies reported adverse events.

We contacted the trial authors if the trial reports did not include the outcomes used in this review. Trial reports do not always report all outcomes assessed in the trial.

Risk of bias in included studies

We assessed trials on whether generation of the allocation sequence, allocation concealment, blinding, and the inclusion of all

randomized participants were adequate, inadequate, or not described (Table 3).

GENERATION OF ALLOCATION SEQUENCE

All studies were reported as randomized. Four studies reported adequate generation of the allocation sequence (Seidlein 98:Gambia; Looareesuwan 99:Thai; Agtmael 99:Europe; Kshirsagar 00:India). The remaining four studies mentioned randomization, but did not report the methods used to generate the allocation sequence.

ALLOCATION CONCEALMENT

Allocation concealment was adequate in six studies, which used a priori numbered or coded drug containers, central randomization, or sequentially numbered sealed opaque envelopes. Two studies reported as randomized did not describe the method of allocation concealment (Agtmael 99:Europe; Lefevre 01:Thailand).

BLINDING

Four studies reported as double blind used the double dummy technique (Seidlein 98:Gambia; Looareesuwan 99:Thai; Agtmael 99:Europe; Kshirsagar 00:India). Four studies were described as open (Hatz 98:Tanzania; Vugt 98:Thailand; Vugt 00:Thailand; Lefevre 01:Thailand).

Three adequately concealed trials reported adequate generation of the allocation sequence and were double blind (Seidlein 98:Gambia; Looareesuwan 99:Thai; Kshirsagar 00:India).

INCLUSION OF ALL PARTICIPANTS

None of the identified studies had complete data for all participants randomized into the trial for the duration of follow up. This was partly because researchers stopped follow up after a participant withdrew. Therefore an intention-to-treat analysis was not possible for the trial investigators or for this review, as data necessary for an intention-to-treat analysis were not collected. All trials gave results of analyses based on evaluable participants (that is, participants still on treatment at each time point); however, five of the studies also claimed to have reported cure rates as an 'intention-to-treat' analysis (Hatz 98:Tanzania; Seidlein 98:Gambia; Agtmael 99:Europe; Kshirsagar 00:India; Lefevre 01:Thailand). These are not the results of an intention-to-treat analysis, and differed from their evaluable participants analysis by assuming that all participants withdrawn from treatment or lost to follow up still had parasitaemia at all remaining time points. At the end of follow up, the number of participants not evaluable for the primary outcome was less than 10% in two trials (Looareesuwan 99:Thai; Lefevre 01:Thailand), 10 to 15% in two trials (Seidlein 98:Gambia; Vugt 00:Thailand), and more than 15% in four trials (Hatz 98:Tanzania; Vugt 98:Thailand; Agtmael 99:Europe; Kshirsagar 00:India) (Table 3).

Effects of interventions

FOUR DOSE REGIMEN

Six trials tested a four dose regimen.

SULFADOXINE-PYRIMETHAMINE: one trial (n = 287). This trial conducted in The Gambia did not report any results for

parasitaemia on day 28 or 42 (Seidlein 98:Gambia). No statistically significant difference was detected in the parasitological failure rate between the two groups on day 14 (8/119 failures in the artemether-lumefantrine group and 3/128 in the sulfadoxine-pyrimethamine group; Relative Risk 2.87; 95% confidence interval 0.78 to 10.56). These confidence intervals are wide and clinically important differences cannot be excluded. In the eight artemether-lumefantrine failures at day 14, polymerase chain reaction (PCR) results were available for six participants. These were all reported as new infections (Appendix 1). No PCR results were available for the three treatment failures in the sulfadoxine-pyrimethamine group.

The time taken to clear half the parasites present (PCT 50) was faster with artemether-lumefantrine (mean of 11.6 hr compared to 21.1 hr; n = 144 artemether-lumefantrine, 143 sulfadoxine-pyrimethamine), which was statistically significant (p < 0.0001, test not stated, trial authors' calculation).

MEFLOQUINE: one trial (n = 252). This trial conducted in Thailand did not report parasitaemia on day 63 (Looareesuwan 99:Thai). Artemether-lumefantrine was associated with an increased risk of parasitological failure on day 28 when compared with mefloquine (35/114 failures compared to 21/119; Relative Risk 1.74; 95% confidence interval 1.08 to 2.80).

The trial authors reported parasite clearance time was faster with artemether-lumefantrine (median of 43 hr compared to 66 hr, n = 126 in each arm), which was statistically significant (p < 0.001, Wilcoxon test, trial authors' calculation) (Table 4). Reported fever clearance time was also faster with artemether-lumefantrine (median of 32 hr compared to 54 hr; n = 75 artemether-lumefantrine, 67 mefloquine) and was statistically significant (p = 0.003, Wilcoxon test, trial authors' calculation) (Table 5).

HALOFANTRINE: one trial (n = 103). Trial participants were travellers returning to France and the Netherlands from the tropics (Agtmael 99:Europe). Artemether-lumefantrine was associated with more failures on day 28 (8/45 compared with 0/41), but this was not statistically significant (Relative Risk 15.52; 95% confidence interval 0.92 to 260.76). The wide confidence interval reflects considerable imprecision, therefore clinically important results cannot be excluded in either direction.

All participants on halofantrine cleared their parasites. The trial authors reported parasite clearance time (Table 4) was faster with artemether-lumefantrine (median of 32 hr compared to 48 hr; n = 51 artemether-lumefantrine, 52 halofantrine), which was statistically significant (p < 0.001, test not stated, trial authors' calculation). Reported fever clearance time was faster with artemether-lumefantrine (median of 24 hr compared to 32 hr; n = 32 artemether-lumefantrine, 39 halofantrine), but this was not statistically significant (p = 0.835, Wilcoxon test, trial authors' calculation) (Table 5).

CHLOROQUINE: two trials (n = 439). One study from India and one study from Tanzania showed artemether-lumefantrine was associated with fewer failures on day 28, but the size of this

effect varied greatly between the two studies ([Hatz 98:Tanzania](#); [Kshirsagar 00:India](#); test for heterogeneity $p = 0.0001$). This heterogeneity could be attributed to age, transmission, or degree of chloroquine resistance. As there is no benefit of increased precision for this meta-analysis, it is more useful to consider the individual trial results. Relative Risks for the individual studies were: 0.38 (95% confidence interval 0.30 to 0.49, [Hatz 98:Tanzania](#)); and 0.06 (95% confidence interval 0.02 to 0.17, [Kshirsagar 00:India](#)). On days 7 and 14, [Hatz 98:Tanzania](#) reported fewer parasitological failures with artemether-lumefantrine. [Kshirsagar 00:India](#), a double blind study, was conducted in an area with an unexpectedly high chloroquine resistance, which resulted in the trial being terminated before completion. [Hatz 98:Tanzania](#), which was an open study, was also conducted in an area of high chloroquine resistance.

The trial authors analysed subsets of treatment failures for PCR on days 14 and 28 (Appendices 1 and 2). Less than half of the failures in one trial were tested therefore any statistical inferences must be made with extreme caution ([Hatz 98:Tanzania](#)). In [Kshirsagar 00:India](#) all treatment failures in the artemether-lumefantrine group were classified as recrudescing infections although no PCR was done.

