

Artesunate versus quinine for treating severe malaria (Review)

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[Intervention Review]

Artesunate versus quinine for treating severe malaria

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ABSTRACT

Background

Severe malaria results in over a million deaths every year, most of them in children aged under five years and living in sub-Saharan Africa. This review examines whether treatment with artesunate, instead of the standard treatment quinine, would result in fewer deaths and better treatment outcomes.

Objectives

To compare artesunate with quinine for treating severe malaria.

Search methods

We searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (*The Cochrane Library*), MEDLINE, EMBASE, LILACS, ISI Web of Science, the *meta*Register of Controlled trials (*mRCT*), conference proceedings, and reference lists of articles to November 2010.

Selection criteria

Randomized controlled trials comparing intravenous, intramuscular, or rectal artesunate with intravenous or intramuscular quinine for treating adults and children with severe malaria who are unable to take medication by mouth.

Data collection and analysis

Two authors independently assessed the eligibility and risk of bias of trials, and extracted and analysed data. The primary outcome was all-cause death. Dichotomous outcomes were summarized using risk ratios (RR) and continuous outcomes by mean differences (MD). Where appropriate, we combined data in meta-analyses.

Main results

Eight trials enrolling 1664 adults and 5765 children are included in this review.

Treatment with artesunate significantly reduced the risk of death both in adults (RR 0.61, 95% Confidence Interval (CI) 0.50 to 0.75; 1664 participants, five trials) and children (RR 0.76, 95% CI 0.65 to 0.90; 5765 participants, four trials)

In children, treatment with artesunate increased the incidence of neurological sequelae at the time of hospital discharge. The majority of these sequelae were transient and no significant difference between treatments was seen at later follow up.

Artesunate versus quinine for treating severe malaria (Review)

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Authors' conclusions

The evidence clearly supports the superiority of parenteral artesunate over quinine for the treatment of severe malaria in both adults and children and in different regions of the world.

PLAIN LANGUAGE SUMMARY

Artesunate reduces death from severe malaria

Severe malaria occurs when infection with the malaria parasite is complicated by serious failure of the body's major organs, and results in over a million deaths every year. Sometimes severe malaria is associated with coma and is known as cerebral malaria. Following cerebral malaria a small proportion of children suffer with long-term neurological disability.

This review of trials assessed the effectiveness of artesunate compared with the standard treatment quinine. Eight trials involving 1664 adults and 5765 children were identified, from study sites in Asia and Africa.

Treating adults in Asia with artesunate instead of quinine would prevent an extra 94 deaths for every 1000 patients treated. In trials involving children, the proportion of deaths was lower than in the trials involving adults. This lower risk of death results in a smaller benefit in children than in adults, but would still save an extra 26 lives for every 1000 children treated.

In the children who survived their illness, there were more neurological problems at the time of hospital discharge in those treated with artesunate than those treated with quinine. However, the majority of these neurological problems had resolved when they were reviewed 28 days later, and at this timepoint there was no difference between the two treatment groups.

Artesunate should be the drug of choice for adults and children with severe malaria worldwide.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Artesunate compared with quinine for treating severe malaria						
Patient or population: Children with severe malaria Settings: Malaria endemic areas Intervention: Artesunate Comparison: Quinine						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Quinine	Artesunate				
Death	109 per 1000	83 per 1000 (71 to 98)	RR 0.76 (0.65 to 0.9)	5765 (4 studies ¹)	high ^{2,3,4,5}	
Neurological sequelae at day 28	11 per 1000	14 per 1000 (8 to 22)	RR 1.23 (0.74 to 2.03)	4857 (1 study ⁶)	moderate ^{7,8,9,10}	
Neurological sequelae at discharge	28 per 1000	38 per 1000 (28 to 51)	RR 1.36 (1.01 to 1.83)	5163 (3 studies ^{1,1})	moderate ^{2,3,4,12}	
Time to hospital discharge (days)	See comment	See comment	Not estimable	113 (3 studies ^{1,1})	moderate ^{2,13,4,14}	
Hypoglycaemia episodes	30 per 1000	19 per 1000 (13 to 26)	RR 0.62 (0.45 to 0.87)	5765 (4 studies ¹)	high ^{2,3,4,15}	

*The **assumed risk** was calculated by dividing the total number of events in the control group (across studies) by the total number of patients in the control group (across studies). This was numerically very similar to the median control group risk but is easier to link with the corresponding forest plot. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk Ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

- ¹ One large multicentre trial (Dondorp 2010) and two small trials (Cao 1997, Eitahir 2010) have assessed artesunate vs quinine in children aged <15 years. In addition one large multicentre study included a subgroup of children in this age group (Dondorp 2005)
- ² No serious study limitations: All the trials adequately concealed allocation to be considered at low risk of bias. The trials were unblinded but this is unlikely to bias this objective outcome
- ³ No serious inconsistency: There was no statistical heterogeneity between the trials ($I^2 = 0\%$).
- ⁴ No serious indirectness: Most of the data is from Dondorp 2010 which had centres in Mozambique, the Gambia, Ghana, Kenya, Tanzania, Nigeria, Uganda, Rwanda and the Democratic Republic of Congo, and used the established standard doses of artesunate and quinine (with loading dose). Of note the median age of children in this trial was 2.9 years in the quinine group and 2.8 in the artesunate group.
- ⁵ No serious imprecision: Both limits of the 95% CI of the pooled effect imply an appreciable clinical benefit with artesunate. The Number Needed To Treat to prevent one childhood death is 38.
- ⁶ Only one large multicentre trial (Dondorp 2010) reports this outcome.
- ⁷ Serious study limitations: 41/170 (24%) patients with neurological sequelae at discharge were not available for assessment at day 28.
- ⁸ No serious inconsistency: Not applicable as only one trial.
- ⁹ No serious indirectness: This trial (Dondorp 2010) had 11 centres throughout Africa and used the standard dosing of artesunate and quinine. The nature of the neurological sequelae is not described.
- ¹⁰ No serious imprecision: The 95% CI around the absolute effect is narrow. The worst case scenario is a 1.2% increase in neurological sequelae at day 28
- ¹¹ Three trials (Dondorp 2010, Dondorp 2005, and Cao 1997) report this outcome
- ¹² Serious imprecision: The effect estimate is of a clinically important harm. However the 95% CI includes the possibility of no clinically important difference between the two interventions.
- ¹³ No serious inconsistency: None of the trials found evidence of an important difference between the two treatment groups
- ¹⁴ Serious imprecision: We were unable to pool the data as they were only reported as medians and range/intra quartile range. There is no evidence of a clinically important benefit with artesunate on this outcome.
- ¹⁵ No serious imprecision: The result is statistically significant in favour of artesunate. The current sample size is adequately powered to detect a 40% risk reduction with 80% power and 95% confidence.

BACKGROUND

Description of the condition

Malaria is a febrile illness caused by infection with the *Plasmodium* parasite, which is transmitted from person to person by mosquitos. Five species of plasmodium are known to cause disease in humans: *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, and *P. knowlesi* (WHO 2010). *P. falciparum* is the most common malaria parasite worldwide, and is responsible for almost all of the severe disease and deaths (WHO 2000; WHO 2008).

Repeated exposure to malaria infection over 5 to 10 years can produce a naturally acquired immunity in humans, which is protective against the most severe forms of the disease (Doolan 2009). Consequently, in high transmission settings as seen in large parts of Africa, young children are most at risk prior to the acquisition of effective immunity, whereas in low transmission settings, or in travellers from non-endemic areas, adults are often equally vulnerable to severe disease (WHO 2000).

Severe malaria is diagnosed on the basis of a positive blood slide or antigen test for malaria, plus the presence of clinical or laboratory markers which indicate vital organ dysfunction. These markers include impaired consciousness, coma, convulsions, respiratory distress, shock (systolic blood pressure < 70 mmHg in adults, < 50 mmHg in children), jaundice, haemoglobinuria, or severe acidosis or anaemia (WHO 2010). Cerebral malaria is a specific type of severe malaria characterised by an unrousable coma. Even with correct treatment cerebral malaria can have a mortality rate approaching 20%, and persistent neurological sequelae are seen in a small proportion of survivors (Jaffar 1997).

The standard treatment for severe malaria has been an intravenous infusion or intramuscular injection of quinine (WHO 2000). A loading dose of 20 mg/kg is recommended to reduce the time needed to reach effective concentrations in the blood, with subsequent dosing at 10 mg/kg at eight hourly intervals (White 1983b; van Der Torn 1996). A Cochrane Review found a significant reduction in fever clearance time and parasite clearance time with a loading dose compared with no loading dose but concluded that data were insufficient to demonstrate an impact on mortality (Lesi 2004).

Adverse effects resulting from quinine therapy are common. Cinchonism (symptoms of quinine overdose) often occurs with conventional dose regimens. This usually mild and reversible symptom complex consists of tinnitus, deafness, dizziness, and vomiting, and may affect adherence (Alkadi 2007). Hypoglycaemia is a less common but more serious adverse effect (White 1983). Toxic levels of quinine can occur following rapid intravenous administration and can result in heart rhythm disturbances, blindness, coma, and even death (Alkadi 2007). In addition, there is limited evidence that the efficacy of quinine in severe malaria may be declining in some parts of South-East Asia (Wongsrichanalai 2002).

Description of the intervention

Artesunate is one of a number of antimalarials derived from artemisinin, the active ingredient in a Chinese herbal remedy for fever, *Artemisia annua*. The artemisinin derivatives are now the recommended treatment for uncomplicated (less severe) malaria, when they are given orally in combination with a partner drug, as Artemisinin-based Combination Therapy (ACT), to delay or prevent the development of artemisinin resistance (WHO 2010). The artemisinin derivatives are generally regarded as safe in humans (Ribeiro 1998; Alkadi 2007; Nosten 2007). Animal studies using very high doses of artemisinins have demonstrated focal brain stem lesions particularly affecting the auditory pathways (Brewer 1994; Nontprasert 1998; Genovese 2000; Nontprasert 2000; Nontprasert 2002), but studies of brain stem function in humans, including audiometry, have failed to show any abnormality following repeated courses (Ribeiro 1998; Kissinger 2000). To date, only one nested case-control study has demonstrated a significant audiometric hearing loss in factory workers treated with artemether-lumefantrine for uncomplicated malaria compared with workers with no history of exposure to malaria infection or artemether-lumefantrine (Toovey 2004). This result needs to be interpreted with caution due to a number of design limitations.

How the intervention might work

Deaths from severe malaria often occur during the first 24 to 48 hours following hospital admission. Consequently, to be effective antimalarial drugs need to achieve rapid therapeutic blood concentrations following administration.

Compared to quinine, the artemisinin derivatives have been shown to clear malaria parasites from the blood faster, and to have a broader spectrum of activity (ter Kuile 1993; Adjuik 2004). Importantly they are effective against young ring forms of the parasite before they sequester in the microcirculation of vital organs, a major pathophysiological step in the development of severe disease (ter Kuile 1993; WHO 2000).

Artesunate is the most studied artemisinin-derivative for the treatment of severe malaria and may be given by intramuscular or intravenous injection. It has been shown to reliably reach peak concentrations within one hour of administration (Nealon 2002; Hien 2004).

Of the alternatives, artemether and arteether are available as oil-based, intramuscular formulations. Artemether is prone to erratic and partial absorption (Karbwang 1997; Murphy 1997; Mithwani 2003), and arteether to low peak concentrations and slow absorption (Looareesuwan 2002; Li 2004). Systematic reviews of artemether and arteether compared to quinine have so far failed to show a reduction in mortality compared to quinine therapy, although the data are limited (AQMSG 2001; Afolabi 2004; Kyu 2009).

