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[Intervention Review]

Artemisinin derivatives for treating uncomplicated malaria

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ABSTRACT

Background

Artemisinin derivatives are a relatively new group of drugs with antimalarial properties. As resistance to other antimalarial drugs continues to increase, artemisinin drugs may be useful alternatives.

Objectives

The objective of this review was to assess the effects of artemisinin drugs for treating uncomplicated falciparum malaria.

Search methods

We searched the Cochrane Infectious Diseases Group Specialized Register, the Cochrane Controlled Trials Register, MEDLINE, EMBASE, Science Citation Index, LILACS, African Index Medicus, conference abstracts, and reference lists of relevant articles. We contacted organisations, researchers in the field, and drug companies.

Selection criteria

Randomised and quasi-randomised trials of artemisinin derivatives, alone or in combination with other antimalarials, compared with standard antimalarial treatments, in adults or children with uncomplicated falciparum malaria. Only trials where treatment was given by mouth or suppository were included. Comparisons between different artemisinin derivatives and treatment regimens were also included.

Data collection and analysis

Eligibility and trial quality were assessed and data were extracted independently by the two reviewers.

Main results

Forty-one trials involving over 5000 patients were included. Variation in study design and quality made synthesis of the data problematic. Allocation concealment was adequate in only two trials. Most data were from areas of multidrug resistant falciparum malaria in South-East Asia. Compared with standard antimalarial treatments, artemisinin drugs showed fast parasite clearance and high cure rates at follow-up, provided the duration of treatment with artemisinin drugs was adequate. Combination with mefloquine improved sustained parasite clearance and was effective in multidrug resistant areas. When doses were adequate, the combination shortened the duration of treatment. We found no evidence that artemisinin drugs are more harmful than standard treatment drugs over a typical trial period of 28 days.

Authors' conclusions

The evidence suggests that artemisinin drugs are effective and safe for treating uncomplicated malaria. There is no evidence from randomised trials that one artemisinin derivative is better than the others. In areas where there is mefloquine resistance, combination therapy with an artemisinin derivative appears to improve sustained parasite clearance compared with either drug alone.

This review summarizes trials up to 1999. For the reasons in the 'What's new' section, this review will no longer be updated.

8 May 2019

No update planned

Review superseded

A wide variety of artemisinin derivative combination treatments are now in use. Please refer to the Cochrane Special Collection: Sinclair 2014 <https://doi.org/10.1002/14651858.SC000007/full>

PLAIN LANGUAGE SUMMARY

Artemisinin drugs for treating uncomplicated malaria are better used in combination therapy

Artemisinin drugs come originally from a plant that has been used since ancient times in China as a traditional medicine for fever and malaria. These drugs act quickly and few side effects have been reported. Malaria parasites have so far not developed resistance to artemisinin drugs. The review shows that artemisinin drugs clear malaria parasites from the blood more effectively than standard treatment drugs. In areas where malaria parasites are more resistant to existing drugs, such as South-East Asia, artemisinin drugs are not better at sustained parasite clearance than standard treatment with quinine or mefloquine. Combination treatment using an artemisinin drug together with the longer-acting antimalarial drug mefloquine improves sustained clearance of parasites, but mefloquine is associated with adverse effects. There are few studies on combination treatment with longer-acting antimalarial drugs that are safer than mefloquine. There is no evidence from trials that any of the several artemisinin derivatives is better than the others.

BACKGROUND

Malaria

The 300-500 million clinical cases of malaria which occur worldwide each year are a heavy social and economic burden on developing countries. Most infections are caused by *Plasmodium falciparum* which is also responsible for almost all of the 2-3 million deaths every year from severe malaria (WHO 1995; PRISM 1996). There are far more uncomplicated infections, which have a large impact on morbidity and the disease burden in endemic areas (Olliaro 1996). The goal of treatment for patients with uncomplicated malaria is rapid and sustained clearance of parasites, as well as clinical symptoms, with a single dose or short course of treatment.

National antimalarial drug policies normally recommend at least two standard treatment regimens for uncomplicated falciparum malaria (WHO 1988, WHO 1996). There is a first-line treatment recommended for routine use, and second-line alternatives for treating infections that are not cured by the first-line treatment, or for which the first-line treatment is contraindicated (WHO 1994). Standard treatment drugs vary according to local policy and local patterns of malaria parasite resistance to the drugs available. The main options recommended by the WHO for first- or second-line oral treatment of uncomplicated malaria are regimens using the drugs chloroquine, sulfadoxine-pyrimethamine, mefloquine and quinine (WHO 1994). However, the decision of which drugs to use is becoming more of a problem in areas where malaria parasites are becoming more resistant to these and other established drugs. In Thailand, for example, there is a high level of resistance to chloroquine, sulfadoxine-pyrimethamine and quinine, and increasing resistance to mefloquine. A similar pattern is emerging in countries neighbouring Thailand, including Myanmar and Cambodia (Wernsdorfer 1994). In Viet Nam, where mefloquine is expensive and not readily available and quinine is still largely effective, the WHO recommend quinine plus tetracycline over 7 days for treatment of uncomplicated malaria in adults (WHO 1990). A similar pattern of decreasing effectiveness of antimalarial drugs (multidrug resistance) is emerging in other malaria endemic areas. One alternative is a relatively new group of antimalarial drugs derived from artemisinin.

Artemisinin drugs

Artemisinin (qinghaosu) is the active principle isolated by Chinese scientists in 1972 from the plant *Artemisia annua*. The plant has been used since ancient times in China as a traditional medicine for fever and malaria (QARCG 1979). In the early 1970s, artemisinin preparations in tablet form did not perform well due to the drug's poor solubility and absorption. Chinese scientists improved the solubility and activity of artemisinin by developing new formulations and by modifying the parent compound to create several semi-synthetic derivatives (CCRGQ 1982; Woerdenbag 1990). Of the many compounds produced by chemical modification of artemisinin only four, dihydroartemisinin (DHA), artesunate (AS), artemether (AM) and arteether (AE), have reached pharmaceutical development for use in humans. Various formulations are now available, or are being developed, in China, Europe, Thailand and Viet Nam.

Formulations of artemisinin derivatives currently available or under development:

- Artemisinin: oral (tablet, capsule), suppository.
- Dihydroartemisinin: oral (tablet).
- Artesunate: oral (tablet, capsule), suppository, intramuscular, intravenous.
- Artemether: oral (tablet, capsule), intramuscular.
- Co-artemether: oral (artemether plus lumefantrine together in tablet form).
- Arteether: intramuscular (not yet commercially available).

The artemisinin derivatives have great potential as antimalarial drugs. They have a novel structure and mode of action amongst antimalarial compounds (Meshnick 1993). Resistance to the drugs has not yet been demonstrated in malaria parasites, nor has cross-resistance with other antimalarial drugs currently used in standard treatment regimens (Olliaro 1995). The first published report of clinical trials appeared in the Chinese Medical Journal in 1979 (QARCG 1979). By 1994, more than 1 million patients with malaria in endemic regions had been treated with various formulations of artemisinin derivatives (White 1994). Despite the limitations of many of the reported clinical studies, a consistent observation is that artemisinin derivatives produce faster relief of clinical symptoms and clearance of parasites from the blood than any other antimalarial drug (Hien 1993, Meshnick 1996).

The problem with artemisinin drugs is that when they are used alone over short periods (less than 5 days), clearance of malaria parasites from the blood is only temporary in up to 50% of patients (Meshnick 1996). This recrudescence has been attributed to the short time it takes for artemisinin drugs to be eliminated from the body. Longer courses of treatment for uncomplicated malaria raise the problem of poor compliance. An alternative is to use artemisinin drugs in combination with other antimalarial drugs which take longer to be eliminated from the body, such as mefloquine or sulfadoxine-pyrimethamine. Combination of a high dose of mefloquine at the end of a full course of artemisinin drug has produced a high cure rate, although this still requires at least 5 days of treatment (Looareesuwan 1994). There is a need for combinations that are effective in shorter courses and suitable for all types of patient (WHO 1990). One drug company (Novartis) has responded by developing a combination tablet of artemether with benflumetol (now called lumefantrine), a longer-acting antimalarial drug also originating in China. Artemisinin drugs are a logical option to clear parasites from the blood quickly, and perhaps combination with a longer-acting drug could allow for a shorter overall course of treatment. An important clinical question, therefore, is whether artemisinin drugs should be combined de novo with a longer-acting antimalarial drug.

Treatment policies

Artemisinin derivatives have come in to use outside China largely by necessity to treat multidrug resistant malaria (Hien 1994, Looareesuwan 1994, Nosten 1994, Meshnick 1996). As a result, they have largely not undergone consistent and rational development and testing. Important clinical questions about their use have yet to be answered: there is still no consensus on which is the best derivative or the best treatment regimen, or if these drugs confer any therapeutic advantage in areas where malaria parasites are still sensitive to existing drugs. Since they have become more widely available they are being used more and more for first-line treatment of malaria, even in areas where standard drugs such as

chloroquine, sulfadoxine-pyrimethamine, quinine and mefloquine are still effective (Meshnick 1996).

In 1996 a WHO report of an informal consultation on management of uncomplicated malaria recommended treatment regimens with artemisinin derivatives as follows (WHO 1996):

Monotherapy

- Artemisinin: 10 mg/kg once a day for 5 days, double divided dose on first day.
- Artesunate: 2 mg/kg once a day for 5 days, double divided dose on first day.
- Artemether: 2 mg/kg once a day for 5 days, double divided dose on first day.
- Dihydroartemisinin: 2 mg/kg once a day for 5 days, double divided dose on first day.

Combination therapy

- Artemisinin: 10 mg/kg once a day for 3 days, plus mefloquine (15-25 mg/kg) as a single dose on second or third day.
- Artesunate: 4 mg/kg once a day for 3 days, plus mefloquine (15-25 mg/kg) as a single dose on second or third day.

The WHO report warns that these prescriptions are based only on available clinical data which in itself is insufficient to formulate treatment regimens. The report also cautions against widespread and uncontrolled use. Inconsistent and indiscriminate use of artemisinin derivatives, particularly for uncomplicated malaria where presumptive treatment, self-treatment and repeated treatment with oral drugs is common in practice, might result in faster development and spread of resistance. Also, toxicological studies in animals (Brewer 1994) and observations of temporary brain dysfunction in humans (Miller 1997) caution repeated exposure in humans until more is known about potential adverse effects of artemisinin drugs on the central nervous system. It is, therefore, essential that these drugs are used in an optimal way and only where they have a significant advantage over established antimalarials. A comprehensive assessment of benefits and risks in different epidemiological settings is needed to inform drug policy decisions on the rational use of these drugs.

The aim of this review is to summarise the existing evidence of effectiveness and safety of artemisinin derivatives, alone and in combination with other antimalarials, in the treatment of uncomplicated falciparum malaria. The following clinical questions will be addressed in terms of parasitological and clinical cure, and tolerability:

1. Are treatment regimens with artemisinin drugs better than other standard treatment regimens for uncomplicated malaria?
2. Do artemisinin drugs have a comparative advantage over other antimalarials in geographical areas where malaria parasites are still sensitive to existing antimalarial drugs, as well as in areas where drug resistance is high?
3. Should artemisinin derivatives be combined de novo with all first-line treatment regimens using longer-acting antimalarials?
4. Is any artemisinin derivative better than the others?
5. For any artemisinin derivative having a comparative advantage over other antimalarial drugs, what is the best formulation, dose and treatment regimen?

The inclusion criteria, therefore, prespecified comparisons that could potentially make a contribution to answering these questions.

OBJECTIVES

To compare the effectiveness and safety of artemisinin drugs versus standard treatment regimens, and the relative performance of each derivative, in treating adults and children with uncomplicated falciparum malaria. Effectiveness is defined in terms of clearance of asexual parasites from the blood (parasitological cure) and relief of clinical symptoms.

The following null hypotheses were explored or tested, depending on the data available:

- There is no difference in effectiveness or tolerability between artemisinin derivatives and existing standard treatment regimens.
- There is no difference in effectiveness or tolerability between different artemisinin derivatives.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or pseudo-randomised trials of treatment comparisons.

Types of participants

Adults and children with falciparum malaria infection confirmed by a blood slide. Asymptomatic individuals and patients with clinical symptoms of uncomplicated malaria will be included, but not patients with signs and symptoms of severe or complicated malaria.

Types of interventions

This review includes only trials in which treatment was given by mouth or suppository. We have excluded trials where patients were given antimalarials by intramuscular injection or intravenous infusion, because the inability to retain oral treatment is a criterion for classifying a case as possibly severe or complicated and treating it as such (Warrell 1990; WHO 1994). We have included suppositories because of their potential advantages in rural situations, particularly in treating children.

Artemisinin drug (dihydroartemisinin, artemisinin, artesunate, artemether) given by mouth or suppository, alone or in combination with other antimalarials:

1. Single drug therapy: artemisinin or derivative drug alone versus WHO recommended standard treatment for uncomplicated malaria (chloroquine, amodiaquine, sulfadoxine-pyrimethamine, mefloquine, quinine, quinine + tetracycline).
2. Combination therapy: artemisinin or derivative drug in combination with a longer-acting antimalarial drug (mefloquine, sulfadoxine-pyrimethamine) versus WHO recommended standard treatment for uncomplicated malaria.

3. Comparisons between artemisinin derivatives:
  - a. Comparisons between derivatives.
  - b. Comparisons between doses of the same derivative.
  - c. Comparisons between regimens of the same derivative.

Types of outcome measures

1. Clinical

Fever clearance time (time for temperature to return to normal as defined by the authors); fever clearance within 48 hours of starting treatment; clinical treatment failure (patients given an alternative treatment because of no clinical improvement under the allocated regimen); other reported indicators of clinical improvement.

2. Parasitological

Parasite clearance at day 7, 14 and 28; parasite clearance time; rate of 50% or 90% parasite clearance (PC50, PC90), as reported; in vivo sensitivity as S (parasite clearance within 7 days of starting treatment and sustained to day 28), RI (parasite clearance within 7 days followed by recrudescence by day 28), RII (temporary marked reduction in parasitaemia), RIII (no marked reduction in parasitaemia) (WHO 1973).

3. Adherence

Number of patients completing treatment.

4. Tolerability

Adverse events:

- mild (vomiting, nausea, diarrhoea, dizziness, other).
- major (neuropsychological disturbances, any other serious adverse events reported).

Search methods for identification of studies

The Cochrane Infectious Diseases Group Specialized Register was searched for any trial or reference to a relevant trial (published, in-press or in progress). The topic search terms used were: malaria, qinghaosu, artemisinin, dihydroartemisinin, artesunate, artemether, arteether. Full details of the CIDG methods and the journals searched are published in *The Cochrane Library* in the section on Collaborative Review Groups.

The reviewer searched the Cochrane Controlled Trials Register, published in *The Cochrane Library* (1999, Issue 4). This is a compilation of about 160,000 published trials identified by hand-searching by various individuals within the Cochrane Collaboration. Full details of the sources and methods used are published in *The Cochrane Library*.

The following databases were also searched: MEDLINE (1966 to December 1999); BIDS Science Citation Index (1980 to December 1999); EMBASE (1988 to October 1999), using the search strategy defined by The Cochrane Collaboration, and detailed in appendix 5c of the Cochrane Handbook; African Index Medicus (February 1998); and LILACS (December 1999). The specific topic search terms used were malaria, qinghaosu, artemisinin, dihydroartemisinin, artesunate, artemether, arteether, co-artemether.

Organisations and individual researchers working in the field were contacted for unpublished data, confidential reports and raw data of published trials. The following drug companies were also

contacted: Arencos, Cotec Company, Mepha, Rhone-Poulenc Rorer, Propharma, Novartis, Sanofi Winthrop, Guilin Pharmaceutical Company, Kunming Pharmaceutical Corporation, Thua Thien Hue Pharmaceutical Company, National Pharmaceutical Plant Company (Hanoi).

The reviewer also handsearched conference abstracts and checked the citations of existing reviews on artemisinin drugs (*Trans R Soc Trop Med Hyg* 1994;88 Suppl 1; *Jpn J Trop Med Hyg* 1996;24 Suppl 1; Woerdenbag 1990; Meshnick 1996; de Vries 1996) and of all trials identified by the above methods.

The advisory panel supporting this review and the external referees were asked to check the completeness of the search and the efforts made to identify unpublished, on-going and planned trials.

Data collection and analysis

Selection of studies

The topic was identified as a priority by the Cochrane Infectious Diseases Group Editors, and resources allocated to the reviewer in consultation with the Group's main funders, the Department for International Development, UK.

