Artemisinin derivatives for treating uncomplicated malaria

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A substantive amendment to this systematic review was last made on 18 February 1999. Cochrane reviews are regularly checked and updated if necessary.

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 strategy: We searched the Cochrane Infectious Diseases Group trials 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.

Reviewers' 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.

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, 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
DIHYDROARTÉMISININ: 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
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: 10mg/kg once a day for 5 days, double divided dose on
first day
ARTESUNATE: 2mg/kg once a day for 5 days, double divided dose on
first day
ARTEMETHER: 2mg/kg once a day for 5 days, double divided dose on
first day
DIHYDROARTEMISININ: 2mg/kg once a day for 5 days, double divided
dose on first day

Combination therapy
ARTEMISININ: 10mg/kg once a day for 3 days, plus mefloquine
(15-25mg/kg) as a single dose on second or third day
ARTESUNATE: 4mg/kg once a day for 3 days, plus mefloquine (15-25mg/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 aims of this review are 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.

Criteria for considering studies for this review
Types of studies
Randomised or pseudorandomised 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 intervention
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, artesinin, artesunate, artemether) given by mouth or suppository, alone or in combination with other antimalarials:


2. Combination therapy: artesinin or derivative drug in combination with a longer-acting antimalarial drug (mefloquine, sulfadoxine-pyrimethamine) versus WHO recommended standard treatment for uncomplicated malaria.

3a. Any artesinin derivative compared with any other
3b. Same derivative, different doses
3c. Same derivative and dose, different regimens.

Types of outcome measures

(i) 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.

(ii) 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).

(iii) Adherence: number of patients completing treatment.

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

Search strategy for identification of studies
See: Collaborative Review Group search strategy
The trials register of the Cochrane Infectious Diseases Group 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, arteether, artemether. 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 on the Cochrane Library. 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 1999; BIDS Science Citation Index 1980 to 1999; EMBASE 1988-99, using the search strategy defined by the Cochrane Collaboration, and detailed in appendix 5c of the Cochrane Handbook; African Index Medicus; LILACS. The specific topic search terms used were malaria, qinghaosu, artemisinin, dihydroartemisinin, artesunate, arteether, artemether, co-artemether.

Dates of latest searches:
Cochrane Controlled Trials Register: Cochrane Library Issue 4 1999
MEDLINE: December 1999
BIDS SCI: December 1999
EMBASE: October 1999
African Index Medicus: February 1998
LILACS: December 1999

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: Arenco, 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.

Methods of the review

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 on 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.

Methodological quality of 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 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 prespecified 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.

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 weighted 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.

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 Table of Included Studies.

STUDIES IDENTIFIED
One hundred and five potentially eligible studies were identified, of which 41 met the inclusion criteria, 53 were excluded and 11 are awaiting assessment. 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

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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
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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 artesinin, 168 patients; four artesunate, 386 patients; three artemether, 347 patients).

There were twelve comparisons with mefloquine alone (one artesinin, 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 750mg vs. 500mg in combination with artemisinin (76 patients), four trials studied mefloquine 1250mg vs. 750mg 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
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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 350 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
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Six studies compared different doses of artemisinin drugs delivered over the same time schedule. Oral artemether: 360mg/7d vs. 640mg/7d (46 patients); 500mg/5d vs. 750mg/7d (111 patients). Oral artesunate: 1600mg/7d vs. 1200mg/5d (91 patients); 1200mg/3d vs. 800mg/3d (34 patients); 1200mg/5d vs. 600mg/5d (in 16 patients in two arms of a trial with nine treatment groups); 440mg/5d vs. 280mg/3d (100 patients).

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

Methodological quality
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 pseudorandomised 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.

**Results**

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 2400mg artemisinin over 3 days, whilst children received 600 to 1200mg 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 700mg artemunate over 5 days (in 102 patients) or 800mg 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 700mg, another used 800mg, over 5 days. Three comparisons used 600mg oral artesunate over 5 days, one used 700mg over 5 days (Thailand and Myanmar), and one used 1000mg 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
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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
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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 artether. 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 vomiting was observed between artesunate and mefloquine in three studies. No artether 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 artether (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 arteether and mefloquine patients. No adverse effect on blood cell count or chemsitry was reported with arteether compared with chloroquine or mefloquine.

Summary
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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), arteether 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 arteether 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 arteether (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 arteether 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
Combination-treated patients received mefloquine before day 7 in all studies. (See Interventions, Table of included studies).