Why it is important to do this review

A Cochrane Review prepared in year 2000 assessed the effects of the artemisinin derivatives, including artesunate, for treating severe malaria (McIntosh 2000). This review has since been superseded by a series of Cochrane Reviews examining the different artemisinin derivatives.

This review was first published in 2006 and demonstrated the superiority of artesunate for treating adults in Asia, but found insufficient data to make firm conclusions in children. This update includes two additional, recently completed trials, focusing on artesunate versus quinine in African children.

OBJECTIVES

To compare artesunate with quinine for treating severe malaria.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials.

Types of participants

Adults and children with severe malaria who are unable to take medication by mouth.

Types of interventions

Intervention

- Intravenous, intramuscular or rectal artesunate.

Control

- Intravenous or intramuscular quinine.

Types of outcome measures

Primary outcomes

- Death.

Secondary outcomes

- Neurological sequelae.
- Coma recovery time.
- Time to hospital discharge.
- Fever clearance time.
- Parasite clearance time.

Adverse effects

- Serious adverse effects resulting in discontinuation of treatment (eg biochemical abnormalities, cardiac effects).
- Hypoglycaemia (symptomatic or asymptomatic).
- Other adverse events, including tinnitus, hearing impairment, nausea, and vomiting.

Search methods for identification of studies

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

Electronic searches

Databases

We searched the following databases using the search terms and strategy described in Table 1: Cochrane Infectious Diseases Group Specialized Register; Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library*; MEDLINE; EMBASE; LILACS; and ISI Web of Science. We also searched the *meta*Register of Controlled trials (*mRCT*) using artesunate and quinine as search terms.

Searching other resources

Conference proceedings

We searched the following conference proceedings for relevant abstracts: The 5th Multilateral Initiative on Malaria (MIM) Pan-African Malaria Conference, 2 to 6 November 2009, Nairobi, Kenya; the 4th MIM Pan-African Malaria Conference, 13 to 18 November 2005, Yaounde, Cameroon; the 4th European Congress on Tropical Medicine, 11 to 15 September 2005, Marseille, France; ACT NOW; the International Symposium on Malaria, 29 to 30 April 2004, Colombia, New York, USA; the 2nd International Malaria Research Conference, John Hopkins Malaria Research Institute, 25 to 26 March 2004, Maryland, USA; the 3rd MIM Pan-African Conference, 18 to 22 November 2002, Arusha, Tanzania; and the 3rd European Congress on Tropical Medicine and International Health, 8 to 12 September 2002, Lisbon, Portugal.

Researchers, organizations, and pharmaceutical companies

We contacted individual researchers working in the field and the World Health Organization (WHO) for details of unpublished and ongoing trials.

Reference lists

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

Data collection and analysis

Selection of studies

All trials identified by the search strategy were screened by two authors working independently (Katharine Jones (KJ), Sarah Donegan (SD) or David Sinclair (DS)) and full reports of potentially relevant trials were obtained. Two authors independently applied the inclusion criteria to the full reports using an eligibility form and scrutinized publications to ensure each trial was included in the review only once. Trial authors were contacted for clarification if necessary. Disagreement was resolved by discussion with David Lalloo (DL).

Data extraction and management

Two authors independently extracted data using a data extraction form. For each outcome we aimed to extract the number of participants randomised and the number analysed in each treatment group. For dichotomous outcomes, we recorded the number of participants experiencing the event and the number assessed in each treatment group. For continuous outcomes, we extracted arithmetic means and standard deviations for each treatment group, together with the numbers assessed in each group. Where medians were used we also extracted the range or intra-quartile range.

Assessment of risk of bias in included studies

DS and SD independently assessed the risk of bias for each trial using 'The Cochrane Collaboration's tool for assessing the risk of bias' (Higgins 2008). We followed the guidance to assess whether adequate steps had been taken to reduce the risk of bias across six domains: sequence generation; allocation concealment; blinding (of participants, personnel, and outcome assessors); incomplete outcome data; selective outcome reporting; and other sources of bias. We have categorized these judgments as 'yes' (low risk of bias), 'no' (high risk of bias), or 'unclear'. Where our judgement is unclear we attempted to contact the trial authors for clarification. This information was used to guide the interpretation of the data that are presented.

Measures of treatment effect

Results were calculated using risk ratio (RR) for dichotomous data, and mean difference (MD) for continuous data. These effect estimates are presented with 95% confidence intervals (CI).

Dealing with missing data

If there was discrepancy between the number randomized and the number analysed, we calculated the percentage loss to follow up for each treatment group and reported this information.

Originally, we aimed to analyse data according to the intention-to-treat principle (all randomized participants should be analysed in the groups to which they were originally assigned). However, since for some trials it was unclear whether there was loss to follow up, we entered the number analysed into [Review Manager 5](#) whenever these figures were available. By attempting to carry out a complete-case analysis in this way, we have tried to avoid making assumptions about the outcomes of participants that were lost to follow up.

Assessment of heterogeneity

We looked for statistical heterogeneity by inspecting the forest plots for overlapping confidence intervals, applying the Chi² test (P value < 0.10 considered statistically significant), and the I² statistic (I² value of 50% used to denote moderate levels of heterogeneity).

Assessment of reporting biases

We planned to construct funnel plots to look for evidence of publication bias, provided there were sufficient included trials to make this informative.

Data synthesis

We analysed the data using [Review Manager 5](#), and where possible and appropriate we combined studies using a fixed-effect model. If heterogeneity was detected but it was still considered clinically meaningful to combine studies, a random-effects model was used. Medians and ranges are only reported in tables.

If arithmetic means were reported, normality of the data was checked by calculating the ratio of the mean over the standard deviation (Altman 1996). If this test suggested the data were skewed (ie if the ratio was less than two), we commented on this in the text but still combined the results in a meta-analysis.

Subgroup analysis and investigation of heterogeneity

We planned to investigate heterogeneity by conducting pre-specified sub-group analyses for the primary outcome. The potential sources of heterogeneity were allocation concealment, blinding, participant age (children versus adults), and drug regimen (loading dose versus no loading dose of quinine and use of any additional antimalarials).

Sensitivity analysis

Post hoc, we conducted a sensitivity analysis to investigate the robustness of the results to differences in trial design, by subgrouping the trials according to allocation concealment, participant age (children versus adults), type of severe malaria (cerebral versus non-cerebral malaria), geographical region, drug regimen (loading dose versus no loading dose of quinine, and use of any additional antimalarials), route of administration (intravenous versus intramuscular route), and time since admission to hospital.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Results of the search

The original search was conducted in November 2005 and identified 22 references of which four were duplicate trial reports. Six unique trials fulfilled the eligibility criteria and were included in the first version of this review.

An update search conducted in November 2010 identified a further six trials of which two were eligible and these are now included.

Included studies

The eight trials that met our inclusion criteria enrolled a total of 7429 participants (1664 adults and 5765 children).

Location

Six trials were conducted in Asia; four took place in single centres in Vietnam (Anh 1989; Anh 1995; Cao 1997; Hien 1992), Newton 2003 had two centres in Thailand; and Dondorp 2005 had 11 centres throughout Bangladesh, Myanmar, India, and Indonesia. Of the two African studies; Eltahir 2010 was conducted at a single study site in Sudan, and Dondorp 2010 had 11 centres in nine African countries (Mozambique, The Gambia, Ghana, Kenya, Tanzania, Nigeria, Uganda, Rwanda, and the Democratic Republic of the Congo).

Source of funding

Four trials were funded by a medical research charity (Cao 1997; Dondorp 2005; Dondorp 2010; Newton 2003), one by the WHO (Anh 1995), one by a private sugar company (Eltahir 2010), and one received the study drugs from a pharmaceutical company (Anh 1989). Funding was not specified for Hien 1992.

Participants

Four trials enrolled only adults (Anh 1989; Anh 1995; Hien 1992; Newton 2003), of which three included only those with a diagnosis of cerebral malaria (Anh 1989, Anh 1995, Hien 1992). Three trials enrolled only children aged less than 15 years (Cao 1997; Dondorp 2010; Eltahir 2010), and one enrolled both adults and children (Dondorp 2005).

Dondorp 2005 and Dondorp 2010 used rapid diagnostic tests to confirm *P. falciparum* parasitaemia, and all the other trials used standard microscopy. Although standardized clinical definitions for severe malaria exist, the entry criteria were not consistent across trials.

Interventions

All trials compared artesunate with quinine, but the exact dosing and route of administration varied between trials.

Three trials (Dondorp 2005; Dondorp 2010; Eltahir 2010) administered both artesunate and quinine using the current recommended dosing schedules (artesunate: 2.4 mg/kg (intravenous or intramuscular) on admission, at 12 hours, at 24 hours, and then once daily until starting oral therapy, quinine: 20 mg/kg intravenous or intramuscular loading dose, then 10 mg/kg every 8 hours until starting oral therapy).

Anh 1989, Anh 1995, and Hien 1992 gave 60 mg artesunate intravenously at admission, 4 hours, 24 hours and 48 hours. Cao 1997 gave 3 mg/kg intramuscular on admission then 2 mg/kg intramuscular at 12, 24, 48, and 72 hours, and Newton 2003 gave 2.4 mg/kg intravenously on admission, 1.2 mg/kg at 12 hours, and then 1.2 mg/kg every 24 hours until able to swallow. Two trials did not give the loading dose of quinine (Anh 1995; Hien 1992).

In addition six trials gave an additional oral antimalarial to at least one of the treatment arms, which was unmatched between the treatment arms (Anh 1989; Anh 1995; Cao 1997; Eltahir 2010; Hien 1992; Newton 2003). Two trials, Hien 1992 and Cao 1997, included an additional rectal artemisinin arm that was not pertinent to this review.

Supportive care

All eight trials reported measuring blood glucose on admission, but only five trials reported any subsequent active monitoring for hypoglycaemia. Newton 2003 tested all participants several times a day, Cao 1997 tested all participants with coma, prostration, jaundice or more than one complication every four hours for the first 24 hours and then every six hours, Anh 1989 tested all participants on days 1, 3, 7, and 14, and Eltahir 2010 tested all participants every six hours. Dondorp 2005 only measured blood glucose in those participants with clinical signs of hypoglycaemia.

Outcome measures (defined in Table 2)

All eight trials reported death as an outcome

Three trials reported neurological sequelae at discharge (Cao 1997; Dondorp 2005; Dondorp 2010). Six trials reported coma recovery time (Anh 1989; Hien 1992; Anh 1995; Cao 1997; Newton 2003; Eltahir 2010), and two trials reported time to eat, sit, and speak (Dondorp 2005; Dondorp 2010).

Five trials reported fever clearance time (Hien 1992; Anh 1995; Cao 1997; Newton 2003; Eltahir 2010). Reporting of parasite clearance time varied between trials and included parasite clearance times of 50%, 90%, 95%, and 100%, of which parasite clearance time of 50% was the most common (Anh 1989; Hien 1992; Anh 1995; Cao 1997; Newton 2003).

Four trials reported time to hospital discharge (Cao 1997; Newton 2003; Dondorp 2005; Dondorp 2010), and four trials reported adverse effects including hypoglycaemia (Cao 1997; Newton 2003; Dondorp 2005; Dondorp 2010).

Length of follow up

Cao 1997 specified that participants were asked to return for a follow up visit three weeks after discharge from hospital, and Dondorp 2010 followed those with neurological sequelae for 28 days. None of the other trials reported the length of follow-up.

Excluded studies

Sixteen trials detected by the search specifications were excluded from the review (see 'Characteristics of excluded studies').

