Artemether-lumefantrine (four-dose regimen) for treating uncomplicated falciparum malaria (Review)

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[Intervention Review]

Artemether-lumefantrine (four-dose regimen) for treating uncomplicated falciparum malaria

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ABSTRACT

Background

The World Health Organization recommends artemether-lumefantrine, an expensive drug, as a treatment for uncomplicated malaria. We sought evidence of the superiority of the four-dose regimen over existing treatments.

Objectives

To evaluate the four-dose regimen of artemether-lumefantrine for treating uncomplicated falciparum malaria.

Search strategy

We searched the Cochrane Infectious Diseases Group Specialized Register (October 2005), CENTRAL (*The Cochrane Library* 2005, Issue 3), MEDLINE (1966 to October 2005), EMBASE (1988 to October 2005), LILACS (1982 to October 2005), conference proceedings, and reference lists of articles. We also contacted experts in malaria research and the pharmaceutical company that manufactures artemether-lumefantrine.

Selection criteria

Randomized controlled trials comparing four doses of artemether-lumefantrine with standard treatment regimens (single drug or combination), or six doses of artemether-lumefantrine, for treating uncomplicated falciparum malaria.

Data collection and analysis

Two authors independently applied inclusion criteria to potentially relevant trials, assessed trial quality, and extracted data, including adverse events. Total failure by day 28 (day 42 for sulfadoxine-pyrimethamine and day 63 for mefloquine) was the primary outcome.

Main results

Seven trials (2057 participants) tested a four-dose regimen. More people tended to fail treatment with artemether-lumefantrine than with other drugs, including sulfadoxine-pyrimethamine (247 participants, 1 trial), halofantrine (86 participants, 1 trial), and mefloquine (233 participants, 1 trial; difference statistically significant for mefloquine). When compared with chloroquine, artemether-lumefantrine was better in two trials (378 participants), but over 50% of the participants treated with chloroquine had total failure by day 28. Fewer people failed treatment with the six-dose regimen compared to the four-dose regimen (RR 7.71, 95% CI 2.99 to 19.88; 306 participants, 1 trial).

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Authors' conclusions

The four-dose regimen of artemether-lumefantrine seems to be less effective than regimens against which it has been tested. The six-dose regimen is superior to four-dose regimen.

2008: This review will not be updated because the four-dose regimen is no longer recommended; see 'What's new' for details.

PLAIN LANGUAGE SUMMARY

Artemether-lumefantrine (four-dose regimen) for treating uncomplicated malaria

Malaria is a parasitic disease spread by mosquitoes. It affects millions of people worldwide and causes significant illness and mortality. Uncomplicated malaria presents with symptoms such as fever, headache, muscle pain, and vomiting. The parasite has become resistant to a number of previously effective drugs, and so combinations of drugs are used to try to prevent further resistance. Artemether-lumefantrine is one such drug combination. This review of trials showed that, although the four-dose artemether-lumefantrine regimen was superior to chloroquine, in general the four-dose regimen was less effective compared with the six-dose regimen or other drug combinations. The fact that the four-dose regimen is generally less effective means it is unlikely that it would be used for treating uncomplicated malaria.

BACKGROUND

Foreword

Since the first Cochrane Review on artemether-lumefantrine was published (Omari 2002), the six-dose regimen treatment has become the standard, since the four-dose regimen is acknowledged to be associated with treatment failures (Nosten 2003). Trials are generally using the six-dose regimen, and the evidence for this regimen is maintained in a separate review (Omari 2005). This review evaluates the four-dose regimen. We do not intend to update this review as the question has been answered.

Malaria

Malaria is a major health problem with at least 300 to 500 million people 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). Children also commonly present with rapid breathing (tachypnoea), cough, and convulsions.

Antimalarial drug resistance

The resistance of malaria parasites to antimalarials emerged in South-East Asia and South America (White 1999a), and then spread to Africa and western Oceania. Sulfadoxine-pyrimethamine has replaced chloroquine as the first-line treatment in some African countries (such as Malawi and Kenya), but resistance to this is also emerging (WHO 2000a). Resistance to sulfadoxine-pyrimethamine is relatively common in South-East Asia (WHO 2001b), where resistance and declining sensitivity to mefloquine have also been reported (WHO 2000a). Mefloquine is contraindicated in areas of intensive malaria transmission, such as sub-Saharan Africa, because its long half life may expose parasites to sub-curative doses that could result in the development of resistant strains (WHO 2000a).

Artemisinin drugs, including artemether and artesunate, are now used as first-line treatments in some countries in South-East Asia, but they are recommended only as combination treatment (WHO 2000a). Such combination therapy affords rapid clinical response and higher cure rates when compared with other antimalarial combinations (White 1999a). Combination therapy may slow the development of resistance (White 1999b).

Artemether-lumefantrine combination

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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 is designed for use against chloroquine-resistant falciparum malaria. Artemether has a rapid onset of action and the short half life of two to three hours (Lefèvre 1999) means that it is rapidly eliminated from the plasma. Lumefantrine is cleared more slowly and has a longer elimination half life of about 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 before 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 thought to be low (Bloland 2000). Artemether-lumefantrine also reduces gametocyte carriage and thus should have an impact on malaria transmission (Van Vugt 1998b).

There has been some concern about the possible risk of neurotoxicity with artemisinin derivatives arose from animal studies using high doses of lipid-soluble preparations given intramuscularly (WHO 1999). No serious adverse or persistent neurotoxic adverse events have been documented (Novartis 2005). There has been concern that the lumefantrine component could have adverse cardiac effects due to its similar structure to halofantrine (Bindschedler 2000). Artemether-lumefantrine causes minimal QTc prolongation, but it was not associated with adverse clinical cardiac events (Novartis 2005). These potential adverse effects have to be considered when assessing the drug combination.

Artemether-lumefantrine has been added to the WHO Model List of Essential Medicines and is being promoted in Africa as first-line treatment for malaria by the World Health Organization. The World Health Organization has commended Novartis for providing the drug at discounted prices for developing countries in malaria endemic areas (WHO 2001a).

This review aims to summarize the existing evidence of different doses of artemether-lumefantrine and how it compares with other antimalarial drugs for treating uncomplicated falciparum malaria, including mefloquine, sulfadoxine-pyrimethamine, and chloroquine.

For our primary outcome measure, we use total failure by day 28 as the primary outcome measure or day 42 for sulfadoxine-pyrimethamine and day 63 for mefloquine because of their long half lives. In areas where malaria transmission is intense, recurrence of parasites by day 28 could also be due to re-infection, so we also examine the polymerase chain reaction (PCR), which is thought to distinguish between a new infection and a recurrence of malaria (recrudescence) due to drug resistance.

OBJECTIVES

To evaluate the four-dose regimen of artemether-lumefantrine for treating uncomplicated falciparum malaria.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials.

Types of participants

Adults and children with acute uncomplicated malaria, as defined in WHO 2000b, with asexual *P. falciparum* parasitaemia confirmed from blood slides.

Types of interventions

Intervention

Four doses of artemether-lumefantrine.

Control

- Standard treatment regimens (single drug or combination).
- Six doses of artemether-lumefantrine.

Types of outcome measures

Primary

Total failure by day 28, day 42 (for sulfadoxine-pyrimethamine), or day 63 (for mefloquine); defined as a recurrent malaria infection with or without clinical malaria.

Secondary

- Total failure adjusted by PCR to exclude new infections (recrudescent infections) by day 28.
- Parasite clearance time (PCT), defined as the time between commencing treatment and the first negative blood test when negativity persists for more than 48 hours; PCT 50, defined as the time taken for parasites to be reduced to 50% of first test value; and PCT 90, defined as the time taken for parasites to be reduced to 10% of first test value.

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- Fever clearance time, defined as the time between starting treatment and the temperature returning back to normal, and remaining normal for more than 48 hours.
- Gametocyte carriage on days 14 and 28.
- Gametocyte clearance time, defined as the time taken for gametocytes to disappear (if present in the blood initially) after commencing treatment.

Adverse events

- Adverse events requiring discontinuation of treatment or are fatal, life-threatening, or require hospitalization.
- Other adverse events (all other adverse events).

Search methods for identification of studies

We attempted to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress).

Databases

We searched the following databases using the search terms and strategy described in Table 1: Cochrane Infectious Diseases Group Specialized Register (October 2005); Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (2005, Issue 3); MEDLINE (1966 to October 2005); EMBASE (1974 to October 2005); and LILACS (1982 to October 2005).

Table 1. Detailed search strategies

Search set	CIDG SR*	CENTRAL	MEDLINE**	EMBASE[a]	LILACS[b]
1	artemether	artemether	artemether	artemether	artemether
2	lumefantrine	lumefantrine	lumefantrine	lumefantrine	lumefantrine
3	benflumetol	benflumetol	benflumetol	benflumetol	benflumetol
4	co-artemether	co-artemether	co-artemether	coartemether	co-artemether
5	coartem	coartem	coartem	coartem	coartem
6	coarteme	coarteme	coarteme	coarteme	1 or 2 or 3 or 4 or 5
7	riamet	riamet	riamet	riamet	malaria
8	CGP56697	CGP56697	CGP56697	CGP56697	6 and 7
9	-	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	-

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Table 1. Detailed search strategies (*Continued*)

10	-	malaria	exp MALARIA	exp MALARIA	-
11	-	9 and 10	malaria	malaria	-
12	-	-	10 or 11	10 or 11	-
13	-	-	9 and 12	9 and 12	-
14	-	-	Limit 13 to human	Limit 13 to human	-

[a] Cochrane Infectious Diseases Group Specialized Register.
[b] Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Higgins 2005); upper case: MeSH or EMTREE heading; lower case: free text term.