An advisory panel was established, comprising individuals with relevant methodological and content knowledge, plus a potential user of the review, to advise on content, quality and dissemination of the review, as set out in Editorial Information about the Infectious Diseases Group in *The Cochrane Library*.

All trials identified were entered in a database register. The inclusion criteria were applied to all identified studies independently by the two reviewers. In the case of disagreement, the opinion of a member of the advisory panel was sought.

Data extraction and management

Data for the pre-specified outcome measures were abstracted onto collection forms by the first reviewer, and checked independently by the second. Whenever possible investigators were asked to provide additional data for pooled analysis using the pre-specified outcome measures. The primary measure of effectiveness is parasite clearance and clinical cure at day 7. Depending on data available, parasite clearance on day 7 was compared in all patients, counting those with a positive blood smear and those who were not evaluable as failures. Due to increasing loss to follow-up over time, parasite clearance beyond day 7 was compared in evaluable patients, including those lost to follow-up in sensitivity analyses of effects observed in evaluable patients. Analysis of single-drug treatment comparisons was restricted to selected outcomes: parasite clearance at day 7 and end of follow-up, clinical treatment failure and tolerability.

Assessment of risk of bias in included studies

The risk of bias in included trials was assessed in terms of allocation concealment, generation of the allocation sequence, and inclusion of all randomised participants according to the Infectious Diseases Group guidelines.

Data synthesis

Analysis was done in Review Manager (Update Software) pooling data where appropriate. Odds ratios for dichotomous data were first calculated using the Mantel-Haenszel method (fixed effect

model); the DerSimonian & Laird method (random effect model) was also used if heterogeneity between studies was evident from the graphical display and the Chi square test for homogeneity. It was not possible to estimate time to parasite clearance and to fever clearance using the Kaplan-Meier procedure, as initially intended, due to lack of data. The mean difference was, therefore, calculated from reported data.

The following comparisons were made:

1. Single drug therapy

Artemisinin drug alone versus WHO recommended standard treatment (chloroquine, amodiaquine, sulfadoxine-pyrimethamine, mefloquine, quinine, quinine + tetracycline/doxycycline).

2. Combination therapy

Artemisinin drug in combination with a longer-acting antimalarial drug (mefloquine, sulfadoxine-pyrimethamine) versus the individual comparator drug.

3. Comparisons between artemisinin drugs

3a. Comparisons between derivatives

Any artemisinin derivative in a randomised comparison with any other artemisinin derivative, for each pre-specified outcome.

3b. Comparisons between doses of the same derivative

Includes studies where a different total dose was delivered according to the same time schedule to each treatment group.

3c. Comparisons between regimens of the same derivative

Includes studies where the same total dose was delivered differently over time to each treatment group.

Where significant statistical heterogeneity was found within these comparisons, with opposite direction of effect between trials or sub-groups, possible explanations were sought through exploring hypotheses addressing differences in the intervention (dose, duration, formulation/route of administration, regimen), and participants (immunity, level of parasitaemia, symptomatic/asymptomatic).

In comparisons of artemisinin derivatives versus existing antimalarial drugs, the effectiveness of the new drug might be greater in areas where resistance to existing drugs has been demonstrated. We pre-specified that they will be stratified according to the existing level of resistance to the comparator drug in the study area if there is heterogeneity evident in these comparisons to explore the following hypothesis:

The effectiveness of artemisinin drugs compared with existing treatment regimens is greater in areas where resistance to the comparator drug(s) has been demonstrated than in areas where it has not been demonstrated.

We pre-specified that additional appropriate subgroup analyses may be identified only through discussion of the initial tabulations with individuals on the advisory panel, provided justification was clear cut.

In addition to comparisons 1 to 3 above, this review summarises three other important issues (4 to 6 below):

4. Effective doses: An overview of cure rates

Although this review primarily examines randomised comparisons, we were able to look at cure rates achieved by individual regimens and draw some conclusions about dosage adequacy.

5. Potentially important effects described in excluded studies

Potentially important effects, such as comparisons between different routes of administration, or with less common but locally recommended standard treatment drugs, were summarised.

RESULTS

Description of studies

Included study code

In this review, each study is given a code name consisting of: 'Name of investigator, Country code, year the study was done'. If the year the study was done is not known, the publication year is given in brackets. Country codes are listed in the footnotes of the 'Characteristics of included studies' tables.

Studies identified

One hundred and five potentially eligible studies were identified, of which 41 met the inclusion criteria (see 'Characteristics of included studies'), 53 were excluded (see 'Characteristics of excluded studies') and 11 are awaiting assessment (see 'Characteristics of studies awaiting classification'). Twenty eight of the included studies are published in English, and one in Portuguese; one unpublished report was obtained from a drug company sponsor, and nine are unpublished data obtained from a principal investigator in Myanmar.

Not all patients reported in those studies included contributed to this review: five of the included studies had treatment groups that were excluded. Groups were excluded because the treatment regimens did not meet the criteria for inclusion (occurred in 4 studies) or patient numbers were questionable (occurred in 1 study).

Location

Thirty-two of the included studies were done in South-East Asia (19 in Thailand, 4 in Viet Nam, 9 in Myanmar), two in China, six in Sub-Saharan African countries and one in South America. Nine studies included adults and children, 29 included only patients over 14 years of age, and three studies included children only.

Artemisinin drugs used

Five different preparations of artemisinin, five of artemether and five of artesunate were reported in the included studies, and two studies used co-artemether (see Notes, Table of Included Studies for details). Ten studies (2 in Thailand, 8 in Myanmar) did not report the source of the drugs used.

Included studies

Single drug therapy

Eight of the included studies compared an artemisinin drug alone with WHO recommended standard treatment drugs:

- Two studies compared an artemisinin derivative with chloroquine (one artesunate comparison, 103 patients; one artemether comparison, 106 patients).
- Two studies compared rectal artemisinin with oral quinine (60 and 62 patients). One study compared artesunate with quinine-tetracycline (64 patients), and one study compared artesunate and artemether with quinine-tetracycline (144 patients).
- Four studies compared an artemisinin derivative with mefloquine (three artesunate comparisons, 120, 101 and 85 patients; one artemether comparison, 46 patients).
- One study (artesunate vs. chloroquine, above) also included a sulfadoxine-pyrimethamine treatment group (53 patients).
- Two studies compared co-artemether with chloroquine (260 patients) or sulfadoxine-pyrimethamine (287 patients).

Combination therapy

Eighteen included studies compared an artemisinin derivative in combination with mefloquine, versus either drug alone:

- There were 11 comparisons with artemisinin derivative alone (one dihydroartemisinin, 50 patients; three artemisinin, 168 patients; four artesunate, 386 patients; three artemether, 347 patients).
- There were twelve comparisons with mefloquine alone (one artemisinin, 240 patients; ten artesunate, 2141 patients; two artemether, 450 patients).
- There was also one comparison of artemisinin plus sulfadoxine-pyrimethamine with artemisinin alone in 93 patients.
- In addition, five trials that compared the same artemisinin drug treatment combined with different doses of mefloquine. One trial studied mefloquine 750 mg vs. 500 mg in combination with artemisinin (76 patients), four trials studied mefloquine 1250 mg vs. 750 mg in combination with artesunate (168, 159, 100 and 27 patients).
- One other trial studied artesunate combined with mefloquine in the same doses, comparing sequential with concomitant treatment in 36 patients.

The latter two categories address questions relevant to combination therapy with mefloquine and so were included.

Comparisons between artemisinin derivatives

Five of the included studies compared one artemisinin derivative with another: artemisinin with artesunate (one comparison; 40 patients), artesunate with artemether (four comparisons; 86, 97, 120 and 358 patients). Three of these comparisons included sequential mefloquine given to both groups). Artemisinin drugs were given orally in three studies, and rectally in one.

Dose, regimen

Six studies compared different doses of artemisinin drugs delivered over the same time schedule.

- Oral artemether: 360 mg/7 d vs. 640 mg/7 d (46 patients); 500 mg/5 d vs. 750 mg/7 d (111 patients).
- Oral artesunate: 1600 mg/7 d vs. 1200 mg/5 d (91 patients); 1200 mg/3 d vs. 800 mg/3 d (34 patients); 1200 mg/5 d vs. 600 mg/5 d (in 16 patients in two arms of a trial with nine treatment groups); 440 mg/5 d vs. 280 mg/3 d (100 patients).

Two studies compared different treatment regimens using the same total dose of artesunate delivered differently over time: 600 mg over 1, 2 or 5 days in 20 patients (in three treatment groups of the nine-arm trial above) and 600 mg daily or twice-daily over 5 days in 59 patients respectively.

Risk of bias in included studies

Methodological criteria were graded A, B or C, in descending order, according to the Cochrane Infectious Diseases Group standard guidelines for assessing trial quality.

Allocation concealment

Of the 41 included studies, allocation concealment as reported was adequate (Grade A) in only two, inadequate in 9 (alternate allocation) and not clearly described in the other 30.

Blinding

Four studies were reported as double-blind, although in one of these, patients in one group were given treatment daily whereas in the other group it was given twice-a-day. Two studies reported that patients were blinded, yet both compared a 3-day with a 5-day treatment regimen. One study specified that parasitological outcomes were blinded. A further eleven studies were described as open or open-label. The remaining 21 studies did not report on blinding, however, in 19 of these blinding would not be possible because of differences in the drug, regimen or route of administration between the treatment groups.

Generation of allocation sequence

All 41 studies were reported as randomised; 23 did not specify the method used, 8 reported using either computer generated random numbers or random numbers tables, one reported using a lottery of the first three patients then repeating the same sequence, and nine studies were pseudo-randomised by alternate allocation.

Inclusion of all randomised participants

Thirty-one of the included studies reported on exclusions and/or loss to follow-up. Thirteen reported that less than 10% of enrolled patients were not evaluable for all outcomes (proportionate loss per treatment group differed by more than 10% in four of these studies). In 11 studies 10-15% of enrolled patients were not evaluable at the end of follow-up (with a disproportionate percentage loss per group in three). In six studies, between 16 and 23 % of enrolled patients were not evaluable for all outcomes. One study reported a 73% loss to follow-up at day 28. For eight unpublished studies we have only outcome data and no details on exclusions or loss to follow-up, although these were military hospital studies where losses to follow-up are usually few.

Effects of interventions

1. Single drug therapy

This review includes nine studies in which artemisinin drugs alone were compared with WHO recommended standard treatment drugs for uncomplicated falciparum malaria.

Parasite clearance

Chloroquine

Chloroquine was the comparator drug in two studies, each in just over 100 Tanzanian or Nigerian adults and children. Parasite clearance at day 7 was markedly better with artesunate in Nigeria (OR 61.04, 95%CI 7.82, 476.76) and artemether in Tanzania (OR 7.52, 95%CI 2.59, 21.85). The comparative advantage of the artemisinin drugs remained at the end of follow-up, 14 days in one study and 28 days in the other.

Quinine

Artemisinin suppositories (same manufacturer) were compared in two studies with oral quinine in a total of 122 Vietnamese adults and children at the same centre. Adults were given 2800 mg artemisinin over 3 days, whilst children received 600 to 1200 mg based on age. Quinine was given for 14 and 10 days respectively. Parasite clearance at day 7 was better with artemisinin (OR 13.70, 95% CI 1.79, 105.06, fixed effect model). The size of the effect was notably different in the two studies, markedly significant in adults, but not in children. By day 28, there was still no difference in children, however, loss to follow-up exceeded 70% in both treatment groups. In adults the benefit shifted in favour of quinine (OR 0.57, 95% CI 0.18, 1.79, fixed effect model) due to a higher rate of recrudescence in the artemisinin group; this effect was stable to sensitivity analysis counting the 20% loss to follow-up as successes or failures.

One study in Thailand showed no difference in parasite clearance, at day 7 or day 28, between quinine-tetracycline (7 days standard treatment) and 700 mg artesunate over 5 days (in 102 patients) or 800 mg artemether over 5 days (in 89 patients).

Mefloquine

Mefloquine was the comparator drug in five studies, four in South-East Asia and one in Brazil. One comparison in Thailand used oral artemether 700 mg, another used 800 mg, over 5 days. Three comparisons used 600 mg oral artesunate over 5 days, one used 700 mg over 5 days (Thailand and Myanmar), and one used 1000 mg over 4 days (Brazil).

Parasite clearance at day 7 was reported in the two comparisons of artemether with mefloquine in Thailand. No difference was shown overall (OR 1.41, 95% CI 0.05, 42.18), although one study tended to favour artemether and the other mefloquine.

At day 28, artemether was significantly more effective in evaluable patients in one study (OR 10.889, 95% CI 0.99, 119.25), but not when losses to follow-up were counted as failures (OR 2.90, 95% CI 0.63, 13.39). The second study showed no difference in parasite clearance at day 28.

Artesunate was not shown to be better than mefloquine at day 7, nor at day 28 in evaluable patients in three studies (OR 0.98, 95% CI 0.49, 1.95, fixed effect model), nor on intention-to-treat analysis (less than 10% loss to follow-up). The Brazilian study reported parasite clearance at day 35 and also found no difference between the treatment groups (45/50 artesunate, 46/51 mefloquine) ([CardosoBRZ93-4](#)).

Sulfadoxine-pyrimethamine

this was a comparator drug in one artesunate study in Nigeria. Artesunate was significantly better at clearing parasites by day 7

(OR 21.08, 95% CI 2.67, 166.68) and the comparative advantage remained to the end of the 14 day follow-up.

Clinical treatment failure

In the Nigerian study, four patients were withdrawn from the sulfadoxine-pyrimethamine group after self-administering other antimalarial drugs because of poor clinical improvement within 24-48h of starting treatment in the study.

Tolerability

All adverse events reported were mild and transient, none resulted in discontinuation of treatment. Dizziness tended to be more frequent with mefloquine than with artesunate or artemether. Nausea, dizziness and ringing in the ears (tinnitus) was more common in quinine-treated patients, although a few artemether patients also experienced nausea and dizziness. No difference in vomiting was observed between artesunate and mefloquine in three studies. No artemether patient vomited compared to one third of mefloquine-treated patients in one study, whereas the other study comparing these drugs showed no difference. Slowing of the heart rate (bradycardia) was more common with artemether (5/12) than mefloquine (10/34) in one study reporting this outcome. All these studies were in adults.

Itching was more commonly associated with chloroquine than artemisinin drugs. Abdominal pain and diarrhoea affected a similar number of artemether and mefloquine patients. No adverse effect on blood cell count or chemistry was reported with artemether compared with chloroquine or mefloquine.

Summary

- Artesunate and artemether clear malaria parasites from the blood more effectively than the standard first-line drugs chloroquine and sulfadoxine-pyrimethamine in Tanzania and Nigeria.
- In South-East Asia, artemisinin drugs tend to be more effective by day 7, although different comparator drugs were used in studies with artemisinin (versus quinine), artemether and artesunate (versus mefloquine). On day 28, however, there appears to be no difference between the artemisinin drugs and the comparator drugs. The same was noted in Brazil at day 35 follow-up.
- It is worth noting that the day 28 cure rates with artemether and artesunate in the South-East Asian studies between 1989 and 1994, calculated on an intention-to-treat basis, are less than 85%, and varied between 67 and 91% with mefloquine. In contrast, both artesunate and mefloquine were highly effective in Brazil in 1994-5.
- Single-agent treatment with artemisinin drugs appears to be well tolerated. Dizziness was notably less common than with mefloquine or quinine.

1b. Co-artemether studies

This review includes 2 published studies of co-artemether.

Chloroquine

Chloroquine was the comparator drug in one study in 260 children in Tanzania. Parasite clearance at day 7 and day 14 was achieved far more successfully with co-artemether than with chloroquine. However, it is clear that chloroquine was alarmingly ineffective in

this trial and therefore, of questionable value as a useful (or ethical) comparator to the new drug in the study area. Co-artemether achieved 84% cure rate by day 7, and 73 to 88% (counting losses to follow-up as failures then as successes) at day 14.

Sulfadoxine-pyrimethamine

Sulfadoxine-pyrimethamine was the comparator drug in one study in 287 children in The Gambia. No difference was shown in parasite clearance at day 4 (OR 1.42, 95% CI 0.63, 3.20) based on intention-to-treat analysis. At day 15 there was no difference in parasite clearance in evaluable patients (OR 0.33, 95% CI 0.09, 1.29), nor when all losses to follow-up were included as successes (OR 0.36, 95% CI 0.09, 1.40). When all losses to follow-up were analysed as treatment failures the odds ratio favoured sulfadoxine-pyrimethamine (OR 0.48, 95% CI 0.26, 0.91). Co-artemether cleared parasitaemia faster than sulfadoxine-pyrimethamine (PC50 11.6h, 95% CI 10.8 to 12.3, compared with 21.1h, 95% CI 17.3 to 25.0).