Risk of bias in included studies

See Figure 1 for a summary of the risk of bias assessments. Further details are presented in the 'Characteristics of included studies' tables.

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias): Objective outcomes: Death	Blinding (performance bias and detection bias): Subjective outcomes: Others	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Anh 1989	+	-	+	-	+	+	+
Anh 1995	+	+	+	-	+	+	+
Cao 1997	+	+	+	-	+	+	+
Dondorp 2005	+	+	+	-	+	+	+
Dondorp 2010	+	+	+	-	+	+	+
Eltahir 2010	+	+	+	-	+	+	+
Hien 1992	+	+	+	-	+	+	+
Newton 2003	+	-	+	-	+	+	+

Allocation

The generation of the allocation sequence was adequate in all eight trials and allocation concealment was adequate in six trials with only [Anh 1989](#) and [Newton 2003](#) using open randomization.

Blinding

In all eight trials, investigators were aware of treatment allocation. Participants were blind to the intervention in [Hien 1992](#), and microscopists and data analysts were blind to the intervention in [Dondorp 2005](#) and [Dondorp 2010](#).

Incomplete outcome data

[Newton 2003](#), [Dondorp 2005](#) and [Dondorp 2010](#) clearly state that no participants were lost to follow-up. We were able to obtain individual patient data for one trial in which primary outcomes were available for all included participants ([Cao 1997](#)). For the remaining trials the number of participants randomized was used as the denominator in the analysis ([Anh 1989](#); [Hien 1992](#); [Anh 1995](#); [Eltahir 2010](#)). As these were inpatient trials significant attrition is unlikely.

Selective reporting

No evidence of selective outcome reporting was detected.

Other potential sources of bias

No other sources of bias were identified.

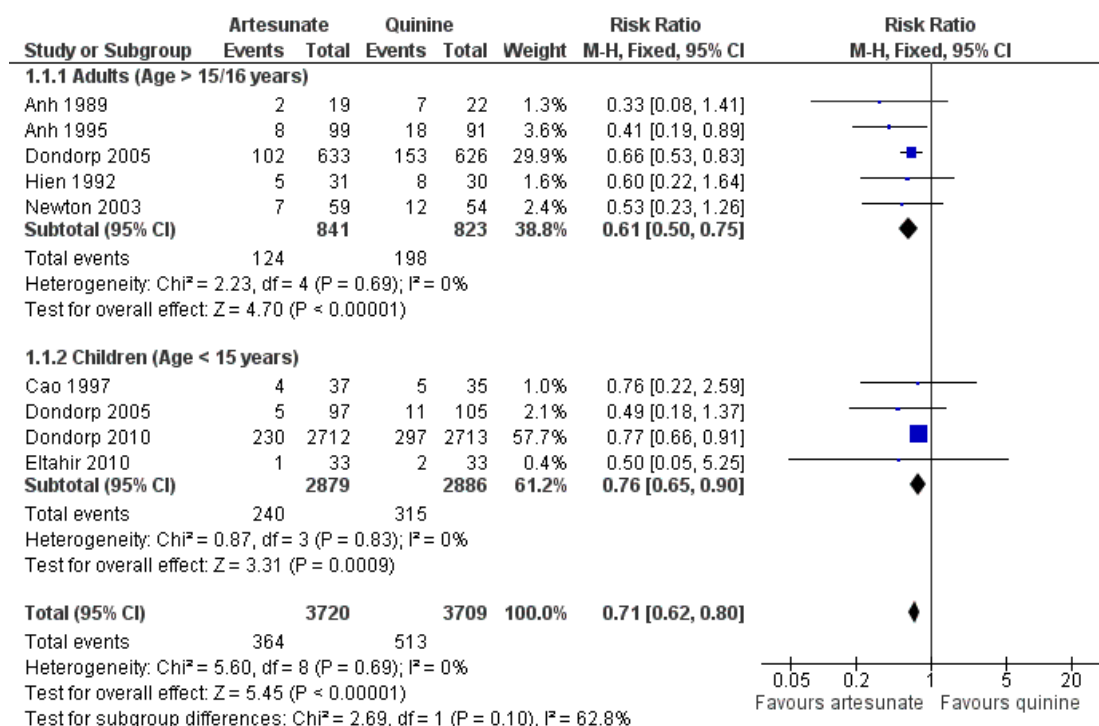
Effects of interventions

See: [Summary of findings for the main comparison](#); [Summary of findings 2](#)

Death

Treatment with artesunate significantly reduced the risk of death both in adults (RR 0.61, 95% CI 0.50 to 0.75; 1664 participants, five trials, [Analysis 1.1, Figure 2](#)) and children (RR 0.76, 95% CI 0.65 to 0.90; 5765 participants, four trials, [Analysis 1.1, Figure 2](#)). This reduction was consistent across all trials regardless of participant age or geographic region (I^2 test for statistical heterogeneity = 0%, [Analysis 1.1](#)).

Figure 2. Forest plot of comparison: 1 Artesunate vs quinine, outcome: 1.1 Death: participant age [Relative effect].



Mortality was lower in the trials recruiting children and consequently the absolute reduction in mortality is lower than that seen in adults (absolute risk reduction: adults: 94 fewer deaths per 1,000 patients, 95% CI 60 fewer to 120 fewer; children: 26 fewer deaths per 1,000 patients, 95% CI 11 fewer to 38 fewer; see [Summary of findings 2](#) and [Summary of findings for the main comparison](#)). This age effect is confounded by region, with the majority of the data in children coming from Africa (where the trial mortality was relatively low), and all the data in adults coming from Asia (where the trial mortality was higher).

Three trials report a subgroup analyses of deaths occurring within the first 48 hours following admission ([Cao 1997](#); [Dondorp 2005](#); [Newton 2003](#)) and one trial reports the number of deaths occurring within the first 24 hours ([Dondorp 2010](#)). Although the difference between groups did not reach statistical significance during these early time periods there were consistently fewer deaths in the groups treated with artesunate (6163 participants, four trials, [Analysis 1.2](#)).

In view of the significant variation in trial design we conducted sensitivity analyses excluding trials with inadequate allocation con-

cealment, trials only included patients with cerebral malaria, and those with no loading dose of quinine, but these did not alter the significance of the result.

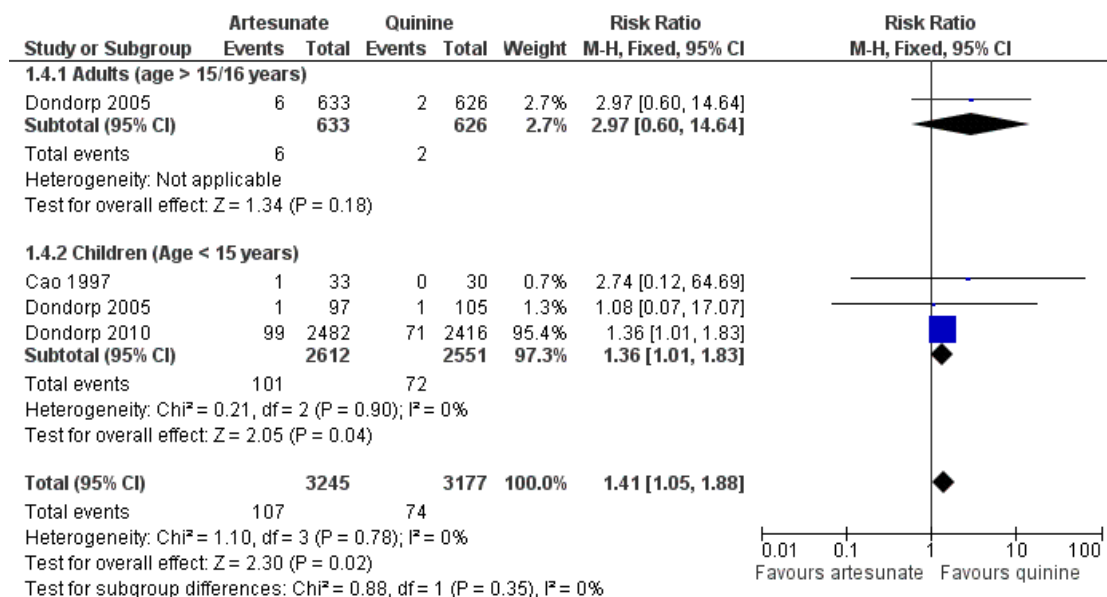
The two large multicentre trials ([Dondorp 2005](#); [Dondorp 2010](#)) conducted multiple subgroup analyses according to the presence or absence of coma, anaemia, shock, acidosis, respiratory distress, or hyperparasitaemia at the time of admission. Mortality was consistently lower with artesunate in all of these subgroups but some were underpowered to show statistically significant differences.

Artesunate appears superior to quinine irrespective of intramuscular or intravenous administration ([Analysis 1.3](#)).

Neurological sequelae

At the time of hospital discharge, neurological sequelae were more common in those treated with artesunate than with quinine (RR 1.41, 95% CI 1.05 to 1.88; 6422 participants, three trials, [Analysis 1.4](#), [Figure 3](#)). Of these three trials, only [Dondorp 2005](#) included adults, and the incidence of neurological sequelae seems to be very low in this group ([Analysis 1.4](#), [Figure 3](#)).

Figure 3. Forest plot of comparison: I Artesunate vs quinine, outcome: I.9 Neurological sequelae at discharge.



One trial in children (Dondorp 2010) followed participants up until day 28 to see if these sequelae resolved. Of the 170 children with sequelae at the time of discharge, 129 (75.9%) were available for assessment on day 28, and 68 of these (52.7%) had fully recovered. At this time point the difference between groups was not statistically significant (RR 1.23, 95% CI 0.74 to 2.03; 4857 participants, one trial, Analysis 1.5).

Coma recovery time

Six trials report a measure of coma recovery time (Anh 1989; Anh 1995; Cao 1997; Eltahir 2010; Hien 1992; Newton 2003). The frequency of clinical monitoring to assess coma recovery varied between these trials and is likely to have influenced the result (see Table 2).

Three trials reported mean coma recovery time but the data from Eltahir 2010 were incompletely reported. There is no evidence of a difference between the groups, the data are skewed and the results inconsistent (231 participants, two trials, Analysis 1.6). Three trials reported median coma recovery time and again the results were inconsistent and no conclusions can be made (see Table 3).

In addition the two large multicentre trials (Dondorp 2005; Dondorp 2010) report median time to speak, and Dondorp 2010 reports median time to localise pain (see Table 3). Dondorp 2010 found the time to speak and localise pain to be slightly prolonged in those treated with artesunate but the clinical significance of this is unclear (Table 3).

Time to hospital discharge

Three trials reported this outcome as a median (Cao 1997; Dondorp 2005, Dondorp 2010). The results were consistent and showed no evidence of a difference between the groups (see Table 3). One trial reported this outcome as a mean (Newton 2003) with no evidence of a difference between the groups, but the data

appeared skewed (113 participants, one trial, Analysis 1.7).

Fever clearance time

Three trials reported this outcome as a mean (Hien 1992; Anh 1995; Eltahir 2010). There is no evidence of a difference between the groups, although the data appeared to be skewed (317 participants, three trials, Analysis 1.8). Two trials reported this outcome as a median (Cao 1997; Newton 2003), and found no statistically significant difference between groups (see Table 3). The frequency with which fever was monitored differed between the trials (Table 2).