Parasite clearance
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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 metaanalysis of weighted 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 (WMD -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 <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 metanalysis of weighted 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 (WMD -10.40 hours, 95% CI -18.08, 2.73, random effect model). This pooled WMD 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
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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
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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
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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 metaanalysis. 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 reports 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  
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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
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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 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 (2500-3000mg over 3-5 days). However, such doses of single-agent artemisinin, although in line with current WHO recommendations (10mg/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 2000mg) cleared parasitaemia in all patients at follow-up when combined with 750mg mefloquine (15mg/kg) in China and Tanzania. In the Viet Nam study, however, a single dose of 500mg artemisinin plus 500mg 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 (2mg/kg/d for 5 days; WHO 1996). However, very different combination regimens were used; short course (1 day), low dose (300mg) artesunate plus 750mg mefloquine is apparently inadequate (KarbwangTHI92c). The Brazilian artesunate study reported a similar finding at day 35 with the combination of 600mg artesunate over 2 days plus 500mg mefloquine (CardosoBRZ93-4).

With artemether, one study used 700mg over 5 days single-agent, one used 800mg over 5 days, and the third tested two doses of artemether in different treatment groups: 500mg over 5 days and 750mg over 7 days (LooareesuwanTHI92b). The lower dose in the latter study is less than the current WHO recommendation (2mg/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 (Looareeesuwan 500mg: 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 800mg) showed no advantage over combination treatment (Looareesuwan 750mg: 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 weighted 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 Table 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 750mg) we combined the data from both groups as they were almost identical and used a weighted 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 weighted 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
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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
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In Thailand, a significant advantage in parasite clearance at day 28 was shown when a 300mg single dose of artemether was combined with 1250mg mefloquine rather than 750mg 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 750mg 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 750mg artemether combined with 500 or 750mg mefloquine, or between 600mg artesunate combined with 750 or 1250mg mefloquine.

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

Only one small Myanmar study (36 patients) compared 600mg artesunate over 3 days with sequential versus concomitant mefloquine (500mg) 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 (500mg single
dose) and sulfadoxine-pyrimethamine (SP) with artemisinin alone (2500mg/5d) 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 metanalysis 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 artemesine 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
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The WHO recommended dose of both artemisinin and artesunate monotherapy produced inadequate cure rates in Tanzania. Both artemether and artesunate (300mg single dose and 600mg over 3 days) appear to be effective in Thailand when combined with 1250mg 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 1200mg artesunate with 600mg 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 1600mg/7days with 1200mg/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 800mg/3 days and 1200mg/3 days in 34 patients.

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

One study comparing artemether combination with mefloquine alone had two groups treated with artemether alone, 500mg over 5 days and 750mg 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 360mg and 640mg
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 600mg given in daily or
twice-daily doses over 5 days in 59 patients (BunnagTHI89b). The
other study compared 600mg 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 (1250mg).
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
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One study in 52 children in Thailand showed artesunate given
rectally (15mg/kg/day for 3 days ) was as effective and safe as
oral treatment (6mg/kg/day for 3 days) when both were combined
with sequential mefloquine (25mg/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 (2500mg over 5days). 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
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Two trials in South East Asia studied combinations of artemisinin
drugs with doxycycline and tetracycline with conflicting results.
Artesunate (300mg over 2.5 days) plus doxycycline was only 80%
effective, and significantly less effective at 28 day follow-up,
than mefloquine (1250mg) plus doxycycline in Thailand
(Looareesuwan THI 92a). Artemether (480mg 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 (750mg over 7days) plus
tetracycline with quinine (6000mg 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.

Summary of analyses

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 unpredicatable 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
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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
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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 applicabilty 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  
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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 has been subject to stringent regulation during development and we cannot assume that they are equivalent in potency or safety.

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

Reviewers' 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 1250mg 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.

Acknowledgements

Heather McIntosh was funded through the Effective Health Care in Developing Countries Project, a grant from the Department for International Development (UK) to the Liverpool School of Tropical Medicine.

We, the reviewers, would like to thank the following members of our advisory panel for their guidance and input throughout the review process: NJ White, S Ebrahim, TE Taylor; also MH Alin, M Liu and P Williamson at the protocol stage. We acknowledge the invaluable contribution of investigators who supplied supplementary data: E Ezedinachi, J Karbwang, Li Guo Qiao, Marlar Than, Kyaw Win; IMPE (Hanoi). Also A Schapira (WHO Hanoi) for assistance in locating Vietnamese studies and Zhou Feng (WCUMS) for Chinese translation. We acknowledge the following drug companies for laudable co-operation: Rhone-Poulec Rorer (JP Helenport), Mepha (M Andrial), Kunming Pharmaceutical Company (Zhang Chu Cheng), Dragon Pharmaceuticals Ltd (GT Williams).

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 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.