2. Combination therapy

2a. Comparison with mefloquine alone

Eleven studies described 13 comparisons of artemisinin drug-mefloquine combination compared with mefloquine alone: one used artemisinin (240 patients), two artemether (450 patients) and ten artesunate (2141 patients). Nine out of the ten studies were done in South-East Asia, one in Brazil.

Treatment regimens varied considerably between studies. The artemisinin and artemether studies, and 7/10 artesunate studies, gave the same dose of mefloquine to both treatment groups within each study. The other three artesunate studies increased the dose of mefloquine when it was given alone. Mefloquine was given to the combination treatment group at the start of artemisinin drug treatment (concomitant) in four comparisons and on completion of artemisinin drug treatment (sequential) in the other nine. Combination-treated patients received mefloquine before day 7 in all studies. (See Interventions, Table of included studies).

Parasite clearance

Day 7: the artemisinin and artemether studies, and 8 artesunate studies reported parasite clearance at day 7. All favoured combination treatment over mefloquine alone (pooled OR 2.58, 95% CI 1.67, 3.13, fixed effect model).

Day 28: at day 28, parasite clearance was significantly better in patients given artemisinin-mefloquine, based on one study in 228 patients, with less than 5% loss to follow-up.

Artemether with mefloquine was more effective in evaluable patients (OR 19.36, 95% CI 6.81, 55.01) in the largest of the two studies (311 patients), even when the 27% of patients lost to follow-up were counted as failures (OR 3.04, 95% CI 1.89, 4.89). The smaller study (76 patients) showed a non-significant tendency in favour of mefloquine. Pooling the data using a random effect model showed no overall difference between treatments (OR 3.08, 95% CI 0.05, 191.18). The wide confidence interval reflects the marked difference in effect between these studies. Both were conducted in Thailand and used artemether from the same source (Kunming) in equivalent doses. The former study gave artemether over 3 days, the latter over 2 days.

Parasite clearance at day 28 was reported in 9 artesunate comparisons, and at day 35 in the tenth. Loss to follow-up was around 10-20% per group, with none in two studies. Analysis of patients evaluable on day 28 showed a tendency to favour combination therapy in seven out of 9 comparisons, significant in five. The overall odds ratio favours artesunate-mefloquine treatment (OR 4.03, 95%CI 1.58, 10.23, random effect model). The difference is still significant if patients lost to follow-up are included as failures. Two studies tended to favour mefloquine alone, however, the difference between the treatment groups was not significant. The study with 35-day follow-up also favoured mefloquine alone, but again the difference between treatment groups was not significant in 88 evaluable patients nor on intention-to-treat analysis (CardosoBRZ93-4). Over all, parasite clearance in patients followed-up for 28 days was significantly better in those treated with a combination of artemisinin drug and mefloquine compared with those given only mefloquine (OR 4.05, 95% CI 1.88, 8.73, random effect model), based on 12 comparisons (2148 patients).

Parasite clearance time: eight out of 11 studies (9 comparisons) reported time to clearance of parasites from the blood. The artemisinin study reported mean and standard deviation, the artemether study reported median and range derived from survival analysis. Four artesunate comparisons reported mean and standard deviation, one reported median and range, two reported percentile ranges, and two did not report this outcome. Our meta-analysis of mean difference in parasite clearance time for all five studies reporting mean and standard deviation shows that parasites are cleared faster when artemisinin or artesunate is combined with mefloquine compared with mefloquine given alone, regardless of variation in the treatment regimen used in different studies (MD -20.70 hours, 95% CI -36.21, -6.48, random effect model). A similar effect was shown in the study using survival analysis (PriceTHI-MYA93-4, reported $P < 0.0001$) and the study reporting percentiles (Nosten[1]THI-MYA92-3; Nosten[2]THI-MYA92-3, reported $P \leq 0.001$). Only one artesunate study reported the mean time to 50% and 90% parasite clearance, the rate was twice as fast in patients treated with artesunate and mefloquine compared with mefloquine alone.

Fever clearance

Eight out of 11 studies (9 comparisons) reported time to clearance of fever. Data were reported in the different studies as described under parasite clearance time. We present a meta-analysis of mean difference in fever clearance time for all five studies reporting mean and standard deviation. It shows that fever resolves faster when an artemisinin drug is combined with mefloquine compared with mefloquine given alone, regardless of variation in the treatment regimen used in different studies (MD -10.40 hours, 95% CI -18.08, 2.73, random effect model). This pooled MD needs to be interpreted with some caution because the different effect sizes across studies reflect heterogeneity in study design. Furthermore, not all studies reporting mean and standard deviation are explicit about the number of patients evaluated, and there is evidence of a skewed distribution in most of the reported data (Altman 1996). Survival analysis is more appropriate for time-to data, one study used it and showed time to fever clearance was significantly faster in patients given artemether or artesunate with mefloquine (PriceTHI-MYA93-4). Similarly, the study reporting percentiles showed a faster response when artesunate was given with mefloquine (Nosten[1]THI-MYA92-3; Nosten[2]THI-MYA92-3).

The remaining study reported the number of patients who's fever had resolved within 48 hours of starting treatment, 98% (259/265) on artesunate-mefloquine and 90% (241/269) on mefloquine only ($P = 0.0002$) ([LuxemburgerTHI-MYA91](#)).

Clinical treatment failure

Clinical treatment failure was reported in two studies: in the artemisinin study one patient in each group was given alternative treatment within 48 hours because of no clinical improvement under the allocated regimen ([HungVNM93-4](#)), in one artesunate study one patient on combination treatment took quinine as self-treatment ([LuxemburgerTHI-MYA91](#)).

Adherence

One study reported that one patient did not come back for the last of three doses of artesunate in the combination treatment group ([LuxemburgerTHI-MYA91](#)).

Tolerability

Major adverse effects

Neuropsychiatric effects were reported in three studies conducted in similar populations in the same area. One mefloquine-only treated patient suffered acute psychosis, recovering without additional treatment in one study ([Nosten\[1\]THI-MYA92-3](#); [Nosten\[2\]THI-MYA92-3](#)); in another study, one artesunate-mefloquine treated patient suffered acute psychosis, and another developed a depressive syndrome, both resolved untreated ([LuxemburgerTHI-MYA91](#)); in the third study, one patient suffered anxiety, palpitations and sleep disturbance one week after combination treatment with artesunate-mefloquine, one epileptic patient given artemether-mefloquine experienced fits (first for 10 years) 24 hours after mefloquine treatment, and one patient in the mefloquine-only group suffered psychosis, delusions and hallucinations requiring hospitalisation and sedation ([PriceTHI-MYA93-4](#)). No other study reported evidence of neurotoxicity.

Severe vomiting was the only adverse event that resulted in discontinuation of treatment. This was reported in four studies. Notably, two studies gave mefloquine sequentially and two concomitantly. The number of events in each study is small (4/834 artesunate-/artemether-mefloquine, 11/657 mefloquine-only), and all tend to favour combination therapy (OR 0.39, 95% CI 0.14, 1.10, fixed effect model).

Mild adverse effects

Vomiting of treatment drugs in patients who tolerated retreatment was reported as an adverse event in 10 studies. Eight reported data that we were able to include in a meta-analysis. All of these studies gave mefloquine sequentially to the combination treatment group. Two reported vomiting when the combination group had been given only the artemisinin drug (early vomiting) compared with mefloquine in the other group, and also vomiting after the combination group had been given both drugs (late vomiting). The other 5 studies simply reported vomiting.

Early vomiting was significantly less common with sequential mefloquine treatment in the larger of the two studies reporting this outcome with either artesunate or artemether ([PriceTHI-MYA93-4](#)). Late vomiting was similar in both treatment groups. The 5 studies that simply reported vomiting showed no difference between treatment groups. One of the remaining two studies reported that

artesunate with concomitant mefloquine made early vomiting less likely compared with mefloquine alone, and that late vomiting was similar in both treatment groups. The last study reported two trials, one using sequential mefloquine ([Nosten\[1\]THI-MYA92-3](#)) and one concomitant ([Nosten\[2\]THI-MYA92-3](#)). The study report aggregates the adverse events data for all mefloquine-only treated patients as one group, although the two trials are separate randomised comparisons.

Nausea was reported in 8 studies. Five reported data for pooled analysis that showed a tendency to favour combination treatment (OR 0.67, 95% CI 0.42 to 1.07, random effect model). Two of the other studies reported nausea as a more frequent complaint of patients treated with mefloquine alone, and the third reported no difference between treatment groups.

Dizziness was reported in seven studies, four with data. The data showed no difference between treatment groups. Two other studies reported more dizziness, associated with nausea, in mefloquine-only treated patients. One study stratified patients according to dizziness before treatment and found no difference between them after treatment ([PriceTHI-MYA93-4](#)).

No difference in diarrhoea or abdominal pain was shown between treatment groups in five studies recording these outcomes. Other adverse effects including headache, rash and arthralgia (joint pain) were reported infrequently and were not shown to be associated with any particular treatment. No abnormalities in haematology or blood chemistry were reported.

Summary

We can summarise our review of combination artemisinin drug-mefloquine compared with mefloquine alone as follows:

- Nine out of 11 studies were done in South-East Asia and one in Brazil between 1991 and 1994, all reported as areas of multidrug resistant falciparum malaria.
- No two studies compared the same treatment regimens, either single-agent or combination.
- The data are consistent with a conclusion that parasite clearance is achieved earlier and faster, and is better at day 28 or 35 follow-up, with combination regimens compared with mefloquine alone.
- Keeping in mind deficiencies in reporting of fever clearance data in some studies and a mixed pattern of effect size across different studies, the available data show that fever clearance is improved by combining mefloquine with an artemisinin derivative.
- Neuropsychiatric adverse reactions were suffered by six patients given mefloquine, either alone or in combination with an artemisinin drug. Severe vomiting is less common with combination treatment regimens, although numbers are small. Data on dizziness are inconclusive.

2b. Comparison with artemisinin drug alone

There were 11 comparisons in 10 studies of artemisinin drug-mefloquine combination compared with artemisinin drug alone, one using dihydroartemisinin (50 patients), three artemisinin (168 patients), four artesunate (386 patients), and three artemether (347 patients). Seven out of the 10 studies were done in South-East Asia, one in China, one in Brazil and one in Tanzania.

In eight out of nine studies, a shorter, lower dose combination regimen was compared with a longer, higher dose single-drug regimen. The treatment regimens used in each study were all different from each other. Mefloquine was given to the combination treatment group concomitantly in 3 studies and sequentially in the other seven. Combination-treated patients received mefloquine before day 5 in all ten studies. (See Interventions, Table of included studies).

Parasite clearance

Day 7: parasite clearance at day 7 was reported in one artemisinin study, two artesunate studies and three using artemether. There was no difference between the treatment groups in any study (data not shown).

Day 28: All three artemisinin studies reported parasite clearance at day 28, all favoured combination treatment in evaluable patients (OR 5.96, 95% CI 2.40, 14.76, fixed effect model). Including all losses to follow-up as failures does not affect the direction of the result. Consistent regimens of single-agent artemisinin were used (2500-3000 mg over 3-5 days). However, such doses of single-agent artemisinin, although in line with current WHO recommendations (10 mg/kg/d for 5 days; WHO 1996), did not achieve adequate cure rates in these studies. In comparison, short-course or single dose artemisinin (1000 or 2000 mg) cleared parasitaemia in all patients at follow-up when combined with 750 mg mefloquine (15 mg/kg) in China and Tanzania. In the Viet Nam study, however, a single dose of 500 mg artemisinin plus 500 mg mefloquine achieved a cure rate of only 85% (HienVNM(94)[1]).

In the three artesunate studies reporting 28 day follow-up there is a marked difference in the direction of effect in evaluable patients: significantly in favour of combination (LooareesuwanTHI91; ThimasarnTHI93-4) and non-significantly in favour of artesunate alone [Karbwang THI 92c]. Intention-to-treat analysis (worst and best case) does not change the opposite direction of effect. Consistent regimens of single-agent artesunate were given in these two studies conducted in Thailand and are in line with current WHO recommendations (2 mg/kg/d for 5 days; WHO 1996). However, very different combination regimens were used; short course (1 day), low dose (300 mg) artesunate plus 750 mg mefloquine is apparently inadequate (KarbwangTHI92c). The Brazilian artesunate study reported a similar finding at day 35 with the combination of 600 mg artesunate over 2 days plus 500 mg mefloquine (CardosoBRZ93-4).

With artemether, one study used 700 mg over 5 days single-agent, one used 800 mg over 5 days, and the third tested two doses of artemether in different treatment groups: 500 mg over 5 days and 750 mg over 7 days (LooareesuwanTHI92b). The lower dose in the latter study is less than the current WHO recommendation (2 mg/kg/d for 5 days; WHO 1996) for any adult weighing over 50kg. When we combined all single-agent artemether groups for analysis, combination with mefloquine appeared to be superior to artemether alone (graph not shown). However, separating the high and low dose groups in the Looareesuwan study shows that the difference is due only to the treatment group that received the lower dose in that study (Looareesuwan 500 mg: OR 4.05, 95% CI 1.47, 11.18, fixed effect model; OR 3.47, 95%CI 0.82, 14.78, random effect model). Pooled analysis of only the high dose groups (700, 750 and 800 mg) showed no advantage over combination treatment (Looareesuwan 750 mg: OR 1.66, 95% CI 0.52, 5.25, fixed effect model) in parasite clearance at day 28 follow-up.

Parasite clearance time: nine studies reported time to clearance of parasites from the blood. One of three studies with artemisinin reported mean and standard deviation, this data was obtained for another study from the investigator, and we estimated a standard deviation in the third study from the reported 95% confidence intervals. Our graph of mean difference in parasite clearance time shows marked heterogeneity between the studies. Parasite clearance was achieved significantly faster in patients treated with artemisinin alone in one study, and with artemisinin-mefloquine combination in another (although time to 50% clearance was similar in both groups), the third artemisinin study showed no difference between the treatment groups in time to 50, 90 or 100% parasite clearance. The treatment regimens used in these studies are diverse (see 'Characteristics of included studies'). There is no evident pattern of effect in relation to sequential or concomitant mefloquine.

One artemether study reported mean and standard deviation, this data was obtained for the other study from the investigator. In the study with two artemether treatment groups (500 and 750 mg) we combined the data from both groups as they were almost identical and used a mean value and the largest standard deviation for analysis. Although neither study showed a significant difference in parasite clearance time, the direction of effect was opposite.

Two of three studies using artesunate reported mean and standard deviation and this data was obtained for the third study from the investigator. These studies show a consistent, but not significant, trend in favour of artesunate-only, although again the treatment regimens vary.

Fever clearance

Nine studies reported time to clearance of fever. Data were reported or obtained for the different studies as described under parasite clearance time. We present a graph of mean difference in fever clearance time using mean and standard deviations. It shows marked heterogeneity between studies which cautions against pooling the data.

Clinical treatment failure

No cases of clinical treatment failure were reported.

Tolerability

Major adverse effects

No adverse event that resulted in discontinuation of treatment was reported.

Only one neuropsychiatric event was reported, one patient treated with artemisinin-mefloquine developed a psychiatric syndrome including restlessness and sleep disturbance one week after treatment, this resolved two weeks later (AlinTAZ94).

Mild adverse effects

Vomiting of treatment drugs was reported as an adverse event in 6 studies that overall showed more vomiting in patients given combination treatment with mefloquine compared with the artemisinin drug alone (OR 1.89, 95% CI 1.07, 3.34). In five of these studies mefloquine was given sequentially to the combination treatment groups, the fifth study is not explicit about this. Vomiting of the first drug was reported only in one artesunate study that

showed no difference between treatment groups. Nausea was reported in 2 studies. It was twice as common in the combination treatment group compared with the artemether group in one study, and associated with vomiting in the other.

Diarrhoea was reported in 6 studies. The heterogeneity in direction of effect could be due to the various artemisinin derivatives used. Only one study showed a marked higher incidence in patients treated with artemether for 5 days compared with a single dose of artemether plus mefloquine ([KarbwangTHI93](#)).

Other adverse effects including headache, rash and arthralgia (joint pain) were reported infrequently and were not shown to be associated with any particular treatment. No abnormalities in haematology or blood chemistry were reported.

