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[Intervention Review]

Artemisinin derivatives for treating severe malaria

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ABSTRACT

Background

Artemisinin derivatives may have advantages over quinoline drugs for treating severe malaria since they are fast acting and effective against quinine resistant malaria parasites.

Objectives

The objective of this review was to assess the effects of artemisinin drugs for severe and complicated falciparum malaria in adults and children.

Search methods

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

Selection criteria

Randomised and pseudo-randomised trials comparing artemisinin drugs (rectal, intramuscular or intravenous) with standard treatment, or comparisons between artemisinin derivatives in adults or children with severe or complicated falciparum malaria.

Data collection and analysis

Eligibility, trial quality assessment and data extraction were done independently by two reviewers. Study authors were contacted for additional information.

Main results

Twenty three trials are included, allocation concealment was adequate in nine. Sixteen trials compared artemisinin drugs with quinine in 2653 patients. Artemisinin drugs were associated with better survival (mortality odds ratio 0.61, 95% confidence interval 0.46 to 0.82, random effects model). In trials where concealment of allocation was adequate (2261 patients), this was barely statistically significant (odds ratio 0.72, 95% CI 0.54 to 0.96, random effects model). In 1939 patients with cerebral malaria, mortality was also lower with artemisinin drugs overall (odds ratio 0.63, 95% CI 0.44 to 0.88, random effects model). The difference was not significant however when only trials reporting adequate concealment of allocation were analysed (odds ratio 0.78, 95% CI 0.55 to 1.10, random effects model) based on 1607 patients. No difference in neurological sequelae was shown. Compared with quinine, artemisinin drugs showed faster parasite clearance from the blood and similar adverse effects.

Authors' conclusions

The evidence suggests that artemisinin drugs are no worse than quinine in preventing death in severe or complicated malaria. No artemisinin derivative appears to be better than the others.

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

23 April 2019

No update planned

Research area no longer active

Further research in this area has focused on specific preparations of arteether and artemether. Trials of these preparations are assessed as separate Cochrane Reviews; therefore it is no longer necessary to update this review. Please refer to the Cochrane Special Collection: Sinclair 2014 https://doi.org/10.1002/14651858.SC000007/full

PLAIN LANGUAGE SUMMARY

Artemisinin derivatives for treating severe malaria

Artemisinin drugs improve survival in severe malaria. Artemisinin drugs come originally from a plant that has been used since ancient times in China as a traditional medicine for fever and malaria. They are fast acting and effective against malaria parasites that have developed resistance to quinine. The review shows that treatment with artemisinin drugs may be better than quinine at preventing death in adults and children with severe and complicated malaria. There is no evidence so far against early treatment with suppositories in rural areas whilst patients are transferred to hospital. Few side effects have been reported with these drugs.

BACKGROUND

This review is related to another by the same authors entitled: Artemisinin derivatives for treating uncomplicated malaria which contains general background information on malaria and the artemisinin derivatives.

Every year severe and complicated malaria results in an estimated 2-3 million deaths caused by Plasmodium falciparum (WHO 1990a; WHO 1995; PRISM 1996). The primary goal of treatment for these patients is to save life and reduce the chance of serious complications developing. The rate of clinical response and clearance of parasites from the blood can provide useful comparative information between alternative treatments, although the clinical significance, particularly in cerebral malaria, is debatable (White 1989). The balance between the risks of drug toxicity and the benefits of antimalarial drug action is also different in severe and complicated malaria compared with uncomplicated infections. Artemisinin derivatives are fast-acting and effective against quinine resistant malaria parasites; available in parenteral and suppository form they can be administered once a day. These drugs may, therefore, have particular advantages over quinoline drugs in the treatment of severe malaria, in preventing clinical deterioration if used early, suppositories in particular being practical for early treatment in rural areas.

The aim of this review is to summarise the existing evidence of effectiveness and safety of artemisinin derivatives, alone and in combination with other antimalarials, in the treatment of severe and complicated falciparum malaria in different epidemiological settings. The following clinical questions will be addressed:

1. Are treatment regimens with artemisinin drugs better than standard treatment regimens for severe and complicated 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 longer-acting antimalarials in the treatment of severe and complicated malaria?
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?

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 severe and complicated falciparum malaria. Effectiveness is defined in terms of survival, time to recover consciousness and resolution of clinical symptoms, clearance of asexual parasites from the blood (parasitological cure) and tolerance.

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

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

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or pseudo-randomised trials of treatment comparisons.

Types of participants

Adults and children with clinical manifestations of severe or complicated falciparum malaria as defined by the WHO (WHO 1990b), and confirmed asexual falciparum parasitaemia.

Types of interventions

Artemisinin derivative administered rectally, intramuscularly or intravenously, alone or in combination with other antimalarial drugs, compared with standard treatment.

Comparisons between different artemisinin derivatives, doses, regimens and routes of administration were also included.

Types of outcome measures

Effectiveness

Clinical

- Death
- Neurological sequelae at follow-up
- Incidence of complications
- Time to recover consciousness (cerebral malaria)
- Time to recover motor response e.g. time to drink, sit, stand
- Time to leave hospital
- Fever clearance time (i.e. time for temperature to return to normal as defined by the authors)

Parasitological

- Parasite clearance at day 7, 28 or at end of follow-up
- Parasite clearance time
- Rate of parasite clearance as time to 50% or 90% clearance (PC50 or PC90) as reported

Tolerance

Clinical

- Discontinuation of treatment
- Gastrointestinal (nausea, vomiting, diarrhoea)
- CNS (dizziness, staggering gait (ataxia), ringing in the ears (tinnitus)
- Local side-effects at injection site

Laboratory and other diagnostic tests

- Haematological
- Metabolic (blood chemistry)

- Cardiovascular (QT changes, arrhythmias)

Search methods for identification of studies

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, artemether, arteether. Full details of the Infectious Diseases Group methods and the journals searched are published in The Cochrane Library in the section on Collaborative Review Groups.

The reviewers searched the Cochrane Controlled Trials Register, published in *The Cochrane Library*. This is a compilation of about 250,000 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; and LILACS. The specific topic search terms used were malaria, qinghaosu, artemisinin, dihydroartemisinin, artesunate, artemether, arteether, and co-artemether.

Dates of latest searches:

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

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

Data collection and analysis

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

Selection of studies

All trials identified were entered in a database register. The inclusion criteria we11re applied to all identified studies independently by the two reviewers. In the event of disagreement, the opinion of a member of the advisory panel was sought.

Data extraction and management

Data for the pre-specified outcome measures was abstracted on to a collection form by the first reviewer, and repeated independently by another person. Whenever possible authors were asked to provide additional data. The primary efficacy parameter is survival. Parasite clearance is compared on days 7 and 28, or at the end of follow-up if longer than 28 days, where data are available. Parasitological cure was calculated from the number of patients evaluable with losses to follow-up included in sensitivity analyses.

Assessment of risk of bias in included studies

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

Data synthesis

Analysis was done in Review Manager (Update Software) pooling data where appropriate. Odds ratios for dichotomous data were first calculated using the Mantel-Haenszel method (fixed effect model); the DerSimonian & Laird method (random effect model) was also used if heterogeneity between studies was evident from the graphical display and the Chi square test for homogeneity. To make interpretation easier we also reported results as risk ratios. It was not possible to estimate time to event outcomes using the Kaplan-Meier procedure, as initially intended, due to lack of data. The mean difference was, therefore, calculated from reported data.

The following comparisons were made:

1. Artemisinin or derivative drug versus WHO recommended standard treatment, for pre-specified outcomes grouped by comparator drug.
2. Any artemisinin derivative versus any other, for each pre-specified outcome.
3. Different dose or route of administration.

Where significant statistical heterogeneity was found within these comparisons, with the direction of effect being different in the various studies, possible explanations were sought through exploring hypotheses addressing differences in the intervention (dose, duration, formulation/route of administration, regimen), and participants (level of disease severity, immunity).

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.

RESULTS

Description of studies

Included study code

In this review, each study is given a code name consisting of: 'Name of investigator, COUNTRY CODE, year the study was done'. If the year the study was done is not known, the publication year is given in brackets. Country codes are listed in the footnotes of the Table of Included Studies.

Studies identified

Thirty studies were identified, of which 23 met the inclusion criteria (see 'Characteristics of included studies'), four were excluded (not including duplicate or interim reports of included studies; see 'Characteristics of excluded studies') and three are awaiting assessment (authors have been contacted; see 'Characteristics of studies awaiting classification'). Twenty of the included study reports are in English, 19 published and one submitted for publication, and one in French (unpublished data) and English (published data); two unpublished studies were obtained from the investigators in Viet Nam. To maximise retrieval of information we used all reports on any study that were consistent in terms of patient numbers. Due to discrepancies between reports, for Taylor MAL 92-4 we abstracted data from the manuscript submitted for publication and used a WHO TDR report for additional information; for Murphy KEN 92-4 we used a WHO TDR report as the main source of data (on the advice of S. Murphy) and the publication for additional information.

Population

Fourteen of the included studies were conducted in South East Asia (7 in Thailand, 5 in Viet Nam, 2 in Myanmar), eight in sub-Saharan African countries and one in Papua New Guinea. Fifteen studies included only adults, seven only children, and one adults and children.

Severe malaria criteria

Ten of the included studies defined severe/complicated malaria according to WHO (WHO 1986; WHO 1990b) criteria. Three others listed criteria that are consistent with WHO guidelines. Nine studies included only patients with cerebral malaria; five in children (Blantyre coma score 2 or less, or defined using the Glasgow or a modified Glasgow coma scale), and five in adults (Glasgow coma score 3-9, or less than 10; or equivalent to 3-6 on the Choray coma scale).

Artemisinin drugs used

Four different preparations of artemisinin, four of artemether and two of artesunate were used in the included studies (see Table of Included Studies for details of manufacturers).

Included studies

Of the 23 included studies:

- Thirteen studies, including a total of 2653 patients, compared artemisinin derivatives with quinine: one study compared artemisinin with quinine; ten studies compared artemether with quinine; two compared artesunate with quinine; one compared artemether and artesunate with quinine; and two compared artemisinin and artesunate with quinine. Artemisinin was given as suppositories and artemether by intramuscular injection in all studies using these drugs. Artesunate was given either by intramuscular injection or intravenous infusion. Eight studies followed artemisinin drug and/or quinine treatment with mefloquine, sulfadoxine-pyrimethamine or tetracycline (see Table of Included Studies for details)
- One study with 43 patients compared artemether with chloroquine.
- One study with 175 patients compared three different artemisinin derivatives (and also included a comparison of intramuscular and intravenous artesunate).
- Two studies (including the one above) compared artesunate given by two different routes, intramuscular and intravenous (giving a total of 109 patients in this comparison).
- Four studies compared different doses of a single artemisinin derivative: two using intramuscular artemether (106 and 28 patients) and two using artesunate suppositories (63 and 54 patients).

Risk of bias in included studies

Allocation concealment

Of the 23 included studies, allocation concealment was adequate (Grade A) in nine, inadequate in one (alternate allocation) and not clearly described in the other 13.

Blinding

One study was reported as double blind, one reported that the physicians and technicians were blinded, and one that only the microscopists who assessed parasitaemia were blind to treatment allocation. Twelve studies were described as either not blinded, open or open-label (in all cases blinding was limited by differences in regimen or route of administration between the treatment groups), of these, three specified that the microscopists were blind to treatment allocation, and one other reported blinding of the assessors of neurological sequelae at follow-up. The remaining nine studies did not report on blinding, however, in five of these, differences in regimen or route of administration between the treatment groups would have precluded blinding of the providers.

Generation of allocation sequence

All 23 studies were reported as randomised; 15 did not specify the method used, four reported using computer generated random numbers, two reported using random number tables, one study used a lottery draw and one was pseudo-randomised by alternate allocation.

Inclusion of all randomised participants

Ten studies reported that less than 10% of enrolled patients were not evaluable. In three studies, 11 to 15% were not evaluable for all outcomes. Three studies reported excluding between 18 and 30%

of enrolled patients, with less than 10% or no subsequent loss to follow-up. Exclusions and loss to follow-up were not reported in the remaining seven studies.

Effects of interventions

Artemisinin drug compared with quinine

Sixteen studies compared an artemisinin derivative with quinine: artemisinin, three comparisons (artemisinin 87 patients, quinine 98); artesunate, five comparisons (artesunate 213 patients, quinine 245); artemether, eleven comparisons (artemether 1069 patients, quinine 1073). In total, 1284 patients treated with an artemisinin derivative were compared with 1284 patients treated with quinine.

Mortality

All sixteen studies reported on mortality. Nine studies admitted only patients with cerebral malaria, whereas seven included both cerebral and non-cerebral malaria patients.

In two comparisons of artemisinin with quinine, deaths were similar in the two groups (artemisinin: 7/50; quinine: 11/63), although one study had unbalanced arms because part-way through the supply of artemisinin ran out and further patients were all recruited into the quinine and artesunate groups (Hien VNM 89-90). In the other study there were slightly fewer deaths in the artemisinin group (2/37 compared with 5/35) (PhuongVNM 92-5). Overall, there was no evidence of a significant difference in effectiveness in the combined estimate (OR 0.68, 95% CI 0.28 to 1.65, fixed effect model).

In five comparisons of artesunate with quinine, two show a significant benefit with artesunate and three a non-significant tendency in favour of artesunate. Pooled analysis shows significantly fewer deaths in patients treated with artesunate over quinine (OR 0.35, 95% CI 0.20 to 0.61). The weight of this evidence comes partly from one study where the researchers stopped using artesunate part-way through, while continuing to recruit patients into the quinine group. Without this study, the meta-analysis result is still statistically significant (OR 0.42, 95% CI 0.23, 0.77).

In eleven comparisons of artemether with quinine, no study showed that artemether was worse than quinine. The two largest studies (both with over 275 patients per group) showed similar numbers of deaths in the artemether and quinine groups. Three studies showed quite large differences in effectiveness between the two drugs, in favour of artemether, but these were based on small numbers of patients, and two scored low on quality assessment for concealment of allocation. The overall odds ratio is marginally in favour of artemether (OR 0.72, 95%CI 0.57, 0.91, random effect model); excluding the three studies with inadequate methods removes the statistical significance (OR 0.79, 95% CI 0.59, 1.05, random effect model).

Pooled analysis of all artemisinin drug comparisons with quinine gives a result in favour of artemisinin drugs, with some heterogeneity between studies (OR 0.61, 95% CI 0.46, 0.82, random effect model). The pooled Risk Ratio Reduction is 48% (95% CI 54% to 18%) using random effect analysis. The pooled data also gives a number needed to treat (NNT) of 25 (95% CI 16, 65). This is an estimate of the number of patients we would need to treat with an artemisinin drug in order to prevent one more death compared with quinine (Gardner 1986; Sackett 1996). These pooled estimates must, however, be interpreted with caution, as there is heterogeneity in the outcome between studies. Furthermore, the statistical difference is barely significant without the six studies that did not report adequate concealment of allocation: RRR 24% (95% CI 40% to 3%); OR 0.72, 95% CI 0.54, 0.96, random effect model.

Mortality: cerebral malaria

Five studies that included both cerebral and non-cerebral malaria patients reported the death rate in these subgroups. Only the smallest study showed an almost significant result in favour of artesunate in cerebral malaria (1/11 artesunate, 3/5 quinine). With artemisinin in two studies 3/15 cerebral malaria patients died compared with 6/12 given quinine, a difference that is not significant. In the largest study, the difference between artemether and quinine approached significance only in the non-cerebral malaria subgroup (Hien VNM 91-6, 15/142 artemether, 23/128 quinine).

Pooling all the available data for only patients with cerebral malaria gives an odds ratio in favour of artemisinin drugs (OR 0.63, 95% CI 0.44, 0.88, random effect model) and a Risk Ratio Reduction of 31% (48% to 10%) but the difference is not significant when only studies reporting adequate concealment of allocation are analysed: RRR 19% (40% to -7%); OR 0.78, 95% CI 0.55, 1.10, random effect model.

Coma recovery and neurological sequelae

All sixteen studies reported time to recovery of consciousness in comatose patients. Six reported median and range (four using survival analysis) two reported mean and range and seven reported mean and standard deviation (of which one also gave 95% confidence intervals).