Conference proceedings

We searched the following conference proceedings for relevant abstracts: The Third Multilateral Initiative on Malaria Pan-African Conference, 18 to 22 November 2002, Arusha, Tanzania; and the Second European Congress on Tropical Medicine (Liverpool, UK, 14 to 18 September 1998).

Researchers, organizations, and pharmaceutical companies

We contacted researchers working in the field, the World Health Organization, and the pharmaceutical company Novartis for unpublished and ongoing trials.

Data collection and analysis

Selection of studies

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

Data extraction and management

AO and CG independently extracted data of trial 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 trial 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). 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 or being excluded from the trial should be documented (WHO 1996).

If the number of participants randomized and the numbers analysed were inconsistent, we calculated the percentage loss to follow up. For dichotomous outcomes, we recorded the number of participants experiencing the event in each group of the trial. For continuous outcomes, we extracted arithmetic means and standard deviations and combined means using mean difference for each group where possible. If the data were reported using geometric means, we extracted standard deviations on the log scale, and extracted and reported the medians and ranges.

Assessment of risk of bias in included studies

We assessed the generation of allocation sequence and concealment of allocation as adequate, inadequate, or unclear according to Jüni 2001. We described whether the trial was open, single blind, or double blind. We assessed the inclusion of all randomized participants in the analysis of the reported primary outcome to be

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adequate if 90% or more were included in the analysis, inadequate if less than 90%, or unclear.

Data synthesis

We analysed data using Review Manager 5. We compared outcome measures for dichotomous data using risk ratio (RR), which is the risk of achieving an outcome in the artemether-lumefantrine group relative to that in the control group, and 95% confidence intervals (CI). We used total failure (clinical or parasitological failure by day 28) as our main outcome, and we also conducted analysis excluding re-infection where PCR data were available. As the value of the risk ratio is constrained to lie between 0 and 1/CGER (control group event rate), large values of the risk ratio are impossible when events are common, so failure is preferred to treatment success.

For total failure with trials that had conducted PCR analysis, we classified the infections into: 1. recrudescent infection (matching genotypes on day 0 and day of recurrence); 2. new infection (different genotypes on day 0 and day of recurrence); and 3. missing values. We conducted an analysis of parasitaemia corrected for PCR on days 14 and 28. We intended to conduct a sensitivity analysis around PCR examining the effect of missing data, but there were too few trials for us to do this.

We intended to explore age, level of malaria transmission, and level of drug resistance as potential sources of heterogeneity, and to conduct sensitivity analyses according to blinding, allocation concealment, whether the trials used an intention-to-treat analysis, and total failure adjusted by PCR to exclude new infections, but data were insufficient.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

We identified 30 potentially relevant studies. Seven trials (2057 participants) met the inclusion criteria (*see* 'Characteristics of included studies'), with one trial, Hatz 1998, reported across two publications. We excluded 19 studies for the reasons given in the 'Characteristics of excluded studies'. We have requested data since 2003 on four studies from Novartis (cited in Novartis 1999) but have not yet received a response.

Trial location

Trials were conducted in The Gambia (Von Seidlein 1998), Tanzania (Hatz 1998), India (Kshirsagar 2000), travellers from the Tropics returning to France and the Netherlands (Van Agtmael 1999a), and Thailand (Van Vugt 1998a; Looareesuwan 1999; Van Vugt 1999).

Trial funding

Four trials reported that they were sponsored by Novartis (Van Vugt 1998a; Von Seidlein 1998; Looareesuwan 1999; Van Vugt 1999). The other three trials did not mention funding.

Participants

Two trials included 547 children aged one to five years (Hatz 1998; Von Seidlein 1998), two trials included 976 adults and children (Van Vugt 1998a; Van Vugt 1999), and three trials included 534 participants over 13 years of age (Looareesuwan 1999; Van Agtmael 1999a; Kshirsagar 2000).

Interventions

All trials gave the four doses of artemether-lumefantrine over 48 hours. Two trials compared it with chloroquine (Hatz 1998; Kshirsagar 2000). Other comparisons were with sulfadoxine-pyrimethamine (Von Seidlein 1998), mefloquine (Looareesuwan 1999), halofantrine (Van Agtmael 1999a), mefloquine plus artesunate (Van Vugt 1998a), and two six-dose regimens of artemether-lumefantrine (Van Vugt 1999).

Antimalarial drug resistance

Multiple-drug resistance was reported for three trials conducted in Thailand; one trial specified resistance to chloroquine, mefloquine, amodiaquine, and sulfadoxine-pyrimethamine (Looareesuwan 1999). Chloroquine resistance was reported in the Tanzanian trial, which was located in Ifakara where 20% of *P. falciparum* strains were resistant in 1988 (Hatz 1998). Kshirsagar 2000, which took place in Mumbai, India, was stopped early because the overall cure rate with chloroquine decreased to 50% due to a higher degree of chloroquine resistance present than expected; it was not clear from the trial report whether this was the result of a formal preplanned stopping rule. The Gambian trial, Von Seidlein 1998, was conducted in an area of chloroquine resistance and less than 5% of the *P. falciparum* strains were resistant to sulfadoxine-pyrimethamine.

Outcome measures

(See Table 2). Total failure by day 28 was the most frequently reported outcome (five of the seven studies). The results of PCR analyses used to exclude new infections were reported in five trials. Five trials reported on fever clearance times. Time to parasite clearance was reported in six trials: two trials reported it as a time-to-event analysis (Looareesuwan 1999; Van Agtmael 1999a); the other trials calculated the time to clearance on those participants in which the event occurred. Six trials reported on gametocyte carriage, and all seven trials reported adverse events.

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Table 2. Reported outcome measures

Trial	Total failure (day)	PCT	FCT	GCT	Gametocyte carriage	PCR analysis	Adverse events
Hatz 1998	7 and 14	No	No	No	Yes	Yes	Yes
Van Vugt 1998a	28 and 63	Yes	Yes	No	Yes	Yes	Yes
Von Seidlein 1998	4 and 15	Yes	No	No	Yes	Yes	Yes
Looareesuwan 1999	28	Yes	Yes	Yes	Yes	No	Yes
Van Agtmael 1999a	28	Yes	Yes	No	Yes	No	Yes
Van Vugt 1999	28	Yes	Yes	No	Yes	Yes	Yes
Kshirsagar 2000	28	Yes	Yes	Yes	No	Yes	Yes

FCT: fever clearance time; GCT: gametocyte clearance time; PCR: polymerase chain reaction; PCT: parasite clearance time.

Risk of bias in included studies

See Table 3 *for the quality assessment and the* 'Characteristics of included studies' *for details.*

Table 3. Risk of bias assessment

Trial	Generation of allocation sequence	Allocation concealment	Blinding	Inclusion of all randomized participant in the analysis[a]
Hatz 1998	Not described	Adequate	No	Inadequate (45%)
Von Seidlein 1998	Adequate	Adequate	Double	Inadequate (86%)
Van Vugt 1998a	Not described	Adequate	No	Inadequate (77%)
Looareesuwan 1999	Adequate	Adequate	Double	Adequate (92%)
Van Agtmael 1999a	Adequate	Not described	Double	Inadequate (83%)
Van Vugt 1999	Not described	Adequate	No	Inadequate (85%)

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Table 3. Risk of bias assessment *(Continued)*

Kshirsagar 2000	Adequate	Adequate	Double	Inadequate (79%)

[a] For primary outcomes. see the 'Data collection and analysis' for the assessment methods, and the 'Characteristics of included studies' for each trial's methods.

Generation of allocation sequence

All the trials were reported as randomized. Four trials reported adequate generation of the allocation sequence. The remaining three trials mentioned randomization, but they did not report the methods used to generate the allocation sequence.

Concealment of allocation

Allocation concealment was adequate in the six trials that used a priori numbered or coded drug containers, central randomization, or sequentially numbered and sealed, opaque envelopes. One trial did not describe the method of allocation concealment (Van Agtmael 1999a).

Blinding

Four trials reported as double blind used the double dummy technique, while the other three trials were described as open. Three of the seven trials used adequate methods to generate the allocation sequence and conceal allocation, and used double blinding (Von Seidlein 1998; Looareesuwan 1999; Kshirsagar 2000).

Inclusion of randomized participants in the analysis

None of seven trials 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. An intention-to-treat analysis was therefore not possible for the trial investigators or for this review because the necessary data were not collected. All trials gave results of analyses based on evaluable participants, that is, participants still on treatment at each time point. Five of the trials, however, also claimed to have reported cure rates as an 'intention-to-treat' analysis (Hatz 1998; Von Seidlein 1998; Van Agtmael 1999a; Van Vugt 1999; Kshirsagar 2000). These are not the results of an intention-to-treat analysis and differed from their analysis of evaluable participants 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 evaluable for the primary outcome was more than 90% in one trial (Looareesuwan 1999), 90% to 85% in two trials (Von Seidlein 1998; Van Vugt 1999), and less than 85% in four trials (Hatz 1998; Van Vugt 1998a; Van Agtmael 1999a; Kshirsagar 2000).

Effects of interventions

1. Versus sulfadoxine-pyrimethamine (287 participants, 1 trial)

Total failure and parasite clearance time

Von Seidlein 1998, which was conducted in The Gambia, did not report any results for total failure by day 28 or 42. By day 14, there was no statistically significant difference in the number of participants with parasites between the two groups, but numbers were small (247 participants, Analysis 1.1). PCR results were available for six of the eight treatment failures in the artemether-lumefantrine group (all new infections), but no PCR results were available for the three treatment failures in the sulfadoxine-pyrimethamine group (Table 4). Adjusting for new infections (with missing samples or failed tests classified as treatment failures) on day 14 did not change the statistical significance, but it did change the direction of the effect (Analysis 1.2). However, parasite clearance time was faster with artemether-lumefantrine compared with sulfadoxine-pyrimethamine (PCT 50 mean 11.6 h, 144 participants; mean 21.1 h, 143 participants), although the trial authors reported that this difference was statistically significant ($P < 0.0001$, test not stated).