The trial authors in [Kshirsagar 00:India](#) reported parasite clearance time was faster with artemether-lumefantrine (median of 36 hr compared to 60 hr; $n = 89$ artemether-lumefantrine, 90 chloroquine), which was statistically significant ($p < 0.001$, Wilcoxon test, trial authors' calculation) ([Table 4](#)). In the same trial the authors reported fever clearance time was faster with artemether-lumefantrine (median of 18 hr compared to 27 hr; $n = 40$ artemether-lumefantrine, 54 chloroquine), which was statistically significant ($p = 0.0456$, Wilcoxon test, trial authors' calculation) ([Table 5](#)).

MEFLOQUINE PLUS ARTESUNATE: one trial ($n = 617$). One trial conducted in Thailand compared artemether-lumefantrine to mefloquine plus artesunate ([Vugt 98:Thailand](#)). Artemether-lumefantrine gave higher parasitological failure rates at day 28 than the mefloquine-artesunate combination (Relative Risk 6.77; 95% confidence interval 3.12 to 14.67). Parasitological failure rate on day 63 was also higher with artemether-lumefantrine (Relative Risk 2.67; 95% confidence interval 1.55 to 4.57).

PCR was conducted on 80% (72/89) of participants with parasites on day 63. In the artemether-lumefantrine group, there was a trend to fewer new infections but more recrudescing infections (new infections: 15/61 compared to 12/28, Relative Risk 0.57, 95% confidence interval 0.31 to 1.06; recrudescing infections: 36/61 compared to 9/28, Relative Risk 1.84, 95% confidence interval 1.03 to 3.27; graphs not displayed).

The authors reported the median parasite clearance times in both groups as two days (range: one to three) and the median fever clearance time as one day (range: one to four) with no difference between the treatment groups.

SIX DOSE REGIMEN

Two trials tested a six dose regimen.

MEFLOQUINE PLUS ARTESUNATE: two trials ($n = 419$). Both trials were conducted in Thailand. Artemether-lumefantrine had higher parasitological failure rates on day 28 (Relative Risk 5.19; 95% confidence interval 0.30 to 89.40 [Lefevre 01:Thailand](#) and Relative Risk 3.20; 95% confidence interval 0.18 to 58.34 [Vugt 00:Thailand](#)). Pooled results were too imprecise to draw any conclusions as to whether this regimen of artemether-lumefantrine is inferior or superior to mefloquine plus artesunate (Relative Risk 4.20; 95% confidence interval 0.55 to 31.93).

PCR analysis was done in both trials. There were no day 28 failures in the mefloquine plus artesunate arm and 11 failures in the artemether-lumefantrine group, with two new infections ([Vugt 00:Thailand](#); [Lefevre 01:Thailand](#), Appendix 2).

The authors in one trial reported no statistically significant difference in the parasite clearance time between artemether-lumefantrine and mefloquine plus artesunate (median of 29 compared to 31 hr; $n = 164$ artemether-lumefantrine, 55 mefloquine-artesunate, no statistical test reported) ([Lefevre 01:Thailand](#)) ([Table 4](#)). Trial authors reported the median fever clearance time for artemether-lumefantrine was 29 hr (95% confidence interval 23 to 37; $n = 76$) compared with 23 hr for mefloquine plus artesunate (95% confidence interval 15 to 30; $n = 29$) in the trial reporting this outcome ([Lefevre 01:Thailand](#), no statistical test reported).

GAMETOCYTES

Gametocyte carriage was not reported for days 14 and 28 in any of the trials. On day 4, a comparison between artemether-lumefantrine and sulfadoxine-pyrimethamine showed fewer participants carrying gametocytes with artemether-lumefantrine (1/41 compared to 10/74; Relative Risk 0.18; 95% confidence interval 0.02 to 1.36). A similar pattern was observed at day 15 (0/125 compared with 37/128; Relative Risk 0.01; 95% confidence interval 0.00 to 0.22; [Seidlin 98:Gambia](#)).

Results were available for gametocyte carriage within the first 72 hours. For mefloquine and halofantrine, individual trial results detected no statistically significant difference in gametocyte carriage (see forest plot). For chloroquine, pooled results from two trials suggested a reduction in gametocyte carriage with artemether-lumefantrine (Relative Risk 0.79; 95% confidence interval 0.63 to 0.99).

Gametocyte clearance time ([Table 6](#)) was reported as medians and percentiles. The trial authors reported gametocyte clearance time was faster with artemether-lumefantrine compared with mefloquine (median of 152 hr compared to 331 hr, $n = 62$ artemether-lumefantrine, 74 mefloquine; Wilcoxon test, $p < 0.001$, authors' calculation) and chloroquine (median of 120 compared to not reached in chloroquine group, $n = 51$ artemether-lumefantrine, 63 chloroquine; Wilcoxon test, $p < 0.001$, authors' calculation). One trial using mefloquine plus artesunate reported this outcome ([Lefevre 01:Thailand](#)). The median time and 95% confidence interval for artemether-lumefantrine was 72 hr (34 to 163; $n = 26$).

compared to 85 hr (46 to 160; $n = 10$) for mefloquine plus artesunate. There is a large overlap of the confidence intervals so it is unlikely that there is a statistically significant difference between these two combination treatments, however the numbers involved for this outcome are small in both trial arms.

ADVERSE EVENTS

All eight trials reported adverse events. The majority of adverse events reported were mild or moderate (Appendices 5 to 9). Reports of severe adverse events are also available on the web site (Appendix 4). No deaths reported by the authors were associated with trial medication (four trials; [Hatz 98:Tanzania](#); [Vugt 98:Thailand](#); [Looareesuwan 99:Thai](#); [Kshirsagar 00:India](#)). Three trials reported occurrences of adverse events that resulted in stopping treatment ([Hatz 98:Tanzania](#); [Agtmael 99:Europe](#); [Vugt 00:Thailand](#)). Four trials reported cardiac monitoring ([Looareesuwan 99:Thai](#); [Agtmael 99:Europe](#); [Kshirsagar 00:India](#); [Lefevre 01:Thailand](#)), and three reported no difference in the QTc interval (difference between the longest and shortest measurable interval on the 12 lead electrocardiogram, corrected for heart rate) between treatment groups ([Looareesuwan 99:Thai](#); [Kshirsagar 00:India](#); [Lefevre 01:Thailand](#)). One trial reported a significant increase in the overall QTc interval in participants treated with halofantrine (52% compared to 16.7%) ([Agtmael 99:Europe](#)). One participant on halofantrine was withdrawn from treatment due to a prolonged QTc interval. Serious neurotoxicity was specifically sought in one trial that reported no such adverse event ([Vugt 98:Thailand](#)).

DISCUSSION

TRIAL METHODS

The methodological quality of the published trials was low. Four out of eight did not describe the generation of the allocation sequence and concealment was not described in two. Four of the trials were not blinded and in three trials less than 80% of the participants were included in the final analysis for the reported primary outcome (Table 3). The 'intention-to-treat' analysis for the primary outcome reported in five trials was actually a limited form of sensitivity analysis because they made the assumption that all participants lost to follow up were treatment failures. As results were not based on an intention-to-treat analysis they are subject to attrition bias and the clinical effectiveness may be biased.