The study reports show no significant difference in coma recovery time between artemisinin suppositories and intravenous quinine (PhuongVNM 92-5, based on 8 children; Hien VNM 89-90, based on 48 adults; Birku ETH 96-7, based on 10 adults).

One large study using survival analysis showed that artemether prolonged coma recovery time (Hien VNM 91-6, 66 h artemether, 48 h quinine, p = 0.003 based on 349 patients). Another large study showed a much less significant difference in favour of quinine (vanHensbroekGAM92-4, 26h artemether, 20h quinine, p = 0.046 based on 444 patients). Of the remaining six studies (accounting for about one third of patients in this comparison) five showed no difference and one reported faster coma recovery with artemether (Ojuawo NIG (98).

Our graphical presentation of MD for the studies reporting mean and standard deviation, or for which we were able to obtain or estimate this data, highlights heterogeneity between studies and evidence of a skewed distribution in most of the data (Altman 1996). Mean difference may, therefore, be an inappropriate statistical method to analyse this data. Only one of four comparisons of artesunate with quinine showed a significant difference in favour of artesunate (Win MYA 89-91, 69 adults). Survival analysis is more appropriate for such time-to data, therefore, using the data as reported we are unable to perform a comprehensive meta-analysis for this outcome.

Neurological sequelae were reported in ten studies comparing an artemisinin derivative with quinine. The time at which sequelae were assessed was not always explicit and varied from study to

study. Four reported on sequelae at discharge. Two others only reported a 7 day follow-up (Karbwang THI 91; Ojuawo NIG (98). Taylor assessed sequelae at 96 hours by which time all patients had recovered consciousness. Win reported at recovery of coma and residual. Karbwang (KarbwangTHI92-4) assessed sequelae at recovery of consciousness, but did not specify how many cerebral malaria patients survived, her data, therefore, are yet to be included in our meta-analysis. Olumese (Olumese NIG 94-6) recorded sequelae within the 28 day study period.

Neurological sequelae reported at recovery or discharge were analysed together as 'neurological sequelae at recovery' using the number of cerebral malaria survivors as the denominator. The type of sequelae recorded by investigators include movement disorders, paralysis, difficulty in walking, speech impairment, blindness, deafness, mental disorders and behavioural abnormalities. The study which compared artemisinin and artesunate assessed less than 20 patients.

For artemether, more patients have been studied, however, there is wide variation in the number of neurological sequelae at recovery in various trials. Van Hensbroek points out that, due to bed shortage, some children in his study were discharged whilst still weak, often not able to stand or walk, and were counted as neurological sequelae cases (MB van Hensbroek, personal communication). Only one study in our meta-analysis reached statistical significance, due to seven cases of transient organic psychosis in the quinine group (Win MYA 89-91). In one study artemether was worse than quinine. Overall, there is no convincing pattern in favour of either drug: RRR 16% (40 to -18%); OR 0.80, 95% CI 0.52, 1.25, random effect model.

One study examined neurological sequelae at one and around five months, to assess whether the deficits were transient or long-term (vanHensbroekGAM92-4). The 23% of patients across both groups with some neurological deficit at discharge fell to 4% at five months, with 92% follow-up: 7/209 artemether, 11/209 quinine. Murphy reported similar persistent deficits in both groups. Karbwang (KarbwangTHI92-4) reported one case of facial palsy persisting for over a month in a patient treated with quinine. Taylor reported blindness lasting up to at least 5 months in one artemether patient. Olumese reported hemiplegia (paralysis of one side of the body) lasting more than 28 days in one quinine-treated patient.

Time to regain motor function

Only one study comparing artemether with quinine reported fully on time to drink, eat, sit, stand and walk (Hien VNM 91-6). No significant difference was shown between the treatment groups. Another study reported no significant difference in time to walk (Olumese NIG 94-6).

Time to leave hospital

Only two studies reported on the duration of hospitalisation for surviving patients. One large study with artemether reported that hospitalisation was longer for patients treated with artemether (Hien VNM 91-6). One study showed no difference between artemisinin, artesunate and quinine in this respect (PhuongVNM 92-5).

Fever clearance time

All sixteen studies reported fever clearance time. Four reported using survival analysis to derive the median and range, two reported median and range but did not mention survival analysis, one reported mean and range and seven reported mean and standard deviation(one of which also gave 95% confidence intervals). In studies where survival analysis was not used the number of patients who were actually assessed for fever clearance is rarely clear in the report. Most studies also mentioned using paracetamol or other fever-reducing interventions but did not discuss the effect that this may have had on the fever clearance time data that they reported.

The reported data show no difference between artemisinin and quinine in three studies. In one study, artesunate cleared fever significantly faster than quinine, whereas two reported no difference. For artemether compared with quinine, five studies showed no difference in fever clearance time, three showed that artemether was faster, and one showed that quinine was faster than artemether.

Parasite clearance

Fifteen studies reported time to clearance of parasites from the blood; time to 50% and/or 90/95% clearance was also reported in 13 studies. Reporting of data was as inconsistent as described previously for fever clearance time.

All three studies comparing artemisinin with quinine concluded that artemisinin reduced parasitaemia significantly faster. All five comparisons of artesunate with quinine showed that artesunate cleared parasitaemia significantly faster. In seven studies, artemether cleared parasitaemia faster than quinine, and two others showed no difference. The three largest artemether studies fell into the first category and all used survival analysis; the median time to parasite clearance reported in these studies was 32 to 72 hours with artemether compared with 40 to 90 hours for quinine.

Eight studies reported parasite clearance at day 7. In our pooled analysis patients who had died by day 7 were counted as failures. The study that examined artemisinin and artesunate showed both were more effective than quinine (PhuongVNM 92-5). In this study, mefloquine was given to all artemisinin and artesunate treated patients on day 4 whereas quinine treated patients received Fansidar on day 7. The second study that tested artemisinin was conducted in Africa and showed no difference (Birku ETH 96-7). With artemether, three studies showed little or no difference, and two showed artemether to be more effective. The pooled odds ratio was 2.20, 95% CI 0.99, 4.91, random effect model).

Parasite clearance at day 28 was reported in five studies. Losses to follow-up were less than 10% in these studies, and were included as failures in our pooled analysis. The only artemisinin study showed no difference (Birku ETH 96-7). There were more failures in the quinine group in the one artesunate study that reported this outcome, although some of the quinine patients were not actually randomised against the artesunate comparator group (Win MYA 89-91, see discussion). No significant difference between artemether and quinine was shown in four trials (OR 1.74, 95% CI 0.75, 4.05, random effect model).

Parasite clearance at day 28 is influenced by adjunctive long-acting antimalarial drugs given after completion of treatment (in one study a single sequential dose of Fansidar was given to all patients, and in another mefloquine was given to the artesunate group whilst tetracycline was given to patients treated with quinine). In the study by Taylor, the one artemether patient and 4/5 quinine patients who had a recrudescence by day 28 did not receive Fansidar at parasite clearance while in hospital as per protocol.

Tolerability, clinical

No study reported adverse effects that resulted in discontinuation of treatment.

Gastrointestinal (nausea, vomiting, diarrhoea, abdominal pain): these were mentioned in six studies. Only three studies reported the number of events which were similar in one study (Murphy KEN 92-4, 10/100 artemether, 9/99 quinine) and higher for quinine in the other two (Birku ETH 96-7, 3/30 artemisinin, 13/30 quinine; KarbwangTHI92-4, 24/47 artemether, 32/50 quinine). Abdominal pain was one of the most common events in patients treated with artemether, but not quinine, in the study by Danis. Win reported nausea in almost all patients treated with quinine but not artemether or artesunate. Phuong noted that there were no reports of diarrhoea or anal discomfort in patients given artemisinin suppositories.

Skin (pruritus, urticaria, rash): these were mentioned in four studies and tended to be associated more with quinine than artemether. The numbers were small: urticaria one case with quinine (vanHensbroekGAM92-4); rash 2/99 quinine (Murphy KEN 92-4); rash 3/50 quinine compared with 1/47 artemether (KarbwangTHI92-4). Danis reported only that pruritus occurred with quinine but not artemether.

Local effects at injection site (pain, abscess): In one study of intramuscular artesunate no local pain or abscess occurred in 37 patients. Pain at the injection site was one of the "most common" adverse events with intramuscular artemether (Danis WAF 93-4), also occurring in 13/47 and 6/15 artemether patients in two other studies (KarbwangTHI92-4; Seaton PNG 92-5). A fourth study, with almost 200 patients, reported no local adverse effects (Murphy KEN 92-4). In two comparisons with intramuscular quinine, pain or abscess was more common with quinine: 6/284 artemether, 12/276 quinine (Hien VNM 91-6, both drugs given every 8 hours); 1/288 artemether, 5/288 quinine (vanHensbroekGAM92-4, artemether given daily, quinine twice daily).

CNS (tinnitus, dizziness): ringing in the ears (tinnitus) affected only quinine patients in six studies. Dizziness or vertigo was reported only in quinine patients in one study and in all groups in another two.

Tolerability, evidence from diagnostic tests

Haematological (blood cell count, haemoglobin, packed cell volume): The only notable difference from blood examination was in the reticulocyte (immature red blood cell) count. One study of artemisinin and artesunate compared with quinine reported a poorer reticulocyte response (the rate of increase towards normal levels) in patients treated with the artemisinin derivatives, based on a subgroup of 56 patients sampled 5 days after treatment had started. Two studies with artemether reported a similar observation at 3 and 7 days (Taylor MAL 92-4, 164 patients; Hien VNM 91-6, 560 patients). No change in daily reticulocyte count was noted by Seaton (Seaton PNG 92-5), and no change in any haematological test was noted in the two artemether studies by Karbwang (Karbwang THI 91; KarbwangTHI92-4).

Metabolic (blood chemistry): Three artemether studies reported no difference in measured biochemical parameters. Eight studies reported post-treatment hypoglycaemia (<2.2mmol/l blood glucose). Quinine was significantly associated with hypoglycaemia in three studies (Birku ETH 96-7, 3/30 artemisinin, 19/30 quinine; Hien VNM 91-6, 31/284 artemether, 69/276 quinine; Seaton PNG 92-5, 0/15 artemether, 11/14 quinine), more likely to cause hypoglycaemia (but not statistically significant) in two others, and noted only in a few quinine patients in one other. The two remaining studies found that a similar number of patients given quinine or artemether developed hypoglycaemia. There is no obvious pattern in terms of study size, location, quinine regimen or route of administration (im or iv).

Cardiovascular (QT changes, arrhythmias): electrocardiogram (ECG) was used in seven studies to monitor adverse effects on the heart. Prolongation of the QT interval, an abnormality in the rhythm of the heart, was the most commonly reported event. The study which looked at artemisinin and artesunate noted a prolongation in 1/12 artemisinin patients and 2/10 on quinine in a subgroup of 32 patients during the study period. Win (Win MYA 89-91) reported slowing of the heart rate (sinus bradycardia) in some patients on intravenous artesunate, this resolved spontaneously. With artemether, a prolongation of the QT interval by more than 25% was more common in quinine patients (11/157 artemether, 12/133 quinine) in one study (Hien VNM 91-6), but more common with artemether (20/82 artemether, 5/80 quinine) in another study (Murphy KEN 92-4). One study showed no difference between artemether and quinine (Danis WAF 93-4, 241 patients).

Artemisinin drug compared with chloroquine

In the one study that compared artemether with chloroquine (White GAM 89), there were more deaths in the chloroquine group (6/22 chloroquine, 2/21 artemether), all patients who died had cerebral malaria on admission. There was no difference in the fever or parasite clearance times, or in the time to recover from coma, based on those patients who survived. There was a non-significant difference in the time to regain motor function in favour of artemether, although the investigators point out that coma score on admission was significantly higher in this group despite randomisation. The study showed no evidence of adverse local, CNS or cardiovascular toxic effects with either drug, nor any difference in haematological or metabolic parameters. Patients were discharged from hospital at around 4 days in both groups, when their fever had cleared, and longer-term toxicity and efficacy was not assessed.

Comparisons between artemisinin drugs

Four studies compared one artemisinin derivative with another: artemisinin versus artesunate (three comparisons); artemisinin versus artemether (one comparison); and artemether versus artesunate (two comparisons). The dose and duration of treatment varied between studies. The treatment arms were unbalanced in the studies by Win (Win MYA 89-91) and Vinh (Vinh VNM 92-4) because recruitment was stopped prematurely in the artemisinin and artesunate (iv) groups respectively, and in the study by Hien (Hien VNM 89-90) with no reason given. Vinh (Vinh VNM

92-4) included two artesunate groups, one intramuscular and one intravenous; we have combined these groups for analysis of artesunate.

There was no significant difference in mortality in the three comparisons of artemisinin suppositories with artesunate (OR 1.29, 95% CI 0.63, 2.65, fixed effect model). Two studies included cerebral and non-cerebral malaria patients, only one separated the mortality data: there was no significant difference in cerebral malaria deaths between the groups (PhuongVNM 92-5, 1/7 artemisinin, 1/11 artesunate).

Two studies used survival analysis to determine time to recover conciousness, and fever and parasite clearance times, one reported median and range, but no method (Hien VNM 89-90), and the fourth reported mean and standard deviation (Win MYA 89-91).

Survival analysis (two studies) showed no significant difference in time to recover consciousness between artemisinin, artesunate and artemether (147 comatose patients). Hien (Hien VNM 89-90) also showed no difference, although the number of patients evaluated is not explicit. Win's study showed artesunate to be slightly faster than artemether, but the groups were only partially randomised (see discussion). Neurological sequelae were reported in two studies, but the numbers were very small (PhuongVNM 92-5, 1/6 artemisinin, 1/10 artesunate; Win MYA 89-91, 1/50 artemether, 0/27 artesunate). Vinh reported that no sequelae occurred, and the fourth study did not mention sequelae as an outcome.

Three studies, two using survival analysis, showed no difference between artemisinin derivatives in the time to clear fever or parasitaemia. Win showed no difference in fever clearance time between artesunate and artemether, but reported that artemether was significantly faster than artesunate at clearing parasites from the blood. Parasite clearance was reported at day 7 by Phuong, mefloquine was given on day 4, the numbers in each group were similar (artemisinin 35/37, artesunate 33/37). Parasite clearance at day 28 was reported by Win, mefloquine was given on day 2 and all survivors in both groups had no parasitaemia at day 28.

Only Phuong reported time to leave hospital and there was no difference between the groups.

Adverse events in the studies by Win and Phuong have been detailed earlier under comparisons with quinine, there were no differences between artemisinin derivatives used. In the studies by Hien (Hien VNM 89-90) and Vinh no adverse events were reported.

Comparisons of same drug, different dose

Two studies compared different doses of intramuscular artemether, and two studies compared different doses of artesunate suppositories.

There were no deaths in these studies. In three, no neurological sequelae were observed in cerebral malaria patients within 28 days (Karbwang THI 92, 8 patients; LooareesuwanTHI95, 12 patients; Thwe MYA 96, 7 patients).

There was no significant difference in parasite clearance at day 28 between the treatment groups in any study, although there was a tendency in favour of the higher dose in three studies where the duration of treatment was the same with both doses, or shorter for the lower dose. In the fourth study, the lower dose, given over a longer time period (7 days) was more effective than the higher dose (given over 5 days). The investigators conclude that the duration of treatment, rather than the dose, is the determinant of cure rate (Karbwang THI 92), however, this is based on a very small number of patients and two variables (dose and duration) differ between the treatment groups.

Mild and transient pain at the injection site was noted in both groups in one artemether study. Mild gastrointestinal events were similar in all treatment groups in all studies, and no adverse effects on the heart or differences in haematological or metabolic parameters were noted.

Comparisons of same drug, different route

Two studies compared intramuscular and intravenous artesunate.

No difference in deaths was shown in either study; both are small studies and although the pooled estimate tends towards favouring the intramuscular route, this comes from the one study with unbalanced arms (Vinh VNM 92-4, as discussed under comparisons between derivatives). Both studies included cerebral and non-cerebral malaria patients, but did not report mortality separately for these groups. Neither study reported neurological sequelae.

Both studies showed no significant difference between intramuscular and intravenous routes in any of the clinical or laboratory measures of therapeutic response. The small study by Hien (Hien VNM 91) reported no local or systemic adverse effects, Vinh did not report on adverse events.