Table 4. Total failure (excludes new infections)

Trial	Comparator	Measure	Day 14		Day 28	
			Artemether-lumefantrine	Comparator	Artemether-lumefantrine	Comparator

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Table 4. Total failure (excludes new infections) *(Continued)*

Hatz 1998	Chloroquine	Number participants failing treatment/number followed up	18/113	106/116	43/118	113/119
		Number with PCR tests/number total failures	7/18	52/106	23/43	44/113
		Missing sample of failed test	0	0	1	1
		Number of recrudescent infections	2	20	3	17
		Number with a new infection	4	5	12	6
		Number with new and recrudescent infections	1	27	7	20
		Corrected failure rate	14/113	101/116	31/118	107/119
Von Seidlein 1998	Sulfadoxine-pyrimethamine	Number participants failing treatment/number followed up	8/119	3/128	20/no data	1/no data
		Number with PCR tests/number total failures	6/8	0/3	16/20	1/1
		Missing sample of failed test	2	3	4	0
		Number of recrudescent infections	0	No results	4	0
		Number with a new infection	6	No results	12	1
		Corrected failure rate	2/119	3/128	8/no data	0/no data

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Table 4. Total failure (excludes new infections) *(Continued)*

Kshirsagar 2000	Chloroquine	Number participants failing treatment/number followed up	-	-	3/65	61/76
		Number with PCR tests/number total failures	-	-	0/3	42/61
		Missing sample of failed test	-	-	3	0
		Number of recrudescent infections	-	-	0	40
		New infections	-	-	0	2
		Corrected day 28 failure rate	-	-	3/65	59/76

Gametocyte carriage

By day four there were fewer participants carrying gametocytes in the artemether-lumefantrine group than in the sulfadoxine-pyrimethamine group (115 participants, Analysis 1.3). A similar pattern was observed at day 15 (253 participants, Analysis 1.4).

Adverse events

Severe adverse events reported by the trialists are documented in Table 5.

Table 5. Severe adverse events

Comparator	Trial	Number with event	
		Artemether-lumefantrine	Comparator
Sulfadoxine-pyrimethamine	Von Seidlein 1998	Anaemia (4), vomiting (1), splenomegaly (1), conjunctivitis (1)	Anaemia (1), fever (1), glomerulonephritis (1), proteinuria (1), haematuria (1)
Mefloquine	Looareesuwan 1999	Severe fatigue (1)	Pneumonia (1), AIDS-related (1)
Halofantrine	Van Agtmael 1999a	Haemolytic anaemia (1), hepatitis A (1)	Prolonged QTc interval (treatment stopped) (1), pneumonia (1)

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Table 5. Severe adverse events *(Continued)*

Chloroquine	Hatz 1998	Treatment stopped (reason not stated) (8), treated for adverse events (7)	Treated for adverse events (7)
	Kshirsagar 2000	None	Died from cerebral malaria (1)

2. Versus mefloquine (252 participants, 1 trial)

Total failure, and parasite, fever, and gametocyte clearance times

Looareesuwan 1999 reported that total failure was higher with artemether-lumefantrine by day 28 (RR 1.74, 95% CI 1.08 to 2.80; 233 participants, Analysis 2.1). However, parasite and fever clearance times were faster with artemether-lumefantrine (Table 6 and Table 7). Gametocyte clearance was also faster with artemether-lumefantrine, but this was not statistically evident in the first 72 hours (252 participants, Analysis 2.2 and Table 8).

Table 6. Parasite clearance time

Trial	Treatment	No. participants	Median	25 to 75 percentile	95% CI	P value
Looareesuwan 1999	Artemether-lumefantrine	126	43	35 to 51	42 to 45	< 0.001[a]
	Mefloquine	126	66	52 to 82	61 to 70	-
Van Agtmael 1999a	Artemether-lumefantrine	51	32	23 to 48	32 to 48	< 0.001
	Halofantrine	52	48	47 to 60	48 to 60	-
Van Vugt 1999	Artemether-lumefantrine (4 doses)	120	44	34 to 51	-	0.96
	Artemether-lumefantrine (6 doses over 60 h)	118	44	22 to 47	-	-
	Artemether-lumefantrine (6 doses over 90 h)	121	44	40 to 47	-	-
Kshirsagar 2000	Artemether-lumefantrine	89	36	24 to 48	30 to 36	< 0.001[a]

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Table 6. Parasite clearance time *(Continued)*

	Chloroquine	90	60	48 to 91	45 to 66	-

CI: confidence interval.
[a] Wilcoxon test.

Table 7. Fever clearance time

Trial	Treatment	No. participants	Median	25 to 75 percentile	95% CI	P value
Looareesuwan 1999	Artemether-lumefantrine	75	32	17 to 54	23 to 37	0.003[a]
	Mefloquine	67	54	29 to 82	36 to 66	-
Van Agtmael 1999a	Artemether-lumefantrine	32	24	12 to 48	18 to 42	0.835
	Halofantrine	39	32	6 to 64	18 to 48	-
Van Vugt 1999	Artemether-lumefantrine (4 doses)	61	23	20 to 44	-	0.38
	Artemether-lumefantrine (6 doses over 60 h)	59	35	20 to 46	-	-
	Artemether-lumefantrine (6 doses over 90 h)	80	22	20 to 44	-	-
Kshirsagar 2000	Artemether-lumefantrine	40	18	6 to 30	12 to 29	0.0456[a]
	Chloroquine	54	27	12 to 48	18 to 36	-

CI: confidence interval.
[a] Wilcoxon test.

Table 8. Gametocyte clearance time

Trial	Treatment	No. participants	Median	25 to 75 percentile	95% CI	P value

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Table 8. Gametocyte clearance time *(Continued)*

Looareesuwan 1999	Artemether-lumefantrine	62	152	68 to 285	89 to 185	< 0.001
	Mefloquine	74	331	128 to 512	281 to 492	-
Kshirsagar 2000	Artemether-lumefantrine	51	120	60 to not reached	-	< 0.001[a]
	Chloroquine	63	Not reached	-	-	-

CI: confidence interval.
[a] Wilcoxon test.

Adverse events

The majority of adverse events reported were mild or moderate (Table 9), but there were reports of some severe adverse events (Table 5). In particular, cardiac monitoring was reported with no difference in the QTc interval between the treatment groups.

Table 9. Mild to moderate adverse events

Comparator	Trial	Adverse event	Artemether-lumefantrine (%)[a]	Comparator (%)[a]
Chloroquine	Hatz 1998	Rashes	5/130 (3.8)	5/130 (3.8)
		Pruritis	1/130 (0.8)	8/130 (6.2)
		Sleep disorders	50/130 (39.0)	48/130 (37.0)
	Kshirsagar 2000	Pruritis	2/89 (2.2)	11/90 (12.2)
		Vomiting	1/89 (1.1)	14/90 (15.3)
		Headache	5/89 (5.6)	7/90 (7.8)
		Diarrhoea	4/89 (9.5)	7/90 (7.8)
		Sleep disorders	3/89 (3.4)	2/90 (2.2)
		Abdominal pain	10/89 (11.2)	10/90 (11.1)
Mefloquine	Looareesuwan 1999	Vomiting	1/126 (0.8)	8/126 (6.3)
		Headache	11/126 (8.7)	14/126 (11.1)
Halofantrine	Van Agtmael 1999a	Vomiting	1/51 (2.0)	7/52 (14.0)

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Table 9. Mild to moderate adverse events *(Continued)*

		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)

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

3. Versus halofantrine (103 participants, 1 trial)

The participants in Van Agtmael 1999a were travellers returning to France and the Netherlands from the tropics.

Total failure

Although the number of participants failing treatment by day 28 was higher with artemether-lumefantrine, it was not statistically significant (86 participants, Analysis 3.1). The wide confidence interval reflects considerable imprecision, therefore clinically important results cannot be excluded in either direction.

Parasite clearance time

All participants on halofantrine cleared their parasites. The trial authors reported that parasite clearance time was statistically significant faster with artemether-lumefantrine (Table 6).

Fever clearance time

Fever clearance was faster with artemether-lumefantrine, but this was not statistically significant (Table 7).

Gametocyte carriage

There was no statistically significant difference between the two treatments within the first 72 hours (14 participants, Analysis 3.2).

Adverse events

Most of the reported adverse events were mild or moderate (Table 9), but four separate severe adverse events were also documented (Table 5). Some of the occurrences resulted in stopping treatment. The results of cardiac monitoring showed a significant increase in the overall QTc interval in participants treated with halofantrine (26/52) compared with artemether-lumefantrine (8/51).

4. Versus chloroquine (439 participants, 2 trials)

Kshirsagar 2000, a double blind trial, was conducted in an area of India with an unexpectedly high chloroquine resistance, which resulted in the trial being terminated before completion. Hatz 1998, which was an open trial in Tanzania, was also conducted in an area of high levels of chloroquine resistance.

Total failure

Both trials showed that artemether-lumefantrine was associated with fewer failures on day 28, but the size of this effect varied greatly between the two trials (Analysis 4.1): Hatz 1998 reported a risk ratio of 0.38 (95% CI 0.30 to 0.49) with 237 participants, and Kshirsagar 2000 reported a risk ratio of 0.06 (95% CI 0.02 to 0.17) with 141 participants. The significant 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. On days seven and 14, Hatz 1998 reported fewer parasitological failures with artemether-lumefantrine.