Where polymerase chain reaction (PCR) results were available, parasitaemia on day 14 and day 28 was corrected for new infections with missing samples or failed tests classified as treatment failures. This had a minimal effect for chloroquine and mefloquine plus artesunate but had a more substantial impact on sulfadoxine-pyrimethamine (on day 14) changing the direction of the effect. However, the result remained statistically insignificant.

FOUR DOSE REGIMEN

For parasitological outcomes, artemether-lumefantrine did not perform better than the other antimalarials apart from chloroquine.

There was no evidence comparing sulfadoxine-pyrimethamine with artemether-lumefantrine for parasitaemia on day 42. The fewer recrudescence and new infections seen in the sulfadoxine-pyrimethamine group may be explained by the long half life of sulfadoxine-pyrimethamine (Appendix 3). Artemether-lumefantrine showed no marked advantage over mefloquine for parasitaemia in one trial of high quality ([Looareesuwan 99:Thai](#)). Halofantrine had fewer treatment failures compared with artemether-lumefantrine, which was not statistically significant. However, this trial was small and the participants had varying degrees of immunity (were from different countries), which could have confounded their response to medication ([Ter Kuile 1995](#)). Artemether-lumefantrine was only superior to chloroquine for parasitaemia on day 28. However, there was a high withdrawal rate (> 50% of the participants in chloroquine group) in both trials and the unexpected higher resistance to chloroquine decreased the cure rate to 50%, in [Kshirsagar 00:India](#). This comparison would have been inappropriate had the actual chloroquine resistance been documented prior to commencing the trial, since a clinical failure rate greater than 25% of a first line antimalarial indicates the treatment should be changed ([WHO 1994](#)).

SIX DOSE REGIMEN

The artemisinin combination therapy of mefloquine plus artesunate was more effective than artemether-lumefantrine at reducing parasitological failure on day 28 and day 63. Apart from the primary outcome, there was no convincing difference between artemether-lumefantrine and mefloquine plus artesunate. This is not unexpected as both are artemisinin combination therapies.

CLEARANCE TIMES

Parasite, fever, and gametocyte clearance times were shorter for artemether-lumefantrine when compared with single therapy, which suggests that clinical symptoms may resolve faster (Table 4; Table 5; Table 6). Most of the trials reported clearance times as medians and percentiles and not time-to-event analyses (apart from [Looareesuwan 99:Thai](#) and [Agtmael 99:Europe](#)). This would have been more informative as data on participants who did not reach the event would have been included in the analysis.

ADVERSE EVENTS

It is important to acknowledge that the trials were not designed with adverse events as primary outcomes and are not sufficiently powered to observe any rare events. In some trials where adverse events were reported, no distinction was made between the treatment groups thereby making comparisons impossible. One trial published adverse cardiac events separately and reported no clinically significant changes in the electrocardiographic intervals ([Vugt 00:Thailand](#)). Although some trials reported adverse cardiac

events, the evidence was insufficient to address concerns about the possible risk of cardiotoxicity. We, therefore, cannot justifiably comment on adverse events reported apart from stating them (Appendices 4 to 9).

AUTHORS' CONCLUSIONS

Implications for practice

FOUR DOSE REGIMEN

This showed no advantage in relation to parasitological cure when compared to mefloquine, halofantrine and sulfadoxine-pyrimethamine (unadjusted result). Given the current evidence, it is potentially harmful to change from any of these drugs to this four dose regimen.

There is evidence to suggest this regimen is superior to chloroquine in areas where chloroquine resistance is common. In these circumstances, artemether-lumefantrine is an alternative to chloroquine as first line treatment where policy makers wish to avoid sulfadoxine-pyrimethamine, amodiaquine, or other standard regimens.

SIX DOSE REGIMEN

There was no difference in cure rate detected when compared to mefloquine plus artesunate (three doses) but studies were small. The limited data available has not demonstrated either superiority or inferiority of artemether-lumefantrine compared to mefloquine plus artesunate.

Studies are conducted with the maximum effort to achieve adherence, and in general service use adherence will fall. This is likely to reduce the effectiveness of artemether-lumefantrine (requiring six doses) when compared with sulfadoxine-pyrimethamine (requiring one dose) or other antimalarial regimens that require fewer than six doses.

As the actual cost of this drug is high, we find it surprising that artemether-lumefantrine has been introduced and approved on

the Essential Drugs List without proper evaluation against standard regimens (WHO 2002). We also find it surprising that comparative effectiveness has not been evaluated in a health service setting, where adherence is more akin to what people are likely to do when the drug is used in practice.

Implications for research

More randomized controlled trials of artemether-lumefantrine are required before this drug can be recommended as an alternative to existing drug regimens. For example, trials could evaluate artemether-lumefantrine against sulfadoxine-pyrimethamine (alone, or combined with either amodiaquine or artesunate) in areas where sulfadoxine-pyrimethamine is failing (WHO 2000a). Trials could also compare artemether-lumefantrine with chloroquine combined with sulfadoxine-pyrimethamine, as this combination is used for first line treatment in several countries (Uganda, Ethiopia, Papua New Guinea). More trials should compare artemether-lumefantrine with other artemisinin-based combinations to determine which, if any, is superior.

As malaria transmission in endemic areas is thought to be related to the presence of gametocytes, and artemisinin derivatives are effective against gametocytes, any new trials conducted in areas of low malaria transmission should collect data on gametocyte carriage.

Trials should be of high quality, with careful attention to concealment of allocation. All participants should be followed up for the duration of the trial regardless of withdrawal from treatment or other protocol violations as this would permit an intention-to-treat analysis. Reasons for all treatment withdrawals should be documented.

Trials should also be pragmatic, so that results more closely represent what will happen in general health service use. This will mean that some people may not fully adhere to all doses of the drugs, but that the trial results will reflect actual cure rates that can be anticipated in a real life situation to help make the results more generalisable.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Agtmael 99:Europe

Methods	Allocation not described. Block randomization (4). Double blind, double dummy.
Participants	103 participants aged 17 to 62 (73 non-immune; 3 immune; 27 possibly immune) Inclusion criteria: microscopically confirmed <i>Plasmodium falciparum</i> (>1000 and <200 000/microL) Excluded: severe malaria.
Interventions	(1) Artemether-lumefantrine: 4 doses over 48 hr (artemether 80 mg/dose, lumefantrine 480 mg/dose). (2) Halofantrine: 3 doses over 12 hr; repeated after 1 week (halofantrine 500mg/dose)
Outcomes	28 day cure. Parasite clearance time. Parasite reduction at 24hr. Fever clearance time. Gametocyte carriage within first 72 hours. Adverse effects. QT interval.
Notes	Study location: Residents of France and the Netherlands returning from 22 African countries and French Guyana 17 not evaluable on day 28: 6 (artemether-lumefantrine); 11(halofantrine) 8 treatment failures: artemether-lumefantrine 8 (RI).

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Hatz 98:Tanzania

Methods	Concealed allocation. Block randomization (6).
Participants	260 children aged 1 to 5 years. Inclusion criteria: weight >5kg; microscopically confirmed <i>Plasmodium falciparum</i> parasitaemia >5000/ml; fever; within 5 km of trial site Excluded: severe malaria; severe malnutrition/kwashiorkor; other antimalarial previous 48 hr; sensitivity to chloroquine; chronic disease.