Summary

We can summarise our review of combination artemisinin drug-mefloquine compared with artemisinin drug alone as follows:

- Seven out of ten studies were done in South-East Asia, one in Brazil and one in Tanzania between 1991 and 1994; one was done in China in 1982-4. Multidrug resistant falciparum malaria occurs in South-East Asia and Brazil.
- No two studies compared the same treatment regimens, either single-agent or combination.
- The data are consistent with a conclusion that giving mefloquine with an artemisinin drug does not result in earlier parasite clearance compared with the artemisinin drug alone.
- We conclude from the available data that sustained parasite clearance is better when mefloquine is combined with an artemisinin derivative, as long as the dose and duration of combination treatment is adequate.
- The available data on fever clearance are inconclusive.
- Only one neuropsychiatric adverse reaction was reported in a patient treated with artemisinin-mefloquine.

Combination mefloquine dose/schedule

In Thailand, a significant advantage in parasite clearance at day 28 was shown when a 300 mg single dose of artemether was combined with 1250 mg mefloquine rather than 750 mg mefloquine ([BunnagTHI92-4a](#); [KarbwangTHI93-4](#)). However, it is worth noting that the author of one of these studies reported a considerably better success rate for the same 750 mg mefloquine-artemether combination in another study (with the same inclusion criteria in the same year) where the combination was shown to be superior to artemether alone ([KarbwangTHI93](#)). The other 2 studies in Thailand failed to show a difference in parasite clearance at day 28 between 750 mg artemether combined with 500 or 750 mg mefloquine, or between 600 mg artesunate combined with 750 or 1250 mg mefloquine.

In Myanmar, a single 400 mg dose of artesunate combined with either 750 mg or 1250 mg mefloquine achieved only 50% cure rates at day 42 follow-up in 1997.

Only one small Myanmar study (36 patients) compared 600 mg artesunate over 3 days with sequential versus concomitant mefloquine (500 mg) and reported a higher parasitaemia cure rate in the concomitant group.

2c. Artemisinin drug in combination with sulfadoxine-pyrimethamine

One study compared a combination of artemisinin (500 mg single dose) and sulfadoxine-pyrimethamine (SP) with artemisinin alone (2500 mg/5 d) in Viet Nam ([HienVNM\(94\)\[1\]](#)). At day 28, artemisinin alone tended to be better in terms of parasite clearance than the combination regimen, but the difference was not statistically significant in 74 patients. Parasite and fever clearance times were similar. There were no patient-reported adverse events. More importantly, neither treatment regimen achieved adequate cure rates (even on intention-to-treat analysis counting losses to follow-up as successes).

3. Comparisons between artemisinin drugs

3a. Comparisons between derivatives

Five studies compared one artemisinin derivative with another: oral artemisinin with artesunate; oral artemether with artesunate, both combined with mefloquine; and rectal artemether with artesunate.

Parasite clearance at day 7 and 28 was similar in both groups in all studies. Parasite clearance and fever clearance time was reported in three studies, in one as mean and standard deviation, in another as mean and standard error (we estimated standard deviation as standard error multiplied by square root sample size), and in the third as mean and range. No study showed a significant difference between the artemisinin derivatives used (caution, as described earlier, regarding meta-analysis of this time-to data applies). There were no cases of clinical treatment failure.

Two studies in which patients were treated with artemisinin derivatives only, reported that there were no adverse effects. Three artesunate versus artemether studies in which mefloquine was also given to all patients reported vomiting, nausea and other mild adverse events affecting similar numbers of patients in both treatment groups. In one of these studies, one patient in each treatment group suffered a neuropsychiatric reaction.

Summary

- The WHO recommended dose of both artemisinin and artesunate monotherapy produced inadequate cure rates in Tanzania.
- Both artemether and artesunate (300 mg single dose and 600 mg over 3 days) appear to be effective in Thailand when combined with 1250 mg mefloquine. However, the effectiveness of the single dose of artemisinin drug here is not consistent with other studies using similar regimens (see summary, Artemisinin drug in combination with mefloquine, comparison with artemisinin drug alone, Results, section 2b.).
- No study has shown one derivative to be better than the others.

3b. Comparisons between doses of the same derivative

One study in Thailand compared 1200 mg artesunate with 600 mg over five days ([BunnagTHI89a](#)). This comparison included only 16 patients and did not show any difference in clinical or parasitological outcome. The only notable adverse event reported was a transient reduction in white blood cell count with the higher dose. A more recent study at the same centre compared 1600 mg/7 days with 1200 mg/5 days showing similar cure rates (over 90% at follow-up) and low incidence of dizziness and nausea in both groups ([LooareesuwanTHI95](#)). In the following year in Myanmar, the

cure rate was 80-90% with 800 mg/3 days and 1200 mg/3 days in 34 patients.

In China in 1987, 440 mg artesunate over 5 days was effective, but not when treatment stopped at 280 mg after 3 days.

One study comparing artemether combination with mefloquine alone had two groups treated with artemether alone, 500 mg over 5 days and 750 mg over 7 days by continuing the same treatment schedule for an additional 2 days ([LooareesuwanTHI92b](#)). Only the higher dose was adequate, resulting in a 98% cure rate at follow-up compared with 74% of patients in the lower dose group.

One study in Myanmar compared oral artemether 360 mg and 640 mg given over 7 days. Both regimens were similarly ineffective, achieving only 60% parasite clearance ([ThanMYA93c](#)).

3c. Comparisons between regimens of the same derivative

Two studies compared the same total dose of artesunate delivered differently over time. One compared 600 mg given in daily or twice-daily doses over 5 days in 59 patients ([BunnagTHI89b](#)). The other study compared 600 mg given over 1, 2 or 5 days in three treatment groups (20 patients) of a nine-arm trial ([BunnagTHI89a](#)). Neither study showed any difference between the treatment groups in any measured outcome of effectiveness or tolerability.

4. Dosage adequacy

Our graphs of parasite clearance show the cure rate achieved in each treatment group in each study at follow-up. Grouping the studies as we have done in this review shows which single-agent and combination treatment regimens appear to be effective and which are not. To achieve at least 90% cure rate at follow-up at least 3 days treatment with an artemisinin derivative is needed when it is combined with a high dose of mefloquine (1250 mg). Shorter regimens with lower doses of mefloquine are not effective. For single-agent treatment with an artemisinin drug, five days treatment is not sufficient to reliably achieve 90% cure rate anywhere in comparative trials with combination therapy.

5. Potentially important effects described in excluded studies

Oral versus rectal route

One study in 52 children in Thailand showed artesunate given rectally (15 mg/kg/day for 3 days) was as effective and safe as oral treatment (6 mg/kg/day for 3 days) when both were combined with sequential mefloquine (25 mg/kg). Cure rates were 92-100% at 28 day follow-up ([SabchareonTHI95-6](#)). Another pharmacokinetic study, in 30 Vietnamese adults, compared oral with rectal artemisinin (2500 mg over 5 days). This showed similar parasite clearance times despite the bioavailability of rectal artemisinin (measured in plasma) being only 30% relative to oral administration ([Ashton VNM \(98\)](#)).

Other combinations

Two trials in South-East Asia studied combinations of artemisinin drugs with doxycycline and tetracycline with conflicting results. Artesunate (300 mg over 2.5 days) plus doxycycline was only 80% effective, and significantly less effective at 28 day follow-up, than mefloquine (1250 mg) plus doxycycline in Thailand ([LooareesuwanTHI 92a](#)). Artemether (480 mg over 5 days) combined with either doxycycline or tetracycline was highly effective in Myanmar and

produced a cure rate at follow-up similar to artemether plus mefloquine ([Than MYA 94b](#)).

In Brazil, one study compared artesunate (750 mg over 7 days) plus tetracycline with quinine (6000 mg over 3 days) plus tetracycline ([Duarte BRZ 92-3](#)). Both regimens were highly effective at follow-up. Patients treated with artesunate were much less affected by dizziness and tinnitus than those treated with quinine.

DISCUSSION

Strength of evidence

Around 10,000 patients were enrolled in the trials we identified as potentially eligible for inclusion in this review. After application of our inclusion criteria approximately 5240 have been included in this review. Despite the large amount of clinical research that has been done, variation in study design and quality makes synthesis of the data problematic.

We cannot be assured that the quality of much of this data is good. Randomisation in a trial should involve both generating an unpredictable allocation sequence and concealing that sequence until allocation occurs; of these, allocation concealment appears to be the most important protector against bias, even more important than blinding which protects the sequence after allocation ([Schulz 1995](#)). Although all of the studies included in this review reported an attempt to randomise allocation of patients to the different treatment groups, only one reported adequate measures to conceal allocation. We therefore have to assume that the twenty-eight studies that were unclearly concealed (did not report on allocation concealment) were potentially open to selection bias.

Most of the included studies reported something about exclusion and, or, loss of randomised patients which allowed us to perform sensitivity analyses on the effect this might have on the results. There is, however, still room for improvement in reporting of patient attrition, the reasons for it and how investigators deal with it ([Begg 1996](#)).

A funnel plot of the primary outcome measure against trial size indicated that publication bias may have influenced the findings in this review ([Egger 1997](#)).

Applicability

Location

Most of the data included in this review are from studies conducted in areas of multidrug resistant falciparum malaria in South-East Asia. This is appropriate because such areas have the greatest need for artemisinin drugs. The Amazon region, where multidrug resistance is also high, is represented by only a few studies in Brazil. The data from Africa comprises a small number of studies in Tanzania and Nigeria comparing the new artemisinin drugs with standard first-line drugs to which resistance is increasing.

Population

Children and adults are represented in the included studies, with blood slide-confirmed uncomplicated falciparum malaria as defined by the investigators. Trials enrolling both children and adults rarely stratify randomisation or report outcome data according to age. It is not clear if some artemisinin drug preparations, such as suppositories, are equally effective in

children and adults at the doses used. No study has included pregnant women.

Malaria endemicity and transmission in the study areas or catchment areas is surprisingly not mentioned in some study reports and only in passing in others. The same applies to the immune status of the patients. This restricts decision making to regions and does not allow wider applicability of results to be assessed.

The issue of residual levels of other antimalarial drugs in the body is dealt with differently across studies and is not clarified at all in some. Resistance to other antimalarials differs in different regions, areas, populations, and with time, therefore, the potential effect of residual drugs is not constant across studies included in this review.

Product

Many formulations of artemisinin drugs are currently available on the market, produced in developed and developing countries. At least 16 different preparations are reported in the included studies. Not all of these drugs have been subject to stringent regulation during development and we cannot assume that they are equivalent in potency or safety.

Regimen

Most data have been generated from studies using artesunate or artemether, there have been significantly fewer studies on artemisinin and very few on dihydroartemisinin. In the majority of studies artemisinin drugs were administered orally, in a few rectally, alone or in combination treatment regimens - mostly with mefloquine.

Differences in treatment regimens cannot be ruled out as a reason for heterogeneity between trials. Regimens vary markedly between studies in terms of dose, schedule, combinations and comparisons. Furthermore, any comparative advantage of one treatment regimen over another reported in any individual study has to be assessed in terms of cure rate which reflects the adequacy of the dose schedules used.

Consecutive and simultaneous studies being conducted in some centres do not appear to follow a logical path of clinical inquiry in terms of the wide range of treatment regimens being tested.

Adherence was hardly ever mentioned in the studies included in this review. Loss to follow-up was either reported without clarification of whether those patients had completed their treatment or not, or with the vague statement that they were lost for "reasons unrelated to their treatment". Some of the treatment regimens used in these studies lasted for a week or more. There are few data to assess how many outpatients actually complete a full treatment course.

Cost

A full cost analysis of artemisinin drugs versus standard treatment is beyond the scope of this review, and can be done better by people developing clinical practice guidelines for national or regional implementation. An example, however, is useful.

The following are approximate retail prices for a full adult treatment course in Viet Nam compared with standard treatment quinine at

the time of writing (March 1998) supplied by A Schapira (WHO, Hanoi):

- Quinine 10,500 mg/7 d (250 mg tablet x 42) = US \$0.97.
- Artemisinin 3000 mg/5 d (250 mg tablet x 12) = US \$ 1.06.
- Artesunate 600 mg/5 d (50 mg tablet x 12) = US \$0.62.

At a rural pharmacy in Lao PDR, drug prices were:

- Quinine (as above) = US \$1.75.
- Artesunate (as above) = US \$1.25.

Thus in areas of South-East Asia the price of artesunate 5 day treatment is now lower than that of quinine standard 7 day treatment, and a full course of artemisinin costs about the same as quinine.

Benefit and risk

From this review, we can say that artemisinin drugs are effective in areas of multidrug resistance provided that the dose is adequate. Combination with an adequate dose of mefloquine can shorten the overall treatment time. There is no strong evidence from randomised trials that artemisinin drugs are harmful as measured by adverse events within a typical study period of 28 days.

An overview of tolerability and safety data on artemisinin drugs gathered from randomised and non-randomised controlled trials, and studies without control groups, concluded that few side effects have been reported with these compounds ([Ribeiro 1998](#)).

AUTHORS' CONCLUSIONS

Implications for practice

1. Are artemisinin drugs better than existing standard treatment for uncomplicated malaria?

- Artemisinin drugs clear parasitaemia more effectively than standard treatment with chloroquine or sulfadoxine-pyrimethamine in Africa.
- In South-East Asia and Brazil, there is no difference in sustained parasite clearance between artemisinin drugs used alone and standard treatment with quinine or mefloquine.
- Single-agent treatment with artemisinin drugs is well tolerated. Dizziness in particular is less common than with mefloquine and quinine.

2. Do artemisinin drugs have a comparative advantage over other antimalarials in geographical areas where malaria parasites are still sensitive to existing antimalarial drugs, as well as in areas where drug resistance is high?

- Data from Tanzania and Nigeria show that artemisinin drugs clear parasitaemia more effectively than standard treatment with chloroquine or sulfadoxine-pyrimethamine in areas where resistance to those drugs is increasing.
- Most data are from areas of multidrug resistant falciparum malaria in South-East Asia and Brazil. When used alone, even at WHO recommended doses, artemisinin derivatives do not improve sustained parasite clearance compared with quinine or mefloquine standard treatment in these areas.

3. Should artemisinin derivatives be combined de novo with all first-line treatment regimens using longer-acting antimalarials?

- Parasite clearance and fever clearance is achieved earlier if mefloquine is combined with an artemisinin drug compared with mefloquine alone. In areas of mefloquine resistance the combination improves sustained parasite clearance compared with either drug alone.
- Neuropsychiatric adverse effects have not been reported in patients given only artemisinin derivatives, but have been reported in patients given mefloquine and artemisinin drug combination treatment. Severe vomiting might be less likely with combination treatment compared with mefloquine alone.
- There are few data on combination treatment with longer-acting antimalarial drugs other than mefloquine.

4. Is any artemisinin derivative better than the others?

- There is no evidence from randomised trials that any artemisinin derivative is better than the others. Most data apply to artesunate and artemether, fewer to artemisinin and very few to dihydroartemisinin.

5. What is the best dose and treatment regimen?

- A wide variety of treatment regimens has been tested in randomised trials. The rationale is often not explained in terms of previous clinical or pharmacokinetic findings. Treatment regimens reported as having a comparative advantage in some studies achieve inadequate cure rates. Overall, it appears that if artemisinin drugs are given alone at least 7 days treatment is needed to reliably achieve adequate cure rates; if they are combined with mefloquine at least 3 days treatment is needed with a dose of 1250 mg mefloquine in mefloquine-resistant areas. The treatment regimens recommended in WHO guidelines from 1996 may be inadequate and should be revised as a matter of priority.

Implications for research

The use of artemisinin derivatives spread before basic questions concerning dose-effect relationship, dose optimisation and standardisation of drug regimens, alone or in combination with other antimalarials, had been addressed. This review highlights the need for clear definition of the clinical questions outstanding and co-ordination of drug trials.