DISCUSSION

Strength of evidence

Despite the volume of clinical research, variation in patient populations, regimen comparisons, and quality of study design makes data synthesis problematic. Variation in the way in which outcome data are reported and lack of information on patient attrition precludes comprehensive metanalysis of all the evidence available. This is a great pity as fundamental clinical questions still do not have clear answers. The most recent overview of primary research this field can be found in: Medecine Tropicale 1998;58(3 suppl) The rational use of qinghaosu and its derivatives.

Artemisinin drugs compared with quinine

The majority of studies in severe malaria have been comparisons of artemisinin drugs, mostly artemether, with standard treatment quinine. Over 2600 patients in thirteen such studies are included in this review so far; 85% (2261/2653) of these patients were treated in trials which reported adequate concealment of allocation. One study was only partly pseudorandomised (alternate allocation): the investigators stopped using artesunate part-way through their study as they were concerned that the preparation was not sterile. However, they continued recruiting patients which means that, whilst the quinine-artemether comparison in this study was randomised, the quinine-artesunate comparison had a randomised element, and a sequential non-randomised element of only quinine patients. The investigators attempted to clarify the design of their study (Kyaw Win, personal communication) which we decided to include, although there is still some doubt as to how many quinine patients were truly randomised.

Metanalysis of mortality, the most important outcome, in this review indicates that a patient treated with an artemisinin drug might have a better chance of survival than a patient treated with quinine. Although the direction of effect is fairly consistent across trials, the statistical significance of the pooled result is sensitive to exclusion of trials with insufficient methods (or reporting) of allocation concealment.

The evidence on coma recovery time and neurological sequelae is not strong or conclusive. Survival analysis is the most appropriate statistical approach to analysing 'time-to' data, and only four studies reported using it. The studies that used other methods, either did not specify what this was, or were not explicit about the number of patients evaluated. Our metanalysis of neurological sequelae "at recovery" may be flawed because we had to make some assumptions about when these were assessed. Furthermore, the extent to which reporting of neurological sequelae varies between studies suggests that investigators are using different criteria to define these deficiencies and their clinical significance. Most of the included studies also had insufficient follow-up, in time or numbers of patients, to assess persistent neurological morbidity.

Time to clearance of fever and parasitaemia are of secondary importance in severe malaria. Here we had the same problem with 'time-to' data discussed above. It is important to note that almost all studies mentioned using mechanical methods (such as tepid sponging, fanning) or antipyretic drugs, such as paracetamol, to reduce fever as necessary, yet none discuss how this was distributed across the treatment groups or the effect it may have had on the reported fever clearance times. An overview of the included comparisons with quinine supports the well established observation that artemisinin drugs clear parasites from the blood faster.

Subsequent to this review, the Artemether-Quinine Meta-analysis Study Group conducted an individual patient data metanalysis of artemether versus quinine using data from the large well-conducted trials included in this review. Their results were similar to ours and they concluded that artemether is a good alternative to quinine for treating severe malaria (IPD 99).

Comparisons between artemisinin drugs

Randomised trials comparing different artemisinin derivatives, doses or routes of administration in severe malaria are few and treatment regimens vary widely. It is clear that there is no general agreement on the conditions under which these drugs should be compared. Investigators, between 1989 and 1996, appear to have conducted small trials in isolation. Each individual study is too small to be conclusive, and the variation between them precludes meaningful metanalysis.

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

Applicability

Location

Data included in this review are gathered from diverse malarious regions of the world. The results do not indicate important variation that might limit applicability to certain geographical areas. However, resistance to quinine varies from region to region, being particularly high in some areas of South East Asia, whereas resistance to artemisinin drugs has not been conclusively demonstrated in clinical practice. It is logical to expect that the relatively new artemisinin drugs will be better at killing malaria parasites than quinine, and for the margin of benefit to be wider in areas where resistance to quinine is high. Monitoring of marginal benefit is warranted as artemisinin drugs become more widely available and subject to unregulated use.

Population

In this review, the least tendency to favour artemether compared with quinine is shown in the six African studies and the largest of the studies done in South East Asia. These studies account for all the children in the mortality metanalysis of artemisinin drugs versus quinine, which could indicate an age-effect.

Coma scores qualifying as cerebral malaria are inconsistent across the included studies. In cerebral malaria the pathological effects are thought to be related to sequestration of red blood cells containing mature parasites in small blood vessels of the brain. By the time this happens it could be, by that time, the pathological changes that cause death are irreversible in some patients (Hien 1993). Notably, only blood slide-positive patients were included in the studies included in this review. Other complications of severe malaria were reported with varying degrees of clarity, and few reports broke-down outcome data according to these subgroups. Since disease severity is a major determinant of outcome in severe malaria, uneven distribution of complications between treatment groups, despite randomisation, could have a profound effect on study results (NJ White, personal communication).

Product

Many formulations of artemisinin drugs are currently available on the market, produced in developed and developing countries. 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

Differences in treatment regimens cannot be ruled out as a contributor to heterogeneity between trials in this review. These vary markedly, although three of the four largest artemether-quinine studies used the same, or similar, regimens.

The studies included in this review also varied considerably in the exclusion criteria cut-off time for previous intake of antimalarial drugs; residual levels of other drugs in the body can only be determined by analysis, and this issue is not clarified in some studies.

Sustained parasite clearance is affected, amongst other things, by longer-acting antimalarial drugs, such as mefloquine and sulfadoxine-pyrimethamine (e.g. Fansidar), given after completion of the artemisinin drug treatment course. This practice is based on earlier observations that recrudescence rates are high when artemisinin derivatives are used alone, and is substantiated by this review.

Cost

A full cost analysis of artemisinin drugs versus standard treatment is beyond the scope of this review, and can be done better by people

developing clinical practice guidelines for national or regional implementation. An example, however, is useful. The preparation of artemether used in 5/9 comparisons with quinine included in this review is Paluther (Rhone-Poulenc Rorer) for intramuscular injection. The manufacturer has provided a total treatment cost comparison for this drug versus intravenous quinine in an African public hospital setting (Ivory Coast) in 1998:

Drug only:

- Paluther (6x80mg IM) US$ 17.59
- Quinine standard dose (1.5g/day IV x 3, then 12 tablets/day x 3) US$ 8.62
- Quinine minimum dose (1.5g/day IV x 3, no oral treatment) US $ 3.43

Drug plus sterile material:

- Paluther (as above) US$ 18.26
- Quinine standard dose (as above) US$ 22.15
- Quinine minimum dose (as above) US$ 10.20

Quinine is the cheaper drug by far, however, sterile solution for intravenous infusion greatly adds to its cost. Intramuscular quinine would compare even more favourably with Paluther in terms of cost. Local preparations of artemisinin drugs would be cheaper in developing countries than imported Paluther, although equivalent potency cannot be assumed.

Benefit and risk

From this review, we can say that there is some evidence that artemisinin drugs (bearing in mind that most of the evidence comes from artemether) may be better than quinine at preventing death from severe malaria. We are less sure about the risks of harm because evidence from randomised trials is lacking.

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

AUTHORS' CONCLUSIONS

Implications for practice

1. Are treatment regimens with artemisinin drugs better than standard treatment regimens for severe and complicated malaria?

Artemisinin drugs are no worse than quinine in preventing death from severe malaria. Aggregate data suggests that at best one more life could be saved in every 25 patients (95% CI 16 to 65) treated with an artemisinin drug compared with quinine, however, this has to be interpreted with caution because of the heterogeneity between studies. Additional supportive care might be more essential to survival than the antimalarial drug in patients with complications of severe malaria, including cerebral malaria.

There is no evidence yet to suggest that early treatment in rural areas with suppositories is inappropriate, being more convenient than parenteral quinolines, whilst patients are being transferred to a higher grade health facility.

2. Do artemisinin drugs have a comparative advantage over other antimalarials in areas where comparator drug resistance is high?

There is a need to determine whether the superiority of artemisinin drugs over quinine is a reflection of reduced sensitivity to quinine.

3. Should artemisinin derivatives be combined de novo with longer-acting antimalarials in the treatment of severe and complicated malaria?

Combination with a longer-acting antimalarial drug such as mefloquine or sulfadoxine-pyrimethamine does reduce the rate of recrudescence according to the available evidence, and could possibly slow development of resistance to artemisinin derivatives. However, the risk of enhanced neurological reactions with mefloquine following severe malaria needs to be considered (NJ White, personal communication).

4 and 5. Is any artemisinin derivative better than the others; what is the best formulation, dose and treatment regimen?

The best derivative, route of administration, dose and treatment regimen has not been established in randomised controlled trials.

Implications for research

Individual patient data (IPD) meta-analysis has been completed for the larger, well-conducted RCTs of artemether versus quinine included in this review. Ideally, all data that address a common clinical question should be analysed in such a thorough and collaborative way.

Most randomised comparisons with quinine have used artemether. In the light of the results of the IPD metanalysis of artemether versus quinine trials, a decision should now follow as to a) is more data on artemether needed? and b) what data?

Prolongation of coma with artemether (and more convulsions, vanHensbroekGAM92-4) compared with quinine indicates a need for active investigation of neurological adverse effects of artemisinin derivatives in humans with cerebral malaria.

There are few data available on artemisinin and artesunate compared with standard treatment. Artesunate is being widely used, and artemisinin suppositories advocated.

Future trials

Co-ordination of trials is desperately needed to standardise inclusion criteria, the definition of severe malaria, monitoring of trials and outcome measures. The lack of agreement between trials to date reflects particularly badly on this aspect of clinical research.

There is a need to clarify the important risk factors for death in severe malaria rather than using post hoc statistical analysis, and to stratify randomisation according to potentially important features.

Researchers have to make their data available if maximum use is to be made of all the existing evidence in order to make an informed decision on appropriate use of artemisinin derivatives in severe malaria.

There is still a need to identify inexpensive, easily administered antimalarial drugs and adjunct therapies that will substantially reduce the rate of death in severe malaria (Hoffman 1996).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Anh VNM 89

Methods	Random number table; open Excluded = 6/47 (13%; < 1000 Pf/µl) Follow-up: 7 to 14 days hospitalisation No loss to follow-up reported
Participants	41 Vietnamese adults 16 to 52 years Cerebral malaria (Choray coma scale 3, equivalent Glasgow 3-6) with or without renal, gastrointestinal, hepatic or pulmonary complications Pf >1000/µl
Interventions	ASiv vs QNNiv: 1. AS240: 60 mg at 0 h, 4 h, 24 h and 48 h 2. QNN (20 mg/kg over 4 h then 10 mg/kg every 8 h to day 7)
Outcomes	1. Mortality 2. Coma recovery time 3. PCT (50, 95 & 100%)
Notes	Quality assessment: B, A, C AS: Guilin No.2 Pharmaceutical Factory, China; supplied by Roche Asian Research Foundation

Anh VNM 92-95

Methods	Centralised randomisation, allocation concealed in opaque sealed envelopes; open No exclusions or loss to follow-up reported Follow-up: 7 to 14 days hospitalisation
Participants	190 Vietnamese adults Cerebral malaria (Choray coma scale 3, equivalent Glasgow 3-6) with or without other visceral complications Pf parasitaemia
Interventions	ASiv vs QNNiv: 1. AS240: 60 mg at 0 h, 4 h, 24 h and 48h, plus MQ15 oral on day 7 2. QNN: 20 mg/kg over 4 h then 10 mg/kg every 8 h to day 7
Outcomes	1. Mortality 2. Coma recovery time 3. PCT (50, 95 & 100%) 4. FCT

Anh VNM 92-95 *(Continued)*

Notes	Quality assessment: A, A, A AS: Guilin No.2 Pharmaceutical Factory, China; supplied by WHO

Birku ETH 96-7

Methods	Open randomisation using lottery draw No withdrawals or exclusions loss to follow-up at 28 d = 3/60 (5%)
Participants	65 Ethiopian adults 23 to 41 years Severe malaria (WHO 1990b), 15 patients had unrousable coma (Glasgow <10) Asexual falciparum parasitaemia Excluded: QNN or SP just before admission; history of liver/kidney disease; pregnant
Interventions	ARTpr vs QNNiv: 1. ART 4250 mg (750 mg at 0 h, 500 mg at 12 h, then 500 mg daily on days 2 to 7) 2. QNN 20 mg/kg over 4 h then 10 mg/kg every 8 h, continued per os when able Tepid sponging for fever (> 39 °C sub-lingual); intravenous fluid for severe dehydration, shock, hypoglycaemia; transfusion for Hb < 5 g/dl and signs of conjestive cardiac failure; dextrose for blood glucose < 2.2 mM/l; nursing care for comatose patients
Outcomes	1. Mortality 2. Coma recovery time 3. PCT 4. PC50 5. FCT 6. Adverse effects
Notes	Quality assessment: B, B, A Artemisinin: Mediplantex, Hanoi, Viet Nam

Bunnag THI 89-90

Methods	Randomised, method not specified No exclusions reported Loss to follow-up at day 28: AM480 = 7/53 (13%), AM600 = 3/53 (7%)
Participants	106 Thai male adults 15 to 45 years Febrile Severe malaria (WHO 1990b)

Bunnag THI 89-90 *(Continued)*

	Asexual falciparum parasitaemia
Interventions	AMim480 vs AMim600: 1. AM480: 160 mg on day 1, 80 mg on days 2 to 5 2. AM600: 200 mg on day 1, 100 mg on days 2 to 5 Patients with Pv during 28 d follow-up given 150 mg chloroquine base
Outcomes	1. FCT 2. PCT 3. Cure rate at day 28 4. Recrudescence (WHO 1973)
Notes	Quality assessment: B, B, B Arthermin

Danis WAF 93-4

Methods	Centralised block randomisation stratified by investigating centre (5 centres), allocation concealed in sealed envelopes, not blinded. Withdrawn = 2/282 (<1%); records lost: 12/180 (4%); excluded after treatment: AM = 7/133 (5%), QNN = 10/135 (7%); loss to follow-up at d14: 37/268 (14%)
Participants	194 West African children, 3 months to 15 years; 74 adults, 16 to 48 years; febrile One or more criteria for severe malaria, or 3 incidents of vomiting in previous 24h, and one other manifestation of severe malaria (WHO 1990b), cerebral Glasgow score 7 or less, Blantyre 3 or less; asexual falciparum parasitaemia. Excluded: MQ, SP in previous 15 d; H, ART derivative in previous 5 d; QNN in previous 24 h; any intramuscular injection in previous 12 h; other systemic infectious disease; non-systemic or intracranial disease; renal insufficiency; circulatory arrest; diffuse haemorrhage; pregnancy, breastfeeding; contraindication for intramuscular injection
Interventions	AMim vs QNNiv: 1. AM: < 50 kg, 9.6 mg/kg (1.6 mg/kg at 0 h, 12 h, days 2 to 5; > 50 kg, 480 mg (80 mg at 0 h, 12 h, days 2 to 5) 2. QNN: 20 mg/kg, then 10 mg/kg every 8 h, per os from days 3 to 7 depending on patient clinical state
Outcomes	1. Mortality 2. Time to total parasite clearance (major endpoint) 3. FCT 4. Resolution of coma (Glasgow score 15 in adults with a score of <12, Blantyre score 5 in children with a score of <4) 5. PC50, PC90 6. Safety by clinical, haematological, biochemical & ECG tests
Notes	Quality assessment: A, A, B Paluther Rhone-Poulenc

Hien VNM 89-90

Methods	Randomised, method not specified

Hien VNM 89-90 *(Continued)*

	No exclusion or loss to follow-up reported
Participants	79 Vietnamese adults 15 to 52 years Cerebral malaria (clinical signs with unrousable coma, Glasgow scale <10) Asexual falciparum parasitaemia
Interventions	ARTpr + MQ10 vs ASiv + MQ10 vs QNNiv: 1. ART 2800 mg (600 mg at 0 h and 4 h, 400 mg at 24 h, 32 h, 48 h and 56 h) + MQ 500 mg (single dose, sequential) 2. AS 240 mg (60 mg at 0 h and 4h, 60 mg at 24 h and 48h) + MQ 500 mg (single dose, sequential) 3. QNN 500 mg, every 8 hours for 14 days All patients managed according to WHO 1986 recommendations
Outcomes	1. Mortality 2. FCT 3. Time to regain full consciousness (Glasgow scale 15) 4. PCT (50, 90, 100%)
Notes	Quality assessment: B, B, C ART & AS: supplied by Prof Guo Qiao Li