Hatz 98:Tanzania (Continued)

Interventions	(1) Artemether-lumefantrine: 4 doses over 48 hr (artemether 1 to 2 mg/kg/dose, lumefantrine 6 to 12 mg/kg/dose) (2) Chloroquine: 4 doses over 48 hr (total dose 25mg/kg). All participants had paracetamol.	
Outcomes	7 day cure. 14 day cure. Parasite reductions on days 1 to 3. Proportion of children with negative slide on days 1 to 3. PCR genotype. Gametocyte carriage on days 0, 1, 2, 3, and 7. Haemoglobin.	
Notes	Study location: Ifakara, Tanzania. 48 not evaluable at day 7 (14 artemether-lumefantrine, 34 chloroquine); 53 not evaluable at day 14 (20 artemether-lumefantrine, 33 chloroquine) Perennial transmission. Chloroquine resistance	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Kshirsagar 00:India

Methods	Concealed allocation. Block randomization (4). Double blind, double dummy parallel.	
Participants	179 adults aged 16 to 70 years. Inclusion criteria: microscopically confirmed Plasmodium falciparum or mixed infection (including Plasmodium falciparum >1000/microL) Excluded: P. falciparum >200,000/microL; severe malaria.	
Interventions	(1) Artemether-lumefantrine: 4 doses over 48 hr (artemether 80 mg/dose, lumefantrine 480 mg/dose). (2) Chloroquine: 4 doses over 48 hr (1st dose 600mg, then 300mg per dose) All: primaquine on day 8 (single dose 45mg).	
Outcomes	28 day cure. Parasite clearance time. Reduction in parasite load at 24 hr. Fever clearance time. Gametocyte carriage within first 72 hours.	

	Gametocyte clearance time. PCR genotype. Adverse events.	
Notes	Study location: Mumbai, India. Participants hospitalized for 8 days. 38 not evaluated on day 28: 24 (artemether-lumefantrine); 14 (chloroquine) 64 treatment failures: 3 artemether-lumefantrine (RI); 61 chloroquine [49 (RI), 8 (RII), 4 (RIII)] Premature termination of trial because of one death (chloroquine group) and decrease in chloroquine cure rate to <50% Perennial transmission. Chloroquine resistance.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Lefevre 01:Thailand

Methods	Allocation not described. Randomization 3:1.
Participants	219 participants aged 12 to 71. Inclusion criteria: microscopically confirmed Plasmodium falciparum Excluded: severe complicated malaria.
Interventions	(1) Artemether-lumefantrine: 6 doses over 48 hr (artemether 80mg/dose, lumefantrine 480mg/dose). (2) Artesunate: doses over 48 hr (artesunate 4mg/kg/dose); mefloquine 2 doses over 48 hr (day 2 - 15mg/kg, day 3 - 10mg/kg)
Outcomes	28 day cure. Parasite clearance time. Fever clearance time. Gametocyte carriage within first 72 hr. Gametocyte clearance time. Parasite reduction at 24 hr. Adverse effects. PCR analysis.
Notes	Study location: Bangkok, Thailand. Trial designed to compare artemether-lumefantrine with historical controls in which artesunate-mefloquine was used 11 not evaluated on day 28: 9 (artemether-lumefantrine); 2 (artesunate-mefloquine)
Risk of bias	

Lefevre 01:Thailand (Continued)

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Looareesuwan 99:Thai

Methods	Concealed allocation. Double blind, double dummy.
Participants	252 adults and children aged 13 to 63. Inclusion criteria: microscopically confirmed Plasmodium falciparum, parasitaemia 1000 to 200,000/ microL (mixed infection acceptable) Excluded: complicated malaria.
Interventions	(1) Artemether-lumefantrine: 4 doses over 48 hr (artemether 80 mg/dose, lumefantrine 480 mg/dose) (2) Mefloquine: 2 doses over 8 hr (1st dose 750 mg, 2nd dose 500 mg)
Outcomes	28 day cure. Parasite clearance time. Fever clearance time. Gametocyte clearance time. Gametocyte carriage within first 72 hours. Adverse effects.
Notes	Study location: Bangkok, Thailand. Inpatients. 19 not evaluated on day 28: 12 (artemether-lumefantrine); 7 (mefloquine) 56 treatment failures: 35 artemether-lumefantrine (RI); 21 mefloquine [12 (RI), 5 (RII), 4 (RIII)] Low transmission. Multidrug resistance.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Seidlein 98:Gambia

Methods	Concealed allocation. Block randomization (4). Double blind, double dummy.
Participants	287 children aged 1 to 5 years. Inclusion criteria: parasitaemia >5000/microL; fever; within 10km of trial centre Excluded: requiring parenteral treatment.

Seidlein 98:Gambia (Continued)

Interventions	(1) Artemether-lumefantrine: 4 doses over 48 hours (artemether 1.3 to 2.6 mg/kg/dose; lumefantrine 8.8 to 17.5 mg/kg/dose) (2) Sulfadoxine-pyrimethamine: single dose (8.8 to 17.5 mg/kg)	
Outcomes	Day 4 cure. Day 15 cure. Parasite clearance time. Proportion of children with fever on days 1 to 4. Gametocyte carriage on days 1, 2, 3, 4, and 15. PCR genotype.	
Notes	Study location: The Gambia. 2 trial centres: semiurban and rural. 40 not evaluated on day 28 : 25 (artemether-lumefantrine), 15 (sulfadoxine-pyrimethamine) Local transmission: seasonal. Local resistance: chloroquine; sulfadoxine-pyrimethamine.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Vugt 00:Thailand

Methods	Concealed allocation. Block randomization (3).	
Participants	200 participants aged 2 to 63. Inclusion criteria: parasitaemia >500/ul. Excluded: severe malaria.	
Interventions	(1) Artemether-lumefantrine: 6 doses over 48 hr (artemether 1.3 to 2.6 mg/kg/dose; lumefantrine 7.8 to 15 mg/kg/dose). (2) Artesunate: 3 doses over 48 hr (4mg/kg/dose); mefloquine 2 doses over 48 hr (day 2, 15 mg/kg; day 3, 10 mg/kg)	
Outcomes	28 day cure. Proportion of patients with fever on days 0 to 3. Proportion of patients with parasitemia on days 0 to 3. Gametocyte carriage within first 72 hours. Adverse events. ECG findings.	