A study group has been established to conduct Individual patient data metaanalyses of all trials of artesunate combination treatment versus existing standard treatment. This project includes a number of new trials being conducted through WHO. 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 being tackled through IPD analysis and the conduct of new dedicated trials. It is, therefore, no longer necessary or expedient to update this review in its existing format. It will continue to appear on the Cochrane Library for a limited number of future issues, new trials being added to those awaiting assessment, for information only.

Characteristics of included studies

Table: Characteristics of included studies

Characteristics of excluded studies

Study : Alin TAZ 93
Artesunate given by intravenous infusion.

Study : 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.

Study : Ashton VNM (98)
RCT comparing oral with rectal administration of artemisinin (500mg/d/5days). Comparison does not fit the inclusion criteria. Outcomes reported: pharmacokinetics and fever clearance time.

Study : Ashton VNM(98)
Compares artemisinin suppositories vs. oral.
Study: Batty VNM 96
Intravenous route of administration does not meet the inclusion criteria, although relevant outcomes reported (fever and 50% parasite clearance time).

Study: Bich VNM 93
Treatment regimens do not fit the inclusion criteria: ART + QNN vs AS + doxycycline vs QNN

Study: Bunnag THI (97)
Treatment regimens do not fit the inclusion criteria: AM 150mg + MQ15 at 0h, followed by either AM 100mg + MQ10 at 6h [Group A] or AM 100mg + MQ10 at 24h [Group B]

Study: Bunnag THI 89-90a
Using placebo in the middle of a treatment regimen, as in this trial, would not be done in clinical practice.
AS600mg/5d (200mg on d1, 100mg on d2, placebo on d3 &4, 100mg AS600mg/5d (200mg on d1, 100mg on d2, placebo on d3 &4, 100mg on d5-7)
AS 600mg/7d (200mg on d1, 100mg on d2-5, placebo on d6 &7) P>

Study: Bunnag THI 89-90b
Comparison of two different doses of artemether given by intramuscular injection.

Study: Chen CHI
Reported as randomised comparison of dihydroartemisinin and quinine. Only outcome reported is gametocyte infectivity.

Study: Duarte BRZ 92-3
Treatment regimens do not fit the inclusion criteria: AS + tetracycline vs. QNN + tetracycline, concomitant treatments.

Study: Duc VNM 93
Artemether given by intramuscular injection compared with oral chloroquine.

Study: Elhassan SUD 91
Artemether versus quinine both given by intramuscular injection.

Study: Fu CHI
Investigators unable to provide data or details concerning design, conduct and analysis of the trial (personal communication).

Study: 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.

Study: Guo CHI (90)
Comparison of non-randomised treatment groups.

Study: Guo CHI 86a
Artemether given by intramuscular injection compared with oral piperaquine, used only in China.

Study: Guo CHI 86b
Artemether given by intramuscular injection compared with oral pyronaridine (+ sulfadoxine pyrimethamine) used only in China.

Study: 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
Study: Irion GAM(98)
Same study as included study Hatz GAM(98). Reports only on distinction of new infections from recrudescences as determined by PCR-RFLP analysis.

Study: Jiang CHI 80
Patients were not allocated randomly to the two treatment groups (personal communication).

Study: Jiao CHI (97)
Treatment regimens do not meet the inclusion criteria: benflumetol vs. CGP 56697 (co-artemether).

Study: Li CHI (82)
No comparator group.

Study: Li CHI (90)
Non-randomised comparison of groups treated at different study sites.

Study: Li CHI (95)
Report does not mention randomisation (DHA 5d vs. 7d).

Study: Li CHI 85
Artesunate given by intravenous infusion.

Study: Li CHI a
Outcome measured (gametocyte infectivity) does not fit inclusion criteria.

Study: Li CHI b
Investigator unable to provide data or details concerning design, conduct and analysis of the trial (personal communication).

Study: Li VNM (95)
Investigator unable to provide details concerning design, conduct and analysis of the trial (personal communication).

Study: Looareesuwan THI 92a
Treatment regimens do not fit the inclusion criteria: MQ + doxycycline vs. AS + doxycycline, both concomitant.

Study: Looareesuwan THI 94
Patients were not randomly assigned to the two treatment groups.

Study: Luxemburger THI-MYA93
Comparison of oral AM+MQ vs. intravenous QNN+MQ in patients with hyperparasitaemia.

Study: Na-Bangchang THI(96)a
Treatment regimens do not fit inclusion criteria: artemether-doxycycline vs. artemether-azithromycin

Study: Na-Bangchang THI(96)b
Treatment regimens do not fit the inclusion criteria: three different regimens of artemether-pyrimethamine.

Study: Nigeria 1988
AM versus CLQ both given by intramuscular injection.

Study: Pang CHI (87)
Not a randomised comparison.