Hien VNM 91

Methods	Patients allocated at random in pairs, method not specified; open No exclusions or loss to follow-up reported
Participants	Vietnamese adults 15 to 45 years Severe falciparum malaria (WHO 1986) Falciparum parasitaemia Excluded: pregnancy; parenteral QNN in previous 4h
Interventions	ASim + MQ10 vs ASiv + MQ10 AS 2 mg/kg at 0 h, 1 mg/kg at 12 h and 24 h, then daily until patient able to take oral medication + MQ 500 mg (single dose, sequential) Unconcious patients: single dose phenobarbitone intramuscular Hypoglycaemia: dextrose 1mg/kg intravenous
Outcomes	1. Mortality 2. Incidence of complications 3. FCT 4. PCT 5. Rate of parasite clearance (graph)
Notes	Quality assessment: B, B, A

Hien VNM 91 *(Continued)*

	AS from Guilin No2 Pharmaceutical Factory, 60 mg ampoules anhydrous powder reconstituted in 0.6 ml sodium bicarbonate, diluted to 5 ml in 5% dextrose

Hien VNM 91-6

Methods	Randomised, method not specified, double blind Excluded = 1/561 No loss to follow-up reported
Participants	560 Vietnamese patients > 14 years Asexual falciparum parasitaemia and one or more of the following: Glasgow coma score <11 (cerebral malaria); anaemia or jaundice with Pf > 100,000/µl; hyperparasitaemia (> 10%); renal impairment; hypoglycaemia; shock (systolic BP > 80 mmHg with cool extremities). Excluded: 1st trimester pregnancy; intravenous drug users; > 3 g QNN or two doses of ART derivative in previous 48 h
Interventions	AMim vs QNNim 1. AM: 4 mg/kg, then 2 mg/kg every 8 h 2. QNN 20 mg/kg, then 10 mg/kg every 8h All patients given isotonic saline to restore/maintain fluid balance Hypoglycaemia managed with aqueous dextrose Blood transfused if PCV<20%
Outcomes	1. Mortality 2. Neurological sequelae 3. FCT 4. PCT 5. Time to coma recovery (Glasgow score 15) 6. Duration of hospitalisation 7. Incidence of complications 8. Side effects
Notes	Quality assessment: A, B, A AM from Kunming Pharmaceutical Co. 3ml ampoule

Karbwang THI 91

Methods	Randomised, method not specified No exclusions or loss to follow-up reported
Participants	26 Thai adults (25 male) 15 to 45 years Severe falciparum malaria (WHO 1990b). Excluded: antimalarials in previous 24 h

Karbwang THI 91 *(Continued)*

Interventions	AMim vs QNNiv: 1. AM: 160 mg on day 1, 80 mg on days 2 to 7) 2. QNN: 20 mg/kg on day 1, 10 mg/kg every 8 h to day 7
Outcomes	1. Mortality by day 7 2. FCT 3. PCT 4. Time to recover conciousness 5. Neurological sequelae 6. Adverse effects
Notes	Quality assessment: B, B, C Arthermin (80 mg ampule)

Karbwang THI 92

Methods	Randomised, method not specified; no exclusions or loss to follow-up reported
Participants	28 Thai male adults 15 to 65 years Severe falciparum malaria (WHO 1990b) Excluded: history of antimalarial treatment; concurrent disease
Interventions	AMim640 vs AMim700: 1. AM640: 160 mg on day 1, 80 mg on days 2 to 7 2. AM700: 300 mg on day 1, 100 mg on days 2 to 5 AM tablets given per os as soon as oral medication possible Acute renal failure managed by dialysis
Outcomes	1. Mortality by day 28 2. FCT 3. PCT 4. Tolerance (clinical & laboratory evaluations)
Notes	Quality assessment: B, B, C Source of AM not reported

KarbwangTHI92-4

Methods	Centralised computer generated randomisation, allocation concealed in sealed envelopes opened in sequence, open-label, microscopists blinded Withdrawn before treatment: AM = 3/50 (6%), QNN = 2/52 (4%); excluded after treatment <10%
Participants	102 Thai adults 15 to 65 years Severe falciparum malaria (WHO 1990b)

KarbwangTHI92-4 *(Continued)*

	Excluded: pregnancy; antimalarials in previous 24h; concurrent diseases
Interventions	AMim vs QNNiv: 1. AM:160 mg on day 1, 80 mg on days 2 to 7 2. QNN: 20 mg/kg on day 1, 10 mg/kg every 8 h to day 7 QNN loading dose not given if history of previous antimalarial treatment Renal failure managed by dialysis; antibiotics, anticonvulsants, antiemetics, ulcer medication, sedative, paracetamol, diuretics, vasopressors, packed RBC as required
Outcomes	1. Mortality by day 7 2. FCT 3. PCT (rate graph) 4. Time to recover conciousness 5. Incidence of complications 6. Neurological sequelae 7. Adverse effects
Notes	Quality assessment: A, A, A AM: Paluther (80 mg/ml) Rhone Poulenc Rorer, manufactured by Kunming, China; Artemetheri for injection, Kunming, starting from patient #41

LooareesuwanTHI95

Methods	Computer generated randomisation in blocks of 10, allocation concealed in sealed envelopes, physicians and technicians blinded No exclusions reported Loss to follow-up at 28 d: AS1600 = 5/32 (16%), AS1200 = 4/31 (13%)
Participants	63 Thai adults > 15 years Severe falciparum malaria (WHO 1990b) 51/63 had not had malaria before Excluded: pregnancy; acute diarrhoea; rectal abnormalities or previous surgery; antimalarials in previous 2 weeks
Interventions	ASpr1200 + MQ25 vs ASpr1600 + MQ25: 1. AS1200: 200 mg at 0 h, 12 h, 24 h, 36 h, 48 h and 60 h + MQ1250 mg (sequential, 750 mg at 72 h & 500 mg at 84 h) 2. AS1600: 200 mg at 0 h, 4 h, 8 h, 12 h, 24 h, 36 h, 48 h and 60 h + MQ1250 (as before)
Outcomes	1. Mortality 2. Time to regain consciousness 3. FCT 4. PCT (50, 90, 100%) 5. Cure rate at day 28 6. Adverse effects
Notes	Quality assessment: A, A, B AS: Plasmotrim, Rectocaps (200 mg capsule) Mepha, Switzerland

Murphy KEN 92-4

Methods	Centralised randomisation using random number table, allocation concealed in sealed envelopes opened sequentially, open-label Excluded from analysis: AM =14/103 (14%), QNN = 26/97 (27%) No loss to follow-up reported
Participants	200 Kenyan children < 12 years Unrousable coma (Blantyre motor response <2) Falciparum parasitaemia with fever Excluded: evidence of head injury; systolic BP < 70 mmHg; prior treatment with QNN, ART derivative, Fansidar or metakelfin
Interventions	AMim vs QNNiv: 1. AM 3.2 mg/kg on day 1, 1.6 mg/kg for 1 to 4 days or until conscious and aparasitaemic, minimum 3 doses 2. QNN 20 mg/kg, then 10 mg/kg every 8 h (minimum 3 intravenous doses, per os when able to drink) Falcidin (25 mg/kg S, 1.25 mg/kg P) given in water when able to take oral fluid and aparasitaemic Fluid balance maintained with intravenous/oral fluids
Outcomes	1. Mortality 2. Mortality with respiratory distress 3. Time to death 4. Time to localise pain 5. Rate of neurological sequelae 6. Time to sit, stand walk, drink 7. PCT (50, 90, 100%), FCT, recrudescence by day 28 8. Tolerance (TESS in 1st week, abnormal lab results)
Notes	Quality assessment: A, A, B Paluther 8% solution, Rhone-Poulenc

Ojuawo NIG (98)

Methods	Randomisation method not reported Exclusions, withdrawals, loss to follow-up not reported
Participants	37 Nigerian children 2 to 6 years Cerebral malaria, unrousable coma (Glasgow scale) Asexual Pf No other identifiable cause of coma
Interventions	AMim vs QNNiv: 1. AM 3.2 mg/kg, then 1.6 mg/kg every 12 h for 3 days 2. QNN 10 mg/kg over 2 h then 8 hourly until conscious, then per os to day 7

Ojuawo NIG (98) *(Continued)*

	Other supportive treatment included: intravenous 10% dextrose; 10% mannitol intravenous for cerebral oedema; ampicillin, gentamicin if clinical evidence of infection and appropriate antibiotics for confirmed infection
Outcomes	1. Mortality 2. Neurological sequelae 3. CRT 4. FCT 5. PC at 72 h & day 7
Notes	Quality assessment: B, B, C Paluther

Olumese NIG 94-6

Methods	Independent randomisation using computer-generated random numbers, allocation concealed in envelopes Withdrawn: 5/108 (5%) reasons given No loss to follow-up at day 28
Participants	103 Nigerian children 11 months to 5 years Cerebral malaria (WHO 1990b) Unrousable coma > 30min (modified Glasgow scale) Peripheral Pf Excluded: abnormal CSF or low blood glucose who responded to glucose infusion only
Interventions	AMim vs QNNiv: 1. AM 9.6 mg/kg (3.2 mg/kg on day 1, then 1.6 mg/kg daily on days 2 to 5) 2. QNN 20 mg/kg, then 10 mg/kg every 8 h until conscious, then per os to complete 21 doses Exposure, fanning, sponging for fever; paraldehyde or diazepam for convulsions; 50% dextrose for hypoglycaemia; 10 ml/kg packed red cells for severe anaemia (Hb < 5 g/dl)
Outcomes	1. Mortality 2. Neurological sequelae 3. CRT 4. PCT 5. FCT 6. Adverse effects
Notes	Quality assessment: A, A, A AM from Kunming Pharmaceuticals

PhuongVNM 92-5

Methods	Randomised, method not specified, open

PhuongVNM 92-5 *(Continued)*

	Withdrawn before treatment = 2/111 (2%) No exclusions reported No loss to follow-up at day 7, 67/98 (68%) at day 28
Participants	109 Vietnamese children 3 months to 14 years More than two thirds had not had malaria before Asexual Pf One or more criteria for severe malaria: Blantyre coma 3 or less; PCV 15% or less with Pf > 10,000/µl; hyperparasitaemia; jaundice; hypoglycaemia; spontaneous bleeding; shock; convulsions; renal impairment Excluded: severe diarrhoea; PfPv; QNN > 60 mg/kg, ART > 20 mg/kg, AS > 2 mg/kg or any antimalarial for more than 48 h for current episode
Interventions	ARTpr + MQ15 vs ASim + MQ15 vs QNNiv + SP: 1. ART 120 mg (40 mg at 0 h, 20 mg at 4 h, 24 h, 48 h and 72h + MQ 750 mg at 96 h) 2. AS 11 mg/kg (3 mg/kg at 0 h, 2 mg/kg at 12 h, 24 h, 48 h and 72 h + MQ 750 mg at 96 h) 3. QNN 20 mg/kg, then 10 mg/kg every 8 h to 7 days + Fansidar single dose on day 7
Outcomes	1. Mortality 2. Neurological sequelae 3. CRT 4. FCT 5. PCT (50, 90, 100%) 6. period in hospital 7. Complications 8. Adverse events
Notes	Quality assessment: A, B, A ART suppositories from Vidipha, Viet Nam; AS from Guilin No.2 Pharmaceutical Factory

Seaton PNG 92-5

Methods	Centralised randomisation, allocation concealed in sealed envelopes opened in sequence, open label, microscopists blinded Excluded: AM = 3/20 (15%), QNN = 2/20 (10%) Loss to follow-up AM = 2/17 (12%)
Participants	40 adults (39 Papua New Guinean, 1 European) Asexual falciparum parasitaemia; One or more criteria of severe/complicated malaria (WHO 1990b) Excluded: < 12 years; pregnant; parenteral antimalarial prior to admission; PfPv; coexisting infection
Interventions	AMim vs QNNiv: 1. AM 9.6 mg/kg (3.2 mg/kg, then 1.6 mg/kg daily on days 2 to 5) 2. QNN 20 mg/kg then 10 mg/kg every 8 h for 7 days; per os after 48 h if tolerated

Seaton PNG 92-5 *(Continued)*

	Tepid sponging & paracetamol as required for pyrexia; oligouric with impaired renal function managed with peritoneal dialysis; blood transfusion when indicated; hypoglycaemia treated with intravenous dextrose
Outcomes	1. Mortality at day 7 & 28 2. CRT 3. FCT 4. PCT (50 & 100%) 5. Tolerance (clinical & laboratory criteria)
Notes	Quality assessment: A, A, B AM: Rhone-Poulenc Rorer

Taylor MAL 92-4

Methods	Centralised computer generated randomisation, allocation concealed in sealed envelopes opened in sequence, open-label, microscopists blinded Withdrawn: AM = 12/95 (13%), QNN = 7/88 (8%) No loss to follow-up reported
Participants	183 Malawian children with cerebral malaria, unrousable coma (Blantyre score 2 or less) and asexual falciparum parasitaemia Excluded: additional diagnosis; QNN or AM in previous week
Interventions	AMim vs QNNiv: 1. AM 3.2 mg/kg, then 1.6 mg/kg daily 2. QNN 20 mg/kg then 10 mg/kg every 8 h (minimum 3 intravenous doses, per os when able to drink) Fansidar (500 mg S, 25 mg P) given at parasite clearance and full recovery
Outcomes	1. Mortality (survival the major criterion for efficacy) 2. Neurological sequelae at 96h 3. FCT 4. PCT (50, 90, 100%) 5. Time to recover full consciousness (Blantyre score 5, or 4 in patients with compromised vision due to malaria) 6. Time to sit, stand, walk, drink, eat 7. Recrudescence at 7 d, 14 d, 21 d and 28 d
Notes	Quality assessment: A, A, A Artemetheri for injection 80 mg/ml, Kunming Pharmaceuticals Paluther 8% solution Rhone-Poulenc, manufactured by Kunming Pharmaceuticals

Thwe MYA 96

Methods	Randomised, method not specified No exclusions reported Loss to follow-up at day 28: AS1200 = 0/27, AS800 = 2/27 (7%)

Thwe MYA 96 *(Continued)*

Participants	54 Burmese male adults 18 to 50 years Clinical features of severe (Glasgow scale 10-14) and complicated falciparum malaria (WHO 1990b) Excluded: concomitant illness; haemorrhoids; gastrointestinal problems or previous rectal surgery; mixed malaria infection; antimalarials in previous 14 days
Interventions	ASpr800 + MQ25 vs ASpr1200 + MQ25: 1. AS 800 mg (200 mg at 0 h, 12 h, 24 h and 36 h) + MQ 1250 mg (sequential, 750 mg at 48 h, 500 mg at 60 h) 2. AS 1200 mg (200 mg at 0 h,12 h, 24 h, 36 h, 48 h and 60 h) + MQ 1250 mg (sequential, 750 mg at 72 h, 500 mg at 84 h)
Outcomes	1. Mortality 2. FCT 3. PCT 4. Recrudescence at day 28 5. Side effects (haematological & biochemical laboratory tests)
Notes	Quality assessment: B, B, A Plasmotrim, Rectocaps 200 mg capsule, Mepha

vanHensbroekGAM92-4

Methods	Randomised, method not specified; stratified by admission coma score and study centre, balanced over time in blocks of 10; allocation concealed in sealed envelopes; open; neurological sequelae assessors blinded Withdrawn before treatment: 3/579 (died) No exclusions or loss to follow-up reported < 5% loss at 5 months follow-up for persistent neurological sequelae
Participants	576 Gambian children 1 to 9 years Cerebral malaria, Blantyre score 2 or less Asexual falciparum parasitaemia Excluded: disease other than malaria; recovered consciousness after correction of hypoglycaemia; QNN treatment before admission
Interventions	AMim vs QNNim: 1. AM 3.2 mg/kg on day 1, 1.6 mg/kg daily 2. QNN 20 mg/kg, then 10 mg/kg every 12 h Fansidar (25mg S, 1.25mg P) given after full recovery (in 2nd and 3rd year of the study); comatose patients given intravenous glucose/saline; hypoglycaemia managed with intravenous glucose; convulsions with diazepam, paraldehyde or phenobarbitone; transfusion if PCV < 15%; secondary infection treated with chloramphenicol
Outcomes	1. Mortality at hospital 2. Persisting neurological sequelae (primary end-points)

vanHensbroekGAM92-4 *(Continued)*

	3. FCT 4. PCT (50, 90, 100%) 5. CRT 6. Neuorological sequelae at discharge, 1 & 5 months
Notes	Quality assessment: A, A, A Paluther Rhone-Poulenc