The trial authors did PCR analyses on subsets of participants who failed treatment on days 14 and 28 (Table 4). Less than half of the treatment failures in Hatz 1998 were tested, so any statistical inferences must be made with extreme caution. In Kshirsagar 2000, all treatment failures in the artemether-lumefantrine group were classified as recrudescent infections although no PCR was done.

Parasite clearance time and fever clearance time

Kshirsagar 2000 reported that parasite and fever clearance times were statistically significantly faster with artemether-lumefantrine (Table 6 and Table 7).

Gametocytes

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The pooled results from the two trials suggested a reduction in gametocyte carriage with artemether-lumefantrine within the first 72 hours (RR 0.79, 95% CI 0.63 to 0.99; 427 participants, Analysis 4.2). Gametocyte clearance was faster with artemether-lumefantrine compared with chloroquine (Table 8).

Adverse events

Most reported adverse events were mild or moderate (Table 9), but a few were severe (Table 5). No deaths reported by either trial were associated with trial medication. Hatz 1998 reported occurrences of adverse events that resulted in stopping treatment. Kshirsagar 2000 reported cardiac monitoring with no difference in the QTc interval between treatment groups. One participant on halofantrine was withdrawn from treatment due to a prolonged QTc interval.

5. Versus mefloquine plus artesunate (617 participants, 1 trial)

Total failure

Van Vugt 1998a, conducted in Thailand, reported that more participants experienced total failure with artemether-lumefantrine at day 28 than with mefloquine plus artesunate (RR 6.77, 95% CI 3.12 to 14.67; 537 participants, Analysis 5.1). The results remained similar when new infections were excluded (RR 6.45, 95% CI 2.78 to 14.95; 537 participants, Analysis 5.2). The total failure on day 63 was also higher with artemether-lumefantrine (RR 2.67, 95% CI 1.55 to 4.57; 478 participants, Analysis 5.3).
PCR was conducted on 80% (72/89) of participants with parasites on day 63. There was a trend to fewer new infections in the artemether-lumefantrine group, but there were more also recrudescent infections in the artemether-lumefantrine group.

Parasite and fever clearance times

The trial 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.

Gametocyte carriage

There was no statistically significant difference in gametocyte carriage within the first 72 hours between the two groups (RR 1.41, 95% CI 0.86 to 2.32; 616 participants, Analysis 5.4).

Adverse events

Van Vugt 1998a specifically sought serious neurotoxicity, but it reported no such adverse event.

6. Versus artemether-lumefantrine (six doses) (359 participants, 1 trial)

Van Vugt 1999, which was conducted in Thailand, compared the four-dose regimen of artemether-lumefantrine with two six-dose regimens given over 60 and 96 hours, respectively.

Total failure and parasite clearance time

The four-dose regimen had higher parasitological failure rates at day 28 compared with six-dose regimen (RR 7.71, 95% CI 2.99 to 19.88; 60 hour and 96 hour regimens combined, 306 participants, Analysis 6.1).
A PCR analysis was conducted during the 28-day follow up, but the results were reported according to the treatment site and not the treatment group. Twenty-four of the 25 treatment failures were evaluated by PCR genotyping. There were no re-infections in the 13 recurrent infections seen in the hospital, and four of the 11 recurrent malaria episodes at the campsite were new infections.

Parasite and fever clearance times

The median parasite clearance time was 44 hours for all three groups (Table 6). There was no statistically significant difference in the median fever clearance times between the four-dose regimen and the two six-dose regimens (Table 7).

Gametocytes

For comparisons with the six-dose regimens, 66 (18.4%) of all the participants had gametocytes detected during the first 72 hours. Gametocyte carriage was reported according to treatment centre. There was no statistically significant difference in the gametocyte clearance time in comparisons between the four-dose and six-dose regimens (P = 0.5; trial authors' calculation).

Adverse events

None were reported.

DISCUSSION

Four of the seven trials described the methods used to generate the allocation sequence, and six trials described the concealment of allocation. Five trials reported an 'intention-to-treat' analysis for total failure, the primary outcome measure, but it 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.

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Where PCR results were available, the total failure by day 14 and day 28 were corrected for new infections, with missing samples or failed tests classified as treatment failures. This did not materially affect the results for chloroquine and mefloquine plus artesunate, but it had a more substantial impact on sulfadoxine-pyrimethamine on day 14 by changing the direction of the effect to favour artemether-lumefantrine.

The four-dose regimen had significantly more treatment failures than the six-dose regimen. There was no significant difference in the parasite, fever, and gametocyte clearance times between the regimens, and the six-dose regimens were not associated with increased adverse events. The trial with the six-dose regimen as the comparator was conducted in an area with multiple-drug resistance, which is one of the recommendations for using this regimen. This review has shown that six-dose regimens are superior to the four-dose regimen in terms of total failure rates.

For parasitological outcomes, artemether-lumefantrine did not perform better than the other antimalarials apart from chloroquine. The trial comparing sulfadoxine-pyrimethamine with artemether-lumefantrine did not report on total failure on day 42. The fewer recrudescent and new infections seen in the sulfadoxine-pyrimethamine group may be explained by the long half life of sulfadoxine-pyrimethamine. Artemether-lumefantrine showed no marked advantage over mefloquine for parasitaemia in one trial of high quality (Looareesuwan 1999). 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 (they were from different countries), which could have confounded their response to medication (ter Kuile 1995).

Artemether-lumefantrine was only superior to chloroquine for total failure on day 28. However, there was a high withdrawal rate (more than 50% of the participants in the chloroquine group) in both trials, and the unexpected higher resistance to chloroquine decreased the cure rate to 50% in Kshirsagar 2000. 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).

Parasite, fever, and gametocyte clearance times were shorter for artemether-lumefantrine when compared with the other antimalarial drugs, which suggests that clinical symptoms may resolve faster. With the exception of Looareesuwan 1999 and Van Agtmael 1999a, the trials reported clearance times as medians and percentiles, and not as time-to-event analyses. Time-to-event analyses are more informative as data on participants who did not reach the event would have been included in the analysis.

It is important to acknowledge that the trials were not designed to evaluate safety. 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 reporting the details.

AUTHORS' CONCLUSIONS

Implications for practice

Artemether-lumefantrine showed no advantage in relation to total failure when compared with mefloquine, mefloquine plus artesunate, halofantrine, and sulfadoxine-pyrimethamine (result not adjusted for new infections).

There is evidence to suggest the four-dose artemether-lumefantrine 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 or other standard regimens.

The six-dose artemether-lumefantrine regimen is superior to the four-dose regimen.

2008: This review will not be updated because the four-dose regimen is no longer recommended. Only the six-dose regimen, reviewed in Omari 2005, is recommended (WHO 2007).

Implications for research

Since the artemether-lumefantrine is no longer used as a four-dose regimen, there is no need for further research.

2008: This review will not be updated because the four-dose regimen is no longer recommended. Only the six-dose regimen, reviewed in Omari 2005, is recommended (WHO 2007).

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REFERENCES

References to studies included in this review

Hatz 1998 *{published data only}*

* Hatz C, Abdulla S, Mull R, Schellenberg D, Gathmann I, Kibatala P, et al.Efficacy and safety of CGP 56697 (artemether and benflumetol) compared with chloroquine to treat acute falciparum malaria in Tanzanian children aged 1-5 years. *Tropical Medicine and International Health* 1998;**3**(6):498–504.

Irion A, Felger I, Abdulla S, Smith T, Mull R, Tanner M, et al.Distinction of recrudescences from new infections by PCR-RFLP analysis in a comparative trial of CPG 56 697 and chloroquine in Tanzanian children. *Tropical Medicine and International Health* 1998;**3**(6):490–7.

Kshirsagar 2000 *{published data only}*

Kshirsagar N, Gogtay NJ, Moorthy NS, Garg MR, Dalvi SS, Chogle AR, et al.A randomized, double-blind, parallel-group, comparative safety, and efficacy trial of oral co-artemether versus oral chloroquine in the treatment of acute uncomplicated Plasmodium falciparum malaria in adults in India. *American Journal of Tropical Medicine and Hygiene* 2000;**62**(3):402–8.

Looareesuwan 1999 *{published data only}*

Looareesuwan S, Wilairatana P, Chokejindachai W, Chalermrut K, Wernsdorfer W, Gemperli B, et al.A randomized, double-blind, comparative trial of a new oral combination of artemether and benflumetol (CGP 56697) with mefloquine in the treatment of acute Plasmodium falciparum malaria in Thailand. *American Journal of Tropical Medicine and Hygiene* 1999;**60**(2):238–43.

Van Agtmael 1999a *{published data only}*

Van Agtmael M, Bouchaud O, Malvy D, Delmont J, Danis M, Barette S, et al.The comparative efficacy and tolerability of CGP 56697 (artemether + lumefantrine) versus halofantrine in the treatment of uncomplicated falciparum malaria in travellers returning from the Tropics to The Netherlands and France. *International Journal of Antimicrobial Agents* 1999;**12**(2):159–69.

Van Vugt 1998a *{published data only}*

Van Vugt M, Brockman A, Gemperli B, Luxemburger C, Gathmann I, Royce C, et al.Randomized comparison of artemether-benflumetol and artesunate-mefloquine in treatment of multidrug-resistant falciparum malaria. *Antimicrobial Agents and Chemotherapy* 1998;**42**(1):135–9.