The experience with artemisinin drugs should be useful as researchers encounter more new antimalarial compounds. It is important they get together at an early stage in a collaborative network and agree research questions, methods, outcomes and reporting of results. In addition, careful attention to trial methodology (allocation concealment, for example) should be ensured.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

AlinTAZ94

Methods	Randomised, method not specified; open Follow-up 28 days No exclusions reported Loss to follow-up day 28: ART = 1/18 (5%), ART+MQ = 3/20 (15%)
Participants	38 adults, male and female, 18 to 25 years; febrile, <i>Plasmodium falciparum</i> >1000/μl Excluded: severe/cerebral malaria; recent antimalarial treatment; pregnancy
Interventions	ARTpo vs ARTpo + MQ15 (C) ART 3000 mg/5 d (500 mg x 2 on d1, 250 mg x 2 on days 2 to 5) ART 2000 mg/2 d (500 + 750 mg on d1, 250 mg x 3 on d2) + MQ 750 mg (250 mg x 3 on d1)
Outcomes	Clinical: FCT Parasitological: PCT, PC50, recrudescence Adverse events Pharmacokinetics
Notes	Quality assessment: B, B, C ART (capsules) from Institute Materia Medica, Hanoi Holoendemic area, drug resistance not reported

AlinTAZ96

Methods	Randomised, method not specified Follow-up 28 days No exclusions reported Loss to follow-up day 28: ART = 0/20, AS = 1/20 (5%)
Participants	40 male and female, 14 to 50 years; febrile, Pf>1000/μl Excluded: severe malaria; recent antimalarials; pregnancy
Interventions	ARTpo vs ASpo ART 3000 mg/6 d (500 mg on d1, 2 x 250 mg on days 2 to 5, 500 mg on d6) AS 600 mg/6 d (100 mg on day 1, 2 x 50 mg on days 2 to 6) Treatment supervised

AlinTAZ96 (Continued)

Outcomes	Clinical: FCT Parasitological: PCT, PC50, recrudescence Pharmacokinetics Adverse events: clinical observation and patient reported
Notes	Quality assessment: B, B, A ART (capsules) from Institute of Materia Medica, Viet Nam; AS (tablets) from Guilin Pharmaceutical Works, China Holoendemic area, drug resistance not reported

ArnoldVNM89

Methods	Randomised using table of random numbers, allocation concealment not reported Follow-up 28 days No exclusions reported Loss to follow-up day 28: ART = 5/32 (16%), QNN = 8/30 (27%)
Participants	62 adults, male and female, 17 to 56 years; Pf asexual 1000 to 150,000/μl; negative Dill-Glazko and lignin urine test. Excluded: antimalarials for current illness; confusion; coma; pregnancy; heart, liver, kidney disease; Pf-Pv
Interventions	ARTpr vs QNNpo ART 2800 mg (600 mg at 0 and 6 h, 400 mg at 24, 32, 48 and 56 h) QNN 21,000 mg (500 mg x 3, daily for 14 days)
Outcomes	Clinical: FCT Parasitological: PCT, PC50; recrudescence Adverse events
Notes	Quality assessment: B, A, C ART supplied by Prof. Li Guo Qiao, Sanya Tropical Medicine Institute, China Endemic catchment area, drug resistance not reported

BunnagTHI89a

Methods	Random allocation reported, method not specified Follow-up 28 days No exclusions reported Loss to follow-up at day 28: AS600/1 d = 0/5, AS600/2 d = 0/5, AS600/5 d = 1/10, AS1200 = 1/6 (17%)
Participants	26 male, >14 years Excluded: PfPv; Pf > 100,000/μl; concurrent disease; recent antimalarials; urine positive for sulfonamides/4-aminoquinolines

BunnagTHI89a (Continued)

Interventions	ASpo dose/regimens AS1200 mg vs 600 mg over 5 days AS 600 mg over 1, 2 or 5 days 150 mg CLQ base if Pv detected during follow-up
Outcomes	Clinical: FCT Parasitological: PCT, cure, recrudescence Adverse events
Notes	Quality assessment: B, B, C AS (50 mg tablet) supplied by Prof. Li Guo Qiao, Sanya Tropical Medicine Institute, China Five treatment groups excluded: AS 650 mg over 5 days; AMim; ASiv; ASpo200+CLQ; ASpo200+SP (total 21 patients) Endemicity and drug resistance not reported

BunnagTHI89b

Methods	Randomised, method not specified; double blind Follow-up 28 days No exclusions reported Loss to follow-up: 9/59 (15%) total Evaluated: AS daily = 25, twice daily = 25
Participants	59 adults, male and= female, 15 to 52 years; acute uncomplicated malaria, Pf asexual < 5% Excluded: history of liver/kidney disease
Interventions	ASpo daily vs twice daily dose AS600 mg/5 d (200 mg on day 1, 100 mg on days 2 to 5) AS600 mg/5 d (100 mg at 0 and 12h, then 8 x 50 mg at 12 h intervals) Treatment supervised; 150 mg CLQ base if Pv detected during follow-up
Outcomes	Clinical: FCT Parasitological: PCT, cure, recrudescence Adverse events
Notes	Quality assessment: B, B, C AS (from Atlantic Laboratories Corp. Ltd, Thailand?) Endemicity not reported, 67% of patients from multidrug resistant areas

BunnagTHI92-4a

Methods	Randomised, method not specified, double blind Follow-up 42 days No exclusions reported

BunnagTHI92-4a (Continued)

Loss to follow-up: MQ25 = 10/80 (12%), MQ15 = 6/79 (8%)

Participants	159 male adults, 15 to 65 years; acute uncomplicated malaria, Pf asexual < 5% Excluded: history of liver/kidney disease
Interventions	ASpo + MQ15 vs ASpo + MQ25 AS300 mg (singles dose) + MQ 750 mg at 24 h, 500 mg at 30 h AS300 mg (singles dose) + MQ 750 mg at 24 h, placebo at 30 h 300 mg CLQ if Pv detected during follow-up
Outcomes	Clinical: Fever clearance within 24 and 48 h Parasitological: Parasite clearance within 24 and 48 h, cure, recrudescence Adverse events
Notes	Quality assessment: B, B, B Source of AS: not reported Endemicity not reported, mentions high resistance to CLQ, SP, increasing resistance to QNN and MQ in Thailand

BunnagTHI92-4b

Methods	Randomised, method not specified Follow-up 42 days No exclusions reported Loss to follow-up day 42: AM = 2/60 (3%), AS = 3/60 (5%)
Participants	120 male, 15 to 57 years; acute uncomplicated malaria; Pf asexual < 5% Excluded: history of liver/kidney disease
Interventions	AMpo + MQ25 vs ASpo + MQ25 (S) AM 300 mg (single dose) + MQ 1250 mg (750 mg at 24 h, 500 mg at 30 h) AS 300 mg (single dose) + MQ 1250 mg (as before)
Outcomes	Clinical: Fever clearance within 24 and 48 h Parasitological: Parasite clearance within 24 and 48 h, cure, recrudescence Adverse events
Notes	Quality assessment: B, B, A AM (50 mg tablet) from Arenco, Belgium; AS (50 mg tablet) from Guilin Pharmaceuticals, China Endemicity not reported, multidrug resistance

CardosoBRZ93-4

Methods	First 3 patients allocated by lottery, followed by sequential application of the same numbers; open Follow-up 35 days Excluded: AS = 1/51 (2%)

Artemisinin derivatives for treating uncomplicated malaria (Review)

CardosoBRZ93-4 (Continued)

Loss to follow-up day 35: AS+MQ = 9/51 (18%), AS = 5/50 (10%), MQ = 5/51 (10%)

Participants	103 male and female, 14 to 60 years; signs and symptoms of uncomplicated malaria; Pf asexual. Excluded: < 12 years; heart, liver, kidney disease; pregnancy; antimalarials in previous 15 days; PfPv; serious associated infection; unable to remain in study area for 35 days
Interventions	ASpo vs ASpo + MQ10(S) vs MQ20 AS 1000 mg/4 d (200 mg at 0 and 12 h; 100 mg x 2 on days 2 to 4) AS 600 mg/2 d (200 mg at 0, 12 and 24 h) + MQ 500 mg (at 36 h) MQ 1000 mg (500 mg at 0 and 8h)
Outcomes	Clinical: FCT Parasitological: PCT, cure, recrudescence Adverse events
Notes	Quality assessment: B, B, C AS: Plasmodium Lactab (50 mg), Mepha, Switzerland High transmission area; CQ, QNN resistance

EzedinachiNIG92

Methods	Randomised, method not specified Follow-up 14 days Excluded: SP = 4/52 (8%) Loss to follow-up not reported
Participants	155 adults and children; Pf parasitaemia; no other visible disease Excluded: unable to take oral medication; concomitant illness
Interventions	ASpo vs CLQpo vs SPpo AS 550 mg (100 mg at 0 h, 50 mg every 12 h for 5 days) CLQ 75 mg/kg (25 mg/kg for 3 days) SP (age-adjusted single dose)
Outcomes	Clinical: symptom clearance rate per group according to a defined scoring system Parasitological: PCT Adverse events
Notes	Quality assessment: B, B, B AS from Guilin Pharmaceutical (sic), Guangxi, China Symptom score: 1 point for each case of fever, headache, bitter mouth, aches and pains, malaise One treatment group excluded: Halfan po 72 mg/kg (24 mg/kg at 6, 12, 18 h), 53 patients Endemicity, drug resistance not reported

GuoCHI87

Methods	Randomised, random number table set up by coin tossing; patients blind Follow-up 28 days No exclusions reported Loss to follow-up day 28: AS280 = 9/50 (18%), AS440 = 5/50 (10%)
Participants	100 male and female, 9 to 60 years; symptoms of malaria; Pf asexual >1000/μl with illness < 5 days or Pf asexual > 5000/μl with illness of > 5days Excluded: serious gastrointestinal symptoms
Interventions	ASpo 280 mg/3 d vs ASpo 440 mg/5 d (80 mg at 0 h, 40 mg at 6 h on day 1, then 80 mg/day for 2 to 4 days; equivalent dose adjusted for age)
Outcomes	Clinical: FCT Parasitological: PCT, cure, recrudescence Adverse events
Notes	Quality assessment: B, B, C AS (20 mg tablet) from Guilin Pharmaceutical Factory, China One treatment group excluded: piperaquine, 50 patients Endemicity, drug resistance not reported

HatzTAZ(98)

Methods	Random allocation in blocks of 6, sequence generation not specified;open Follow-up 14 days for major outcomes reported, follow-up also at day 28 Exclusions/Loss to follow-up at day 7: Co-AM = 14/130 (11%); CLQ = 34/130 (26%); at day 14: Co-AM = 20/130 (15%); CLQ = 33/130 (25%); Total premature discontinuation: Co-AM = 24/130 (18.5%), CLQ = 94/130 (72.3%)
Participants	260 children 1 to 5 years; febrile; >5kg; acute uncomplicated malaria; Pf > 5000/μl Excluded: intolerance of oral medication; signs of severe malaria; malnutrition; antimalarials in previous 48 h; sensitivity to chloroquine; underlying chronic disease
Interventions	Co-AMpo vs CLQpo Co-AM/2 d: 5 to10 kg body weight given AM40 mg + Lumifantrine 240 mg;10 to15 kg given x 2 dose; 15 to 20 kg given x 3 dose; 20 to 25 kg given x 4 dose (4 equal doses at 0, 8, 24 and 48 h) 25 Co-AM and 93 CLQ patients received other antimalarials in the 28 day study period (118 discontinued prematurely) All received paracetamol 250 mg x 2/d in first 3 to 4 days; 2 CLQ patients received cotrimoxazole; 183/260 had other medication for pneumonia, anaemia, ulcers, rash CLQ 25 mg/kg/3 d (10, 5, 5, 5 mg/kg)
Outcomes	Clinical: fever at 48 h; Hb Parasitological: cure at 7 d and 14 d; % parasite reduction on days 1, 2 and 3; gametocytaemia on days 0, 1, 2, 3 and 7 Adverse events
Notes	Quality assessment: B, B, C

HatzTAZ(98) (Continued)

Co-AM (CGP56697) from Novartis Pharma A.G.

Permanent transmission area

HienVNM(94)[1]

Methods	Computer generated block randomisation table, allocation concealed in sealed envelopes; open Follow-up 28 days No exclusions reported Loss to follow-up ART = 9/45 (20%), ART+MQ = 5/45 (11%), ART+SP = 10/48 (21%)
Participants	138 adults, 16 to 62 years; acute uncomplicated malaria; Pf asexual 1000 to 500,000/μl; no underlying disease Excluded: PfPv; pregnancy; severe or complicated malaria
Interventions	ARTpo vs ARTpo + MQ10 vs ARTpo + SP ART 2500 mg (500 mg/d for 5 days) ART 500 mg (single dose) + MQ 500 mg (single dose at 6 h) ART 500 mg (as before) + SP 1.5 g/75 mg (single dose at 6 h)
Outcomes	Clinical: FCT Parasitological: PCT (50, 90, 100%), recrudescence
Notes	Quality assessment: A, A, C Source of ART not reported (Roche?) No local transmission, mentions CLQ, SP resistance and increasing resistance to QNN in Viet Nam

HienVNM90

Methods	Randomised, method not specified Follow-up 28 days No exclusions reported Loss to follow-up day 28: ART = 21/30 (70%), QNN = 23/30 (77%)
Participants	60 children, male and female, 4 to 13 years; Pf asexual 1000 to 150,000/μl; negative Dill-Glaxo and lignin urine test Excluded: antimalarials for current illness; confusion; coma; pregnancy; heart, liver, kidney disease; Pf-Pv
Interventions	ARTpr vs QNNpo ART 600 to 1200 mg/3 d adjusted for age (100 to 600 mg at 0 h, 100 to 400 mg at 4h, 100 to 300 mg on day 2 and day 3) QNN 300 mg/kg (10 mg/kg every 8 h for 10 days)
Outcomes	Clinical: FCT Parasitological: PCT (50, 90, 100%); recrudescence Adverse events

HienVNM90 (Continued)

Notes	Quality assessment: B, B, C ART supplied by Prof. Li Guo Qiao, Sanya Tropical Medicine Institute, China Endemic area, drug resistance not reported

HungVNM93-4

Methods	Randomised, method not specified; double blind Follow-up 28 days Excluded: ART+MQ = 5/122 (4%), MQ = 4/118 (3%) Loss to follow-up day 28: 2/117 (2%), 2/114 (2%)
Participants	240, adults and children, male and female, 6 to 59 years; Pf 1000 to 100,000/μl Excluded: complicated malaria; PfPv; pregnancy; lactation; unable to take oral drug; known allergy to treatment; recent ART, QNN, MQ, Tc, Dox
Interventions	ARTpo + MQ10 vs MQ10 (S) ART 500 mg (single dose) + MQ 500 mg (at 2 h) Placebo + MQ 500 mg (at 2 h)
Outcomes	Clinical: FCT Parasitological: PCT, cure, recrudescence Adverse events
Notes	Quality assessment: B, B, A ART from ACF-Chemie, The Netherlands Endemic area, mentions CLQ and SP resistance in Viet Nam

KarbwangTHI91

Methods	Randomised, method not specified; open Follow-up AM 28 days, MQ 42 days No exclusions reported Loss to follow-up: AM (day 28) = 4/34 (12%), MQ (day 42) = 1/12 (8%)
Participants	46 adult male, 17 to 48 years; febrile, acute uncomplicated malaria; Pf < 5% asexual Excluded: liver/kidney disease; antimalarials for current illness
Interventions	AMpo vs MQ25 AM 700 mg/5 d (200 mg at 0 and 6 h; 100 mg on days 2 to 5) MQ 1250 mg (750 mg at 0 h, 500 mg at 6 h) Treatment supervised; 150 mg CLQ base if Pv detected during follow-up
Outcomes	Clinical: FCT Parasitological: PCT, PC50, cure, recrudescence

KarbwangTHI91 (Continued)

Adverse events

Notes	Quality assessment: B, B, B AM supplied by United Medical Ltd, Bangkok No local transmission, mentions multidrug resistance in Thailand

KarbwangTHI92a

Methods	Randomised, method not specified Follow-up 42 days Excluded: 2/22 (9%) total No loss to follow-up reported
Participants	20 adult male, 17 to 48 years; acute uncomplicated Pf malaria; Pf asexual < 5% Excluded: history of liver/kidney disease
Interventions	ASpo + MQ25 (S) vs MQ25 AS (200 mg single dose) + MQ 1250 mg (750 mg at 6 h, 500 mg at 12 h) MQ 1250 mg (as before) Treatment supervised
Outcomes	Clinical: FCT Parasitological: PCT, cure, recrudescence Adverse events
Notes	Quality assessment: B, B, B AS supplied by Atlantic Co. Ltd, Thailand Patients with CLQ resistant malaria

KarbwangTHI92b

Methods	Randomised, method not specified; open Follow-up 28 days No exclusions reported Loss to follow-up day 28: AS = 1/31 (3%), QNN+Tc = 3/33 (9%)
Participants	64 male adults, 15 to 35 years; acute uncomplicated malaria, Pf asexual < 5% Excluded: severe malaria (WHO 1990); history of liver/kidney disease; antimalarials for current episode
Interventions	ASpo vs QNN+Tc po AS 700 mg/5 d (200 mg at 0 h, 100 mg at 12 h then daily for 4 d) QNN 600 mg 8 hourly + Tc 250 mg 6 hourly for 7 d
Outcomes	Clinical: FCT Parasitological: PCT, cure, recrudescence