Vinh VNM 92-4

Methods	Randomised, method not specified (randomisation to ASiv stopped at 30 patients), open Excluded: AMim = 2/47 (4%), ART = 1/52 (2%), ASim = 1/50 (2%), ASiv = 1/31 (3%) No loss to follow-up
Participants	180 Vietnamese 15 to 66 years Clinical severe malaria Asexual falciparum parasitaemia One of following: coma (Glasgow < 11), hypoglycaemia, renal failure, jaundice, anaemia (PVC < 20% with Pf > 100,000/µl), hyperparasitaemia (Pf > 500,000/µl), shock Excluded: 1st trimester pregnancy; concomitant disease; Pv or Pf Pv; > 3 g QNN or 2 doses ART derivative recorded
Interventions	ARTpr vs AMim vs ASim vs ASiv: ART 2800 mg (1200 mg at 0 h, 400 mg at 4 h, 24 h, 48 h and 72 h) AM 500 mg (200 mg at 0 h, 100 mg at 24 h, 48 h and 72 h) AS 300 mg (120 mg at 0 h, 60 mg at 24 h, 48 h and 72 h) All patients received MQ 750 mg on regaining consciousness or on day 4; fluid, electrolytes, antipyretics when needed (WHO 1990a); dialysis for acute renal failure
Outcomes	1. Mortality 2. Time to regain full consciousness 3. FCT 4. PCT
Notes	Quality assessment: A, B, A AM from Kunming Pharmaceutical Factory, China; ART from Viet Nam Industrial Development of Pharmaceutics; AS from Guilin No.2 Factory, China

White GAM 89

Methods	Randomised, method not specified, open No exclusions No loss to follow-up

White GAM 89 *(Continued)*

Participants	43 Gambian children; severe malaria (WHO 1990b) Excluded: antimalarials in previous 4 h
Interventions	AM intramuscular vs CLQ intramuscular: 1. AM 4 mg/kg on day 1, 2 mg/kg daily 2. CLQ 3.5 mg/kg every 6 h (per os when able to take fluids by mouth) Temperature > 38.5 °C treated with fanning, sponging and paracetamol; intravenous fluids, ampicillin, benzylpenicillin, gentamicin, diazepam, paraldehyde given as indicated clinically; all comatose patients given intramuscular phenobarbitone; blood transfusion if PCV < 15%
Outcomes	1. Mortality 2. FCT 3. PCT (50, 90, 100%) 4. Time to reach coma score 5; time to drink, sit, stand, walk; 5. Incidence of recurrent seizures, hypoglycaemia, septicaemia, transfusion 6. Adverse effects
Notes	Quality assessment: B, B, A Artemether 80 mg/ml Kunming Pharmaceuticals

Win MYA 89-91

Methods	Alternate allocation (allocation to AS treatment was stopped early due to concerns about sterility of the ampuoles; referred patients already on intravenous QNN were kept in the QNN treatment group but later excluded from analysis), microscopists blinded Excluded: 36/180 (20%) Evaluated: AM = 50, AS = 27, QNN = 67 No loss to follow-up
Participants	144 Burmese male adults 17 to 50 years Unrousable coma (Glasgow scale 3-9) without other severe complications Falciparum parasitaemia Excluded: other causes of coma; parenteral antimalarial in previous 48h; other complications of malaria; concomitant chronic illness
Interventions	AMim + MQ20 vs ASiv + MQ20 vs QNNiv + Tc: 1. AM 600 mg (200 mg, then 100 mg at 12 h, 24 h, 36 h and 48 h) + MQ 1000 mg at 48 h (sequential, single dose) 2. AS 240 mg (120 mg, then 60 mg at 12 h, 24 h and 48 h) + MQ 1000 mg (as before) 3. QNN 600 mg every 8 h for up to 10 days + Tc (250 mg at 48 h then every 6 h for 7 days)
Outcomes	1. Mortality 2. FCT 3. PCT 4. Time to regain conciouness 5. Incidence of complications 6. Recrudescence

Win MYA 89-91 *(Continued)*	7. Side effects
Notes	Quality assessment: C, B, B AM (100 mg/amp) from State Pharmaceutical Factory, Yunan; AS (60 mg/ml) from Guilin Pharmaceutical Factory No.2

Study code: Name of investigator, COUNTRY CODE, year the study was done (if the year the study was done is not known, the publication date is given in brackets).
ETH: Ethiopia; GAM: Gambia; KEN: Kenya; MAL: Malawi; MYA: Myanmar; NIG: Nigeria; PNG: Papua New Guinea; THI: Thailand; VNM: Viet Nam; WAF: West Africa; Pf: *Plasmodium falciparum*; Pv: *Plasmodium vivax*; PfPv: mixed falciparum & vivax infection; ART: artemisinin; AM: artemether; AS: artesunate; QNN: quinine; CLQ: chloroquine; MQ: mefloquine; H: halofantrine; S: sulfadoxine; P: pyrimethamine; Tc: tetracycline; (S): sequential MQ; (C): concomitant MQ; FCT: fever clearance time; PCT: parasite clearance time; PC50/90: time to 50%/90% parasite clearance; CRT: coma recovery time; TESS: treatment emergent signs and symptoms; RBC: red blood cells.
Risk of bias (methodological quality) assessment: used the Cochrane Infectious Diseases Group standard guidelines in terms of allocation concealment, generation of allocation sequence, and inclusion of all randomised participants.

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

Study	Reason for exclusion
Karbwang THI 92-4i	Interim report of included study Karbwang THI 92-4
LuxemburgerTHI-MYA93	Uncomplicated hyperparasitaemic falciparum malaria
Molyneux MAL	Interim results from included study Taylor MAL 92-4
Salako NIG 92	Comparison: artemether intramuscular vs sulfadoxine-pyrimethamine intramuscular; moderately severe malaria defined as persistent nausea or vomiting which made it impossible to retain oral therapy
Salako NIG 94	Duplicate publication of data from Salako NIG 92 and Walker NIG 91-4
Sowumni NIG 93-4	Observational study of three non-randomised groups of patients treated with intramuscular artemether
Taylor MAL 92i	Interim results from included study Taylor MAL 92-4
Walker NIG 91-4i	This study has a number of major flaws including: lack of consistency in administration of study drugs; no set schedule for symptom assessment; poor follow-up; haphazard administration of concomitant medications Methods: centralised computer generated randomisation, allocation concealed in sealed envelopes opened in sequence, open-label. Excluded from analysis: AM = 30/52 (58%), QNN = 29/47 (62%); up to 70% loss to follow-up reported Participants: 40 Nigerian children 9m-10y; cerebral malaria (WHO 1990), unrousable coma on Blantyre scale; falciparum parasitaemia; no other cause of coma. Excluded: antimalarials in previous week Interventions: artemether intramuscular vs vs quinine intravenous; artemether 3.2 mg/kg on d1, 1.6mg/kg daily on d2-5 or until conscious and aparasitaemic, minimum 4 injections; quinine QNN 20 mg/kg, then 10 mg/kg every 8h, minimum 3 intravenous doses, then per oral when able to drink Outcomes: mortality; time to regain full consciousness; time to Blantyre score 5; neurological sequelae; recrudescence at d7 & d28; fever clearance time; parasite clearance time; time to sit, stand, drink

Study	Reason for exclusion
	Artemetheri for injection 80 mg/ml, Kunming Pharmaceuticals
Walker NIG 91-4ii	Interim results of excluded study Walker NIG 91-4

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

Myint MYA 85

Methods	—
Participants	—
Interventions	—
Outcomes	—
Notes	—

Shwe MYA 87-91

Methods	—
Participants	—
Interventions	—
Outcomes	—
Notes	—

Vinh VNM 92

Methods	—
Participants	—
Interventions	—
Outcomes	—
Notes	—

DATA AND ANALYSES

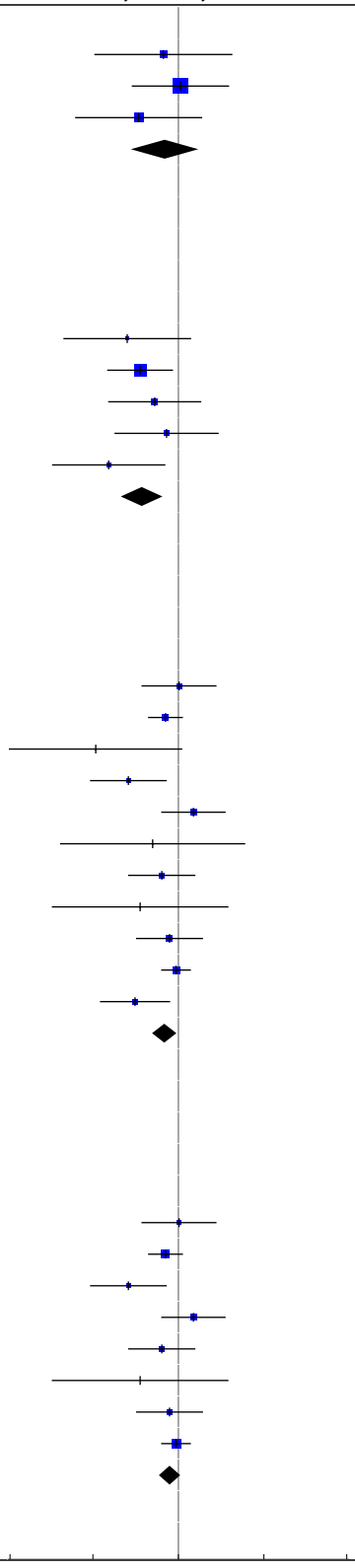
Comparison 1. Artemisinin drug vs quinine

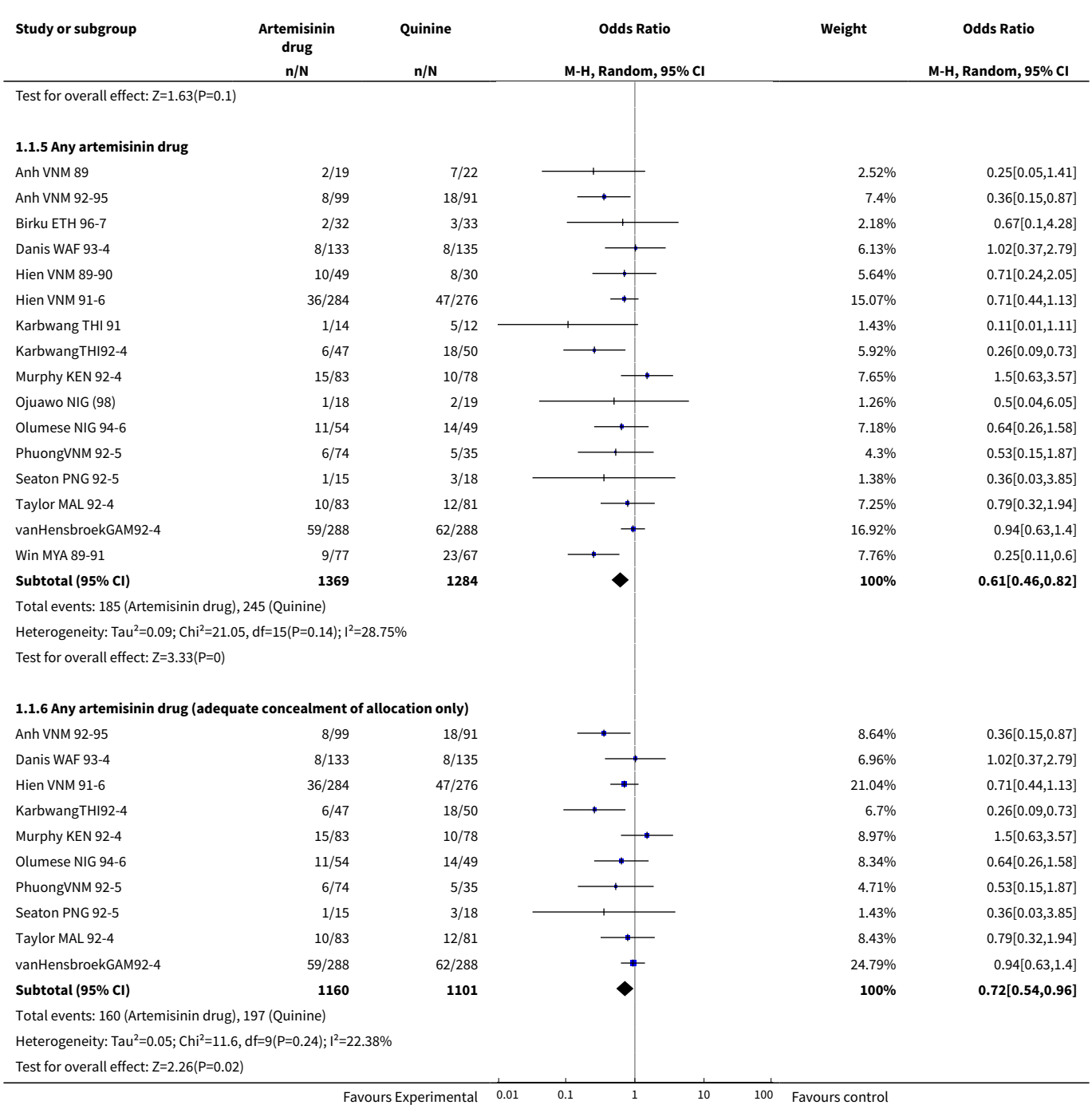
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	16		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Artemisinin	3	185	Odds Ratio (M-H, Random, 95% CI)	0.69 [0.28, 1.71]
1.2 Artesunate	5	458	Odds Ratio (M-H, Random, 95% CI)	0.37 [0.21, 0.65]
1.3 Artemether	11	2142	Odds Ratio (M-H, Random, 95% CI)	0.68 [0.49, 0.95]
1.4 Artemether (adequate concealment of allocation only)	8	1962	Odds Ratio (M-H, Random, 95% CI)	0.79 [0.59, 1.05]
1.5 Any artemisinin drug	16	2653	Odds Ratio (M-H, Random, 95% CI)	0.61 [0.46, 0.82]
1.6 Any artemisinin drug (adequate concealment of allocation only)	10	2261	Odds Ratio (M-H, Random, 95% CI)	0.72 [0.54, 0.96]
2 Mortality subgrouped as cerebral or non-cerebral malaria	14		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Artemisinin, cerebral malaria	2	27	Odds Ratio (M-H, Random, 95% CI)	0.26 [0.05, 1.45]
2.2 Artemisinin, non-cerebral malaria	2	110	Odds Ratio (M-H, Random, 95% CI)	0.48 [0.04, 5.63]
2.3 Artesunate, cerebral malaria	1	16	Odds Ratio (M-H, Random, 95% CI)	0.07 [0.00, 1.02]
2.4 Artesunate, non-cerebral malaria	1	56	Odds Ratio (M-H, Random, 95% CI)	1.83 [0.28, 11.88]
2.5 Artemether, cerebral malaria	5	546	Odds Ratio (M-H, Random, 95% CI)	0.75 [0.47, 1.20]
2.6 Artemether, non-cerebral malaria	3	448	Odds Ratio (M-H, Random, 95% CI)	0.60 [0.32, 1.14]
2.7 Any artemisinin drug, all cerebral malaria patients	14	1939	Odds Ratio (M-H, Random, 95% CI)	0.63 [0.44, 0.88]
2.8 Any artemisinin drug, all cerebral malaria patients (adequate concealment of allocation only)	8	1607	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.55, 1.10]
3 Neurological sequelae (cerebral malaria)	10		Odds Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Artemisinin, at recovery	2	18	Odds Ratio (M-H, Random, 95% CI)	1.36 [0.04, 46.65]
3.2 Artesunate, at recovery	1	12	Odds Ratio (M-H, Random, 95% CI)	0.79 [0.02, 25.90]
3.3 Artemether, at recovery	8	1315	Odds Ratio (M-H, Random, 95% CI)	0.80 [0.52, 1.25]
3.4 Artemether, at 1 month	2	510	Odds Ratio (M-H, Random, 95% CI)	0.79 [0.41, 1.51]
3.5 Artemether, at 5 months	1	418	Odds Ratio (M-H, Random, 95% CI)	0.62 [0.24, 1.64]
4 Parasite clearance at day 7	7		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Artemisinin, all patients	2	132	Odds Ratio (M-H, Random, 95% CI)	2.04 [0.18, 23.75]
4.2 Artesunate, all patients	1	72	Odds Ratio (M-H, Random, 95% CI)	6.06 [1.21, 30.43]
4.3 Artemether, all patients	5	925	Odds Ratio (M-H, Random, 95% CI)	2.20 [0.99, 4.91]
5 Parasite clearance at day 28	5		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Artemisinin, all patients	1	57	Odds Ratio (M-H, Random, 95% CI)	0.46 [0.04, 5.43]
5.2 Artesunate, all patients	1	69	Odds Ratio (M-H, Random, 95% CI)	10.2 [0.56, 186.60]
5.3 Artemether, all patients	4	362	Odds Ratio (M-H, Random, 95% CI)	1.74 [0.75, 4.05]
6 Coma recovery time	9		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 Artemisinin	2	58	Mean Difference (IV, Random, 95% CI)	-9.01 [-19.71, 1.68]
6.2 Artesunate	4	326	Mean Difference (IV, Random, 95% CI)	-2.94 [-13.92, 8.04]
6.3 Artemether	5	423	Mean Difference (IV, Random, 95% CI)	-3.65 [-7.37, 0.06]

Analysis 1.1. Comparison 1 Artemisinin drug vs quinine, Outcome 1 Mortality.