Van Vugt 1999 *{published data only}*

Van Vugt M, Wilairatana P, Gemperli B, Gathmann I, Phaipun L, Brockman A, et al.Efficacy of six doses of artemether-lumefantrine (benflumetol) in multidrug-resistant Plasmodium falciparum malaria. *American Journal of Tropical Medicine and Hygiene* 1999; **60**(6):936–42.

Von Seidlein 1998 *{published data only}*

Von Seidlein, Bojang K, Jones P, Jaffar S, Pinder M, Obaro S, et al.A randomized controlled trial of artemether/benflumetol, a new antimalarial and pyrimethamine/sulfadoxine in the treatment of uncomplicated falciparum malaria in African children. *American Journal of Tropical Medicine and Hygiene* 1998;**58**(5):638–44.

References to studies excluded from this review

Espino 2002 *{unpublished data only}*

Espino FE. Efficacy studies of chloroquine+sulfadoxine-pyrimethamine, sulfadoxine-pyrimethamine and artemether-lumefantrine for uncomplicated malaria in Mindanao Island, Philippines. 2002.

Falade 2005 *{published data only}*

Falade C, Makanga M, Premji Z, Ortmann CE, Stockmeyer M, de Palacios PI. Efficacy and safety of artemether-lumefantrine (Coartem) tablets (six-dose regimen) in African infants and children with acute uncomplicated falciparum malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2005;**99**(6):459–67.

Jiao 1997 *{unpublished data only}*

Jiao XQ, Liu EY, Shan CQ, Dal P, Gathmann I, Mull R, et al.A double-blind comparative trial of benflumetol, a novel antimalaria, and CGP 56697, a combination of benflumetol and artemether, in the treatment of acute P. falciparum malaria in adults in China. Proceedings of the 5th International Conference of Travel Medicine; 1997 Mar 24-27; Geneva (Switzerland). 1997:Abstract 108.

Karbwang 2002 *{unpublished data only}*

Karbwang J. Coartemether safety and efficacy evaluation of the six dose regimen in the treatment of uncomplicated malaria in children and infants. 2002.

Krudsood 2003 *{published data only}*

Krudsood S, Chalermrut K, Pengruksa C, Srivilairit S, Silachamroon U, Treeprasertsuk S, et al.Comparative clinical trial of two-fixed combinations dihydroartemisinin-napthoquine-trimethoprim (DNP) and artemether-lumefantrine (Coartem/Riamet) in the treatment of acute uncomplicated falciparum malaria in Thailand. *Southeast Asian Journal of Tropical Medicine and Public Health* 2003;**34**(2):316–21.

Lefevre 2001 *{published data only}*

Lefevre G, Looareesuwan S, Treeprasertsuk S, Krudsood S, Silachamroon U, Gathmann I, et al.A clinical and pharmacokinetic trial of six doses of artemether-lumefantrine for multidrug-resistant Plasmodium falciparum malaria in Thailand. *American Journal of Tropical Medicine and Hygiene* 2001;**64**(5-6):247–56.

Lefevre 2002 *{published data only}*

Lefevre G, Carpenter P, Souppart C, Schmidli H, Martin JM, Lane A, et al.Interaction trial between artemether-lumefantrine (Riamet) and quinine in healthy subjects. *Journal of Clinical Pharmacology* 2002;**42**(10):1147–58.

Mayxay 2004 *{published data only}*

Mayxay M, Khanthavong M, Lindegardh N, Keola S, Barends M, Pongvongsa T, et al.Randomized comparison of chloroquine plus sulfadoxine-pyrimethamine versus artesunate plus mefloquine versus artemether-lumefantrine in the treatment of uncomplicated falciparum malaria in the Lao People's Democratic Republic. *Clinical Infectious Diseases* 2004;**39**(8):1139–47.

Mutabingwa 2005 *{published data only}*

Mutabingwa TK, Anthony D, Heller A, Hallett R, Ahmed J, Drakeley C, et al.Amodiaquine alone, amodiaquine+sulfadoxine-pyrimethamine, amodiaquine+artesunate, and artemether-lumefantrine for outpatient treatment of malaria in Tanzanian

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children: a four-arm randomised effectiveness trial. *Lancet* 2005; **365**(9469):1474–80.

Ndayiragije 2004 ***{published data only}***
Ndayiragije A, Niyungeko D, Karenzo J, Niyungeko E, Barutwanayo M, Ciza A, et al.Efficacy of therapeutic combinations with artemisinin derivatives in the treatment of non complicated malaria in Burundi [Efficacité de combinaisons thérapeutiques avec des dérivés de l'artémisinine dans le traitement de l'accès palustre non–complique au Burundi]. *Tropical Medicine & International Health* 2004;**9**(6):673–9.

Piola 2005 ***{published data only}***
Piola P, Fogg C, Bajunirwe F, Biraro S, Grandesso F, Ruzagira E, et al.Supervised versus unsupervised intake of six-dose artemether-lumefantrine for treatment of acute, uncomplicated Plasmodium falciparum malaria in Mbarara, Uganda: a randomised trial. *Lancet* 2005;**365**(9469):1467–73.

Popov 2002 ***{published data only}***
Popov AF, Morokov VS, Chirkov VP, Popova NI, Lama N. Efficacy of mefloquine, halofantrine, and coarteme in the treatment of tropical malaria. *Meditsinskaia Parazitologiia i Parazitarnye Bolezni* 2002;**Jan-Mar**(1):28–9.

Stohrer 2004 ***{published data only}***
Stohrer JM, Dittrich S, Thongpaseuth V, Vanisaveth V, Phetsouvanh R, Phompida S, et al.Therapeutic efficacy of artemether-lumefantrine and artesunate-mefloquine for treatment of uncomplicated Plasmodium falciparum malaria in Luang Namtha Province, Lao People's Democratic Republic. *Tropical Medicine & International Health* 2004;**9**(11):1175–83.

Sun 2000 ***{published data only}***
Sun ZW, Shan CQ, Li GF, Ding DB, Liu GY, Wang JY, et al.Clinical comparative trial of co-artemether and benflumetol (two formulations) in the treatment of falciparum malaria. *Zhongguo Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zhi [Chinese Journal of Parasitology & Parasitic Diseases]* 2000;**18**(3):159–61.

Sutherland 2005 ***{published data only}***
Sutherland CJ, Ord R, Dunyo S, Jawara M, Drakeley CJ, Alexander N, et al.Reduction of malaria transmission to anopheles mosquitoes with a six-dose regimen of co-artemether. *PLoS Medicine* 2005;**2**(4):338–49.

Van Agtmael 1999b ***{published data only}***
* Van Agtmael MA, Cheng-Qi S, Qing JX, Mull R, van Boxtel CJ. Multiple dose pharmacokinetics of artemether in Chinese patients with uncomplicated falciparum malaria. *International Journal of Antimicrobial Agents* 1999;**12**(2):151–8.

Van Vugt 2000 ***{published data only}***
Van Vugt M, Ezzet F, Nosten F, Gathmann I, Wilairatana P, Looareesuwan S, et al.No evidence of cardiotoxicity during antimalarial treatment with artemether-lumefantrine. *American Journal of Tropical Medicine and Hygiene* 1999;**61**(6):964–7.
* Van Vugt M, Looareesuwan S, Wilairatana P, McGready R, Villegas L, Gathmann I, et al.Artemether-lumefantrine for the treatment of multidrug-resistant falciparum malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2000;**94**(5): 545–8.

Von Seidlein 1997 ***{published data only}***
Von Seidlein L, Jaffer S, Pinder M, Haywood M, Snounou G, Gemperli B, et al.Treatment of African children with uncomplicated falciparum malaria with a new antimalarial drug, CGP 56697. *Journal of Infectious Diseases* 1997;**176**(4):1113–6.

Zhiwei 1999 ***{published data only}***
Zhiwei S, Chengqi S, Guofu L, Jingyan W, Deben D, Guangyu L, et al.Treatment effects of Co-artemether and Benflumetol capsule in naturally occuring falciparum malaria patients. *Journal of Practical Parasitic Diseases* 1999;**7**(2):49–51.

Additional references

Bindschedler 2000
Bindschedler M, Lefevre G, Ezzet F, Schaffer N, Meyer I, Thomsen MS. Cardiac effects of co-artemether (artemether/lumefantrine) and mefloquine given alone or in combination to healthy volunteers. *European Journal of Clinical Pharmacology* 2000;**56**(5):375–81.

Bloland 2000
Bloland PB, Ettling M, Meek S. Combination therapy for malaria in Africa: hype or hope?. *Bulletin of the World Health Organization* 2000;**78**(12):1378–88.

Ezzet 1998
Ezzet F, Mull R, Karbwang J. Population pharmacokinetics and therapeutic response of CGP 56697 (artemether + benflumetol) in malaria patients. *British Journal of Clinical Pharmacology* 1998;**46** (6):553–61.

Higgins 2005
Higgins J, Green S, editors. Highly sensitive search strategies for identifying reports of randomized controlled trials in MEDLINE. Cochrane Handbook for Systematic Reviews of Interventions 4.2.5 [updated May 2005]; Appendix 5b. http://www.cochrane.org/resources/handbook/hbook.htm (accessed 1 October 2005).

Jüni 2001
Jüni P, Altman DG, Egger M. Systematic reviews in health care: Assessing the quality of controlled clinical trials. *BMJ* 2001;**323** (7303):42–6.

Nosten 2003
Nosten F. Letters to the Editor. *The Newsletter of the East African Network for Monitoring Antimalarial Treatment* 2003;**6**(1):10.

Novartis 1999
Novartis. *A novel antimalarial combination: one product, two concepts Coartem / Riamet. Product monograph*. Basel, Switzerland: Novartis Pharma AG, 1999.