Vugt 00:Thailand (Continued)

Notes	Study location: Bangkok and Karen, Thailand. 2 trial centres: Bangkok - inpatients for 28 days; Karen - outpatients. 19 not evaluated on day 28: 16 (artemether-lumefantrine), 3 (artemether plus mefloquine) Low transmission.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Vugt 98:Thailand

Methods	Concealed allocation. Block randomization (4).	
Participants	617 participants aged 5 to 66 years. Inclusion criteria: microscopically confirmed malaria. Excluded: severe malaria.	
Interventions	(1) Artemether-lumefantrine: 4 doses over 48 hr (artemether 1 to 2mg/kg/dose, lumefantrine 6 to 12mg/kg/dose). (2) Artesunate: 3 doses over 48 hr (4mg/kg/dose); mefloquine 2 doses over 48 hr (day 2, 15mg/kg; day 3, 10mg/kg)	
Outcomes	63 day cure. 28 day cure. Parasite clearance time. Fever clearance time. Gametocyte carriage. PCR analysis. Adverse effects.	
Notes	Study location: Karen, Thailand. 139 not evaluated on day 63: 61(artemether-lumefantrine); 78 (artemether plus mefloquine) Low transmission. Multidrug resistance.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

ECG: electrocardiogram

PCR: polymerase chain reaction

QT interval: difference between the longest and shortest measurable interval on the 12 lead electrocardiogram

RI: (drug resistance) Recrudescence of infection between 7 and 28 days of completing treatment following initial resolution of symptoms and parasite clearance

RII: (drug resistance) Reduction of parasitaemia of >75% at 48 hours but failure to clear parasites within 7 days

RIII: (drug resistance) Parasitaemia does not fall by >75% within 48 hours

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

Study	Reason for exclusion
Jiao 1997	Compared artemether-lumefantrine with lumefantrine, which is not a recommended standard therapy for uncomplicated malaria Randomized double blind trial in China with adults. Interventions: Artemether-lumefantrine compared to lumefantrine Results: 28 day cure rates were 98% (artemether-lumefantrine) and 92% (lumefantrine). Median fever clearance times were 21 hours (artemether-lumefantrine) and 36 hours (lumefantrine)
Karbwang 2002	Artemether-lumefantrine not compared with another antimalarial 600 children in multicentre trial (Kenya, Nigeria and Tanzania) Intervention: Artemether-lumefantrine 6-dose regimen. Results: On-going study.
Seidlein 1997	Not a randomized control trial (safety trial). Safety trial in The Gambia with 60 children (age 1 to 6 years) Intervention: Artemether-lumefantrine 4-dose regimen. Results: All children cleared parasites within 72 hours. Median parasite clearance time was 36 hours. No neurological, cardiac or other adverse reactions reported. 16 (27%) children had a reappearance of parasites. 12 out of 14 second episodes were reinfections (by polymerase chain reaction (PCR) analysis)
Vugt 1999a	Artemether-lumefantrine was not compared with another antimalarial. Compared four dose and six dose regimens Randomized double blind trial in Thailand with 359 participants (age 3 to 75 years) Interventions: 3 different dose regimens of artemether-lumefantrine. One 4-dose regimen and two 6-dose regimens Results: No difference in parasite and fever clearance times and reported adverse effects. Adjusted 28 day cure rate was 96.9% and 99.12% for 6-dose regimens and 83.3% for 4-dose regimen (p<0.001)
Zhiwei 1999	Compared artemether-lumefantrine with lumefantrine, which is not recommended standard therapy for uncomplicated malaria. Randomized double blind trial in Hainan Province, China with 100 participants Intervention: Artemether-lumefantrine compared with lumefantrine Results: 28 day cure rates were 98% (artemether-lumefantrine) and 95.9% (lumefantrine). Mean parasite clearance times were 29.7 +/- 8.9 hours (artemether-lumefantrine) and 54.7 +/- 17.4 hours (lumefantrine). Mean fever clearance times were 17.1 +/- 8.6 hours (artemether-lumefantrine) and 29.4 +/- 24.9 hours (lumefantrine)

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

Espino 2002

Trial name or title	Efficacy studies of chloroquine+ sulfadoxine-pyrimethamine (SP), SP and artemether-lumefantrine for uncomplicated malaria in Mindanao Island, Philippines
Methods	
Participants	146 patients
Interventions	(1) Artemether-lumefantrine (2) Chloroquine+ sulfadoxine-pyrimethamine (3) Sulfadoxine-pyrimethamine
Outcomes	(1) Adequate clinical response (2) Early treatment failures (3) Late treatment failures
Starting date	July 2001
Contact information	Dr Fe Esperanza Espino, Medical Department, Institute for Tropical Medicine, Alabang, Muntinlupa City, Philippines
Notes	Allocation not concealed

DATA AND ANALYSES

Comparison 1. Artemether-lumefantrine (4 doses) vs any other antimalarial drug regimen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitaemia by day 28	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 AL vs. sulfadoxine-pyrimethamine	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 AL vs. mefloquine	1	233	Risk Ratio (M-H, Fixed, 95% CI)	1.74 [1.08, 2.80]
1.3 AL vs. halofantrine	1	86	Risk Ratio (M-H, Fixed, 95% CI)	15.52 [0.92, 260.75]
1.4 AL vs. chloroquine	2	378	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.21, 0.35]
1.5 AL vs. mefloquine plus artesunate	1	537	Risk Ratio (M-H, Fixed, 95% CI)	6.77 [3.12, 14.67]
2 Parasitaemia by day 63	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 AL vs. mefloquine plus artesunate	1	478	Risk Ratio (M-H, Fixed, 95% CI)	2.67 [1.55, 4.57]
3 Parasitaemia by day 14	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 AL vs. sulfadoxine-pyrimethamine	1	247	Risk Ratio (M-H, Fixed, 95% CI)	2.87 [0.78, 10.56]
3.2 AL vs. chloroquine	1	229	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.11, 0.27]
4 Parasitaemia by day 7	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 AL vs. sulfadoxine-pyrimethamine	1	270	Risk Ratio (M-H, Fixed, 95% CI)	0.05 [0.00, 0.92]
4.2 AL vs. chloroquine	1	233	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.06, 0.21]
5 Gametocyte carriage within the first 72 hours	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 AL vs. mefloquine	1	252	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.67, 1.05]
5.2 AL vs. halofantrine	1	14	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.04, 1.32]
5.3 AL vs. chloroquine	2	427	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.63, 0.99]
5.4 AL vs. mefloquine plus artesunate	1	616	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.86, 2.32]
6 Gametocyte carriage by day 4	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 AL vs. sulfadoxine-pyrimethamine	1	115	Risk Ratio (M-H, Fixed, 95% CI)	0.18 [0.02, 1.36]
7 Gametocyte carriage by day 15	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 AL vs. sulfadoxine-pyrimethamine	1	253	Risk Ratio (M-H, Fixed, 95% CI)	0.01 [0.00, 0.22]

Comparison 2. Artemether-lumefantrine (6 doses) vs any other antimalarial drug regimen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitaemia by day 28	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 AL vs. mefloquine plus artesunate	2	389	Risk Ratio (M-H, Fixed, 95% CI)	4.20 [0.55, 31.93]
2 Gametocyte carriage within the first 72 hours	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 AL vs. mefloquine plus artesunate	2	240	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.58, 2.06]

Comparison 3. AL vs chloroquine, PCR sensitivity analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitaemia on day 28	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 AL vs. chloroquine, adjusted for new infections	2	378	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.16, 0.29]
1.2 AL vs. chloroquine, not adjusted for new infections	2	378	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.21, 0.35]
2 Parasitaemia on day 14	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 AL vs. chloroquine, adjusted for new infections	1	229	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.09, 0.23]
2.2 AL vs. chloroquine, not adjusted for new infections	1	229	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.11, 0.27]