Study: Price THI 93-5
Hyperparasitaemic falciparum malaria.

Study: QACRG CHI 75
Unable to obtain detailed information on this study from 1975
summarised in a review of antimalarial 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 oral chloroquine; PCT and recrudescence at day 28 reported.

Study : 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)

Study : Shen 1989
Retrospective comparison of separate study groups.

Study : 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.

Study : Simooya ZIM 91
Artemether given by intramuscular injection vs. oral chloroquine.

Study : Sowunmi NIG 93
Artemether given by intramuscular injection vs. oral mefloquine in hyperparasitaemic falciparum malaria.

Study : Sowunmi NIG 94-7
Artemether given by intramuscular injection.

Study : Than MYA 94b
Treatment regimens do not fit the inclusion criteria.
Alternate allocation. Outcomes: (cure rate d7 and 28).
AM 480mg/5d + Dox 200mg/7d; 30 patients (30/30; 29/30)
AM 480mg/5d + Tc 1000mg/7d; 28 patients (28/28, 27/28)
AM 480/5d + MQ20; 30 patients (30/30; 30/30).

Study : ThanMYA95
Treatment groups treated with different artesunate regimens and different mefloquine schedules (sequential or concomitant).
AS600/2+MQ20(S) vs. AS600/3+MQ20(C).

Study : ThanMYA96b
Unexplained uneven group numbers in a study supposedly using alternate allocation. Dihydroartemisinin (Cotexin) regimen comparison: 480mg/3d (32 patients) vs. 480mg/7d (21 patients).

Study : Thwe MYA 93
Investigators unable to provide data or details concerning design, conduct and analysis of the trial (personal communication, Kyaw Win).

Study : 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.

Study : Wang CHI (81)
Observational study, no comparator group.

Study : Wang CHI (95)
Investigator unable to provide details concerning design, conduct and analysis of the trial (personal communication).
Study: Wang CHI 79-80
Patients were not allocated randomly to the three treatment groups (personal communication).

Study: Wang CHI 94
Investigator unable to provide details concerning design, conduct and analysis of the trial (personal communication).

Study: 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.

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KarbwangTHI92b (published data only)


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Li CHI82-4 (published data only)


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LooareesuwanTHI93 (published data only)

Looareesuwan THI95 {published data only}


Luxemburger THI-MYA91 {published data only}


Nosten[1] THI-MYA92-3 {published data only}


Nosten[2] THI-MYA92-3 {published data only}


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Than MYA94a {unpublished data only}

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Than MYA96a {unpublished data only}

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Than MYA97 {unpublished data only}

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von Seidlein GAM96 {published data only}


Win MYA94-5 {published data only}


* indicates the major publication for the study

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Li CHI 85


Li CHI a


Li CHI b

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Li VNM (95)

Li GQ, Wang XH, Guo XB, Jian HX, Anh

Looareesuwan THI 92a


Looareesuwan THI 94


Luxemburger THI-MYA93


Na-Bangchang THI (96) a


Na-Bangchang THI (96) b


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Honrado THI 94-5


LooareesuwanTHI(99)


Novartis CHI

This unpublished study, conducted in Chinese children aged 5-14 years, comparing artemether monotherapy with co-artemether (artemether-benflumetol/lumefantrine) is mentioned in the discussion section of two published reports of co-artemether trials (Hatz TAZ (98), vonSeidlein GAM 96). The reviewers have been unable to obtain unpublished data from Novartis Pharma A.G.

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IHM 1998


McIntosh 1998


Coversheet

Title

Artemisinin derivatives for treating uncomplicated malaria

Reviewer(s)

McIntosh HM, Olliaro P

Date of most recent amendment: 31 May 2000

Date of most recent substantive amendment: 18 February 1999

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For information on the editorial group see: Cochrane Infectious Diseases Group

Extramural sources of support to the review

European Commission (Directorate General XII) BELGIUM
Department for International Development UK

Intramural sources of support to the review

Liverpool School of Tropical Medicine UK

Synopsis

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.

Keywords

HUMAN; MALARIA-FALCIPARUM / drug-therapy; ANTIMALARIALS / therapeutic-use; ANTIMALARIALS / analogs- &-derivatives; ARTEMISININE / therapeutic-use; ARTEMISININE / analogs- &-derivatives; DRUG-THERAPY-COMBINATION; ARTEMISININE / administration- &-dosage; ANTIMALARIALS / administration- &-dosage; ANTIMALARIALS / adverse-effects; ARTEMISININE / adverse-effects; CHLOROQUINE / therapeutic-use; QUININE / therapeutic-use; MEFLOQUINE / therapeutic-use; AMODIAQUINE / therapeutic-use;

CRG Code: HM-INFECTN
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