Novartis 2005
Novartis. *Coartem monograph*. 4th Edition. Basel: Novartis Pharma AG, 2005.

Omari 2005
Omari AAA, Gamble C, Garner P. Artemether-lumefantrine (six doses) for treating uncomplicated falciparum malaria. *Cochrane Database of Systematic Reviews* 2005, Issue 4. [DOI: 10.1002/14651858.CD005564]

Review Manager 5
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ter Kuile 1995

ter Kuile FO, Luxemburger C, Nosten F, Thwai KL, Chongsuphajaisiddhi T, White NJ. Predictors of mefloquine treatment failure: a prospective study of 1590 patients with uncomplicated falciparum malaria. *Transactions of the Royal Society of Medicine and Hygiene* 1995;**89**(6):660–4.

Van Vugt 1998b

Van Vugt M, Nosten F, Price RN, Looareesuwan S, White NJ. Antimalarial drug resistance: Treatment and prevention. Proceedings of the Second European Congress on Tropical Medicine. 1998 Sept 14-18; Liverpool (UK). 1998:Abstract 463.

White 1999a

White N. Antimalarial drug resistance and combination chemotherapy. *Philosophical Transactions of the Royal Society of London Series B, Biological Sciences* 1999;**354**(1384):739–49.

White 1999b

White NJ, Nosten F, Looareesuwan S, Watkins WM, Marsh K, Snow RW, et al.Averting a malaria disaster. *Lancet* 1999;**353** (9168):1965–7.

WHO 1994

World Health Organization. Division of Control of Tropical Diseases. *Antimalarial drug policies: data requirements, treatment of uncomplicated malaria and management of malaria in pregnancy. Report of an informal consultation, Geneva, 14-18 March 1994*. Geneva: World Health Organization, 1994. [: WHO/MAL/ 94.1070]

WHO 1996

World Health Organization. Division of Control of Tropical Diseases. *Assessment of therapeutic efficacy of antimalarial drugs: for uncomplicated falciparum malaria in areas with intense transmission*. Geneva: World Health Organization, 1996. [: WHO/MAL/ 96.1077]

WHO 1999

World Health Organization. Department of Communicable Disease Research and Development. *WHO informal consultation on clinical neurological investigations required for patients treated with artemisinin compounds and derivatives. Report of an informal consultation convened by WHO, Geneva, 20 July 1998*. Geneva: World Health Organization, 1998. [: TDR/TDF/99.1]

WHO 2000a

World Health Organization. WHO Expert Committee on Malaria (1998 : Geneva, Switzerland). WHO expert committee on malaria: twentieth report. World Health Organization Technical Report Series 2000; Vol. 892.

WHO 2000b

World Health Organization. Communicable Diseases Cluster. Severe falciparum malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2000;**94**(Suppl 1):1–90.

WHO 2001a

World Health Organization. Office of Press and Public Relations. WHO and Novartis join forces to combat drug resistant malaria. http://www.who.int/inf-pr-2001/en/pr2001-26.html (accessed 23 May 2001).

WHO 2001b

World Health Organization. Global Partnership to Roll Back Malaria. *The use of antimalarial drugs. Report of a WHO informal consultation, 13-17 November 2000*. Geneva: World Health Organization, 2001. [: WHO/CDS/RBM/2001.33]

WHO 2007

World Health Organization. WHO Essential Medicines Library: artemether + lumefantrine. www.who.int/emlib/ March 2007 (accessed 18 July 2008).

References to other published versions of this review

Omari 2002

Omari AAA, Gamble C, Garner P. Artemether-lumefantrine for treating uncomplicated falciparum malaria. *Cochrane Database of Systematic Reviews* 2002, Issue 3. [DOI: 10.1002/ 14651858.CD003125.pub2]

Omari 2003

Omari AAA, Gamble C, Garner P. Artemether-lumefantrine for treating uncomplicated falciparum malaria. *Cochrane Database of Systematic Reviews* 2003, Issue 2. [DOI: 10.1002/ 14651858.CD003125.pub2]

Omari 2004

Omari AAA Gamble C, Garner P. Artemether-lumefantrine for uncomplicated malaria: a systematic review. *Tropical Medicine & International Health* 2004;**9**(2):192–9.

* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

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

Hatz 1998

Methods	Generation of allocation sequence: not described Allocation concealment: concealed allocation, numbered blister packs Blinding: none Inclusion of all randomized participants in the analysis of reported primary outcome: 45% (118/260) Number of blocks used in randomization: 6
Participants	Number: 260 children aged 1 to 5 years Inclusion criteria: weight > 5 kg; microscopically confirmed *P. falciparum* parasitaemia > 5000/mL; fever; within 5 km of trial site Exclusion criteria: severe malaria; severe malnutrition/kwashiorkor; other antimalarial previous in 48 h; sensitivity to chloroquine; chronic disease
Interventions	1. Artemether-lumefantrine: 4 doses over 48 h; artemether 1 to 2 mg/kg/dose; lumefantrine 6 to 12 mg/kg/dose 2. Chloroquine: 4 doses over 48 h; total dose 25 mg/kg All participants had paracetamol
Outcomes	1. Day 7 cure 2. Day 14 cure 3. Parasite reductions on days 1 to 3 4. Proportion of children with negative slide on days 1 to 3 5. PCR genotype 6. Gametocyte carriage on days 0, 1, 2, 3, and 7 7. Haemoglobin
Notes	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) Malaria transmission: perennial Chloroquine resistance

Kshirsagar 2000

Methods	Generation of allocation sequence: computer-generated Allocation concealment: concealed allocation, central randomization Blinding: double dummy parallel, blinding not specified Inclusion of all randomized participants in the analysis of reported primary outcome: 21% (38/179) Number of blocks used in randomization: 4
Participants	Number: 179 adults aged 16 to 70 years Inclusion criteria: microscopically confirmed *P. falciparum* or mixed infection (including *P. falciparum* > 1000/µL) Exclusion criteria: *P. falciparum* > 200,000/µL; severe malaria

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Kshirsagar 2000 (*Continued*)

Interventions	1. Artemether-lumefantrine: 4 doses over 48 h; artemether 80 mg/dose; lumefantrine 480 mg/dose 2. Chloroquine: 4 doses over 48 h; first dose 600 mg, then 300 mg per dose All had primaquine on day 8 (single dose of 45 mg)
Outcomes	1. Day 28 cure 2. Parasite clearance time 3. Reduction in parasite load at 24 h 4. Fever clearance time 5. Gametocyte carriage within first 72 h 6. Gametocyte clearance time 7. PCR genotype 8. Adverse events
Notes	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 1 death (chloroquine group) and decrease in chloroquine cure rate to < 50% Malaria transmission: perennial Chloroquine resistance

Looareesuwan 1999

Methods	Generation of allocation sequence: computer-generated Allocation concealment: concealed allocation, central randomization Blinding: double dummy, participants and all personnel Inclusion of all randomized participants in the analysis of reported primary outcome: 8% (19/252)
Participants	Number: 252 adults and children aged 13 to 63 Inclusion criteria: microscopically confirmed *P. falciparum*; parasitaemia 1000 to 200,000/µL (mixed infection acceptable) Exclusion criteria: complicated malaria
Interventions	1. Artemether-lumefantrine: 4 doses over 48 h; artemether 80 mg/dose; lumefantrine 480 mg/dose 2. Mefloquine: 2 doses over 8 h; first dose 750 mg; second dose 500 mg
Outcomes	1. Day 28 cure 2. Parasite clearance time 3. Fever clearance time 4. Gametocyte clearance time 5. Gametocyte carriage within first 72 h 6. Adverse effects
Notes	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))

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	Malaria transmission: low transmission Multiple-drug resistance

Van Agtmael 1999a

Methods	Generation of allocation sequence: computer-generated Allocation concealment: not described Blinding: double dummy, participants and all personnel Inclusion of all randomized participants in the analysis of reported primary outcome: 17% (17/103) Number of blocks used in randomization: 4
Participants	Number: 103 participants aged 17 to 62 (73 non-immune; 3 immune; 27 possibly immune) Inclusion criteria: microscopically confirmed *P. falciparum* (> 1000 and < 200,000/µL) Exclusion criteria: severe malaria
Interventions	1. Artemether-lumefantrine: 4 doses over 48 h; artemether 80 mg/dose; lumefantrine 480 mg/dose 2. Halofantrine: 3 doses over 12 h; repeated after 1 week; 500 mg/dose
Outcomes	1. Day 28 cure 2. Parasite clearance time 3. Parasite reduction at 24 h 4. Fever clearance time 5. Gametocyte carriage within first 72 h 6. Adverse effects 7. QT interval
Notes	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)

Van Vugt 1998a

Methods	Generation of allocation sequence: not described Allocation concealment: concealed allocation, numbered sealed opaque packets Blinding: none Inclusion of all randomized participants in the analysis of reported primary outcome: 23% (139/617) Number of blocks used in randomization: 4
Participants	Number: 617 participants aged 5 to 66 years Inclusion criteria: microscopically confirmed malaria Exclusion criteria: severe malaria
Interventions	1. Artemether-lumefantrine: 4 doses over 48 h; artemether 1 to 2 mg/kg/dose; lumefantrine 6 to 12 mg/kg/dose 2. Artesunate: 3 doses over 48 h (4 mg/kg/dose); mefloquine 2 doses over 48 h (15 mg/kg on day 2; 10 mg/kg on day 3)

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Van Vugt 1998a (*Continued*)