Comparison 4. AL vs sulfadoxine-pyrimethamine, PCR sensitivity analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitaemia on day 14	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 AL vs. SP, adjusted for new infections	1	247	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.12, 4.22]
1.2 AL vs. SP, not adjusted for new infections	1	247	Risk Ratio (M-H, Fixed, 95% CI)	2.87 [0.78, 10.56]

Comparison 5. AL (4 doses) vs mefloquine plus artesunate, PCR sensitivity analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitaemia on day 28	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 AL vs. mefloquine plus artesunate, adjusted for new infections	1	537	Risk Ratio (M-H, Fixed, 95% CI)	6.45 [2.78, 14.95]
1.2 AL vs. mefloquine plus artesunate, not adjusted for new infections	1	537	Risk Ratio (M-H, Fixed, 95% CI)	6.77 [3.12, 14.67]

Comparison 6. AL (6 doses) vs mefloquine plus artesunate, PCR sensitivity analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitaemia on day 28	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 AL vs. mefloquine plus artesunate, adjusted for new infections	2	389	Risk Ratio (M-H, Fixed, 95% CI)	3.50 [0.45, 27.03]
1.2 AL vs. mefloquine plus artesunate, not adjusted for new infections	2	389	Risk Ratio (M-H, Fixed, 95% CI)	4.20 [0.55, 31.93]

Analysis 1.1. Comparison 1 Artemether-lumefantrine (4 doses) vs any other antimalarial drug regimen, Outcome 1 Parasitaemia by day 28.

Review: Artemether-lumefantrine for treating uncomplicated falciparum malaria

Comparison: 1 Artemether-lumefantrine (4 doses) vs any other antimalarial drug regimen

Outcome: 1 Parasitaemia by day 28

Analysis 1.2. Comparison 1 Artemether-lumefantrine (4 doses) vs any other antimalarial drug regimen, Outcome 2 Parasitaemia by day 63.

Review: Artemether-lumefantrine for treating uncomplicated falciparum malaria

Comparison: 1 Artemether-lumefantrine (4 doses) vs any other antimalarial drug regimen

Outcome: 2 Parasitaemia by day 63

Analysis 1.3. Comparison 1 Artemether-lumefantrine (4 doses) vs any other antimalarial drug regimen, Outcome 3 Parasitaemia by day 14.

Review: Artemether-lumefantrine for treating uncomplicated falciparum malaria

Comparison: 1 Artemether-lumefantrine (4 doses) vs any other antimalarial drug regimen

Outcome: 3 Parasitaemia by day 14

Analysis 1.4. Comparison 1 Artemether-lumefantrine (4 doses) vs any other antimalarial drug regimen, Outcome 4 Parasitaemia by day 7.

Review: Artemether-lumefantrine for treating uncomplicated falciparum malaria

Comparison: 1 Artemether-lumefantrine (4 doses) vs any other antimalarial drug regimen

Outcome: 4 Parasitaemia by day 7

Analysis 1.5. Comparison 1 Artemether-lumefantrine (4 doses) vs any other antimalarial drug regimen, Outcome 5 Gametocyte carriage within the first 72 hours.

Review: Artemether-lumefantrine for treating uncomplicated falciparum malaria

Comparison: 1 Artemether-lumefantrine (4 doses) vs any other antimalarial drug regimen

Outcome: 5 Gametocyte carriage within the first 72 hours

Analysis 1.6. Comparison 1 Artemether-lumefantrine (4 doses) vs any other antimalarial drug regimen, Outcome 6 Gametocyte carriage by day 4.

Review: Artemether-lumefantrine for treating uncomplicated falciparum malaria

Comparison: 1 Artemether-lumefantrine (4 doses) vs any other antimalarial drug regimen

Outcome: 6 Gametocyte carriage by day 4

Analysis 1.7. Comparison 1 Artemether-lumefantrine (4 doses) vs any other antimalarial drug regimen, Outcome 7 Gametocyte carriage by day 15.

Review: Artemether-lumefantrine for treating uncomplicated falciparum malaria

Comparison: 1 Artemether-lumefantrine (4 doses) vs any other antimalarial drug regimen

Outcome: 7 Gametocyte carriage by day 15

Analysis 2.1. Comparison 2 Artemether-lumefantrine (6 doses) vs any other antimalarial drug regimen, Outcome 1 Parasitaemia by day 28.

Review: Artemether-lumefantrine for treating uncomplicated falciparum malaria

Comparison: 2 Artemether-lumefantrine (6 doses) vs any other antimalarial drug regimen

Outcome: 1 Parasitaemia by day 28

Analysis 2.2. Comparison 2 Artemether-lumefantrine (6 doses) vs any other antimalarial drug regimen, Outcome 2 Gametocyte carriage within the first 72 hours.

Review: Artemether-lumefantrine for treating uncomplicated falciparum malaria

Comparison: 2 Artemether-lumefantrine (6 doses) vs any other antimalarial drug regimen

Outcome: 2 Gametocyte carriage within the first 72 hours

Analysis 3.1. Comparison 3 AL vs chloroquine, PCR sensitivity analysis, Outcome 1 Parasitaemia on day 28.

Review: Artemether-lumefantrine for treating uncomplicated falciparum malaria

Comparison: 3 AL vs chloroquine, PCR sensitivity analysis

Outcome: 1 Parasitaemia on day 28

Analysis 3.2. Comparison 3 AL vs chloroquine, PCR sensitivity analysis, Outcome 2 Parasitaemia on day 14.

Review: Artemether-lumefantrine for treating uncomplicated falciparum malaria

Comparison: 3 AL vs chloroquine, PCR sensitivity analysis

Outcome: 2 Parasitaemia on day 14

Analysis 4.1. Comparison 4 AL vs sulfadoxine-pyrimethamine, PCR sensitivity analysis, Outcome 1 Parasitaemia on day 14.

Review: Artemether-lumefantrine for treating uncomplicated falciparum malaria

Comparison: 4 AL vs sulfadoxine-pyrimethamine, PCR sensitivity analysis

Outcome: 1 Parasitaemia on day 14

Analysis 5.1. Comparison 5 AL (4 doses) vs mefloquine plus artesunate, PCR sensitivity analysis, Outcome 1 Parasitaemia on day 28.

Review: Artemether-lumefantrine for treating uncomplicated falciparum malaria

Comparison: 5 AL (4 doses) vs mefloquine plus artesunate, PCR sensitivity analysis

Outcome: 1 Parasitaemia on day 28

Analysis 6.1. Comparison 6 AL (6 doses) vs mefloquine plus artesunate, PCR sensitivity analysis, Outcome 1 Parasitaemia on day 28.