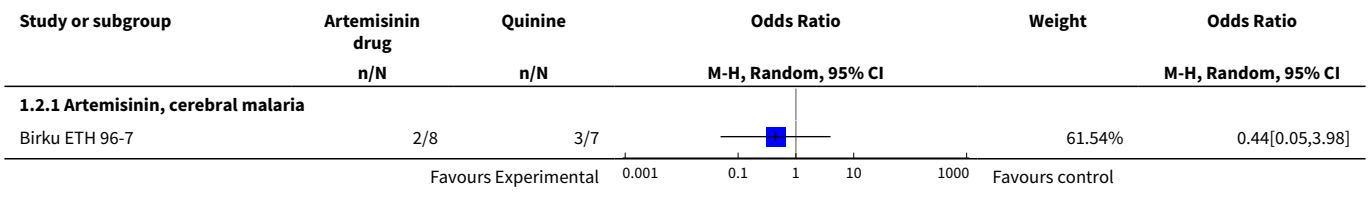
Study or subgroup	Artemisinin drug n/N	Quinine n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1 Artemisinin					
Birku ETH 96-7	2/32	3/33		23.85%	0.67[0.1,4.28]
Hien VNM 89-90	5/18	8/30		47.98%	1.06[0.29,3.92]
PhuongVNM 92-5	2/37	5/35		28.17%	0.34[0.06,1.9]
Subtotal (95% CI)	**87**	**98**		**100%**	**0.69[0.28,1.71]**
Total events: 9 (Artemisinin drug), 16 (Quinine)					
Heterogeneity: Tau^2=0; Chi^2=1.05, df=2(P=0.59); I^2=0%					
Test for overall effect: Z=0.8(P=0.42)					
1.1.2 Artesunate					
Anh VNM 89	2/19	7/22		10.65%	0.25[0.05,1.41]
Anh VNM 92-95	8/99	18/91		39.89%	0.36[0.15,0.87]
Hien VNM 89-90	5/31	8/30		20.02%	0.53[0.15,1.85]
PhuongVNM 92-5	4/37	5/35		15.94%	0.73[0.18,2.96]
Win MYA 89-91	2/27	23/67		13.5%	0.15[0.03,0.7]
Subtotal (95% CI)	**213**	**245**		**100%**	**0.37[0.21,0.65]**
Total events: 21 (Artemisinin drug), 61 (Quinine)					
Heterogeneity: Tau^2=0; Chi^2=2.72, df=4(P=0.61); I^2=0%					
Test for overall effect: Z=3.46(P=0)					
1.1.3 Artemether					
Danis WAF 93-4	8/133	8/135		7.95%	1.02[0.37,2.79]
Hien VNM 91-6	36/284	47/276		19.6%	0.71[0.44,1.13]
Karbwang THI 91	1/14	5/12		1.85%	0.11[0.01,1.11]
KarbwangTHI92-4	6/47	18/50		7.69%	0.26[0.09,0.73]
Murphy KEN 92-4	15/83	10/78		9.93%	1.5[0.63,3.57]
Ojuawo NIG (98)	1/18	2/19		1.64%	0.5[0.04,6.05]
Olumese NIG 94-6	11/54	14/49		9.33%	0.64[0.26,1.58]
Seaton PNG 92-5	1/15	3/18		1.79%	0.36[0.03,3.85]
Taylor MAL 92-4	10/83	12/81		9.41%	0.79[0.32,1.94]
vanHensbroekGAM92-4	59/288	62/288		22.01%	0.94[0.63,1.4]
Win MYA 89-91	7/50	23/67		8.8%	0.31[0.12,0.8]
Subtotal (95% CI)	**1069**	**1073**		**100%**	**0.68[0.49,0.95]**
Total events: 155 (Artemisinin drug), 204 (Quinine)					
Heterogeneity: Tau^2=0.08; Chi^2=14.69, df=10(P=0.14); I^2=31.91%					
Test for overall effect: Z=2.28(P=0.02)					
1.1.4 Artemether (adequate concealment of allocation only)					
Danis WAF 93-4	8/133	8/135		7.35%	1.02[0.37,2.79]
Hien VNM 91-6	36/284	47/276		25.41%	0.71[0.44,1.13]
KarbwangTHI92-4	6/47	18/50		7.06%	0.26[0.09,0.73]
Murphy KEN 92-4	15/83	10/78		9.65%	1.5[0.63,3.57]
Olumese NIG 94-6	11/54	14/49		8.93%	0.64[0.26,1.58]
Seaton PNG 92-5	1/15	3/18		1.44%	0.36[0.03,3.85]
Taylor MAL 92-4	10/83	12/81		9.02%	0.79[0.32,1.94]
vanHensbroekGAM92-4	59/288	62/288		31.13%	0.94[0.63,1.4]
Subtotal (95% CI)	**987**	**975**		**100%**	**0.79[0.59,1.05]**
Total events: 146 (Artemisinin drug), 174 (Quinine)					
Heterogeneity: Tau^2=0.03; Chi^2=8.33, df=7(P=0.3); I^2=15.98%					



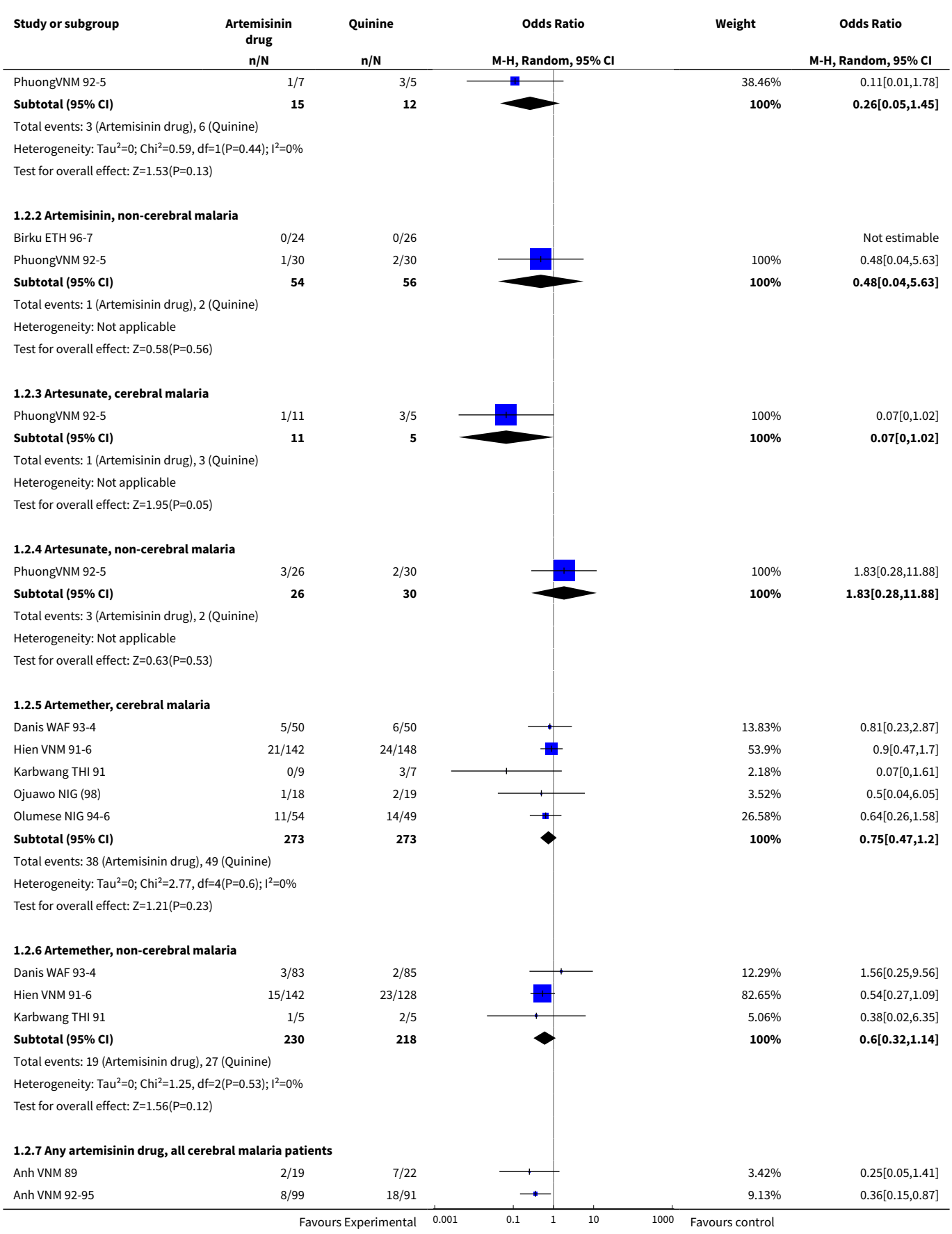


Study or subgroup	Artemisinin drug n/N	Quinine n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Test for overall effect: Z=1.63(P=0.1)					
1.1.5 Any artemisinin drug					
Anh VNM 89	2/19	7/22		2.52%	0.25[0.05,1.41]
Anh VNM 92-95	8/99	18/91		7.4%	0.36[0.15,0.87]
Birku ETH 96-7	2/32	3/33		2.18%	0.67[0.1,4.28]
Danis WAF 93-4	8/133	8/135		6.13%	1.02[0.37,2.79]
Hien VNM 89-90	10/49	8/30		5.64%	0.71[0.24,2.05]
Hien VNM 91-6	36/284	47/276		15.07%	0.71[0.44,1.13]
Karbwang THI 91	1/14	5/12		1.43%	0.11[0.01,1.11]
KarbwangTHI92-4	6/47	18/50		5.92%	0.26[0.09,0.73]
Murphy KEN 92-4	15/83	10/78		7.65%	1.5[0.63,3.57]
Ojuawo NIG (98)	1/18	2/19		1.26%	0.5[0.04,6.05]
Olumese NIG 94-6	11/54	14/49		7.18%	0.64[0.26,1.58]
PhuongVNM 92-5	6/74	5/35		4.3%	0.53[0.15,1.87]
Seaton PNG 92-5	1/15	3/18		1.38%	0.36[0.03,3.85]
Taylor MAL 92-4	10/83	12/81		7.25%	0.79[0.32,1.94]
vanHensbroekGAM92-4	59/288	62/288		16.92%	0.94[0.63,1.4]
Win MYA 89-91	9/77	23/67		7.76%	0.25[0.11,0.6]
Subtotal (95% CI)	**1369**	**1284**		**100%**	**0.61[0.46,0.82]**
Total events: 185 (Artemisinin drug), 245 (Quinine)					
Heterogeneity: Tau^2=0.09; Chi^2=21.05, df=15(P=0.14); I^2=28.75%					
Test for overall effect: Z=3.33(P=0)					
1.1.6 Any artemisinin drug (adequate concealment of allocation only)					
Anh VNM 92-95	8/99	18/91		8.64%	0.36[0.15,0.87]
Danis WAF 93-4	8/133	8/135		6.96%	1.02[0.37,2.79]
Hien VNM 91-6	36/284	47/276		21.04%	0.71[0.44,1.13]
KarbwangTHI92-4	6/47	18/50		6.7%	0.26[0.09,0.73]
Murphy KEN 92-4	15/83	10/78		8.97%	1.5[0.63,3.57]
Olumese NIG 94-6	11/54	14/49		8.34%	0.64[0.26,1.58]
PhuongVNM 92-5	6/74	5/35		4.71%	0.53[0.15,1.87]
Seaton PNG 92-5	1/15	3/18		1.43%	0.36[0.03,3.85]
Taylor MAL 92-4	10/83	12/81		8.43%	0.79[0.32,1.94]
vanHensbroekGAM92-4	59/288	62/288		24.79%	0.94[0.63,1.4]
Subtotal (95% CI)	**1160**	**1101**		**100%**	**0.72[0.54,0.96]**
Total events: 160 (Artemisinin drug), 197 (Quinine)					
Heterogeneity: Tau^2=0.05; Chi^2=11.6, df=9(P=0.24); I^2=22.38%					
Test for overall effect: Z=2.26(P=0.02)					

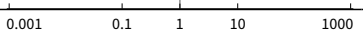
Analysis 1.2. Comparison 1 Artemisinin drug vs quinine, Outcome 2 Mortality subgrouped as cerebral or non-cerebral malaria.