Outcomes	1. Day 63 cure 2. Day 28 cure 3. Parasite clearance time 4. Fever clearance time 5. Gametocyte carriage 6. PCR analysis 7. Adverse effects
Notes	Location: Karen, Thailand 139 not evaluated on day 63: 61(artemether-lumefantrine); 78 (artemether plus mefloquine) Malaria transmission: low Multiple-drug resistance

Van Vugt 1999

Methods	Generation of allocation sequence: not described Allocation concealment: concealed allocation, numbered sealed opaque packets Blinding: none Inclusion of all randomized participants in the analysis of reported primary outcome: 15% (53/359) Number of blocks used in randomization: 6
Participants	Number: 359 adults and children age 3 to 75 Inclusion criteria: microscopically confirmed *P. falciparum* Exclusion criteria: severe malaria, children < 2 years
Interventions	1. Artemether-lumefantrine: 4 doses over 48 h 2. Artemether-lumefantrine: 6 doses over 60 h 3. Artemether-lumefantrine: 6 doses over 90 h Single dose: 4 tablets for 15 kg; 8 tablets for 15 to 25 kg; 12 tablets for 25 to 35 kg; 16 tablets if > 35 kg
Outcomes	1. Day 28 cure 2. Parasite clearance time 3. PCR analysis 4. Adverse effects 5. Fever clearance time 6. Gametocyte carriage
Notes	Location: Thailand 2 trial centres: Bangkok (inpatients for 28 days); Karen (outpatients) Multiple-drug resistance

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Von Seidlein 1998

Methods	Generation of allocation sequence: computer-generated Allocation concealment: concealed allocation, central randomization Blinding: double dummy, participants and all personnel Inclusion of all randomized participants in the analysis of reported primary outcome: 14% (40/287) Number of blocks used in randomization: 4
Participants	Number: 287 children aged 1 to 5 years Inclusion criteria: parasitaemia > 5000/µL; fever; within 10 km of trial centre Exclusion criteria: requiring parenteral treatment
Interventions	1. Artemether-lumefantrine: 4 doses over 48 h; 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	1. Day 4 cure 2. Day 15 cure 3. Parasite clearance time 4. Proportion of children with fever on days 1 to 4 5. Gametocyte carriage on days 1, 2, 3, 4, and 15 6. PCR genotype
Notes	Location: The Gambia 2 trial centres: semi-urban and rural 40 not evaluated on day 28: 25 (artemether-lumefantrine); 15 (sulfadoxine-pyrimethamine) Local malaria transmission: seasonal Local drug resistance: chloroquine; sulfadoxine-pyrimethamine

ECG: electrocardiogram; *P. falciparum*: *Plasmodium falciparum*; 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 d of completing treatment following initial resolution of symptoms and parasite clearance; RII: (drug resistance) reduction of parasitaemia of > 75% at 48 h but failure to clear parasites within 7 d; RIII: (drug resistance) parasitaemia does not fall by > 75% within 48 h.

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

Espino 2002	Data in unpublished report are not interpretable
Falade 2005	Not a randomized controlled trial
Jiao 1997	Compared artemether-lumefantrine with lumefantrine, which is not a recommended standard therapy for uncomplicated malaria
Karbwang 2002	Artemether-lumefantrine (6-dose regimen) not compared with another antimalarial

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(*Continued*)

Krudsood 2003	Used 6-dose artemether-lumefantrine regimen
Lefevre 2001	Used 6-dose artemether-lumefantrine regimen
Lefevre 2002	Investigated electrocardiographic and pharmacokinetic interactions between artemether-lumefantrine and quinine
Mayxay 2004	Used 6-dose artemether-lumefantrine regimen
Mutabingwa 2005	Used 6-dose artemether-lumefantrine regimen
Ndayiragije 2004	Used 6-dose artemether-lumefantrine regimen
Piola 2005	Used 6-dose artemether-lumefantrine regimen
Popov 2002	Not a randomized controlled trial
Stohrer 2004	Used 6-dose artemether-lumefantrine regimen
Sun 2000	Compared artemether-lumefantrine with lumefantrine, which is not a recommended standard therapy for uncomplicated malaria
Sutherland 2005	Used 6-dose artemether-lumefantrine regimen
Van Agtmael 1999b	Compared artemether
Van Vugt 2000	Used 6-dose artemether-lumefantrine regimen
Von Seidlein 1997	Not randomized control trial (safety trial)
Zhiwei 1999	Compared artemether-lumefantrine with lumefantrine, which is not a recommended standard therapy for uncomplicated malaria

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DATA AND ANALYSES

Comparison 1. Artemether-lumefantrine (4 doses) versus sulfadoxine-pyrimethamine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total failure by day 14	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2 Total failure by day 14 (excluding new infections)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Gametocyte carriage by day 4	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4 Gametocyte carriage by day 15	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Comparison 2. Artemether-lumefantrine (4 doses) versus mefloquine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total failure by day 28	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2 Gametocyte carriage within the first 72 h	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Comparison 3. Artemether-lumefantrine (4 doses) versus halofantrine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total failure by day 28	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2 Gametocyte carriage within the first 72 h	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Comparison 4. Artemether-lumefantrine (4 doses) versus chloroquine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total failure by day 28	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2 Gametocyte carriage within the first 72 h	2	427	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.63, 0.99]

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Comparison 5. Artemether-lumefantrine versus mefloquine plus artesunate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total failure by day 28	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2 Total failure by day 28 (excluding new infections)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Total failure by day 63	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4 Gametocyte carriage within the first 72 h	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Comparison 6. Artemether-lumefantrine (4 doses) versus artemether-lumefantrine (6 doses)

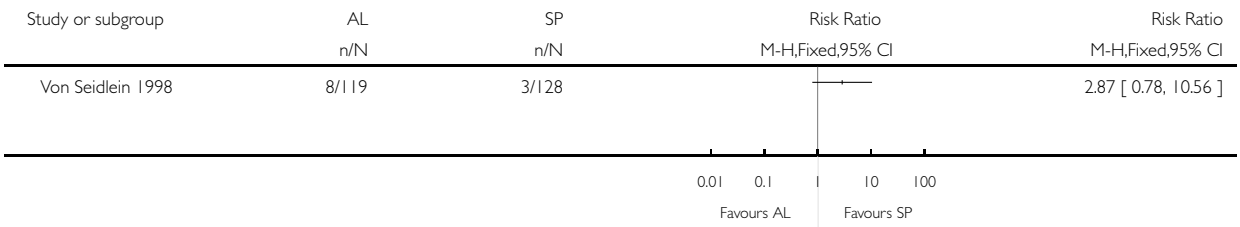
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total failure by day 28	1	306	Risk Ratio (M-H, Fixed, 95% CI)	7.71 [2.99, 19.88]
1.1 6-dose regimen taken over 60 h	1	148	Risk Ratio (M-H, Fixed, 95% CI)	6.15 [1.77, 21.38]
1.2 6-dose regimen taken over 96 h	1	158	Risk Ratio (M-H, Fixed, 95% CI)	10.19 [2.32, 44.84]

Analysis 1.1. Comparison 1 Artemether-lumefantrine (4 doses) versus sulfadoxine-pyrimethamine, Outcome 1 Total failure by day 14.

Review: Artemether-lumefantrine (four-dose regimen) for treating uncomplicated falciparum malaria

Comparison: 1 Artemether-lumefantrine (4 doses) versus sulfadoxine-pyrimethamine

Outcome: 1 Total failure by day 14



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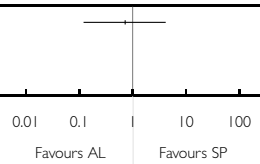
Analysis 1.2. Comparison 1 Artemether-lumefantrine (4 doses) versus sulfadoxine-pyrimethamine, Outcome 2 Total failure by day 14 (excluding new infections).

Review: Artemether-lumefantrine (four-dose regimen) for treating uncomplicated falciparum malaria

Comparison: 1 Artemether-lumefantrine (4 doses) versus sulfadoxine-pyrimethamine

Outcome: 2 Total failure by day 14 (excluding new infections)

Study or subgroup	AL n/N	SP n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Von Seidlein 1998	2/119	3/128		0.72 [0.12, 4.22]



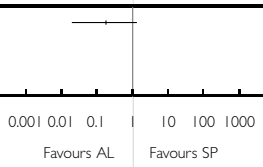
Analysis 1.3. Comparison 1 Artemether-lumefantrine (4 doses) versus sulfadoxine-pyrimethamine, Outcome 3 Gametocyte carriage by day 4.

Review: Artemether-lumefantrine (four-dose regimen) for treating uncomplicated falciparum malaria

Comparison: 1 Artemether-lumefantrine (4 doses) versus sulfadoxine-pyrimethamine

Outcome: 3 Gametocyte carriage by day 4

Study or subgroup	AL n/N	SP n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Von Seidlein 1998	1/41	10/74		0.18 [0.02, 1.36]



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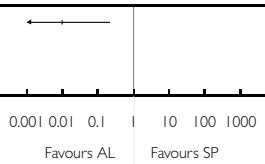
Analysis 1.4. Comparison 1 Artemether-lumefantrine (4 doses) versus sulfadoxine-pyrimethamine, Outcome 4 Gametocyte carriage by day 15.

Review: Artemether-lumefantrine (four-dose regimen) for treating uncomplicated falciparum malaria

Comparison: 1 Artemether-lumefantrine (4 doses) versus sulfadoxine-pyrimethamine

Outcome: 4 Gametocyte carriage by day 15

Study or subgroup	AL n/N	SP n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Von Seidlein 1998	0/125	37/128		0.01 [0.00, 0.22]



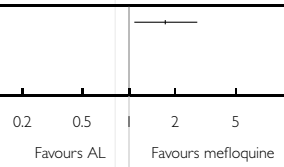
Analysis 2.1. Comparison 2 Artemether-lumefantrine (4 doses) versus mefloquine, Outcome 1 Total failure by day 28.