Parasite clearance time (PCT)

Five trials report a measure of mean parasite clearance time. Artesunate appears superior to quinine at reducing the mean 50% PCT (MD -8.14 hrs, 95% CI -11.55 to -4.73; 292 participants, three trials, Analysis 1.9), mean 90% PCT (MD -18.50 hrs, 95% CI -24.13 to -12.87; 61 patients; one trial, Analysis 1.9), mean 95% PCT (MD -10.69 hrs, 95% CI -20.27 to -1.10, 231 patients; two trials; Analysis 1.9), and mean 100% PCT (MD -9.77h 95% CI -18.11 to -1.44, 419 patients; four trials; Analysis 1.9).

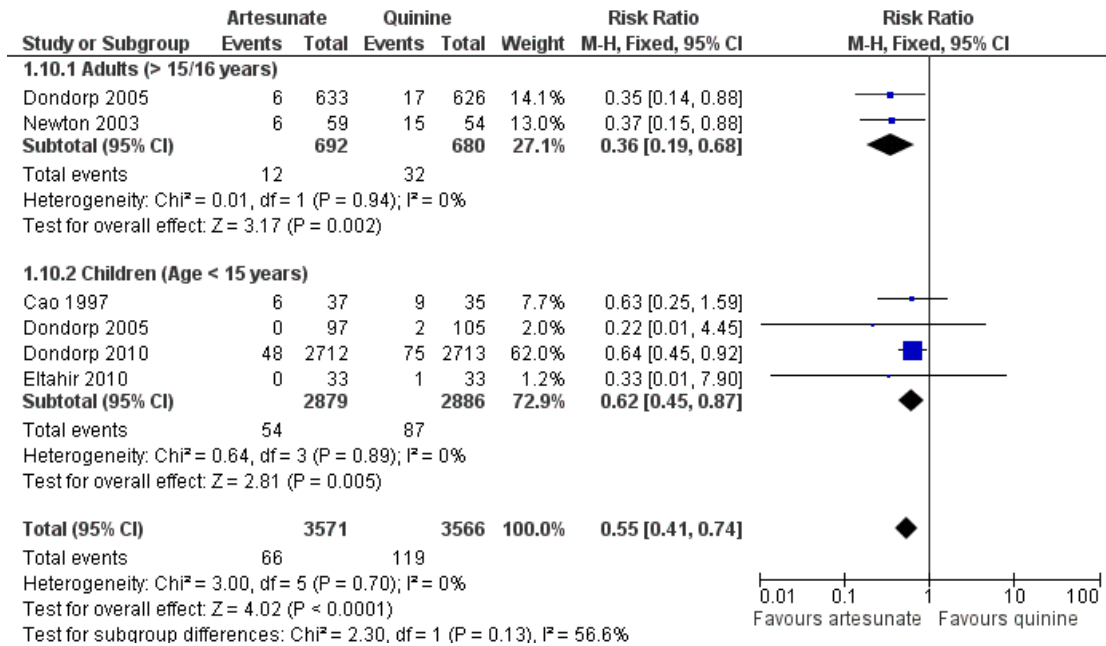
Two additional trials (Newton 2003; Cao 1997) reported median 50% and 90% PCT (see Table 3).

The frequency with which trials repeated malaria blood films differed between the trials (see Table 2).

Adverse effects

No trial reported discontinuation of medication. With the exception of hypoglycaemia and tinnitus, all adverse effects reported could be attributable to malaria. Artesunate was associated with a statistically significant reduction in episodes of hypoglycaemia (RR 0.55, 95% 0.41 to 0.74; 7137 participants, 4 trials, Analysis 1.10, Figure 4).

Figure 4. Forest plot of comparison: I Artesunate vs quinine, outcome: I.15 Hypoglycaemia episodes: by age of participants.



Additional comments on adverse events taken from the original trial reports are given in [Table 4](#).

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Artesunate compared with quinine for treating severe malaria					
Patient or population: Adults with severe malaria Settings: Malaria endemic areas Intervention: Artesunate Comparison: Quinine					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Quinine	Artesunate			
Death	241 per 1000	147 per 1000 (121 to 181)	RR 0.61 (0.5 to 0.75)	1664 (5 studies ¹)	high ^{4,2,3,4,5}
Neurological sequelae at day 28	-	-	-	-	Not reported
Neurological sequelae at discharge	3 per 1000	9 per 1000 (2 to 44)	RR 2.97 (0.6 to 14.64)	1259 (1 study ⁶)	moderate ^{7,8,9,10}
Time to hospital discharge (days)	See comment	See comment	Not estimable	113 (2 studies ¹¹)	moderate ^{12,13,14,15}
Hypoglycaemia episodes	47 per 1000	17 per 1000 (9 to 32)	RR 0.36 (0.19 to 0.68)	1372 (2 studies ¹¹)	high ^{12,16,14,17}

*The **assumed risk** was calculated by dividing the total number of events in the control group (across studies) by the total number of patients in the control group (across studies). This was numerically very similar to the median control group risk but is easier to link with the corresponding forest plot. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk Ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

- ¹ One large multicentre trial ([Dondorp 2005](#)) and four smaller trials ([Anh 1989](#), [Anh 1995](#), [Hien 1992](#), [Newton 2003](#)) have assessed artesunate vs quinine in adults
- ² No serious study limitations: two of the smaller studies did not conceal allocation and none of the studies were blinded. However the majority of the data is from studies which did conceal allocation and the lack of blinding is unlikely to introduce bias for an objective outcome such as death.
- ³ No serious inconsistency: The point estimates of all five trials favoured artesunate. No significant statistical heterogeneity was detected ($I^2 = 0\%$).
- ⁴ No serious indirectness: All five trials were from Asia, but from a variety of settings (Vietnam, Bangladesh, India, Myanmar, Indonesia and Thailand), and included age groups above 15/16 years. Of the four small trials; two did not give the loading dose of quinine, but there was no statistical heterogeneity between these two trials and the large multicentre trial which did give the loading dose.
- ⁵ No serious imprecision: Both limits of the 95% CI imply a clinically important benefit with artesunate.
- ⁶ Only one trial reported the incidence of neurological sequelae in adults ([Dondorp 2005](#)). This is unpublished data received from the authors.
- ⁷ No serious study limitations: This trial was unblinded but the nature of the sequelae makes an observer or reporting bias unlikely
- ⁸ No serious inconsistency: Not applicable as only one trial
- ⁹ No serious indirectness: This trial had sites in four different countries in Asia and used the established standard doses of artesunate and quinine (with loading dose). Of the 10 sequelae which occurred in this trial (the additional two were in children): Five were psychiatric sequelae, four were a persistent problem with balance, and two had a hemiparesis.
- ¹⁰ Serious imprecision: Neurological sequelae appear to be a rare event following severe malaria in adults. However the 95% CI includes the possibility of a clinically important harm with artesunate.
- ¹¹ Two trials ([Dondorp 2005](#) and [Newton 2003](#)) report this outcome.
- ¹² No serious study limitations: [Dondorp 2005](#) adequately concealed allocation to be considered at low risk of bias. [Newton 2003](#) did not but is a much smaller trial. Neither trial was blinded
- ¹³ No serious inconsistency: Neither trial found a statistically significant difference in time to hospital discharge
- ¹⁴ No serious indirectness: This evidence is from multiple sites within Asia (Bangladesh, India, Myanmar and Indonesia) and both trials used standard drug doses. The data from [Dondorp 2005](#) does include some children.
- ¹⁵ Serious imprecision: We were unable to pool data due to the way data were presented but there is no evidence of a benefit on this outcome with artesunate.
- ¹⁶ No serious inconsistency: There was no statistical heterogeneity ($I^2 = 0\%$)
- ¹⁷ No serious imprecision: This result is statistically significant in favour of artesunate. The current sample size is adequately powered to detect a 75% risk reduction with 80% power and 95% confidence.

DISCUSSION

Summary of main results

Potential benefits of treating severe malaria with artesunate instead of quinine

Treating severe malaria with artesunate instead of quinine reduces the risk of death by 39% in adults (95% CI 25% to 50%), and 24% in children (95% CI 10% to 35%).

Artesunate also reduces episodes of hypoglycaemia during treatment by 45% (95% CI 26% to 59%).

Potential harms of treating severe malaria with artesunate instead of quinine

In adults neurological sequelae following treatment for severe malaria appears to be very low (< 1%) and no difference has been shown between artesunate and quinine.

In children, treatment with artesunate appears to increase the incidence of neurological sequelae at the time of hospital discharge but the majority of these sequelae seem to resolve with time, and there is no evidence of a difference between the two treatments 28 days later.

Overall completeness and applicability of evidence

This review includes trials from multiple countries within Africa and Asia where malaria is most prevalent. Although there are no trials from South America it would be reasonable to generalise these findings to all geographic regions.

There is now adequate evidence to be confident of the results in both adults and children. However, it should be noted that these trials did not include a significant number of pregnant women.

Based on this trial data the absolute benefit in children appears lower than that seen in adults, primarily due to the lower mortality seen in children. This observation may be related to regional differences rather than participant age as the majority of child data is from Africa, and all the adult data is from Asia. Potential reasons for the lower risk of mortality seen in children in [Dondorp 2010](#) include: inclusion of 'less severe' malaria, increased efficacy of quinine in Africa or true differences in the risk of death related to acquisition of partial immunity in Africa.

Quality of the evidence

Although several of the smaller trials suffer from methodological problems such as open randomization, unmatched additional oral antimalarials, or non-standard dosing, these do not affect the overall quality of the evidence as the majority of the data is from large multicentre trials which do not suffer the same problems.

We consider the evidence for a reduction in mortality with artesunate to be high quality, and further research to establish this is

unnecessary (see [Summary of findings for the main comparison](#) and [Summary of findings 2](#)).

The increase in neurological sequelae is of a smaller magnitude than the reduction in deaths and seems to be temporary. The balance of benefits and harms is in favour of benefit with artesunate.

Economic commentary

To supplement the main systematic review of the effects on artesunate in the management of severe malaria, we sought to identify economic evaluations which compared the use of artesunate with the use of quinine. Systematic supplementary searches of the NHS Economic Evaluation Database (NHS EED) and the Health Economic Evaluations Database (HEED) identified four articles using the search terms outlined in [Table 1](#). The articles were then screened for inclusion and two were discarded as they evaluated the use of rectal artesunate.

[Lubell 2009](#) is a cost-effectiveness analysis based on the large multicentre trial of artesunate in Asia ([Dondorp 2005](#)), and [Lubell 2011](#) is based on the large multicentre trial from sub-Saharan Africa ([Dondorp 2010](#)). Both studies take the service-provider's perspective, calculating the total costs to the health service, and no estimate was made of the economical benefit to the individual or society.

In both studies, the total cost of care using artesunate was marginally higher per patient than using quinine (in Asia: US\$43.0 vs. US\$32.4; in Africa: US\$66.5 vs. US\$63.5). However, given the large treatment effect of artesunate, the incremental cost per additional death averted was less than US\$140 in both studies. For a brief summary of these two studies see [Table 5](#).

It is important to highlight that neither of the identified economic evaluations were subjected to any formal critical appraisal and we do not attempt to draw any firm or general conclusions regarding the relative costs or efficiency of artesunate compared with quinine for the treatment of severe malaria. However, the available evidence indicates that, from an economic perspective, the use of artesunate for the treatment of severe malaria is a promising strategy when compared with quinine. Combined with the clinical data and the WHO treatment guidelines, this information may prove useful to those with responsibility for making local, regional, or national decisions regarding the management of individuals with severe malaria. However, end users of this review will need to assess the extent to which the economic evidence presented here may be applicable to their own setting.

AUTHORS' CONCLUSIONS

Implications for practice

Intravenous artesunate should be the treatment of choice for adults

and children presenting with severe malaria in any geographical region.