KarbwangTHI92b (Continued)

Adverse events

Notes	Quality assessment: B, B, B AS (50 mg tablet) China Mentions multidrug resistance in Thailand

KarbwangTHI92c

Methods	Randomised, method not specified Follow-up AS 28 days, AS+MQ 42 days No exclusions reported Loss to follow-up: AS (day 28) = 1/32 (3%), AS+MQ (day 42) = 6/34 (18%)
Participants	66 male, 15 to 58 years; acute uncomplicated malaria, Pf asexual < 5% Excluded: history of liver/kidney disease
Interventions	ASpo vs ASpo + MQ15 (S) AS 700 mg/5 d (200 mg at 0 h, 100 mg at 12 h, 100 mg on days 2 to 5) AS 300 mg/1 d (200 mg at 0 h, 100 mg at 12 h) + MQ 750 mg (at 24 h) 300 mg CLQ base if Pv detected during follow-up
Outcomes	Clinical: FCT Parasitological: PCT, cure, recrudescence Adverse events
Notes	Quality assessment: B, B, C AS: China (50 mg tablet) CLQ resistant malaria

KarbwangTHI93

Methods	Randomised, method not specified Follow-up AM 28 days, AM+MQ 42 days No exclusions reported Loss to follow-up: AM+MQ = 6/56 (11%), AM = 3/53 (6%)
Participants	109 male, 13 to 47 years; febrile; Pf < 5% Excluded: history of liver/kidney disease
Interventions	AMpo vs AMpo + MQ15 (S) AM 700 mg/5 d (300 mg on day 1, 100 mg on days 2 to 5) AM 300 mg (single dose) + MQ 750 mg (at 24 h) 300 mg CLQ base if Pv detected during follow-up
Outcomes	Clinical: FCT

KarbwangTHI93 (Continued)

	Parasitological: PCT, recrudescence Adverse events
Notes	Quality assessment: B, B, B AM: Artesam, Arengo, Belgium Mentions multidrug resistant malaria in Thailand

KarbwangTHI93-4

Methods	Randomised, method not specified Follow-up 42 days No exclusions reported Loss to follow-up day 42: MQ25 = 2/30 (7%), MQ15 = 0/27
Participants	57 male adults, 13 to 47 years; acute uncomplicated malaria, Pf asexual < 5% Excluded: history of liver/kidney disease
Interventions	AM + MQ15 (S) vs AM + MQ25 (S) AM 300 mg/sd + MQ 750 mg at 24 h AM 300 mg/sd + MQ 750 mg at 24 h, 500 mg at 30 h
Outcomes	Clinical: FCT Parasitological: PCT, cure, recrudescence Adverse events
Notes	Quality assessment: B, B, B AM: Artesam, Profarma n.v., Belgium Mentions multidrug resistant malaria in Thailand

Li CHI82-4

Methods	Randomised, random number table set up by coin tossing Follow-up 28 days No exclusions reported Loss to follow-up day 28: ART = 3/20 (15%), ART+MQ = 0/20
Participants	40 male and female, 8 to 60 years; febrile; clinical diagnosis of malaria; Pf asexual > 1000/μl (or > 5000/μl if febrile > 5 days) Excluded: treated; other serious disease
Interventions	ARTpo vs ARTpo + MQ15 ART 3000 mg/3 d (1000 mg/day) ART 1000 mg (single dose) + MQ 750 mg Treatment supervised

Li CHI82-4 (Continued)

Outcomes	Clinical: FCT Parasitological: PCT, PC95, cure, recrudescence Adverse events
Notes	Quality assessment: B, B, C ART produced by Institute for Chinese Pharmacy, Academy of Traditional Chinese Medicine Endemicity not reported, chloroquine resistance

LooareesuwanTHI91

Methods	Randomised, method not specified; open label Follow-up 28 days Excluded after treatment: MQ = 2/43 (5%) Loss to follow-up day 28: AS+MQ = 3/42 (7%), AS 2/42 (5%), MQ = 4/41 (10%)
Participants	127 male and female, 16 to 60 years; febrile; acute uncomplicated malaria; Pf asexual 100 to 200,000/μl Excluded: severe malaria; pregnancy; antimalarials in previous week
Interventions	ASpo vs ASpo + MQ25(S) vs MQ25 AS 600 mg/5 d (100 mg at 0 h, 50 mg every 12 h for 5 days) AS (as before) + MQ 1250 mg (750 mg 12 h after last dose of AS, 500 mg 6 h later) MQ25 (750 mg at 0 h, 500 mg at 6 h)
Outcomes	Clinical: FCT Parasitological: PCT, cure, recrudescence Adverse events
Notes	Quality assessment: B, B, B AS (tablet) from Atlantic Pharmaceutical Co. Ltd, Thailand No local transmission, multidrug resistance, 24/127 (19%) patients with first attack of malaria

LooareesuwanTHI92b

Methods	Randomised, method not specified; open label Follow-up 28 days Enrollment to AM5d stopped early when cure rate fell below 80%, so only partially randomised No exclusions reported Loss to follow-up day 28: AM5d = 2/40 (5%), AM7d = 9/58 (16%), AM+MQ = 9/53 (17%)
Participants	151, male and female, 16 to 50 years; acute uncomplicated malaria; Pf 1000 to 200,000/μl Excluded: severe malaria; pregnancy; lactating; MQ in previous 2 weeks
Interventions	AMpo vs AMpo + MQ25 AM500 mg/5 d (100 mg, then 50 mg every 12 h for 5 days)

Artemisinin derivatives for treating uncomplicated malaria (Review)

LooareesuwanTHI92b (Continued)

AM750 mg/7 d (100 mg, then 50 mg every 12 h for 7 days)
AM600 mg/1 d (200 mg at 0, 8 and 16 h) + MQ 1250 mg (at 24 h, 2 doses 6 h apart)

Outcomes	Clinical: FCT Parasitological: PCT, cure, recrudescence Adverse events
Notes	Quality assessment: B, B, C AM (50 mg capsule) from Kunming Pharmaceutical Factory, China No local transmission, multidrug resistance

LooareesuwanTHI93

Methods	Randomised, method not specified; open label Follow-up 28 days No exclusions reported Loss to follow-up day 28: AS+MQ = 12/62 (19%), MQ 6/63 (10%)
Participants	125 male and female, 16 to 60 years; acute uncomplicated malaria Excluded: severe malaria; pregnancy; antimalarials in previous week
Interventions	ASpo + MQ15 (S) vs MQ25 AS 800 mg/2 d (200 mg every 12 h) + MQ 750 mg (6 h later) MQ 1250 mg (750 mg at 0 h, 500 mg at 6 h)
Outcomes	Clinical: FCT Parasitological: PCT, cure, recrudescence Adverse events
Notes	Quality assessment: B, B, C AS: Plasmotrim Lactab, Mepha, Switzerland Endemicity, transmission not reported

LooareesuwanTHI95

Methods	Computer generated randomisation in blocks of ten; open label Follow-up 28 days No exclusions reported Loss to follow-up day 28: AS1200 = 3/45 (7%), AS1600 = 6/46 (13%)
Participants	91 male and female, 16 to 60 years; acute uncomplicated malaria (65/91 first attack of malaria); Pf 500 to 200,000/μl Excluded: severe malaria; pregnancy; antimalarials in previous 2 weeks
Interventions	ASpo1200 vs 1600

Artemisinin derivatives for treating uncomplicated malaria (Review)

LooareesuwanTHI95 (Continued)

AS 1200 mg/5 d (200 mg x 2 on day 1, 200 mg on days 2 to 5)
AS 1600 mg/7 d (200 mg x 2 on day 1, 200 mg on days 2 to 7)

Outcomes	Clinical: FCT Parasitological: PCT (50, 90, 100%), cure, recrudescence Adverse events
Notes	Quality assessment: B, A, B AS: Plasmotrim, Lactab, Mepha, Switzerland Endemicity, transmission not reported

LuxemburgerTHI-MYA91

Methods	Patients allocated at random in pairs, method not specified; open Follow-up 28 days Excluded: AS+MQ 4/274 (1%), MQ = 5/278 (2%) Loss to follow-up day 28: 59/270 (22%), 47/273 (17%)
Participants	552 adults > 15 years and children < 6 years; febrile or history of fever; Pf asexual positive Excluded: severe malaria; concomitant disease; antimalarials in previous week; pregnancy; children < 6 kg; history of neuropsychiatric disorder
Interventions	ASpo + MQ15 (C) vs MQ25 AS 10 mg/kg (3 doses at 8 h intervals) + MQ 750 mg (single dose) MQ 1250 mg (single dose) Treatment supervised, drugs given after temperature reduced by paracetamol and tepid sponging
Outcomes	Clinical: number afebrile at 24 and 48 h; symptomatic treatment failure Parasitological: asymptomatic treatment failure Adverse events
Notes	Quality assessment: B, B, C AS (tablet) from Guilin No.1 Factory, China Seasonal unstable transmission, multidrug resistance

Nosten[1]THI-MYA92-3

Methods	Randomised in pairs, method not specified Follow-up 28 days Excluded: AS+MQ = 5/151 (3%), MQ = 2/153 (1%) Loss to follow-up day 28: 27/146 (18%), 31/151 (20%)
Participants	304 adults and children, 6 months to 88 years; slide positive Pf Excluded: severe malaria; pregnancy; children < 5kg; antimalarials in previous month

Nosten[1]THI-MYA92-3 (Continued)

Interventions	ASpo + MQ25 (C) vs MQ25 AS 4 mg/kg (single dose) + MQ 1250 mg (concomitant single dose) MQ 1250 mg (single dose) Treatment supervised; patients with high temperature cooled and given acetaminophen before mefloquine
Outcomes	Clinical: % patients febrile at each follow-up; haematological recovery Parasitological: % patients parasitaemic at each follow-up; failure rate; recrudescence Adverse events
Notes	Quality assessment: B, B, C AS (tablet) from Guilin Pharmaceutical Factory No1, China Seasonal hypoendemic to mesoendemic, multidrug resistance

Nosten[2]THI-MYA92-3

Methods	Randomised, method not specified Follow-up 63 days No exclusions reported Loss to follow-up day 28: AS+MQ = 26/179 (14%), MQ = 15/169 (9%); day 63: 71/179 (40%), 40/169 (24%)
Participants	348 adults and children, 4 months to 58 years; slide positive Pf Excluded: severe malaria; pregnancy; children < 5kg; antimalarials in previous month
Interventions	ASpo + MQ25 (S) vs MQ25 AS 10 mg/kg/3 d (4 mg/kg initially, then 2 mg/kg once daily (n = 112) or 1 mg/kg twice daily (n = 67)) + MQ 1250 mg (on day 2) MQ 1250 mg Treatment supervised; patients with high temperature cooled and given acetaminophen before mefloquine
Outcomes	Clinical: % patients febrile at each follow-up; haematological recovery Parasitological: % patients parasitaemic at each follow-up; failure rate; recrudescence Adverse events
Notes	Quality assessment: B, B, C AS (tablet) from Guilin Pharmaceutical Factory No1, China Seasonal hypoendemic to mesoendemic, multidrug resistance

PriceTHI-MYA93-4

Methods	Patients randomised in blocks of three using a random number generator; open-label Follow-up 63 days Excluded: AM+MQ = 4/178 (2%), AS+MQ = 5/180 (3%), MQ = 1/182 (< 1%) Loss to follow-up day 28: 17%, 15%, 10%; d63: 37%, 30%, 24%

PriceTHI-MYA93-4 (Continued)

Participants	540 adults and children; slide positive Pf Excluded: severe disease; pregnancy; children < 5kg; antimalarials in last 63 days; concomitant disease; history of neuropsychiatric disorder
Interventions	AMpo + MQ25 (S) vs ASpo + MQ25 (S) vs MQ25 AM 12 mg/kg (4 mg/kg/d for 3 d) + MQ 1250 mg (single dose on day 2) AS 12 mg/kg (4 mg/kg/d for 3 d) + MQ 1250 mg (single dose on day 2) MQ 1250 mg (single dose) Treatment supervised, drugs given after temperature reduced by paracetamol and tepid sponging
Outcomes	Clinical: % patients febrile at each follow-up; haematological recovery Parasitological: % patients parasitaemic at each follow-up; failure rate; recrudescence Adverse events
Notes	Quality assessment: B, B, C AS from Guilin No.1 factory; AM from Kunming Pharmaceutical factory, China Seasonal low transmission, multidrug resistance

RugemalilaTAZ(97)

Methods	Randomised using random numbers, allocation concealment not specified; patients and assessors reported as blind (however, 5 d vs 3 d regimen), nurses giving drug not blinded Follow-up 28 days No exclusions reported Loss to follow-up day 28: AM = 13/52 (25%), CLQ = 11/54 (20%)
Participants	106 adults and children; Pf parasitaemia Excluded: < 5 years; pregnancy; lactation; antimalarials in previous 14 days; positive Dill-Glazko urine test; concurrent illness
Interventions	AMpo vs CLQpo AM 9.6 mg/kg if < 15 years (3.2 mg/kg on day 1, 1.6 mg/kg on days 2 to 5), 700 mg if >15y (300 mg on day 1, 100 mg on days 2 to 5) CLQ 25 mg/kg over 3 days
Outcomes	Clinical: proportion of febrile patients examined on days 0, 3, 7, 14, 21 and 28; prevalence rate of malaria-related symptoms Parasitological: proportion of examined patients cleared of parasitaemia on days 2 to 7, 14, 21 and 28 Adverse events
Notes	Quality assessment: B,A,C AM: Artemam (tablet, 50 mg B-artemether) Holoendemic area, 13% CLQ and 15% MQ resistance in vivo

ThanMYA90-91

Methods	Alternate allocation Follow-up 28 days No exclusions or loss to follow-up reported
Participants	120 adults, military hospital
Interventions	ASpo vs MQ20 AS 600 mg/5 d
Outcomes	Parasitological: parasite clearance at day 7 and 28
Notes	Quality assessment: C, B, C Source of AS: not reported One treatment group excluded: Halofantran, 60 patients Endemicity, transmission not reported

ThanMYA91

Methods	Alternate allocation Follow-up 28 days No exclusions or loss to follow-up reported
Participants	118 adults, military hospital
Interventions	ASpo + MQ20 vs MQ20 AS 600 mg/5 d
Outcomes	Parasitological: parasite clearance at day 7 and 28
Notes	Quality assessment: C, B, C Source of AS: not reported Endemicity, transmission not reported

ThanMYA93a

Methods	Alternate allocation; parasitological outcomes blinded Follow-up 28 days No exclusions reported Loss to follow-up: ART = 2/10 (20%), ART+MQ15 = 2/33 (6%)
Participants	76 male adults, military hospital, 18 to 50 years; febrile; Pf asexual > 500 < 100,000/μl Excluded: severe malaria symptoms; PfPv; concomitant systemic illness; antimalarials in previous 2 weeks

ThanMYA93a (Continued)

Interventions	ART + MQ10 vs ART + MQ15 (C) ART 750 mg (250 mg at 0 h, 4 h and 24h) + MQ 500 mg (at 0 h) ART 750 mg (as before) + MQ 750 mg (at 0 h)
Outcomes	Clinical: FCT Parasitological: PCT, cure rate, recrudescence Adverse events
Notes	Quality assessment: C, B, C ART: Lactab (250 mg) Mepha, Switzerland Endemicity, transmission not reported

ThanMYA93b

Methods	Alternate allocation Follow-up 28 days No exclusions or loss to follow-up reported
Participants	36 adults, military hospital
Interventions	AS + MQ10 (C) vs AS + MQ10 (S) AS 600 mg/3 d
Outcomes	Parasitological: parasite clearance at day 7 and 28
Notes	Quality assessment: C, B, C Source of AS: not reported Endemicity, transmission not reported

ThanMYA93c

Methods	Alternate allocation Follow-up 28 days No exclusions or loss to follow-up reported
Participants	46 Burmese adults, military hospital
Interventions	AMpo dose AM 360 mg/7 d (80 mg at 0 h, 40 mg at 12 h, then 40 mg/d); 20 patients AM 640 mg/7 d (80 mg at 0 h and 12 h, then 80 mg/d); 26 patients
Outcomes	Parasitological: parasite clearance at day 7 and 28
Notes	Quality assessment: C, B, C Source of AM: not reported Two treatment groups excluded, uneven numbers (alternate allocation):

ThanMYA93c (Continued)