Study or subgroup	Artemisinin drug n/N	Quinine n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
1.2.1 Artemisinin, cerebral malaria					
Birku ETH 96-7	2/8	3/7		61.54%	0.44[0.05,3.98]

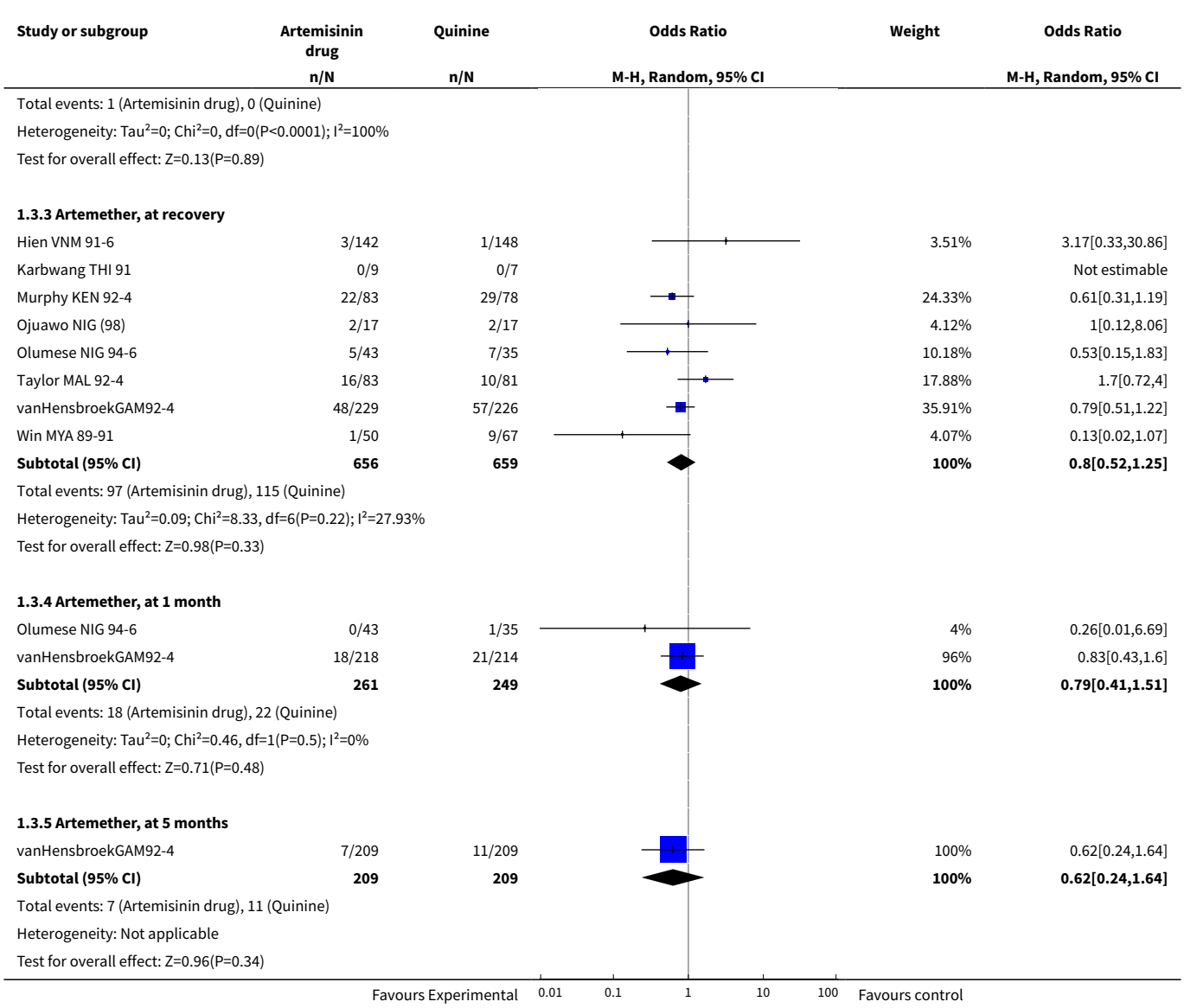


Study or subgroup	Artemisinin drug n/N	Quinine n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Birku ETH 96-7	2/8	3/7		2.22%	0.44[0.05,3.98]
Danis WAF 93-4	5/50	6/50		5.66%	0.81[0.23,2.87]
Hien VNM 89-90	10/49	8/30		7.19%	0.71[0.24,2.05]
Hien VNM 91-6	21/142	24/148		12.97%	0.9[0.47,1.7]
Karbwang THI 91	0/9	3/7		1.12%	0.07[0,1.61]
Murphy KEN 92-4	15/83	10/78		9.39%	1.5[0.63,3.57]
Ojuawo NIG (98)	1/18	2/19		1.76%	0.5[0.04,6.05]
Olumese NIG 94-6	11/54	14/49		8.9%	0.64[0.26,1.58]
PhuongVNM 92-5	2/18	3/5		2.01%	0.08[0.01,0.84]
Taylor MAL 92-4	10/83	12/81		8.97%	0.79[0.32,1.94]
vanHensbroekGAM92-4	59/288	62/288		17.75%	0.94[0.63,1.4]
Win MYA 89-91	9/77	23/67		9.51%	0.25[0.11,0.6]
Subtotal (95% CI)	**997**	**942**		**100%**	**0.63[0.44,0.88]**
Total events: 155 (Artemisinin drug), 195 (Quinine)					
Heterogeneity: Tau^2=0.13; Chi^2=20.31, df=13(P=0.09); I^2=35.99%					
Test for overall effect: Z=2.67(P=0.01)					
1.2.8 Any artemisinin drug, all cerebral malaria patients (adequate concealment of allocation only)					
Anh VNM 92-95	8/99	18/91		11.33%	0.36[0.15,0.87]
Danis WAF 93-4	5/50	6/50		6.44%	0.81[0.23,2.87]
Hien VNM 91-6	21/142	24/148		17.9%	0.9[0.47,1.7]
Murphy KEN 92-4	15/83	10/78		11.73%	1.5[0.63,3.57]
Olumese NIG 94-6	11/54	14/49		10.97%	0.64[0.26,1.58]
PhuongVNM 92-5	2/18	3/5		2.1%	0.08[0.01,0.84]
Taylor MAL 92-4	10/83	12/81		11.07%	0.79[0.32,1.94]
vanHensbroekGAM92-4	59/288	62/288		28.46%	0.94[0.63,1.4]
Subtotal (95% CI)	**817**	**790**		**100%**	**0.78[0.55,1.1]**
Total events: 131 (Artemisinin drug), 149 (Quinine)					
Heterogeneity: Tau^2=0.07; Chi^2=9.8, df=7(P=0.2); I^2=28.56%					
Test for overall effect: Z=1.41(P=0.16)					

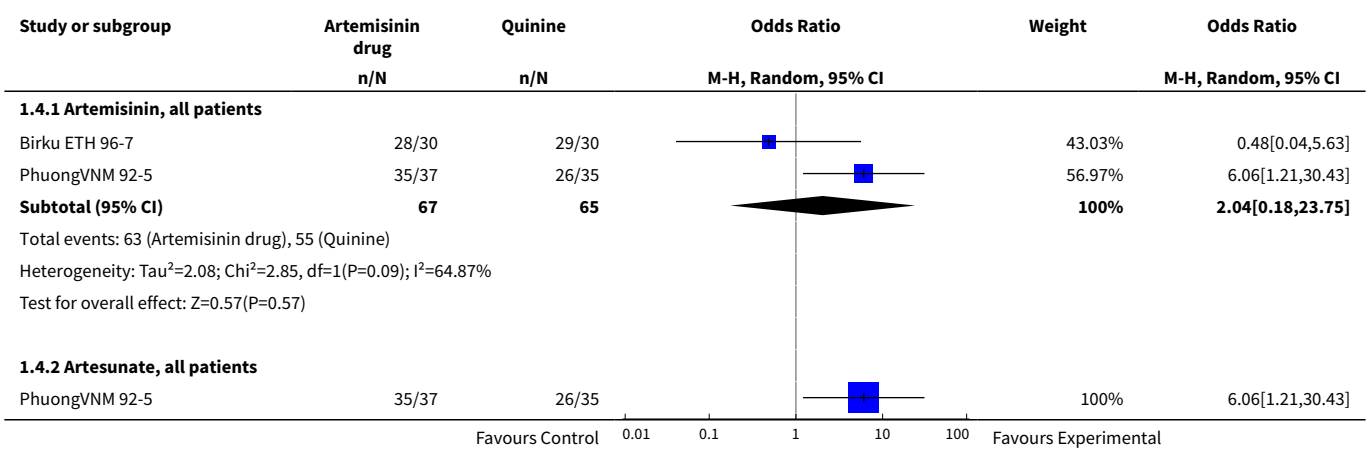


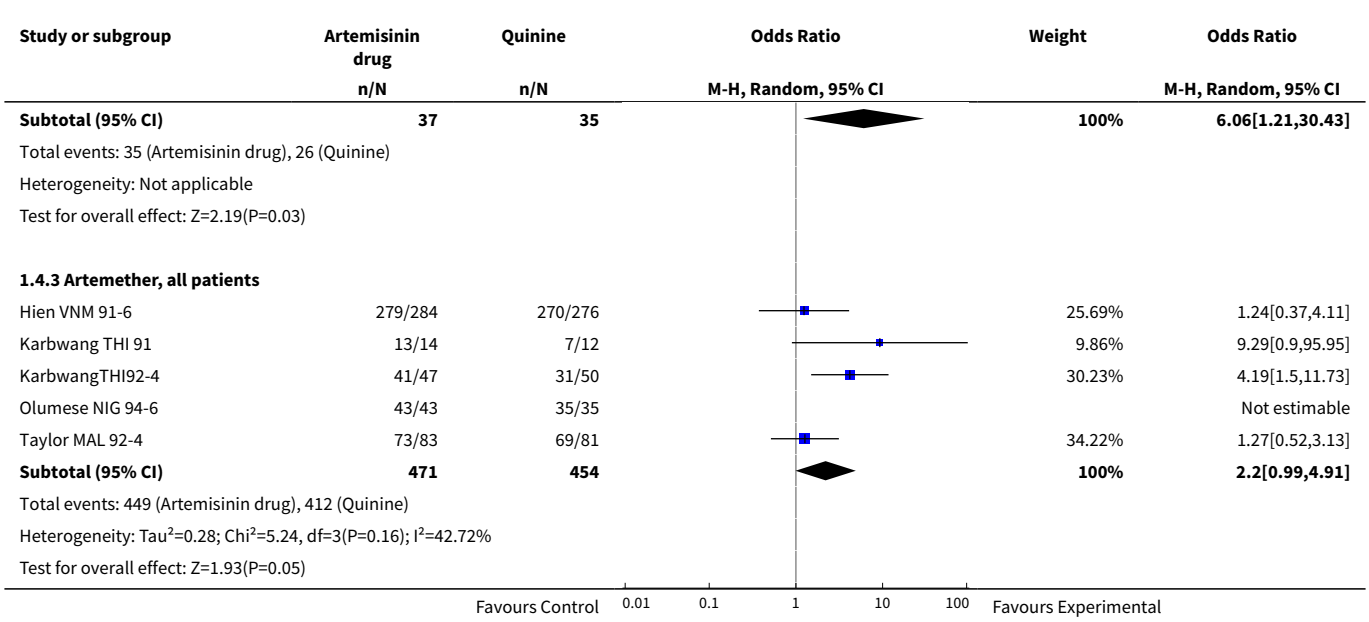
Analysis 1.3. Comparison 1 Artemisinin drug vs quinine, Outcome 3 Neurological sequelae (cerebral malaria).

Study or subgroup	Artemisinin drug n/N	Quinine n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
1.3.1 Artemisinin, at recovery					
Birku ETH 96-7	0/6	0/4			Not estimable
PhuongVNM 92-5	1/6	0/2		100%	1.36[0.04,46.65]
Subtotal (95% CI)	**12**	**6**		**100%**	**1.36[0.04,46.65]**
Total events: 1 (Artemisinin drug), 0 (Quinine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.17(P=0.86)					
1.3.2 Artesunate, at recovery					
PhuongVNM 92-5	1/10	0/2		100%	0.79[0.02,25.9]
Subtotal (95% CI)	**10**	**2**		**100%**	**0.79[0.02,25.9]**

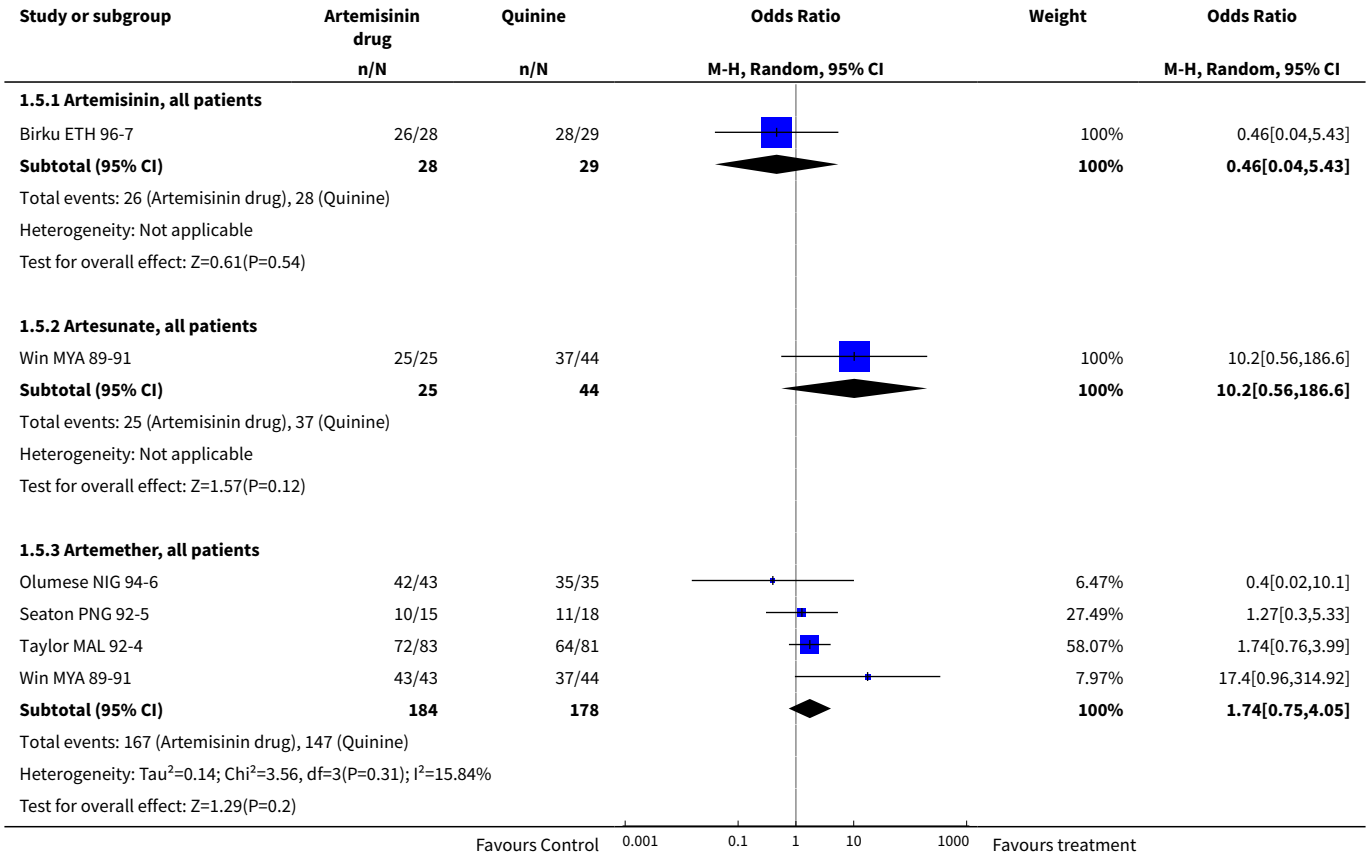


Analysis 1.4. Comparison 1 Artemisinin drug vs quinine, Outcome 4 Parasite clearance at day 7.





Analysis 1.5. Comparison 1 Artemisinin drug vs quinine, Outcome 5 Parasite clearance at day 28.



Analysis 1.6. Comparison 1 Artemisinin drug vs quinine, Outcome 6 Coma recovery time.