Implications for research

Further research to examine the efficacy of artesunate versus quinine in children and adults is unnecessary. The safety of artesunate in pregnancy still needs to be determined, and trials are underway to examine the effects of artesunate when given repeatedly for multiple episodes of malaria. Toxicity from repeated dosing can not be ruled out on the basis of the evidence included in this review. Particular attention should be paid to the incidence of neurological sequelae.

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- * Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Anh 1989

Methods	Study design: An open label randomized controlled trial Study dates: Feb to Dec 1989
Participants	Number: 41 enrolled Inclusion criteria: adults > 16 yr old with cerebral malaria (<i>P. falciparum</i> parasitaemia > 1000/mm ³ and Glasgow Coma Scale of 14 or less not attributable to any cause other than malaria) Exclusions: not specified
Interventions	1. Artesunate: 60 mg intravenous (IV) at 0, 4, 24, and 48 h 2. Quinine: 20 mg/kg IV loading dose over 4 h at 0 h then 10 mg/kg IV every 8 h until able to swallow then 10 mg/kg by mouth every 8 h until day 7 Additional antimalarials: none reported
Outcomes	1. Death 2. Coma recovery time 3. Parasite clearance time of 50% 4. Parasite clearance time of 95%
Notes	Location: Vietnamese hospital Transmission: not specified Funding: Roche Asian Research Foundation supplied artesunate (personal communication from author)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Personal communication with author: Random numbers table
Allocation concealment (selection bias)	High risk	Comment: Not done
Blinding (performance bias and detection bias) Objective outcomes: Death	Low risk	Comment: An open-label trial is unlikely to bias an objective outcome like death
Blinding (performance bias and detection bias) Subjective outcomes: Others	High risk	Comment: An open label trial. No attempt was made to blind participants, providers or outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up occurred

Anh 1989 (Continued)

Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	No other bias identified

Anh 1995

Methods	Study design: An open label randomized controlled trial Study dates: Jul 1992 to May 1995
Participants	Number: 190 enrolled Inclusion criteria: adults 15 to 65 yr with cerebral malaria (asexual <i>P. falciparum</i> parasitaemia and clinical signs of cerebral malaria alone or associated with other visceral complications) Exclusion criteria: associated <i>P. vivax</i> parasitaemia, pregnancy, and concomitant diseases such as diabetes mellitus, stroke, meningitis, head trauma, pulmonary tuberculosis, or AIDS
Interventions	1. Artesunate: 60 mg intravenous (IV) at 0, 4, 24, and 48 h 2. Quinine: 10 mg/kg IV over 4 h at 0 h then 10 mg/kg IV every 8 h until able to swallow then quinine by mouth at similar doses every 8 h until day 7 Additional antimalarials: artesunate treatment arm given one dose of mefloquine by mouth 15 mg/kg at day 7; quinine none
Outcomes	1. Death within 24 h 2. Death after 24 h 3. Coma recovery time 4. Fever clearance time 5. Parasite clearance time of 50% 6. Parasite clearance time of 95% 7. Parasite clearance time of 100% Not included in the review: 8. Time to sit 9. Time to take oral by self medication
Notes	Location: Vietnamese clinical research centre Transmission: not specified Funding: World Health Organization

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Personal communication with author: Central randomization
Allocation concealment (selection bias)	Low risk	Personal communication with author: Central randomization

Anh 1995 (Continued)

Blinding (performance bias and detection bias) Objective outcomes: Death	Low risk	Comment: An open-label trial is unlikely to bias an objective outcome like death
Blinding (performance bias and detection bias) Subjective outcomes: Others	High risk	Comment: An open label trial. No attempt was made to blind participants, providers or outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up are recorded
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	No other bias identified

Cao 1997

Methods	Study design: A 3-arm open label randomized controlled trial Study dates: Aug 1992 to Mar 1995
Participants	Number: 72 enrolled Inclusion criteria: children < 15 yr with severe malaria (asexual <i>P. falciparum</i> parasitaemia plus at least 1 of the following: coma (Blantyre Coma Scale less than or equal to 3), severe anaemia (capillary haematocrit < 15%) with parasitaemia (> 10,000/μL); hyperparasitaemia (> 10% parasitized red blood cells or parasitaemia > 500,000/μL); jaundice (obvious clinically or serum bilirubin > 48 μmol/L); hypoglycaemia (blood glucose < 2.2 mmol/L); spontaneous bleeding (eg gastrointestinal haemorrhage); shock (systolic blood pressure < 50 mmHg if aged < 6 yr, or < 70 mmHg if aged 6 to 14 yr); repeated generalized convulsions (3 or more in 24 h despite cooling); renal impairment (serum creatinine > 177 μmol/L, or urine output < 12 mL/kg/24 h that fails to improve despite rehydration) Exclusion criteria: severe diarrhoea, mixed infection with <i>P. vivax</i> , prior treatment with quinine > 60 mg/kg, artemisinin > 20 mg/kg, or artesunate > 2 mg/kg during the illness episode, or any antimalarial treatment continuing for > 48 h
Interventions	1. Artesunate: 3 mg/kg intramuscular (IM) at 0 h then 2 mg/kg IM at 12, 24, 48, and 72 h 2. Quinine: 20 mg/kg intravenous (IV) loading dose over 4 h (omitted if pretreatment with quinine) then 10 mg/kg IV every 8 h up to day 7 3. [Not relevant to review: rectal artemisinin] Additional antimalarials given: artesunate treatment arm received one dose of mefloquine by mouth 15 mg/kg at 96 h; quinine treatment arm given one dose of sulfadoxine-pyrimethamine 500 mg/25 mg on day 7
Outcomes	1. Death 2. Number survived with neurological sequelae 3. Fever clearance time (all patients, excluding superinfections) 4. Coma resolution

	<ul style="list-style-type: none"> 5. Parasite clearance time of 50% 6. Parasite clearance time of 90% 7. Parasite clearance time of 100% 8. Period in hospital 9. Hypoglycaemia 10. Adverse effects <p>Not included in this review:</p> <ul style="list-style-type: none"> 11. Number survived well 12. Time to death from admission 13. Number with acute renal failure 14. Shock 15. Convulsions 16. Deterioration of coma score 17. Gastrointestinal bleeding 18. Anaemia 19. Chest infection 20. Urinary tract infection 21. Other infection 22. Reticulocyte count at admission, on day 5, at discharge 23. Haematocrit at admission, on day 5, at discharge 	
Notes	<p>Location: Vietnamese hospital Transmission: not specified Funding: Wellcome Trust of Great Britain</p>	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Personal communication with author: Computer generated
Allocation concealment (selection bias)	Low risk	Quote: 'Randomization slips were kept in sealed, consecutively numbered envelopes and opened only after a decision to include the patient in the study had been made'
Blinding (performance bias and detection bias) Objective outcomes: Death	Low risk	Comment: An open-label trial is unlikely to bias an objective outcome like death
Blinding (performance bias and detection bias) Subjective outcomes: Others	High risk	Comment: An open label trial. No attempt was made to blind participants, providers or outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Personal communication from author: 100% analysed, no losses to follow-up

Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	No other bias identified

Dondorp 2005

Methods	Study design: An open label multi-centre randomized controlled trial Study dates: Jun 2003 to May 2005
Participants	Number: 1461 enrolled Inclusion criteria: adults and children > 2 yr with severe malaria (positive blood antigen stick test for <i>P. falciparum</i> and a diagnosis of severe malaria, according to the admitting physician) Exclusion criteria: convincing history of full treatment with quinine (40 mg/kg on the first day and 30 mg/kg on any subsequent day) or an artemisinin derivative for more than 24 h before admission, known allergy to 1 of the artemisinin derivatives or quinine
Interventions	1. Artesunate: 2.4 mg/kg intravenous (IV) at 0, 12, and 24 h then 2.4 mg/kg IV every 24 h until able to swallow then 2 mg/kg by mouth until day 7 2. Quinine: 20 mg/kg IV loading dose then 10 mg/kg every 8 h until able to swallow then 10 mg/kg by mouth every 8 h until day 7 Additional antimalarials: both arms except in India and Bangladesh were given doxycycline (100 mg every 12 h for 7 d) once able to swallow
Outcomes	1. In-hospital death 2. Death within 48 h of entry 3. Death after 48 h of entry 4. In-hospital death (blood-smear positive) 5. Neurological sequelae 6. Time to discharge (median, intra quartile range, and range) 7. Hypoglycaemia after entry Not included in the review: 8. Combined outcome: in hospital death or neurological sequelae 9. Fetal death 10. Time to speak (median, intra quartile range, and range) 11. Time to eat (median, intra quartile range, and range) 12. Time to sit (median, intra quartile range, and range) 13. Convulsions after entry 14. Shock developing after entry 15. Blackwater fever developing after entry 16. Dialysis after entry 17. Vasopressor treatment after entry 18. Mechanical ventilation after entry
Notes	Location: hospitals in Bangladesh, Myanmar, India, and Indonesia Transmission: not specified Funding: Wellcome Trust grant

Dondorp 2005 (Continued)

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: 'The two-step randomisation was produced with a computer generated randomisation list'
Allocation concealment (selection bias)	Low risk	Quote: 'After informed consent was obtained, we signed and dated a numbered sealed envelope across the seal, then opened it to reveal a unique study number. This number did not indicate the treatment allocation, but referred to a separate sealed hardcover box, containing the study drug, case record form, and all disposables needed for drug administration and blood sampling'
Blinding (performance bias and detection bias) Objective outcomes: Death	Low risk	Comment: An open-label trial is unlikely to bias an objective outcome like death
Blinding (performance bias and detection bias) Subjective outcomes: Others	High risk	Comment: An open label trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up are recorded.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	No other bias identified

Dondorp 2010

Methods	Study design: An open label, multi-centre randomized controlled trial Study dates: Oct 2005 to July 2010
Participants	Number: enrolled Inclusion criteria: Age < 15 years (age criteria varied slightly between sites at the request of the respective ethics review boards), a positive rapid diagnostic test for <i>P. falciparum</i> , severe malaria (physicians opinion), written consent Exclusions: Prior full treatment with parenteral quinine, or an artemisinin derivative for more than 24 h

Interventions	<p>Each study site used either the intravenous or intramuscular route for both treatment arms</p> <ol style="list-style-type: none"> 1. Artesunate (Guilin, China): 2.4 mg/kg on admission, at 12 h, at 24 h, and then once daily until starting oral therapy. 2. Quinine dihydrochloride (Indus Pharma, Pakistan): 20 mg salt per kg loading dose infused over 4 h (in 5-10 mL/kg of 5% dextrose), followed by a 10 mg salt per kg infusion over 2-8 h three times daily until starting oral therapy (For intramuscular treatment the doses were the same as for intravenous treatment; quinine was diluted in normal saline to a concentration of 60 mg/mL, and injected into the anterior thigh. The loading dose was given as a split dose into each thigh) Once able to tolerate oral medication (but after a minimum of 24 h of parenteral treatment), all participants received oral artemether-lumefantrine (Novartis, Switzerland) for 3 days with milk or fat)
Outcomes	<ol style="list-style-type: none"> 1. Death 2. Death or sequelae at 28 days 3. Malaria attributable mortality 4. Case fatality in HIV +ve children 5. Time to discharge 3. Neurological sequelae 4. Adverse events <p>Not included in the review:</p> <ol style="list-style-type: none"> 1. Development of coma 2. Convulsions developing after 6 hours 3. Severe anaemia after admission 4. Blackwater fever 5. Time to speak (median, intra quartile range) 6. Time to eat (median, intra quartile range) 7. Time to sit unsupported (median, intra quartile range) 8. Time to localise pain (median, intra quartile range)
Notes	<p>Location: 11 centres in nine African countries (Mozambique, The Gambia, Ghana, Kenya, Tanzania, Nigeria, Uganda, Rwanda, and Democratic Republic of the Congo)</p> <p>Transmission: variable</p> <p>Funding: The Wellcome Trust</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: 'Randomisation was done by people unrelated to the study and provided to the study sites in blocks of 20'
Allocation concealment (selection bias)	Low risk	Quote: 'Study numbers were kept inside opaque sealed paper envelopes. After full informed written consent was obtained, the