AM 480 mg/5 d (80 mg at 0 h and 12h, then 80 mg/d); 24 patients
AM 960 mg/5 d (160 mg at 0 h, 80 mg every 12 h); 40 patients

Patients from areas of varying resistance, all CLQ resistant

ThanMYA94a

Methods	Alternate allocation Follow-up 28 days No exclusions or loss to follow-up reported
Participants	50 adults, military hospital
Interventions	DHApo vs DHApo + MQ20 DHA 360 mg/5 d
Outcomes	Parasitological: parasite clearance at day 7 and 28
Notes	Quality assesment: C, B, C Source of DHA: not reported Endemicity, transmission not reported

ThanMYA96a

Methods	Alternate allocation Follow-up 28 days No exclusions or loss to follow-up reported
Participants	34 adults, military
Interventions	ASpo dose AS 800 mg/3 days + MQ25 AS 1200 mg/3 days + MQ25
Outcomes	Parasitological: parasite clearance at day 7 and 28
Notes	Quality assessment: C, B, C Source of AS: not reported Endemicity, transmission not reported

ThanMYA97

Methods	Alternate allocation Follow-up 28 days

ThanMYA97 (Continued)

	No exclusions or loss to follow-up reported
Participants	100 adults, military hospital
Interventions	ASpo + MQ15 vs ASpo + MQ25 AS 400 mg both groups
Outcomes	Parasitological: parasite clearance at day 7 and 42
Notes	Quality assessment: C, B, C Source of AS: not reported Endemicity, transmission not reported

ThimasarnTHI93-4

Methods	Randomised, method not specified; no blinding Follow-up 28 days 12/394 excluded due to treatment error Loss to follow-up day 7: AS = 7/55 (13%); AM = 8/42 (19%); AS+MQ(1) = 2/80 (2%); AS+MQ(2) = 4/68 (6%); AM+MQ = 5/45 (11%); MQ = 2/45 (4%); QNN+Tc = 6/47 (13%) Loss to follow-up day 28: AS = 8/55 (14%); AM = 11/42 (26%); AS+MQ(1) = 5/80 (6%); AS+MQ(2) = 6/68 (9%); AM+MQ = 10/45 (22%); MQ = 4/45 (9%); QNN+Tc = 8/47 (17%)
Participants	394 Thai and Cambodian male and female 15 to 70 years; febrile; uncomplicated malaria; Pf 500 to 400,000/μl Excluded: complications; pregnancy; antimalarials in previous 2 weeks
Interventions	ASpo vs AMpo vs ASpo+MQ vs AMpo+MQ vs MQ vs QNN+Tc AS 700 mg/5 d (300 mg day 1, 100 mg days 2 to 5) AM 800 mg/5 d (320 mg day 1, 120 mg days 2 to 5) AS 600 mg/2 d+MQ25 (AS 300 mg + MQ750 mg at 6 h on day 1, AS 300 mg + MQ500 mg at 6 h on day 2) AS 600 mg/2 d+MQ15 (AS 300 mg + MQ750 mg at 1 h on day 1, AS 300 mg on day 2) AM 640 mg/2 d+MQ25 (AM 320 mg + MQ750 mg at 6 h on day 1, AM 320 mg + MQ500 mg at 6 h on day 2) MQ25/2 d (750 mg on day 1, 500 mg on day 2) QNN+Tc/7 d (QNN 600 mg 3 x daily + Tc 500 mg x 2 daily)
Outcomes	Parasitological: Parasitaemia on day 7 and day 28 Adverse events
Notes	Quality assessment: B, B, C AS 50 mg tablet from Guilin Co., China AM40 mg capsule from Kunming Co., China MQ 250 mg tablet from Hoffman La Roche Endemic area, MDR Pf 4 centre trial

vonSeidleinGAM96

Methods	Computer generated block (size 4) randomisation, investigators blind to treatment code Double-dummy placebo blinded Follow-up 15 days (passive follow-up to day 29) Excluded: at day 4 Co-AM = 7/144 (5%), SP = 2/143 (1%), at day 15 Co-AM = 8/144 (6%), SP = 8/143 (6%) Loss to follow-up: at day 4 Co-AM = 4/144 (3%), SP = 4/143 (3%), at day 15 Co-AM = 17/144 (12%), SP = 7/143 (5%)
Participants	287 children 1 to 5 years; history of fever; Pf > 5000/μl Excluded: required parenteral treatment; SP in previous 2 weeks; PCV < 25%; malnutrition; chronic disease
Interventions	Co-AMpo vs SPpo Co-AM/2 d: AM 80 mg/kg+Lumefantrine 480 mg/kg given for body weight < 15 kg; x 2 dose given to body weight > 15 kg (4 equal doses at 0 h, 8 h, 24 h and 48 h) SP single dose: S 250 mg+ P 12.5 mg given to body weight < 15 kg; x 2 dose given to body weight > 15kg Paracetamol 15 mg/kg/6 h while febrile
Outcomes	Clinical: episodes of malaria in 29 days; new infections vs recrudescence by genotyping; PCV Parasitological: PCT; cure rate at day 4 and day 15; gametocytaemia Adverse events
Notes	Quality assessment: A, A, C Co-AM (CGP56697) from Novartis Pharma A.G. Seasonal transmission

WinMYA94-5

Methods	Alternate allocation; double blind Follow-up 28 days Excluded: AM = 2/43 (5%), AS = 3/43 (7%) No loss to follow-up
Participants	86 adult male, 15 to 50 years; uncomplicated Pf malaria; Pf asexual > 500/μl Excluded: concomitant illness; severe manifestations; mixed infection; antimalarial in previous 14 days; diarrhoea
Interventions	AMpr vs ASpr AM 600 mg (200 mg/d for 3 days) AS 600 mg (200 mg/d for 3 days)
Outcomes	Clinical: FCT Parasitological: PCT, S/R Adverse events
Notes	Quality assessment: C, B, B AM, AS: Rectocaps (200 mg), Mepha, Switzerland

WinMYA94-5 (Continued)

Malaria free study area

Study code: Name of investigator, COUNTRY CODE, year the study was done (study publication date in brackets if the year the study was done is not known).

Small letters a, b code studies done in the same year chronologically.

Numbers [1], [2] code separate randomised controlled trials reported in one study.

BRZ-Brazil; CHI-China; MYA-Myanmar; NIG-Nigeria; TAZ-Tanzania; THI-Thailand; VNM-Viet Nam; ART-artemisinin; AS-artesunate; AM-artemether; DHA-dihydroartemisinin; MQ-mefloquine; CLQ-chloroquine; SP-sulfadoxine-pyrimethamine; MQ10 = 500 mg; MQ15 = 750 mg; MQ20 = 1000 mg; MQ25 = 1250 mg; (S)-sequential MQ; (C)-concomitant MQ; MDR-multidrug resistant; *Pf-Plasmodium falciparum*; *Pv-Plasmodium vivax*; po-per; os pr-per rectum; PCT-parasite clearance time; FCT-fever clearance time; PC50/90/95-time to 50%/90%/95% reduction in parasitaemia; S/R-sensitive/resistant; (WHO 1973).

Quality assessment: the risk of bias in the trials was assessed using the Cochrane Infectious Diseases Group standard guidelines in terms of 1) allocation concealment, 2) generation of allocation sequence, 3) inclusion of all randomised participants. Graded A, B, C, in descending order of quality.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Alin TAZ 93	Artesunate given by intravenous infusion.
Anh VNM 92b	Although this study is titled an open randomised comparison the data we have suggest that it is comparing data from three different regimens tested in patients at one site which was collected from three individual studies comparing the same three regimens at three different sites.
Ashton VNM (98)	RCT comparing oral with rectal administration of artemisinin (500 mg/d/5 days). Comparison does not fit the inclusion criteria. Outcomes reported: pharmacokinetics and fever clearance time.
Batty VNM 96	Intravenous route of administration does not meet the inclusion criteria, although relevant outcomes reported (fever and 50% parasite clearance time).
Bich VNM 93	Treatment regimens do not fit the inclusion criteria: ART + QNN vs AS + doxycycline vs QNN
Bunnag THI (97)	Treatment regimens do not fit the inclusion criteria: AM 150 mg + MQ15 at 0h, followed by either AM 100 mg + MQ10 at 6h [Group A] or AM 100 mg + MQ10 at 24h [Group B]
Bunnag THI 89-90a	Using placebo in the middle of a treatment regimen, as in this trial, would not be done in clinical practice. AS600 mg/5 d (200 mg on day 1, 100 mg on day 2, placebo on day 3 and day 4, 100 mg on days 5 to 7) AS 600 mg/7 d (200 mg on d1, 100 mg on days 2 to 5, placebo on days 6 and 7)
Bunnag THI 89-90b	Comparison of two different doses of artemether given by intramuscular injection.
Chen CHI	Reported as randomised comparison of dihydroartemisinin and quinine. Only outcome reported is gametocyte infectivity.
Duarte BRZ 92-3	Treatment regimens do not fit the inclusion criteria: AS + tetracycline vs. QNN + tetracycline, concomitant treatments.
Duc VNM 93	Artemether given by intramuscular injection compared with oral chloroquine.
Elhassan SUD 91	Artemether versus quinine both given by intramuscular injection.
Fu CHI	Investigators unable to provide data or details concerning design, conduct and analysis of the trial (personal communication).

Study	Reason for exclusion
Fu CHI 88-90	Artesunate given by intramuscular injection compared with oral piperaquine, used only in China; also intramuscular AS dose comparison, different dose given over a different time period in each treatment group.
Guo CHI (90)	Comparison of non-randomised treatment groups.
Guo CHI 86a	Artemether given by intramuscular injection compared with oral piperaquine, used only in China.
Guo CHI 86b	Artemether given by intramuscular injection compared with oral pyronaridine (+ sulfadoxine pyrimethamine) used only in China.
Hien VNM [2-4] (94)	Treatment regimens do not fit the inclusion criteria: Study [2]: ART + MQ vs. Fansimef vs. QNN + SP Study [3]: ART + MQ vs. Fansimef Study [4]: ART + MQ vs. Fansimef vs. ART + SP
Irion GAM(98)	Same study as included study Hatz GAM(98). Reports only on distinction of new infections from re-crudescences as determined by PCR-RFLP analysis.
Jiang CHI 80	Patients were not allocated randomly to the two treatment groups (personal communication).
Jiao CHI (97)	Treatment regimens do not meet the inclusion criteria: benflumetol vs. CGP 56697 (co-artemether).
Li CHI (82)	No comparator group.
Li CHI (90)	Non-randomised comparison of groups treated at different study sites.
Li CHI (95)	Report does not mention randomisation (DHA 5d vs. 7d).
Li CHI 85	Artesunate given by intravenous infusion.
Li CHI a	Outcome measured (gametocyte infectivity) does not fit inclusion criteria.
Li CHI b	Investigator unable to provide data or details concerning design, conduct and analysis of the trial (personal communication).
Li VNM (95)	Investigator unable to provide details concerning design, conduct and analysis of the trial (personal communication).
Looareesuwan THI 92a	Treatment regimens do not fit the inclusion criteria: MQ + doxycycline vs. AS + doxycycline, both concomitant.
Looareesuwan THI 94	Patients were not randomly assigned to the two treatment groups.
LuxemburgerTHI-MYA93	Comparison of oral AM+MQ vs. intravenous QNN+MQ in patients with hyperparasitaemia.
Na-BangchangTHI(96)a	Treatment regimens do not fit inclusion criteria: artemether-doxycycline vs. artemether-azithromycin
Na-BangchangTHI(96)b	Treatment regimens do not fit the inclusion criteria: three different regimens of artemether-pyrimethamine.
Nigeria 1988	AM versus CLQ both given by intramuscular injection.
Pang CHI (87)	Not a randomised comparison.

Study	Reason for exclusion
Price THI 93-5	Hyperparasitaemic falciparum malaria.
QACRG CHI 75	Unable to obtain detailed information on this study from 1975 summarised in a review of anti-malarial studies on qinghaosu by the Qinghaosu Antimalaria Co-ordinating Research Group [China]. Design not specified; 18 patients treated with qinghaosu tablets, 18 with oral chloroquine; PCT and recrudescence at day 28 reported.
SabchareonTHI95-6	Compares artesunate suppositories vs. oral. ASpr 45(30-57) mg/kg over 48h + MQ25 (S) 6h apart (total 3 days) ASpo 18(15-21) mg/kg over 48h+ MQ25(S) 6h apart (total 3 days)
Shen 1989	Retrospective comparison of separate study groups.
Shwe MYA (98)	Report of three community based studies: 1. Retrospective study to characterise current use of artemisinin derivatives 2. Random cohort study on use of subsidised mefloquine with artesunate 3. Double blind study of compliance and effectiveness of combined packaging (artesunate 5 days + MQ vs. artesunate 5 days + paracetamol placebo) at six health centres, two selling intervention, four placebo.
Simooya ZIM 91	Artemether given by intramuscular injection vs. oral chloroquine.
Sowunmi NIG 93	Artemether given by intramuscular injection vs. oral mefloquine in hyperparasitaemic falciparum malaria.
Sowunmi NIG 94-7	Artemether given by intramuscular injection.
Than MYA 94b	Treatment regimens do not fit the inclusion criteria. Alternate allocation. Outcomes: (cure rate d7 and 28). AM 480 mg/5 d + Dox 200 mg/7 d; 30 patients (30/30; 29/30) AM 480 mg/5 d + Tc 1000 mg/7d; 28 patients (28/28, 27/28) AM 480/5 d + MQ20; 30 patients (30/30; 30/30).
ThanMYA95	Treatment groups treated with different artesunate regimens and different mefloquine schedules (sequential or concomitant). AS600/2+MQ20(S) vs. AS600/3+MQ20(C).
ThanMYA96b	Unexplained uneven group numbers in a study supposedly using alternate allocation. Dihydroartemisinin (Cotexin) regimen comparison: 480 mg/3 d (32 patients) vs. 480 mg/7 d (21 patients).
Thwe MYA 93	Investigators unable to provide data or details concerning design, conduct and analysis of the trial (personal communication, Kyaw Win).
van Vugt THI 95-6	Compares co-artemether (AM + lumefantrine/benflumetol) vs AS + MQ. Does not meet the inclusion criteria as both the artemisinin derivative and the combination drug differ between the treatment groups.
Wang CHI (81)	Observational study, no comparator group.
Wang CHI (95)	Investigator unable to provide details concerning design, conduct and analysis of the trial (personal communication).
Wang CHI 79-80	Patients were not allocated randomly to the three treatment groups (personal communication).
Wang CHI 94	Investigator unable to provide details concerning design, conduct and analysis of the trial (personal communication).

Study	Reason for exclusion
Yen VNM 96	Pseudorandomisation of patients (choosing a closed odd-even ticket) with uncomplicated falciparum malaria to supervised versus unsupervised treatment with artemisinin at one study site and artesunate at another site.