Review: Artemether-lumefantrine (four-dose regimen) for treating uncomplicated falciparum malaria

Comparison: 2 Artemether-lumefantrine (4 doses) versus mefloquine

Outcome: 1 Total failure by day 28

Study or subgroup	AL n/N	Mefloquine n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Looareesuwan 1999	35/114	21/119		1.74 [1.08, 2.80]



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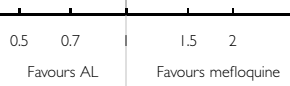
Analysis 2.2. Comparison 2 Artemether-lumefantrine (4 doses) versus mefloquine, Outcome 2 Gametocyte carriage within the first 72 h.

Review: Artemether-lumefantrine (four-dose regimen) for treating uncomplicated falciparum malaria

Comparison: 2 Artemether-lumefantrine (4 doses) versus mefloquine

Outcome: 2 Gametocyte carriage within the first 72 h

Study or subgroup	AL n/N	Mefloquine n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Looareesuwan 1999	62/126	74/126		0.84 [0.67, 1.05]



Analysis 3.1. Comparison 3 Artemether-lumefantrine (4 doses) versus halofantrine, Outcome 1 Total failure by day 28.

Review: Artemether-lumefantrine (four-dose regimen) for treating uncomplicated falciparum malaria

Comparison: 3 Artemether-lumefantrine (4 doses) versus halofantrine

Outcome: 1 Total failure by day 28

Study or subgroup	AL n/N	Mefloquine n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Van Agtmael 1999a	8/45	0/41		15.52 [0.92, 260.75]

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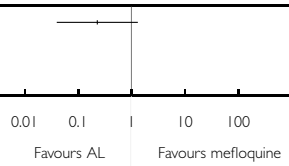
Analysis 3.2. Comparison 3 Artemether-lumefantrine (4 doses) versus halofantrine, Outcome 2 Gametocyte carriage within the first 72 h.

Review: Artemether-lumefantrine (four-dose regimen) for treating uncomplicated falciparum malaria

Comparison: 3 Artemether-lumefantrine (4 doses) versus halofantrine

Outcome: 2 Gametocyte carriage within the first 72 h

Study or subgroup	AL n/N	Mefloquine n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Van Agtmael 1999a	1/5	8/9		0.23 [0.04, 1.32]



Analysis 4.1. Comparison 4 Artemether-lumefantrine (4 doses) versus chloroquine, Outcome 1 Total failure by day 28.

Review: Artemether-lumefantrine (four-dose regimen) for treating uncomplicated falciparum malaria

Comparison: 4 Artemether-lumefantrine (4 doses) versus chloroquine

Outcome: 1 Total failure by day 28

Study or subgroup	AL n/N	Chloroquine n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Hatz 1998	43/118	113/119		0.38 [0.30, 0.49]
Kshirsagar 2000	3/65	61/76		0.06 [0.02, 0.17]

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Analysis 4.2. Comparison 4 Artemether-lumefantrine (4 doses) versus chloroquine, Outcome 2 Gametocyte carriage within the first 72 h.

Review: Artemether-lumefantrine (four-dose regimen) for treating uncomplicated falciparum malaria

Comparison: 4 Artemether-lumefantrine (4 doses) versus chloroquine

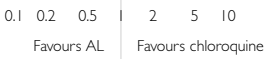
Outcome: 2 Gametocyte carriage within the first 72 h

Study or subgroup	AL n/N	Chloroquine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hatz 1998	12/130	15/130		19.8 %	0.80 [0.39, 1.64]
Kshirsagar 2000	51/89	57/78		80.2 %	0.78 [0.63, 0.98]
Total (95% CI)	**219**	**208**		**100.0 %**	**0.79 [0.63, 0.99]**

Total events: 63 (AL), 72 (Chloroquine)

Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.96); I^2 =0.0%

Test for overall effect: Z = 2.04 (P = 0.041)



Analysis 5.1. Comparison 5 Artemether-lumefantrine versus mefloquine plus artesunate, Outcome 1 Total failure by day 28.

Review: Artemether-lumefantrine (four-dose regimen) for treating uncomplicated falciparum malaria

Comparison: 5 Artemether-lumefantrine versus mefloquine plus artesunate

Outcome: 1 Total failure by day 28

Study or subgroup	AL n/N	Mef plus art n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Van Vugt 1998a	49/273	7/264		6.77 [3.12, 14.67]

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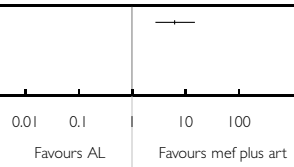
Analysis 5.2. Comparison 5 Artemether-lumefantrine versus mefloquine plus artesunate, Outcome 2 Total failure by day 28 (excluding new infections).

Review: Artemether-lumefantrine (four-dose regimen) for treating uncomplicated falciparum malaria

Comparison: 5 Artemether-lumefantrine versus mefloquine plus artesunate

Outcome: 2 Total failure by day 28 (excluding new infections)

Study or subgroup	AL n/N	Mef plus art n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Van Vugt 1998a	40/273	6/264		6.45 [2.78, 14.95]



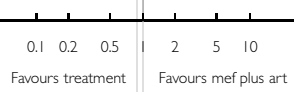
Analysis 5.3. Comparison 5 Artemether-lumefantrine versus mefloquine plus artesunate, Outcome 3 Total failure by day 63.

Review: Artemether-lumefantrine (four-dose regimen) for treating uncomplicated falciparum malaria

Comparison: 5 Artemether-lumefantrine versus mefloquine plus artesunate

Outcome: 3 Total failure by day 63

Study or subgroup	Treatment n/N	Mef plus art n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Van Vugt 1998a	46/248	16/230		2.67 [1.55, 4.57]



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Analysis 5.4. Comparison 5 Artemether-lumefantrine versus mefloquine plus artesunate, Outcome 4 Gametocyte carriage within the first 72 h.

Review: Artemether-lumefantrine (four-dose regimen) for treating uncomplicated falciparum malaria

Comparison: 5 Artemether-lumefantrine versus mefloquine plus artesunate

Outcome: 4 Gametocyte carriage within the first 72 h

Study or subgroup	AL n/N	Mef plus art n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Van Vugt 1998a	34/309	24/307		1.41 [0.86, 2.32]

0.1 0.2 0.5 1 2 5 10

Favours AL | Favours mef plus art

Analysis 6.1. Comparison 6 Artemether-lumefantrine (4 doses) versus artemether-lumefantrine (6 doses), Outcome 1 Total failure by day 28.

Review: Artemether-lumefantrine (four-dose regimen) for treating uncomplicated falciparum malaria

Comparison: 6 Artemether-lumefantrine (4 doses) versus artemether-lumefantrine (6 doses)

Outcome: 1 Total failure by day 28

Study or subgroup	AL (4 doses) n/N	AL (6 doses) n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 6-dose regimen taken over 60 h					
Van Vugt 1998a	10/52	3/96		61.6 %	6.15 [1.77, 21.38]
Subtotal (95% CI)	**52**	**96**		**61.6 %**	**6.15 [1.77, 21.38]**
Total events: 10 (AL (4 doses)), 3 (AL (6 doses))					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.86 (P = 0.0042)					
2 6-dose regimen taken over 96 h					
Van Vugt 1998a	10/52	2/106		38.4 %	10.19 [2.32, 44.84]
Subtotal (95% CI)	**52**	**106**		**38.4 %**	**10.19 [2.32, 44.84]**
Total events: 10 (AL (4 doses)), 2 (AL (6 doses))					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.07 (P = 0.0021)					
Total (95% CI)	**104**	**202**		**100.0 %**	**7.71 [2.99, 19.88]**
Total events: 20 (AL (4 doses)), 5 (AL (6 doses))					
Heterogeneity: Chi^2 = 0.26, df = 1 (P = 0.61); I^2 =0.0%					
Test for overall effect: Z = 4.22 (P = 0.000024)					

0.01 0.1 1 10 100

Favours AL (4 doses) | Favours AL (6 doses)

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WHAT'S NEW

Last assessed as up-to-date: 19 January 2006.

18 July 2008	Review declared as stable	This review will not be updated because the four-dose regimen is no longer recommended. Only the six-dose regimen, reviewed in Omari 2005, is recommended (WHO 2007).
18 July 2008	Amended	Converted to new review format with minor editing.

HISTORY

Protocol first published: Issue 3, 2001

Review first published: Issue 2, 2006

12 April 2006	New citation required and conclusions have changed	2006, Issue 2: We have divided the original review into two separate reviews, one for the four-dose regimen (this review) and the other for the six-dose regimen (Omari 2005). We have excluded quasi-randomized controlled trials as the Cochrane Infectious Diseases Group no longer recommends their inclusion. The primary outcome measure has changed from 'parasitaemia on day 28' to 'total failure by day 28' to include any failures (clinical symptoms or parasitaemia) before this point and also anyone who is parasitaemic on day 28 when the blood slide is taken.

CONTRIBUTIONS OF AUTHORS

Aika Omari and Carrol Gamble extracted and analysed data, and drafted the review. Paul Garner helped write the review.

DECLARATIONS OF INTEREST

Paul Garner and Carrol Gamble (né Preston) were unpaid technical advisers to a World Health Organization meeting (19 and 20 February 2001) considering efficacy and effectiveness studies of artemether-lumefantrine. The World Health Organization paid for their travel and accommodation, and a representative of Novartis chaired the international meeting.

Aika Omari: none known.

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SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK.

External sources

- Department for International Development, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Humans

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