Dondorp 2010 (Continued)

		next envelope, which contained a unique study box number, was opened by the study physician or nurse. Then the corresponding numbered sealed box was opened. This box contained the study drug, case record form (labelled with the unique study number), and all disposables needed for drug administration and blood sampling’.
Blinding (performance bias and detection bias) Objective outcomes: Death	Low risk	Comment: An open-label trial is unlikely to bias an objective outcome like death
Blinding (performance bias and detection bias) Subjective outcomes: Others	High risk	Quote: ‘Although the trial was open label at each site, none of the investigators or triallists, apart from for the trial statistician (TEP), had access to the summaries of treatment allocations. When notes or case record forms were reviewed, all study drug details were removed to preserve masking’
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants are included in the primary analysis. A secondary per-protocol analysis including only those with proven malaria who received the full course of treatment excluded 149 (5.5%) from the artesunate arm and 161 (5.9%) from the quinine arm
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	One study site did study adults as well as children but these participants are not reported in the paper, or analysis

Eltahir 2010

Methods	Study design: An open label randomized controlled trial Study dates: Aug to Sep 2009
Participants	Number: 66 enrolled Inclusion criteria: Children with slide-confirmed, severe <i>P. falciparum</i> malaria, written informed consent Exclusions: None stated
Interventions	1. Intravenous artesunate (Guilin; China): 2.4 mg/kg body weight given at 0, 12, and 24 h, and then daily.

	2. Intravenous quinine (Shanghai; China): 20 mg/kg loading dose infused over 4 h then 10 mg/kg infused over 2-4 h three times a day Once oral therapy was tolerated participants received artesunate+ sulfadoxine-pyrimethamine or quinine tablets to complete treatment
Outcomes	1. Death 2. Coma recovery time 3. Parasite clearance time 4. Fever clearance time 5. Adverse events Not included in the review:
Notes	Location: Sudan Transmission: unstable Funding: Sudanese Sugar Company and Assalaya Sugar Factory, Sudan

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: 'Individuals were randomised (by computer-generated numbers)'
Allocation concealment (selection bias)	Low risk	Quote: 'computer generated numbers were sealed in individual envelopes and securely stored'
Blinding (performance bias and detection bias) Objective outcomes: Death	Low risk	Comment: An open-label trial is unlikely to bias an objective outcome like death
Blinding (performance bias and detection bias) Subjective outcomes: Others	High risk	Comment: An open label trial. No attempt was made to blind participants, providers or outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	No other bias identified

Hien 1992

Methods	Study design: A 3-arm open label randomized controlled trial Study dates: 1989 to 1990
Participants	Number: 61 enrolled Inclusion criteria: cerebral malaria (<i>P. falciparum</i> parasitaemia with clinical signs of malaria and a Glasgow Coma Scale < 10) Exclusion criteria: not specified
Interventions	1. Artesunate: 60 mg intravenous (IV) at 0, 4, 24, and 48 h 2. Quinine: 500 mg IV over 4 h then 500 mg IV every 8 h until able to swallow then 500 mg by mouth every 8 h until day 14 3. [Not relevant to review: rectal artemisinin] Additional antimalarials: artesunate treatment arm given one dose of mefloquine (by mouth 500 mg) once able to swallow
Outcomes	1. Fever clearance time 2. Parasite clearance time of 50% 3. Parasite clearance time of 90% 4. Parasite clearance time of 100% 5. Time to regain full consciousness 6. Death Not included in the review:
Notes	Location: intensive care unit in Vietnam Transmission: not specified Funding: artesunate was provided by Professor Li Guo Qiao

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Personal communication from author: We did randomization by hand using tables of randomization from a statistic book
Allocation concealment (selection bias)	Low risk	Personal communication from author: All treatment codes were sealed in opaque envelopes which were only opened when patients had been recruited into trial based on inclusion criteria
Blinding (performance bias and detection bias) Objective outcomes: Death	Low risk	Comment: An open-label trial is unlikely to bias an objective outcome like death
Blinding (performance bias and detection bias) Subjective outcomes: Others	High risk	Comment: An open label trial. No attempt was made to blind participants, providers or outcome assessors

Hien 1992 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up are recorded
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	No other bias identified

Newton 2003

Methods	Study design: An open label randomized controlled trial Study dates: May to July 1994 and 1995 to 2001
Participants	Number: 113 enrolled, 100 analysed Inclusion criteria: adults aged 15 yr or above with severe malaria (single-species <i>P. falciparum</i> parasitaemia > 0.1% plus at least 1 of following: Glasgow Coma Scale < 11; haematocrit < 20% with asexual parasitaemia > 100,000/μL; total serum bilirubin > 50 μmol/L with asexual parasitaemia > 100,000/μL; serum creatinine > 264 μmol/L with urine output < 400 mL/24 h; systolic blood pressure < 80 mmHg with cool extremities; asexual parasitaemia > 10%; plasma lactate level > 4 mmol/L; plasma glucose level < 2.2 mmol/L; plasma venous bicarbonate level < 15 mmol/L Exclusion criteria: pregnancy, contraindications to study drugs, artesunate, mefloquine, or significant quinine (> 2 g) intake in the previous 24 h
Interventions	1. Artesunate: 2.4 mg/kg intravenous (IV) at 0 h then 1.2 mg/kg at 12 h then 1.2 mg/kg every 24 h until able to swallow then 12 mg/kg by mouth every 24 h over 7 days 2. Quinine: 20 mg/kg IV over 4 h loading dose then 10 mg/kg IV every 8 until able to swallow then 10 mg/kg by mouth until day 7 Additional antimalarials: once able to swallow some participants in both arms were given additional antimalarials, but the drug given varied during the trial; AS: no additional antimalarial (n = 22), mefloquine 15 mg/kg (n = 1), mefloquine 25 mg/kg in 2 doses (n = 22), doxycycline 100 mg every 12 h for 7 d (n = 14); quinine: no additional antimalarial (n = 20), tetracycline 250 mg every 12 h for 7 d (n = 19), doxycycline 100 mg every 12 h for 7 days (n = 15)
Outcomes	1. Fever clearance time 2. Parasite clearance time of 50% 3. Parasite clearance time of 90% 4. Parasite clearance time of 100% 5. Time to regain full consciousness 6. Death 6. Hypoglycaemia 7. Adverse effects Not included in the review:
Notes	Location: 2 hospitals in Thailand Transmission: seasonal low intensity Funding: Wellcome Trust of Great Britain

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Personal communication with author: Random codes were created in Excel using the 'Randbetween' command
Allocation concealment (selection bias)	High risk	Quote: 'The randomization was open'
Blinding (performance bias and detection bias) Objective outcomes: Death	Low risk	Comment: An open-label trial is unlikely to bias an objective outcome like death
Blinding (performance bias and detection bias) Subjective outcomes: Others	High risk	Comment: An open label trial. No attempt was made to blind participants, providers or outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	13 patients were excluded after randomization for not meeting the criteria for severe malaria 5 (%) in the artesunate arm and 8 (%) in the quinine arm
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	No other bias identified

n: number of participants.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Aguwa 2010	Artemether versus quinine
Awad 2003	Not a randomized controlled trial
Barnes 2004	Not severe malaria
Bounyasong 2001	Not severe malaria
Haroon 2005	A quasi-randomized controlled trial in which the first patient was allocated a treatment at random and then future patients were allocated their treatment using an alternating pattern

(Continued)

Krudsood 2003	Not a randomized controlled trial
Li 1990	Not severe malaria
McGready 2001a	Not severe malaria
McGready 2001b	Not a randomized controlled trial
Mohanty 2004	Not a randomized controlled trial (quasi-randomized)
Newton 2001	Treatment comparison is artesunate versus artesunate and quinine
Osanuga 2009	Artemether versus quinine
Phu 2010	Artesunate versus artemether
Pukrittayakamee 2004	Not severe malaria
Win 1992	Not a randomized controlled trial
Zhao 2001	Not severe malaria