Review: Artemether-lumefantrine for treating uncomplicated falciparum malaria

Comparison: 6 AL (6 doses) vs mefloquine plus artesunate, PCR sensitivity analysis

Outcome: 1 Parasitaemia on day 28

ADDITIONAL TABLES

Table 1. Characteristics of included studies

Study	Comparator	Dose regimen	Location	Participants	Age range (years)
Hatz 1998	Chloroquine	4	Tanzania	Children	1 to 5
Kshirsagar 2000	Chloroquine	4	India	Adults	16 to 70
von Seidlein 1998	Sulfadoxine-pyrimethamine	4	The Gambia	Children	1 to 5
Looareesuwan 1999	Mefloquine	4	Thailand	Adults	13 to 63

Table 1. Characteristics of included studies (Continued)

van Agtmael 1999	Halofantrine		4	Travellers from the Tropics returning to France and the Netherlands	Adults	17 to 62
van Vugt 1998	Mefloquine artesunate	plus	6	Thailand	Adults and children	5 to 66
van Vugt 2000	Mefloquine artesunate	plus	6	Thailand	Adults and children	2 to 63
Lefevre 2001	Mefloquine artesunate	plus	6	Thailand	Adults	12 to 71

Table 2. Outcomes reported

Study	Failure rate day(s)	PCT	FCT	GCT	Gametocyte carriage	PCR analysis	Adverse events
Hatz 1998	D7, D14	N	N	N	Y	Y	Y
Kshirsagar 2000	D28	Y	Y	Y	N	Y	Y
von Seidlein 1998	D4, D15	Y	N	N	Y	Y	Y
Looareesuwan 1999	D28	Y	Y	Y	Y	N	Y
van Agtmael 1999	D28	Y	Y	N	Y	N	Y
van Vugt 1998	D28, D63	Y	Y	N	Y	Y	Y
van Vugt 2000	D28	N	N	N	Y	Y	Y
Lefevre 2001	D28	Y	Y	Y	Y	Y	Y
FOOT-NOTES	PCT - parasite clearance time; FCT - fever clearance time; GCT - gametocyte clearance time; PCR - poly-						

Table 2. Outcomes reported (Continued)

	merase chain reaction; D - day; Y - yes; N - no						
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Table 3. Methodological quality of included studies

Study	Concealed allocation	Generated allocation	Blinding	Excluded
Hatz 1998	Adequate	Not described	No	55%
Kshirsagar 2000	Adequate	Computer	Double	21%
von Seidlein 1998	Adequate	Computer	Double	14%
Looareesuwan 1999	Adequate	Computer	Double	8%
van Agtmael 1999	Not described	Computer	Double	17%
van Vugt 1998	Adequate	Not described	No	23%
van Vugt 2000	Adequate	Not described	No	10%
Lefevre 2001	Not described	Not described	No	5%

Table 4. Parasite clearance time

Study	Treatment	N	Median	25-75th percentile	95% CI	P-value
Looareesuwan 1999	Artemether-lumefantrine	126	43	35 - 51	42 to 45	<0.001*
	Mefloquine	126	66	52 - 82	61 to 70	
van Agtmael 1999	Artemether-lumefantrine	51	32	23 - 48	32 to 48	<0.001
	Halofantrine	52	48	47 - 60	48 to 60	
Kshirsagar 2000	Artemether-lumefantrine	89	36	24 - 48	30 to 36	<0.001*
	Chloroquine	90	60	48 - 91	45 to 66	
Lefevre 2001	Artemether-lumefantrine	164	29	18 - 40	29 to 32	

Table 4. Parasite clearance time (Continued)

	Mefloquine-artesunate	55	31	24 - 35	26 to 31	
FOOTNOTES	CI - confidence interval; N - group size examined for the event; * Wilcoxon test					

Table 5. Fever clearance time

Study	Treatment	N	Median	25-75th percentile	95%CI	P-value
Looareesuwan 1999	Artemether-lumefantrine	75	32	17 - 54	23 to 37	0.003*
	Mefloquine	67	54	29 - 82	36 to 66	
van Agtmael 1999	Artemether-lumefantrine	32	24	12 - 48	18 to 42	0.835
	Halofantrine	39	32	6 - 64	18 to 48	
Kshirsagar 2000	Artemether-lumefantrine	40	18	6 - 30	12 to 29	0.0456*
	Chloroquine	54	27	12 - 48	18 to 36	
Lefevre 2001	Artemether-lumefantrine	76	29	8 - 51	23 to 37	
	Mefloquine-artesunate	29	23	15 - 31	15 to 30	
FOOTNOTES	CI - confidence interval; N - group size examined for the event; * Wilcoxon test					

Table 6. Gametocyte clearance time

Study	Treatment	N	Median	25-75th percentile	95% CI	P-value
Looareesuwan 1999	Artemether-lumefantrine	62	152	68 - 285	89 to 185	<0.001
	Mefloquine	74	331	128 - 512	281 to 492	
Kshirsagar 2000	Artemether-lumefantrine	51	120	60-not reached		<0.001
	Chloroquine	63	Not reached			
Lefevre 2001	Artemether-lumefantrine	26	72	32 - 320	34 to 163	
	Mefloquine-artesunate	10	85	46 - 328	46 to 160	
FOOTNOTES	CI - confidence interval; N - group size examined for the event					

APPENDICES

Appendix I. Polymerase chain reaction (PCR) analysis on day 14

Parasitological failure rates corrected for new infections. Any missing samples or failed tests have been classified as treatment failures.

Comparator	Study		Artemether-lumefantrine	Comparator
Sulfadoxine-pyrimethamine	von Seidlein 1998	Day 14 failures/follow up	8/119	3/128
		PCR tested day 14/total failures day 14	6/8	0/3
		Missing sample or failed test	2	3
		Recrudescence	0	No results

(Continued)

		New infections	6	No results
		Corrected day 14 failure rate	2/119	3/128
Chloroquine	Hatz 1998	Day 14 failures/follow up	18/113	106/116
		PCR tested day 14/total failures day 14	7/18	52/106
		Missing sample or failed test	0	0
		Recrudescence	2	20
		New infections	4	5
		New and recrudescence infections	1	27
		Corrected day 14 failure rate	14/113	101/116

Appendix 2. Polymerase chain reaction (PCR) analysis on day 28

Parasitological failure rates adjusted for new infections. Any missing samples or failed tests have been classified as treatment failures.

Comparator	Study		Artemether-lumefantrine	Comparator
Chloroquine	Hatz 1998	Day 28 failures/follow up	43/118	113/119
		PCR tested day 28/total failures day 28	23/43	44/113
		Missing sample or failed test	1	1
		Recrudescence infections	3	17
		New infections	12	6
		New and recrudescence infections	7	20
		Corrected day 28 failure rate	31/118	107/119

(Continued)

	Kshirsagar 2000	Day 28 failures/follow up	3/65	61/76
		PCR tested day 28/total failures day 28	0/3	42/61
		Missing sample or failed test	3	0
		Recrudescence infections	0	40
		New infections	0	2
		Corrected day 28 failure rate	3/65	59/76
Mefloquine-artesunate	Van Vugt 2000	Day 28 failures/follow up	4/134	0/47
		PCR tested day 28/total failures day 28	3/4	0/0
		Missing sample or failed test	1	0
		Recrudescence infections	2	0
		New infections	1	0
		Corrected day 28 failure rate	3/134	0/47
	Lefevre 2001	Day 28 failures/follow up	7/155	0/53
		PCR tested day 28/total failures day 28	7/7	0/0
		Missing sample or failed test	0	0
		Recrudescence infections	6	0
		New infections	1	0
		Corrected day 28 failure rate	6/155	0/53

Appendix 3. Polymerase chain reaction (PCR) analysis on day 28 for sulfadoxine-pyrimethamine

In von Seidlein 1998, PCR analysis was reported for treatment failures by day 28. Follow up after day 14 was passive with participants being encouraged to return to clinic if symptomatic.