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

[Anh VNM 92a](#)

Methods	—
Participants	—
Interventions	—
Outcomes	—
Notes	—

[Bunnag THI \(97\)b](#)

Methods	—
Participants	—
Interventions	—
Outcomes	—
Notes	—

[Coker NIG](#)

Methods	—
Participants	—
Interventions	—
Outcomes	—
Notes	—

[Doherty GAM \(99\)](#)

Methods	—
Participants	—

Doherty GAM (99) *(Continued)*

Interventions	—
Outcomes	—
Notes	—

Hamisi THI (97)

Methods	—
Participants	—
Interventions	—
Outcomes	—
Notes	—

Honrado THI 94-5

Methods	—
Participants	—
Interventions	—
Outcomes	—
Notes	—

LooareesuwanTHI(99)

Methods	—
Participants	—
Interventions	—
Outcomes	—
Notes	—

Novartis CHI

Methods	—
Participants	—

Artemisinin derivatives for treating uncomplicated malaria (Review)

Novartis CHI (Continued)

Interventions	—
Outcomes	—
Notes	—

Price THI (98)

Methods	—
Participants	—
Interventions	—
Outcomes	—
Notes	—

Salcedo BRZ (97)

Methods	—
Participants	—
Interventions	—
Outcomes	—
Notes	—

Villalobos (97)

Methods	
Participants	
Interventions	
Outcomes	
Notes	

DATA AND ANALYSES

Comparison 1. Single drug

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasite clearance at day 7	8		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Artesunate vs chloroquine	1	103	Odds Ratio (M-H, Random, 95% CI)	61.04 [7.82, 476.74]
1.2 Artemether vs chloroquine	1	106	Odds Ratio (M-H, Random, 95% CI)	7.52 [2.59, 21.85]
1.3 Artemisinin vs quinine	3	182	Odds Ratio (M-H, Random, 95% CI)	10.62 [1.15, 98.05]
1.4 Artesunate vs quinine	1	102	Odds Ratio (M-H, Random, 95% CI)	1.2 [0.39, 3.71]
1.5 Artemether vs quinine	1	89	Odds Ratio (M-H, Random, 95% CI)	0.74 [0.24, 2.26]
1.6 Artesunate vs mefloquine	2	220	Odds Ratio (M-H, Random, 95% CI)	1.41 [0.05, 42.18]
1.7 Artemether vs mefloquine	2	133	Odds Ratio (M-H, Random, 95% CI)	0.70 [0.06, 8.52]
1.8 Artesunate vs sulfadoxine-pyrimethamine	1	105	Odds Ratio (M-H, Random, 95% CI)	21.08 [2.67, 166.67]
2 Parasite clearance at day 28	5		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Artemisinin vs quinine	1	49	Odds Ratio (M-H, Random, 95% CI)	0.57 [0.18, 1.79]
2.2 Artesunate vs quinine	1	86	Odds Ratio (M-H, Random, 95% CI)	3.83 [0.38, 38.42]
2.3 Artemether vs quinine	1	70	Odds Ratio (M-H, Random, 95% CI)	2.5 [0.25, 25.30]
2.4 Artesunate vs mefloquine	3	285	Odds Ratio (M-H, Random, 95% CI)	0.98 [0.49, 1.95]
2.5 Artemether vs mefloquine	2	113	Odds Ratio (M-H, Random, 95% CI)	1.91 [0.05, 80.17]
3 Adverse events (artemisinin drug vs mefloquine)	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Vomiting	4	387	Odds Ratio (M-H, Random, 95% CI)	0.80 [0.28, 2.30]
3.2 Dizziness	3	222	Odds Ratio (M-H, Random, 95% CI)	0.16 [0.02, 1.14]

Analysis 1.1. Comparison 1 Single drug, Outcome 1 Parasite clearance at day 7.

Analysis 1.2. Comparison 1 Single drug, Outcome 2 Parasite clearance at day 28.

Analysis 1.3. Comparison 1 Single drug, Outcome 3 Adverse events (artemisinin drug vs mefloquine).

Comparison 2. Co-artemether vs standard treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasite clearance at day 4 or day 7	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Co-artemether vs sulfadox-ine-pyrimethamine (day 4)	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Co-artemether vs chloroquine (day 7)	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Parasite clearance at day 14/15	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Co-artemether vs sulfadoxine-pyrimethamine	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Co-artemether vs chloroquine	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 Co-artemether vs standard treatment, Outcome 1 Parasite clearance at day 4 or day 7.

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.1.1 Co-artemether vs sulfadoxine-pyrimethamine (day 4)				
vonSeidleinGAM96	133/144	128/143		1.42[0.63,3.2]
2.1.2 Co-artemether vs chloroquine (day 7)				
HatzTAZ(98)	109/130	34/130		14.66[7.97,26.95]
			Favours Ctrl 0.01 0.1 1 10 100 Favours Expt	

Analysis 2.2. Comparison 2 Co-artemether vs standard treatment, Outcome 2 Parasite clearance at day 14/15.

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.2.1 Co-artemether vs sulfadoxine-pyrimethamine				
vonSeidleinGAM96	111/119	125/128		0.33[0.09,1.29]
2.2.2 Co-artemether vs chloroquine				
HatzTAZ(98)	95/110	10/97		55.1[23.52,129.09]
			Favours Ctrl 0.001 0.1 1 10 1000 Favours Expt	

Comparison 3. Combination with mefloquine vs mefloquine alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasite clearance at day 7	8		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Artemisinin	1	240	Odds Ratio (M-H, Fixed, 95% CI)	1.46 [0.57, 3.78]
1.2 Artesunate	7	1829	Odds Ratio (M-H, Fixed, 95% CI)	2.28 [1.67, 3.13]
1.3 Artemether	2	450	Odds Ratio (M-H, Fixed, 95% CI)	2.58 [1.37, 4.83]
2 Parasite clearance at day 28	10		Odds Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Artemisinin	1	228	Odds Ratio (M-H, Random, 95% CI)	2.62 [1.40, 4.91]
2.2 Artesunate	9	1737	Odds Ratio (M-H, Random, 95% CI)	4.03 [1.58, 10.23]
2.3 Artemether	2	387	Odds Ratio (M-H, Random, 95% CI)	3.08 [0.05, 191.17]
3 Parasite clearance time	5	532	Mean Difference (IV, Random, 95% CI)	-20.70 [-31.56, -9.85]
3.1 Artemisinin	1	213	Mean Difference (IV, Random, 95% CI)	-20.0 [-26.23, -13.77]
3.2 Artesunate	4	319	Mean Difference (IV, Random, 95% CI)	-21.35 [-36.21, -6.48]
4 Fever clearance time	5	554	Mean Difference (IV, Random, 95% CI)	-10.40 [-18.08, -2.73]
4.1 Artemisinin	1	231	Mean Difference (IV, Random, 95% CI)	-9.0 [-14.57, -3.43]
4.2 Artesunate	4	323	Mean Difference (IV, Random, 95% CI)	-12.33 [-24.93, 0.26]
5 Adverse events	9		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Vomiting, treatment discontinued	4	1491	Odds Ratio (M-H, Random, 95% CI)	0.39 [0.14, 1.11]
5.2 Vomiting, early	2	625	Odds Ratio (M-H, Random, 95% CI)	0.48 [0.06, 3.83]
5.3 Vomiting, late	2	625	Odds Ratio (M-H, Random, 95% CI)	1.02 [0.39, 2.69]
5.4 Vomiting	5	627	Odds Ratio (M-H, Random, 95% CI)	1.40 [0.66, 2.98]
5.5 Dizziness	4	318	Odds Ratio (M-H, Random, 95% CI)	0.80 [0.41, 1.56]
5.6 Diarrhoea	5	481	Odds Ratio (M-H, Random, 95% CI)	1.27 [0.53, 3.06]
5.7 Nausea	5	481	Odds Ratio (M-H, Random, 95% CI)	0.67 [0.42, 1.07]

Analysis 3.1. Comparison 3 Combination with mefloquine vs mefloquine alone, Outcome 1 Parasite clearance at day 7.

Analysis 3.2. Comparison 3 Combination with mefloquine vs mefloquine alone, Outcome 2 Parasite clearance at day 28.

Analysis 3.3. Comparison 3 Combination with mefloquine vs mefloquine alone, Outcome 3 Parasite clearance time.

Analysis 3.4. Comparison 3 Combination with mefloquine vs mefloquine alone, Outcome 4 Fever clearance time.

Analysis 3.5. Comparison 3 Combination with mefloquine vs mefloquine alone, Outcome 5 Adverse events.

Comparison 4. Combination with mefloquine vs artemisinin drug alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasite clearance at day 28	9		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Artemisinin	3	147	Odds Ratio (M-H, Fixed, 95% CI)	5.96 [2.40, 14.76]
1.2 Artesunate	3	261	Odds Ratio (M-H, Fixed, 95% CI)	1.14 [0.42, 3.13]
1.3 Artemether (Looareesuwan 500mg)	3	248	Odds Ratio (M-H, Fixed, 95% CI)	4.05 [1.47, 11.18]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4 Artemether (Looareesuwan 750mg)	3	259	Odds Ratio (M-H, Fixed, 95% CI)	1.66 [0.52, 5.25]
1.5 Dihydroartemisinin	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.14, 3.59]
2 Parasite clearance time	8		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Artemisinin	3	168	Mean Difference (IV, Random, 95% CI)	1.75 [-10.07, 13.58]
2.2 Artemether	2	240	Mean Difference (IV, Random, 95% CI)	-0.20 [-7.36, 6.97]
2.3 Artesunate	3	246	Mean Difference (IV, Random, 95% CI)	0.91 [-1.18, 3.01]
3 Time to 50/90% parasite clearance	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Artemisinin, PC50	2	128	Mean Difference (IV, Fixed, 95% CI)	-1.82 [-3.71, 0.07]
3.2 Artemisinin, PC90	1	90	Mean Difference (IV, Fixed, 95% CI)	-1.10 [-5.14, 2.94]
4 Fever clearance time	8		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Artemisinin	3	168	Mean Difference (IV, Random, 95% CI)	-0.02 [-8.65, 8.60]
4.2 Artesunate	3	251	Mean Difference (IV, Random, 95% CI)	-2.68 [-5.42, 0.06]
4.3 Artemether	2	260	Mean Difference (IV, Random, 95% CI)	-2.62 [-13.15, 7.91]
5 Adverse events	6		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Vomiting	6	601	Odds Ratio (M-H, Random, 95% CI)	1.89 [1.07, 3.34]
5.2 Diarrhoea	5	535	Odds Ratio (M-H, Random, 95% CI)	0.59 [0.13, 2.60]

Analysis 4.1. Comparison 4 Combination with mefloquine vs artemisinin drug alone, Outcome 1 Parasite clearance at day 28.

Analysis 4.2. Comparison 4 Combination with mefloquine vs artemisinin drug alone, Outcome 2 Parasite clearance time.

Analysis 4.3. Comparison 4 Combination with mefloquine vs artemisinin drug alone, Outcome 3 Time to 50/90% parasite clearance.

Analysis 4.4. Comparison 4 Combination with mefloquine vs artemisinin drug alone, Outcome 4 Fever clearance time.

Analysis 4.5. Comparison 4 Combination with mefloquine vs artemisinin drug alone, Outcome 5 Adverse events.

Comparison 5. Combination with mefloquine: mefloquine dose/schedule

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasite clearance at day 28	5		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Artemether (AM) 300 mg + mefloquine (MQ) 15 vs AM 300 mg + MQ 25	2	198	Odds Ratio (M-H, Fixed, 95% CI)	0.17 [0.04, 0.66]
1.2 Artemether (AM) 750 mg + mefloquine (MQ) 10 vs AM 750 mg + MQ 15	1	63	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.32, 2.47]
1.3 Artesunate (AS) 600 mg + mefloquine (MQ) 15 vs AS 600 mg + MQ 25	1	138	Odds Ratio (M-H, Fixed, 95% CI)	3.81 [0.39, 37.61]
1.4 Artesunate (AS) 600 mg + mefloquine (MQ) 10 concomitant vs sequential	1	36	Odds Ratio (M-H, Fixed, 95% CI)	7.5 [0.78, 72.44]

Analysis 5.1. Comparison 5 Combination with mefloquine: mefloquine dose/schedule, Outcome 1 Parasite clearance at day 28.

Comparison 6. Combination with sulfadoxine-pyrimethamine vs artemisinin drug alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasite clearance at day 28	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Artemisinin	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 6.1. Comparison 6 Combination with sulfadoxine-pyrimethamine vs artemisinin drug alone, Outcome 1 Parasite clearance at day 28.

Comparison 7. Comparison between artemisinin drugs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasite clearance at day 7	5		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Artemisinin vs artesunate	1	40	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Artemether vs artesunate	4	661	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.57, 1.74]
2 Parasite clearance at day 28	5		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Artemisinin vs artesunate	1	39	Odds Ratio (M-H, Fixed, 95% CI)	0.50 [0.12, 2.08]
2.2 Artemether vs artesunate	4	578	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.51, 1.94]
3 Parasite clearance time	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Artemisinin vs artesunate	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 Artemether vs artesunate	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Fever clearance time	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 Artemisinin vs artesunate	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Artemether vs artesunate	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 7.1. Comparison 7 Comparison between artemisinin drugs, Outcome 1 Parasite clearance at day 7.

Analysis 7.2. Comparison 7 Comparison between artemisinin drugs, Outcome 2 Parasite clearance at day 28.

Analysis 7.3. Comparison 7 Comparison between artemisinin drugs, Outcome 3 Parasite clearance time.

Analysis 7.4. Comparison 7 Comparison between artemisinin drugs, Outcome 4 Fever clearance time.

WHAT'S NEW

Date	Event	Description
9 November 2009	Review declared as stable	The research questions raised in this review have now been answered and priorities have changed. It is therefore considered no longer necessary to update this review. This decision was taken in August 2008, prior to the introduction of a formal Cochrane policy, hence the necessity to republish now. Further details of reasoning can be found in the 'History' section of this review.

HISTORY

Protocol first published: Issue 3, 1997

Review first published: Issue 3, 1998

Date	Event	Description
25 October 2008	Amended	Converted to new review format with minor editing.
4 August 2008	Review declared as stable	This review was first published in 1998, Issue 3, and was undertaken to provide a comprehensive assessment of the benefits and risks of this new class of antimalarial drugs in different epidemiological settings. It aimed to inform drug policy decisions on their rational use, and the clinical questions addressed by the review were based on what needed clarifying at that time. In April 1998, research findings on artemisinin and its derivatives, including this review, were presented at a conference attended by representatives of the World Health Organization, non-governmental organizations, researchers in the field, and the pharmaceutical industry. Current knowledge and priorities for future research were clarified at the conference 'The rational use of qinghaosu and its derivatives' convened by the International Laveran Association, Annecy, France, 19-22 April 1998 (<i>Médecine Tropicale</i> 1998;58 Suppl 3). The clinical effectiveness of artemisinin drugs is no longer in question and a safety overview showed them to be well tolerated. It is not a priority to continue to review comparisons of artemisinin drugs used alone with standard non-artemisinin drug treatments; nor whether one derivative is better than the others. The way forward is combination therapy and the main goal is to optimize clinical effectiveness in areas of high and lower parasite resistance to standard antimalarial regimens. In conclusion, this systematic review has served its intended purpose. Most of the questions addressed have now been answered and research priorities have, as a result, moved forward. The foremost outstanding clinical questions are around artemisinin combination regimens, and these will be managed within separate Cochrane Reviews. It is, therefore, no longer necessary or expedient to update this review in its existing format. It will continue to appear in the <i>Cochrane Database of Systematic Reviews</i> for information only.
25 May 2005	New search has been performed	Minor update.
18 February 1999	New citation required and conclusions have changed	Substantive amendment.

DECLARATIONS OF INTEREST

We certify that we have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of the review (e.g. employment, consultancy, stock ownership, honoraria, expert testimony).

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK.

External sources

- European Commission (Directorate General XII), Belgium.
- Department for International Development, UK.

NOTES

This review was first published in issue 3 1998 of the Cochrane Library. The original review was undertaken to provide a comprehensive assessment of benefit and risk in different epidemiological settings in order to inform drug policy decisions on the rational use of this new class of antimalarial drugs. The clinical questions addressed by the review were based on what needed clarifying at that time.

In April 1998 a conference was held on The Rational use of Qinghaosu and its Derivatives (*Médecine Tropicale* 1998;58(3 suppl). Research findings to date were presented and discussed among representatives of WHO, non-governmental organisations, researchers in the field and the pharmaceutical industry. Our original systematic review served as a working document at that meeting.

The published conclusions relating to treatment of uncomplicated falciparum malaria include the following:

1. It is clear that artemisinin drugs are fast and effective against uncomplicated *Plasmodium falciparum* malaria in adults and children in all areas of the world
2. All artemisinin derivatives investigated have comparable efficacy
3. These drugs should be used in combination with a second, longer-acting antimalarial to minimise recrudescence and development of resistance
4. In multidrug resistance areas artemisinin drugs (in combination therapy) should be given for at least 3 days to prevent recrudescence.
5. There have been few studies in areas where there is not multidrug resistance, however, there is a strong theoretical basis for always using longer acting antimalarial drugs concurrently with artemisinin derivatives.

As a result current knowledge and priorities for future research were clarified. The clinical effectiveness of artemisinin drugs is no longer in question and a safety overview showed them to be well tolerated. It is not a priority to continue to review comparisons of artemisinin drugs used alone versus standard non-artemisinin drug treatments; nor whether one derivative is better than the others. The way forward is combination therapy and the main goal is to optimise clinical effectiveness in areas of high and lower parasite resistance to standard antimalarial regimens.

In conclusion, this systematic review has served its intended purpose. Most of the questions addressed have now been answered and research priorities have, as a result, moved forward. The foremost outstanding clinical questions are around artemisinin combination regimens, and these will be managed within separate Cochrane Reviews. It is, therefore, no longer necessary or expedient to update this review in its existing format. It will continue to appear in *The Cochrane Library* for a limited number of future issues, new trials being added to those awaiting assessment, for information only.

INDEX TERMS

Medical Subject Headings (MeSH)

*Artemisinins; Antimalarials [*therapeutic use]; Malaria [*drug therapy]; Malaria, Falciparum [drug therapy]; Sesquiterpenes [*therapeutic use]

MeSH check words

Adult; Humans