DATA AND ANALYSES

Comparison 1. Artesunate vs quinine

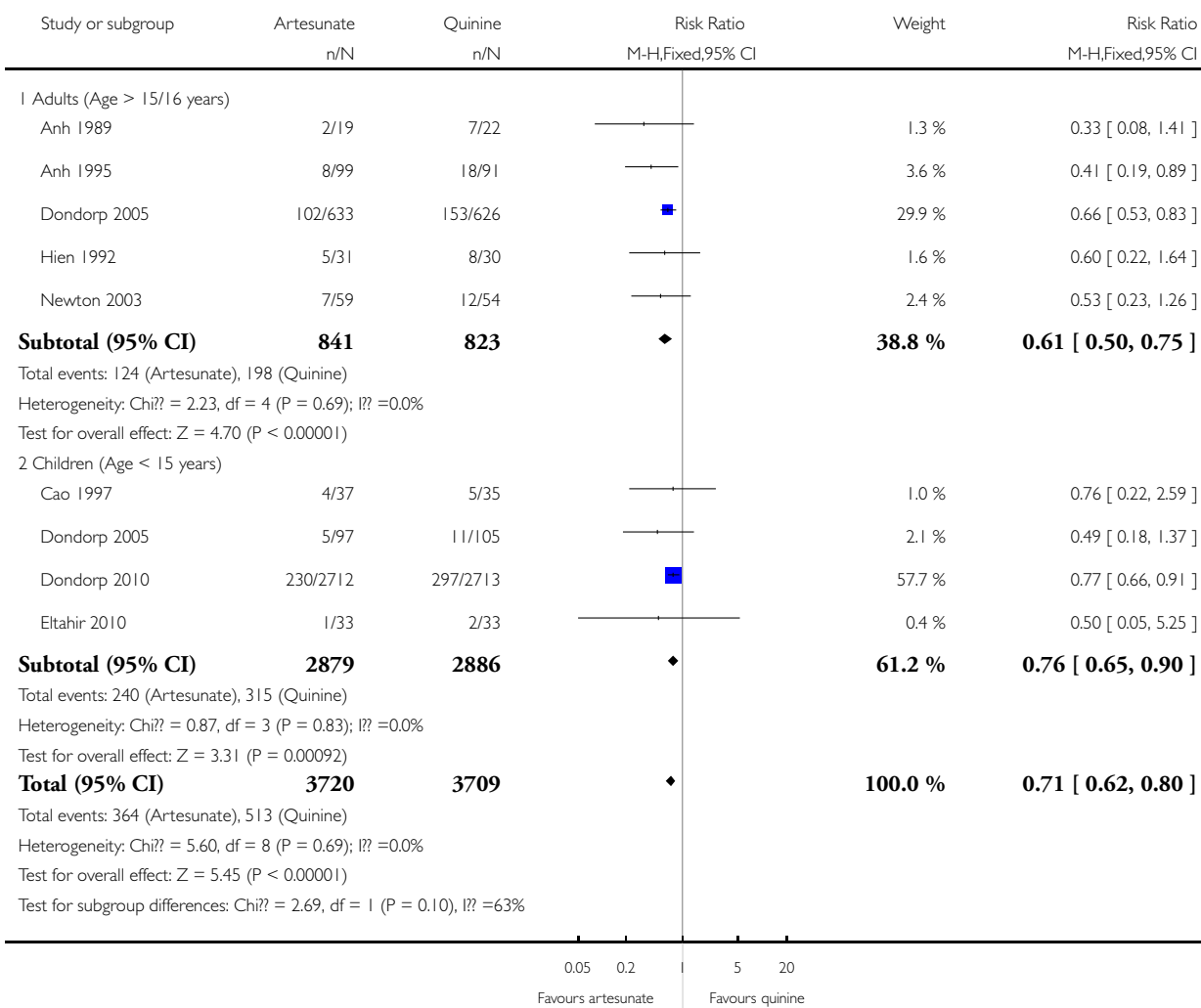
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death: participant age	8	7429	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.62, 0.80]
1.1 Adults (Age > 15/16 years)	5	1664	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.50, 0.75]
1.2 Children (Age < 15 years)	4	5765	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.65, 0.90]
2 Death: time since admission to hospital [sensitivity analysis]	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Death within 24 hours	1	5417	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.69, 1.04]
2.2 Death after 24 hours	1	5072	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.48, 0.88]
2.3 Death within 48 hours	3	1646	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.57, 1.05]
2.4 Death after 48 hours	3	1646	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.38, 0.74]
3 Death: intravenous vs intramuscular artesunate [sensitivity analysis]	8	7429	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.63, 0.80]
3.1 Intravenous artesunate	7	5435	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.60, 0.80]
3.2 Intramuscular artesunate	2	1994	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.60, 0.98]
4 Neurological sequelae at discharge	3	6422	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [1.05, 1.88]
4.1 Adults (age > 15/16 years)	1	1259	Risk Ratio (M-H, Fixed, 95% CI)	2.97 [0.60, 14.64]
4.2 Children (Age < 15 years)	3	5163	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [1.01, 1.83]
5 Neurological sequelae at day 28	1	4857	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.74, 2.03]
5.1 Adults (Age > 15/16 years)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Children (Age < 15 years)	1	4857	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.74, 2.03]
6 Coma recovery time (hours)	2	231	Mean Difference (IV, Random, 95% CI)	2.11 [-19.17, 23.40]
7 Time to hospital discharge (days)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8 Fever clearance time (hours)	3	317	Mean Difference (IV, Random, 95% CI)	-2.74 [-14.07, 8.60]
9 Parasite clearance time (hours)	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
9.1 Time to clear 50% of parasites	3	292	Mean Difference (IV, Random, 95% CI)	-8.14 [-11.55, -4.73]
9.2 Time to clear 90% of parasites	1	61	Mean Difference (IV, Random, 95% CI)	-18.5 [-24.13, -12.87]
9.3 Time to clear 95% of parasites	2	231	Mean Difference (IV, Random, 95% CI)	-10.69 [-20.27, -1.10]
9.4 Time to clear all parasites	4	419	Mean Difference (IV, Random, 95% CI)	-9.77 [-18.11, -1.44]
10 Hypoglycaemia episodes: by age of participants	5	7137	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.41, 0.74]
10.1 Adults (> 15/16 years)	2	1372	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.19, 0.68]
10.2 Children (Age < 15 years)	4	5765	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.45, 0.87]
11 Hypoglycaemia episodes: by method of monitoring	5	7137	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.41, 0.74]
11.1 Routine monitoring	3	251	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.25, 0.85]
11.2 Clinical monitoring	1	1461	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.13, 0.79]
11.3 Unclear	1	5425	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.45, 0.92]

Analysis I.1. Comparison I Artesunate vs quinine, Outcome I Death: participant age.

Review: Artesunate versus quinine for treating severe malaria

Comparison: I Artesunate vs quinine

Outcome: I Death: participant age

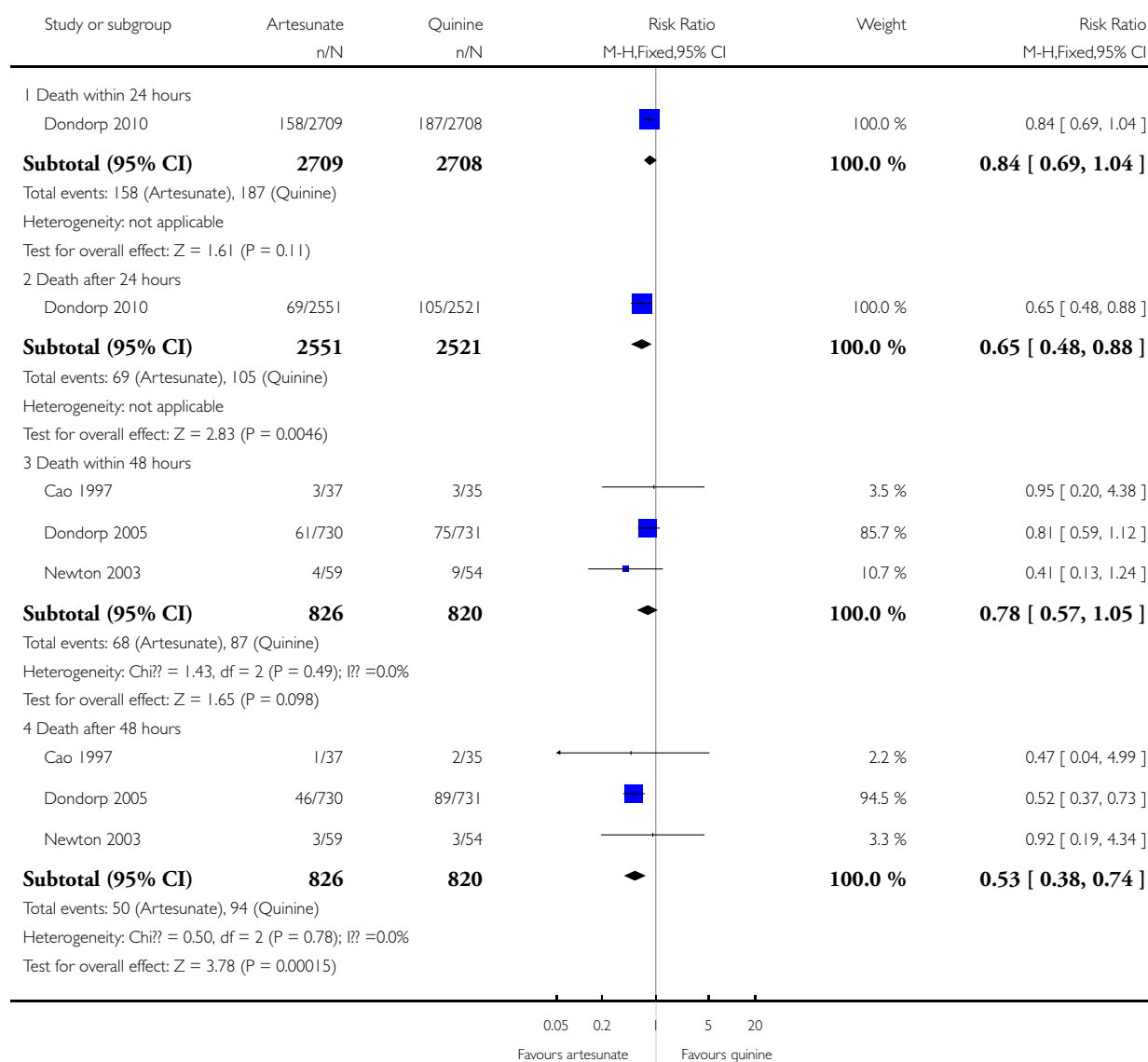


Analysis 1.2. Comparison 1 Artesunate vs quinine, Outcome 2 Death: time since admission to hospital [sensitivity analysis].

Review: Artesunate versus quinine for treating severe malaria

Comparison: 1 Artesunate vs quinine

Outcome: 2 Death: time since admission to hospital [sensitivity analysis]

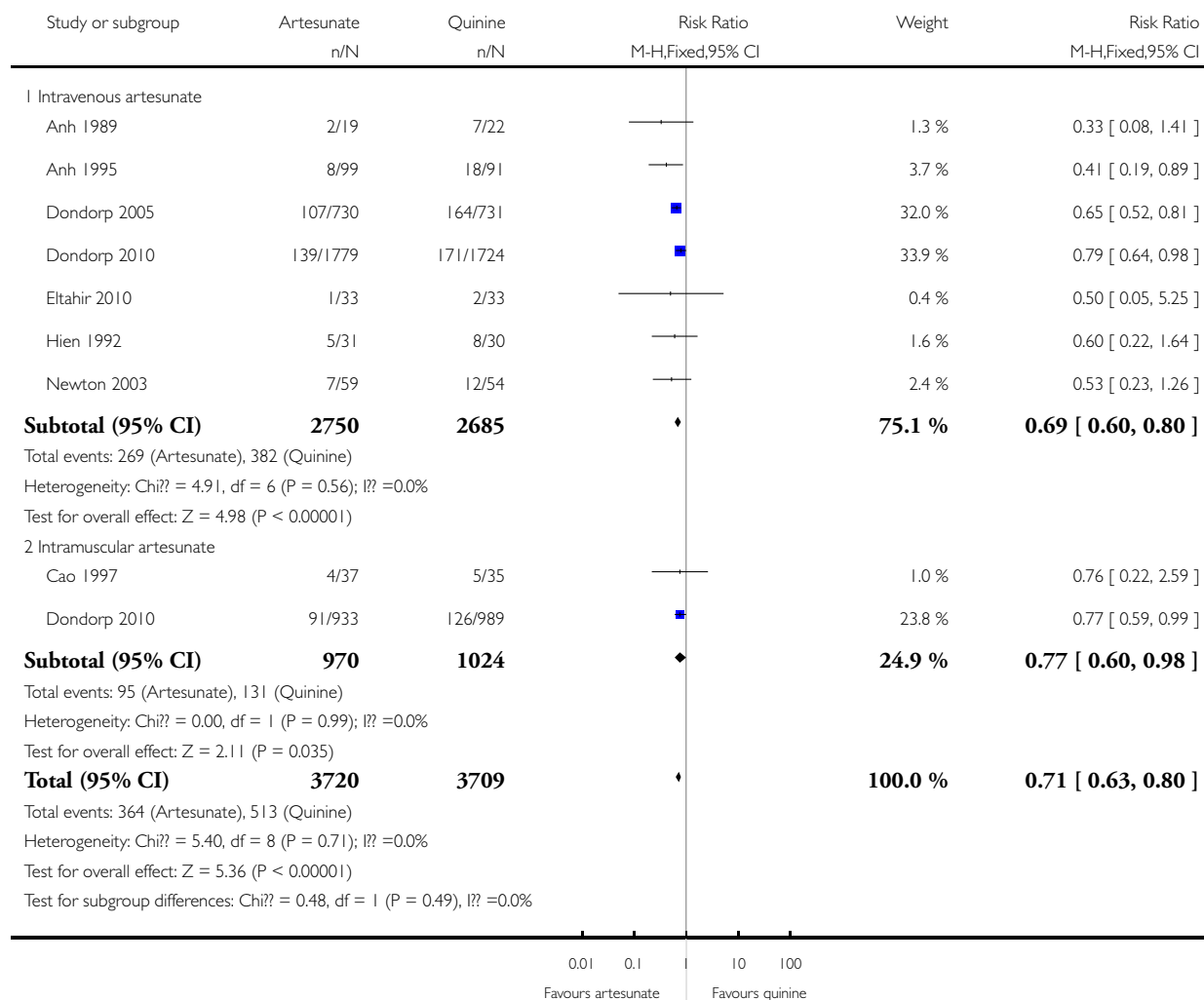


Analysis 1.3. Comparison 1 Artesunate vs quinine, Outcome 3 Death: intravenous vs intramuscular artesunate [sensitivity analysis].