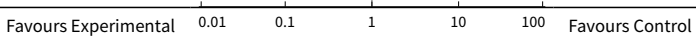
Study or subgroup	Artemisinin drug N	Artemisinin drug Mean(SD)	Quinine N	Quinine Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.6.1 Artemisinin							
Birku ETH 96-7	6	45.6 (11.5)	4	58.8 (10.1)		62.61%	-13.2[-26.71,0.31]
Hien VNM 89-90	18	56.1 (27)	30	58.1 (34.3)		37.39%	-2[-19.49,15.49]
Subtotal ***	**24**		**34**			**100%**	**-9.01[-19.71,1.68]**
Heterogeneity: Tau^2=0; Chi^2=0.99, df=1(P=0.32); I^2=0%							
Test for overall effect: Z=1.65(P=0.1)							
1.6.2 Artesunate							
Anh VNM 89	17	45.2 (30.4)	15	53.6 (25.9)		21.03%	-8.43[-27.93,11.07]
Anh VNM 92-95	91	71.3 (81)	73	58 (49)		20.21%	13.3[-6.78,33.38]
Hien VNM 89-90	31	68.9 (112)	30	58.1 (34.3)		6.35%	10.8[-30.49,52.09]
Win MYA 89-91	25	33.8 (9.4)	44	42.5 (16.4)		52.41%	-8.66[-14.74,-2.58]
Subtotal ***	**164**		**162**			**100%**	**-2.94[-13.92,8.04]**
Heterogeneity: Tau^2=50.24; Chi^2=4.93, df=3(P=0.18); I^2=39.13%							
Test for overall effect: Z=0.52(P=0.6)							
1.6.3 Artemether							
Danis WAF 93-4	44	26.6 (23.2)	44	33 (33.6)		8.63%	-6.34[-18.42,5.74]
Murphy KEN 92-4	68	22.8 (23.5)	68	18.6 (22.8)		18.49%	4.2[-3.58,11.98]
Ojuawo NIG (98)	17	12.5 (5.8)	17	17.4 (7.2)		41.31%	-4.9[-9.29,-0.51]
Olumese NIG 94-6	43	35.1 (27.1)	35	42.4 (31.6)		7.29%	-7.3[-20.54,5.94]
Win MYA 89-91	43	37 (14.7)	44	42.5 (16.4)		24.27%	-5.46[-12,1.08]
Subtotal ***	**215**		**208**			**100%**	**-3.65[-7.37,0.06]**
Heterogeneity: Tau^2=3.67; Chi^2=4.99, df=4(P=0.29); I^2=19.77%							
Test for overall effect: Z=1.93(P=0.05)							

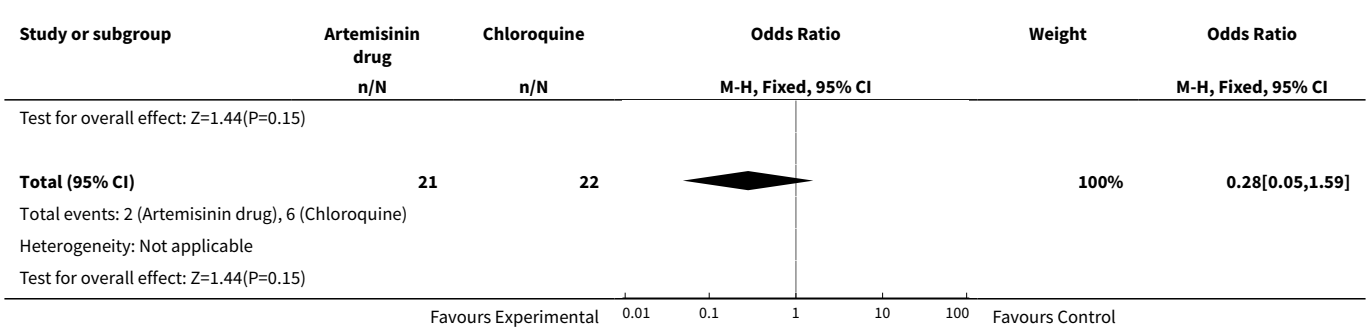
Comparison 2. Artemisinin drug vs chloroquine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	1	43	Odds Ratio (M-H, Fixed, 95% CI)	0.28 [0.05, 1.59]
1.1 Artemether	1	43	Odds Ratio (M-H, Fixed, 95% CI)	0.28 [0.05, 1.59]

Analysis 2.1. Comparison 2 Artemisinin drug vs chloroquine, Outcome 1 Mortality.

Study or subgroup	Artemisinin drug n/N	Chloroquine n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.1.1 Artemether					
White GAM 89	2/21	6/22		100%	0.28[0.05,1.59]
Subtotal (95% CI)	**21**	**22**		**100%**	**0.28[0.05,1.59]**
Total events: 2 (Artemisinin drug), 6 (Chloroquine)					
Heterogeneity: Not applicable					

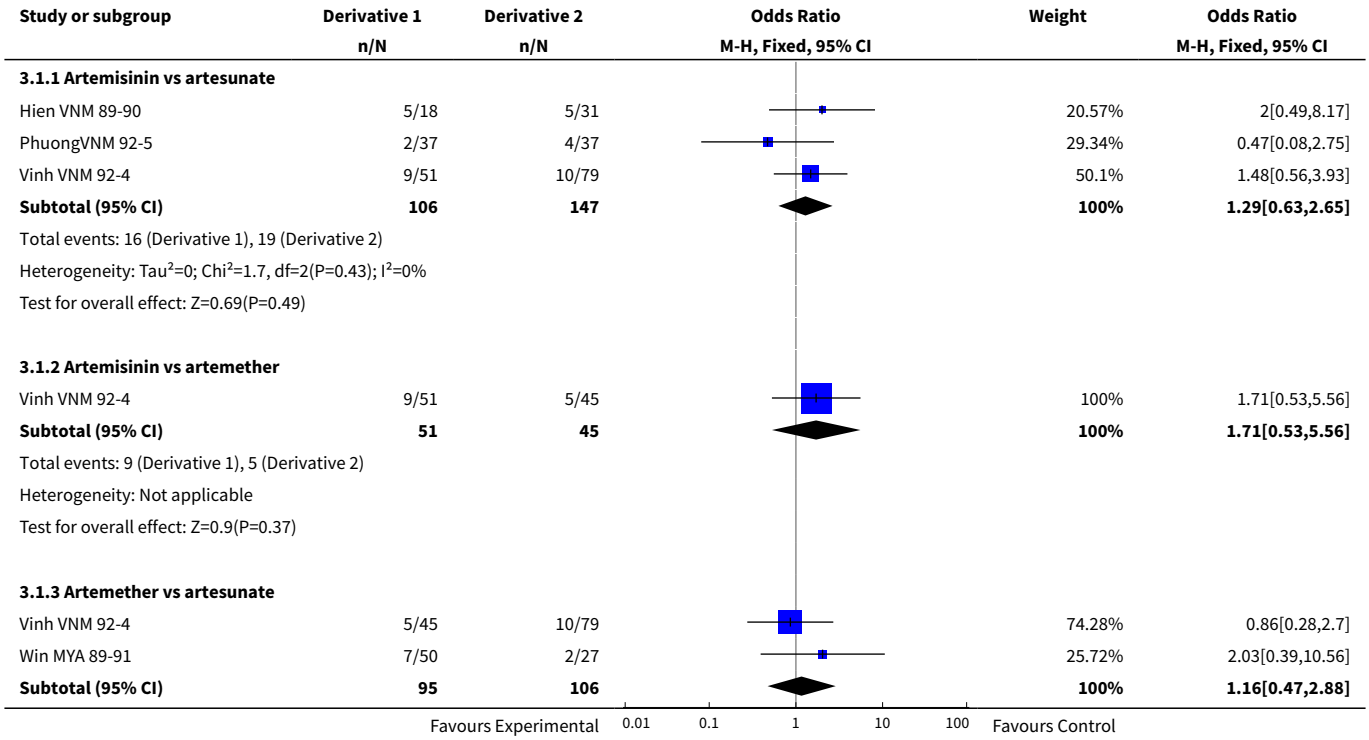


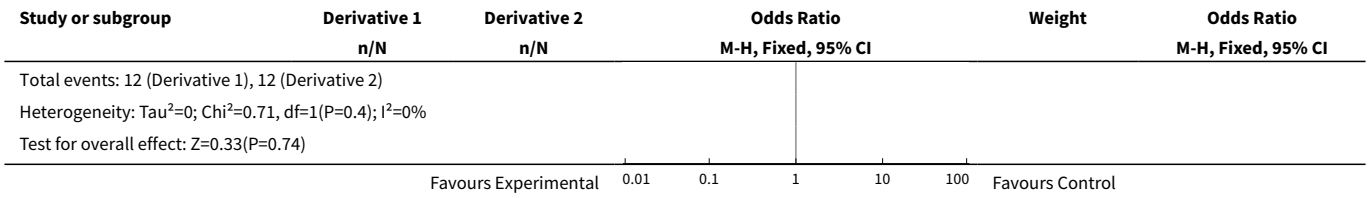


Comparison 3. Artemisinin derivative comparison

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	4		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Artemisinin vs artesunate	3	253	Odds Ratio (M-H, Fixed, 95% CI)	1.29 [0.63, 2.65]
1.2 Artemisinin vs artemether	1	96	Odds Ratio (M-H, Fixed, 95% CI)	1.71 [0.53, 5.56]
1.3 Artemether vs artesunate	2	201	Odds Ratio (M-H, Fixed, 95% CI)	1.16 [0.47, 2.88]

Analysis 3.1. Comparison 3 Artemisinin derivative comparison, Outcome 1 Mortality.

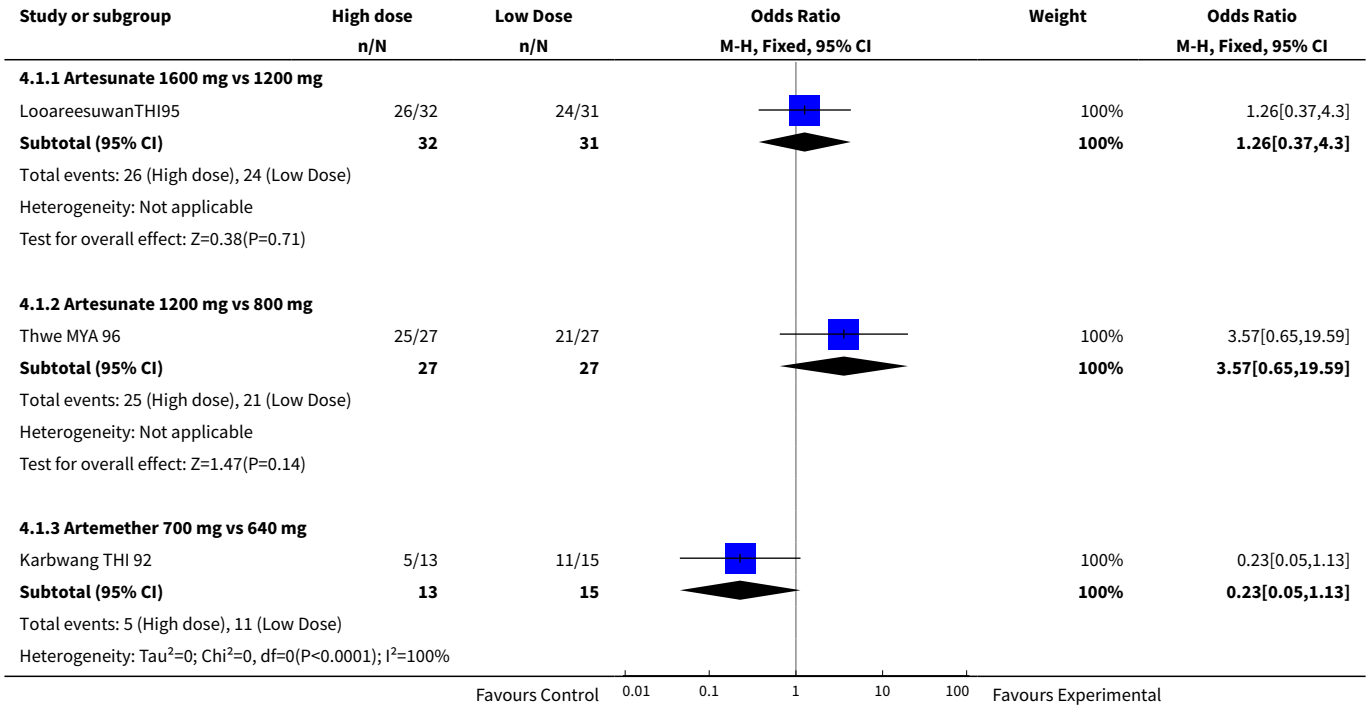


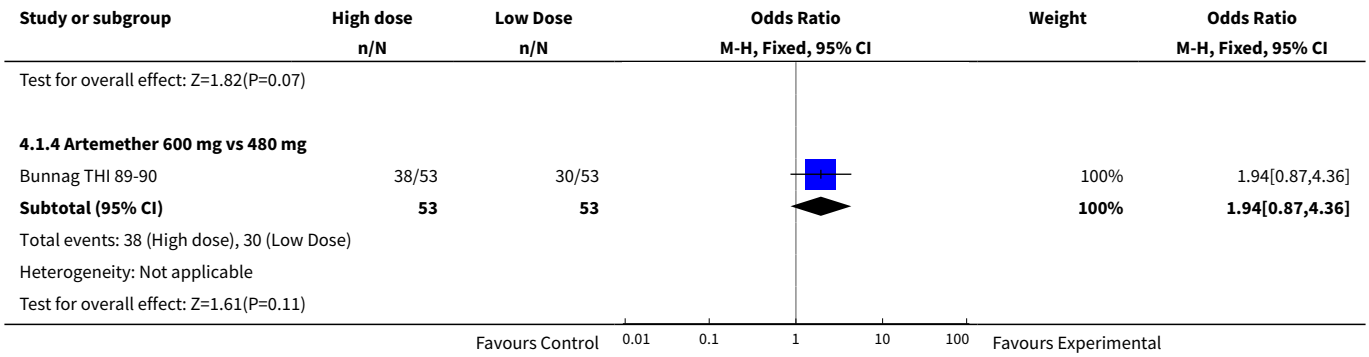


Comparison 4. Artemisinin derivative dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasite clearance at day 28	4		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Artesunate 1600 mg vs 1200 mg	1	63	Odds Ratio (M-H, Fixed, 95% CI)	1.26 [0.37, 4.30]
1.2 Artesunate 1200 mg vs 800 mg	1	54	Odds Ratio (M-H, Fixed, 95% CI)	3.57 [0.65, 19.59]
1.3 Artemether 700 mg vs 640 mg	1	28	Odds Ratio (M-H, Fixed, 95% CI)	0.23 [0.05, 1.13]
1.4 Artemether 600 mg vs 480 mg	1	106	Odds Ratio (M-H, Fixed, 95% CI)	1.94 [0.87, 4.36]

Analysis 4.1. Comparison 4 Artemisinin derivative dose, Outcome 1 Parasite clearance at day 28.

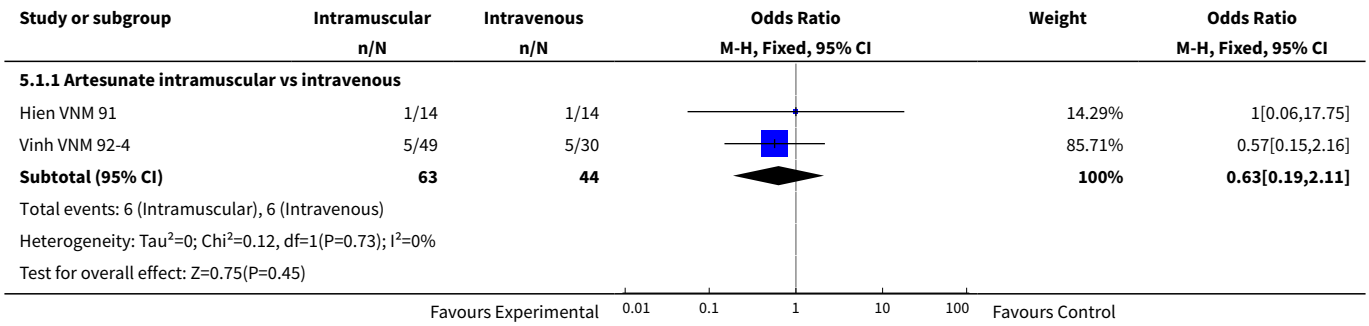




Comparison 5. Route of administration

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Artesunate intramuscular vs intravenous	2	107	Odds Ratio (M-H, Fixed, 95% CI)	0.63 [0.19, 2.11]

Analysis 5.1. Comparison 5 Route of administration, Outcome 1 Mortality.



WHAT'S NEW

Date	Event	Description
9 November 2009	Review declared as stable	Further research in this area has focused on specific preparations of arteether and artemether. Trials of these preparations are assessed as separate Cochrane reviews. The authors therefore consider that it is no longer necessary to update this review.

HISTORY

Protocol first published: Issue 4, 1997
Review first published: Issue 2, 1998

Date	Event	Description
29 July 2008	Review declared as stable	This review was first published in 1999, Issue 2, and was undertaken to provide a comprehensive assessment of the benefits and risks of this new class of antimalarial drugs in different epidemiological settings. It aimed to inform drug policy decisions on their rational use, and the clinical questions addressed by the review were based on what needed clarifying at that time. The comparison of artemether versus quinine for treating severe malaria was subsequently assessed in a meta-analysis of individual patient data (Artemether-Quinine Meta-analysis Study Group. A meta-analysis using individual patient data of trials comparing artemether with quinine in the treatment of severe falciparum malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 2001;95(6):637-50), which supported the findings of this review of summary data. Further research and development in this area has focused on specific preparations of arteether and artemether. Trials of these preparations, including new trials conducted through the World Health Organization, are now assessed as separate Cochrane Reviews. It is, therefore, no longer necessary or expedient to update this review in its existing format. It will continue to appear in the *Cochrane Database of Systematic Reviews* for information only.
29 July 2008	Amended	Converted to new review format with minor editing.
24 May 2005	Amended	Minor update.
10 January 2000	New citation required and conclusions have changed	Substantive amendment.
16 December 1999	New search has been performed	New studies found and included or excluded.

DECLARATIONS OF INTEREST

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

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK.

External sources

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

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Adult; Child; Humans