Comparator	Study		Artemether-lumefantrine	Comparator
Sulfadoxine-pyrimethamine	Von Seidlein 1998	Day 28 failures/follow up	20/No data	1/No data
		PCR tested day 28/total failures day 28	16/20	1/1
		Missing sample or failed test	4	0
		Recrudescence infections	4	0
		New infections	12	1
		Corrected day 28 failure rate	8/No data	0/No data

Appendix 4. Chloroquine: adverse events (mild to moderate)

Adverse Event	Study			
	*Hatz 1998		*Kshirsagar 2000	
	Artemether-lumefantrine (%)	Chloroquine (%)	Artemether-lumefantrine (%)	Chloroquine (%)
Rashes	5/130 (3.8)	5/130 (3.9)		
Pruritis	1/130 (0.8)	8/130 (6.2)	2/89 (2.2)	11/90 (12.2)
Vomiting			1/89 (1.1)	14/90 (15.6)
Headache			5/89 (5.6)	7/90 (7.8)
Diarrhoea			4/89 (4.5)	7/90 (7.8)
Sleep disorders	50/130 (39.0)	48/130 (37.0)	3/89 (3.4)	2/90 (2.2)
Abdominal pain			10/89 (11.2)	10/90 (11.1)

Number of participants with event calculated from percentage using the total number of participants randomized to each group originally

Appendix 5. Mefloquine: adverse events (mild to moderate)

Adverse event	Study	
	*Looareesuwan 1999	
	Artemether-lumefantrine (%)	Mefloquine (%)
Vomiting	1/126 (0.8)	8/126 (6.3)
Headache	11/126 (8.7)	14/126 (11.1)

*Number of participants with event calculated from percentage using the total number of participants randomized to each group originally.

Appendix 6. Halofantrine: adverse events (mild to moderate)

Adverse event	Study	
	*Van Agtmael 1999	
	Artemether-lumefantrine (%)	Halofantrine (%)
Vomiting	1/51 (2.0)	7/52 (14.0)
Headache	7/51 (14.0)	4/52 (8.0)
Sleep disorders	4/51 (8.0)	6/52 (12.0)
Diarrhoea	3/51 (6.0)	6/52 (12.0)

*Number of participants with event calculated from percentage using the total number of participants randomized to each group originally.

Appendix 7. Mefloquine-artesunate: adverse events (mild to moderate) Lefevre 2001*

Adverse event	Study	
	Artemether-lumefantrine (%)	Mefloquine-artesunate (%)
Skin reactions	8/184 (4.9)	2/55 (3.6)
Headache, dizziness, sleep disorder	45/164 (27.4)	9/55 (6.4)

(Continued)

Jaundice	3/164 (1.8)	0/55 (0.0)
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*Number of participants with event calculated from percentage using the total number of participants randomized to each group originally.

Appendix 8. Mefloquine-artesunate: adverse events (mild to moderate) van Vugt 1998, 2000*

Adverse Event	Study			
	Artemether-lumefantrine (%)	Mefloquine-artesunate (%)	Artemether-lumefantrine (%)	Mefloquine-artesunate (%)
Pruritis	12/309 (4.0)	9/308 (3.0)		
Nausea	19/309 (6.0)	52/308 (17.0)	4/150 (2.5)	6/50 (12.0)
Vomiting	10/309 (3.1)	40/308 (13.0)	4/150 (2.7)	5/50 (10.0)
Sleep disorders	37/309 (12.0)	77/308 (25.0)	2/150 (1.5)	8/50 (16.0)
Dizziness	46/309 (15.0)	108/308 (35.0)	8/150 (5.0)	18/50 (36.0)

*Number of participants with event calculated from percentage using the total number of participants randomized to each group originally.

Appendix 9. Adverse events (severe)

Comparator	Study	Artemether-Lumefantrine	Comparator
Chloroquine	Hatz 1998	Treatment stopped - reason not stated (8) Treated for adverse events (7)	Treated for adverse events (7)
Chloroquine	Kshirsagar 2000		Died from cerebral malaria (1)
Sulfadoxine-pyrimethamine	von Seidlein 1998	Anaemia (4) Vomiting (1) Splenomegaly (1) Conjunctivitis (1)	Anaemia (4) Fever (1) Glomerulonephritis (1) Proteinuria (1) Haematuria (1)
Mefloquine	Looareesuwan 1999	Severe fatigue (1)	Pneumonia (1) AIDs related (1)

(Continued)

Halofantrine	van Agtmael 1999	Haemolytic anaemia (1) Hepatitis A (1)	Prolonged QTc interval-treatment stopped (1) Pneumonia (1)
Mefloquine-artesunate	van Vugt 2000	Fever and coma (1)	Urticaria - treatment stopped (1)

WHAT'S NEW

Date	Event	Description
6 August 2009	Amended	Tables 07 to 15 for this review formerly available on the Infectious Diseases' web site - http://cidg.cochrane.org/en/related_reviews.html have been added to the Appendix of the review as Appendices 1 to 9

HISTORY

Protocol first published: Issue 3, 2001

Review first published: Issue 3, 2002

Date	Event	Description
9 November 2008	Amended	Converted to new review format.
11 August 2005	Amended	Review withdrawn as of Issue 4, 2005
9 May 2005	Amended	Date new studies found but not yet included/excluded
26 February 2003	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Aika Omari wrote the protocol, extracted data, analysed data, and drafted the review. Carrol Preston extracted and analysed data, and drafted the review. Paul Garner advised on the draft protocol and helped write the review.

DECLARATIONS OF INTEREST

Aika Omari has no affiliations with or involvement in any organization or entity with a direct financial interest in the subject matter of the review (eg, employment, consultancy, stock ownership, honoraria, expert testimony).

Paul Garner and Carrol Preston were unpaid technical advisers to a World Health Organization meeting on 19-20 February 2001 considering efficacy and effectiveness studies of coartemether. The World Health Organization paid for their travel and accommodation and a representative of Novartis chaired the meeting.

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Internal sources

- Liverpool School of Tropical Medicine, UK.

External sources

- Department for International Development, UK.

NOTES

This review has been superseded by two reviews that have been published as:

Omari AAA, Gamble C, Garner P. Artemether-lumefantrine (four-dose regimen) for treating uncomplicated falciparum malaria. Cochrane Database of Systematic Reviews 2006, Issue 2. Art. No.: CD005965. DOI: 10.1002/14651858.CD005965.

Omari AAA, Gamble C, Garner P. Artemether-lumefantrine (six-dose regimen) for treating uncomplicated falciparum malaria. Cochrane Database of Systematic Reviews 2005, Issue 4. Art. No.: CD005564. DOI: 10.1002/14651858.CD005564.

INDEX TERMS

Medical Subject Headings (MeSH)

Antimalarials [*therapeutic use]; Artemisinins [*therapeutic use]; Drug Combinations; Ethanolamines [*therapeutic use]; Fluorenes [*therapeutic use]; Malaria, Falciparum [*drug therapy]; Randomized Controlled Trials as Topic; Sesquiterpenes [*therapeutic use]

MeSH check words

Humans