Review: Artesunate versus quinine for treating severe malaria

Comparison: 1 Artesunate vs quinine

Outcome: 3 Death: intravenous vs intramuscular artesunate [sensitivity analysis]

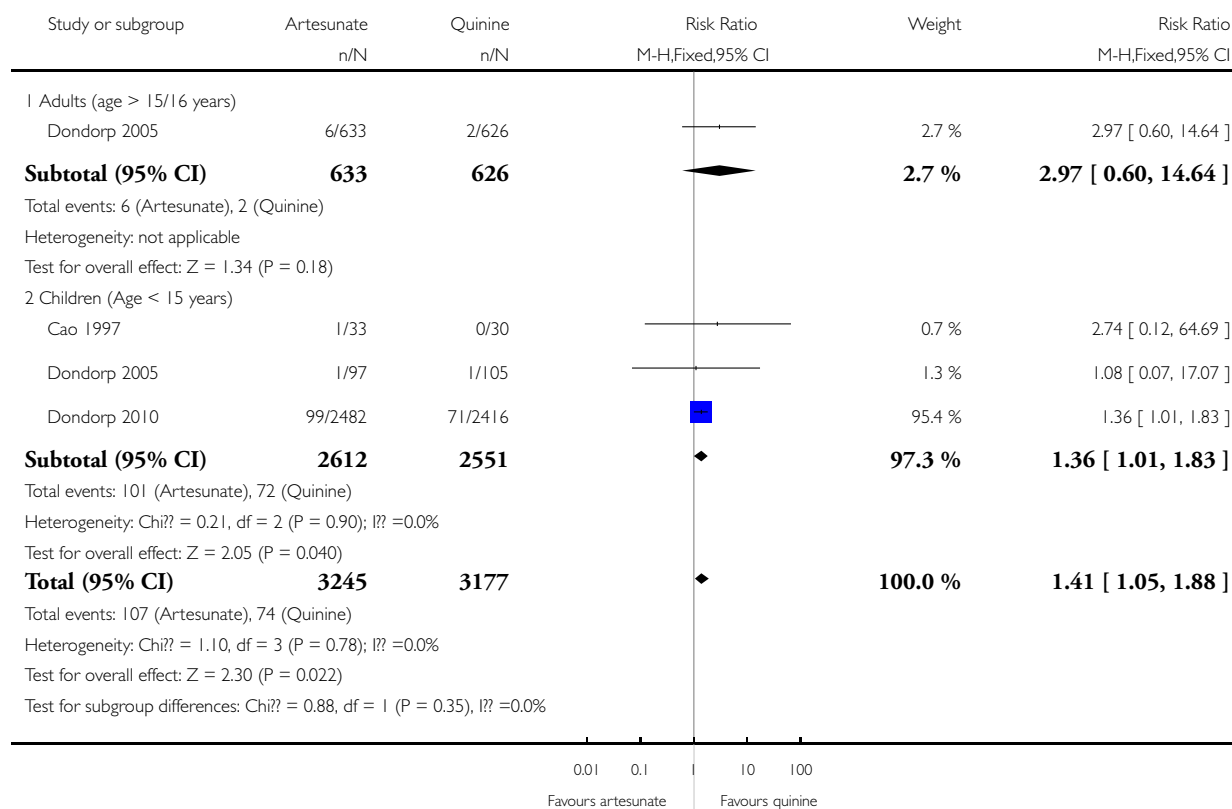


Analysis 1.4. Comparison 1 Artesunate vs quinine, Outcome 4 Neurological sequelae at discharge.

Review: Artesunate versus quinine for treating severe malaria

Comparison: 1 Artesunate vs quinine

Outcome: 4 Neurological sequelae at discharge

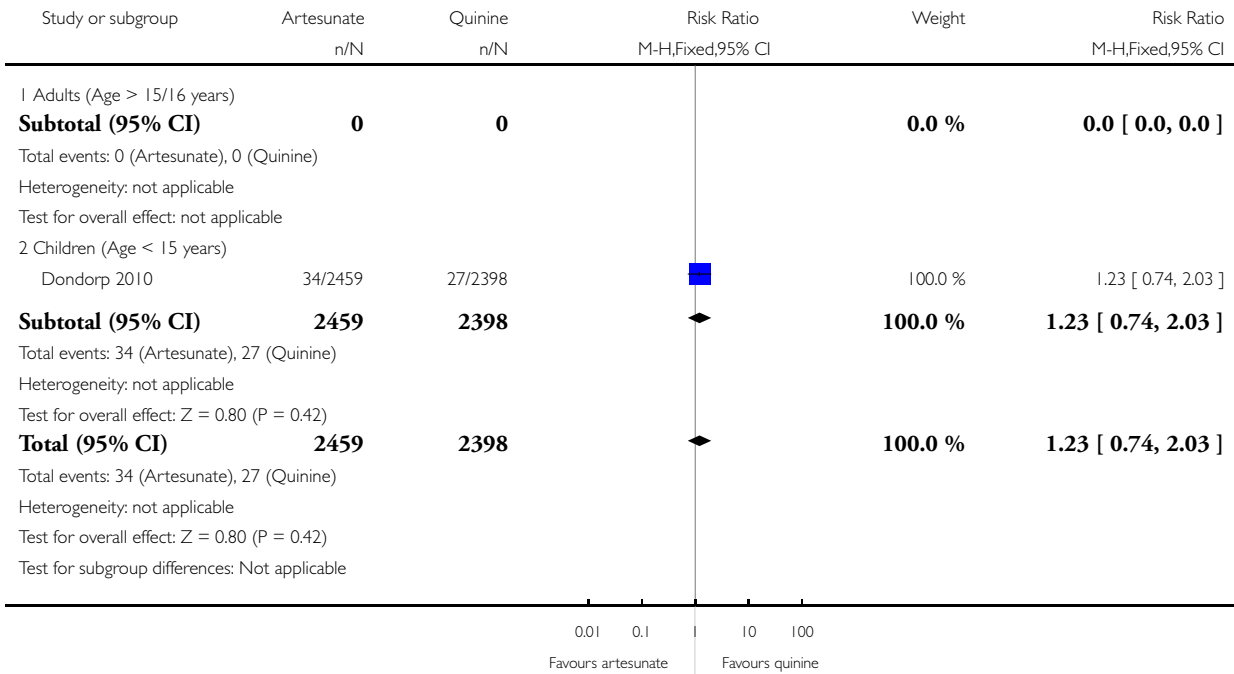


Analysis 1.5. Comparison 1 Artesunate vs quinine, Outcome 5 Neurological sequelae at day 28.

Review: Artesunate versus quinine for treating severe malaria

Comparison: 1 Artesunate vs quinine

Outcome: 5 Neurological sequelae at day 28

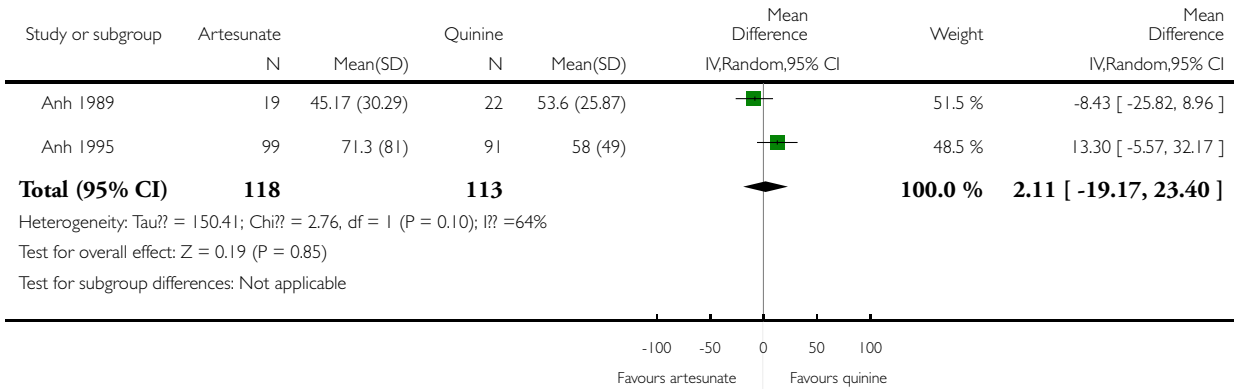


Analysis I.6. Comparison I Artesunate vs quinine, Outcome 6 Coma recovery time (hours).

Review: Artesunate versus quinine for treating severe malaria

Comparison: I Artesunate vs quinine

Outcome: 6 Coma recovery time (hours)

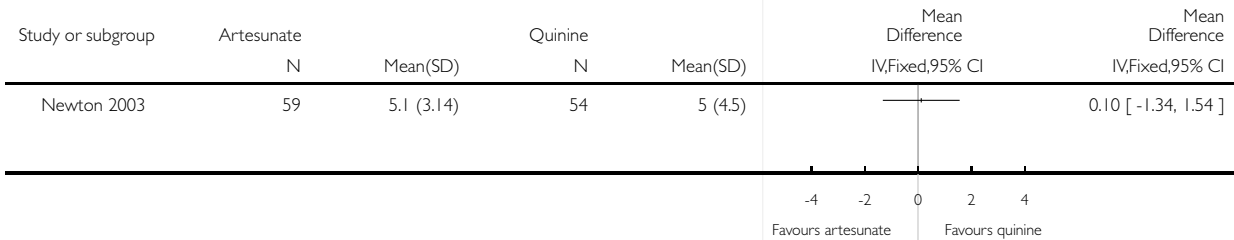


Analysis I.7. Comparison I Artesunate vs quinine, Outcome 7 Time to hospital discharge (days).

Review: Artesunate versus quinine for treating severe malaria

Comparison: I Artesunate vs quinine

Outcome: 7 Time to hospital discharge (days)

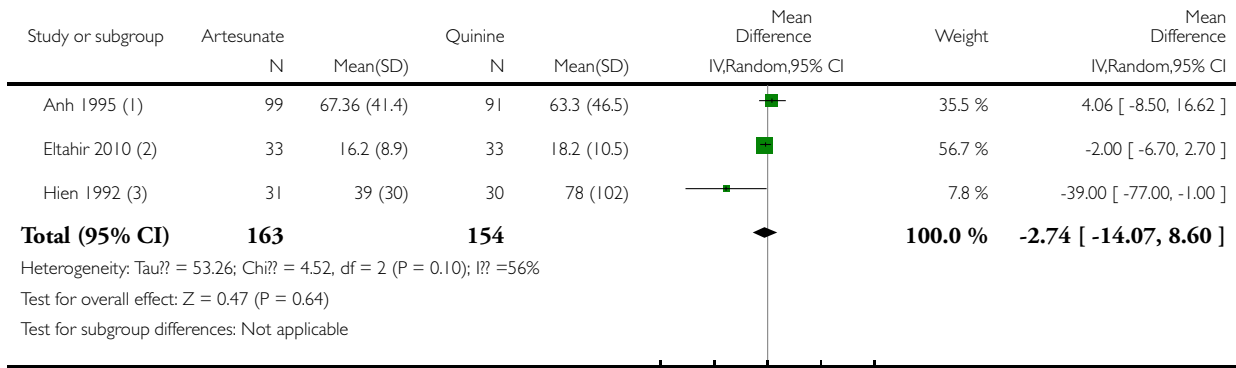


Analysis 1.8. Comparison 1 Artesunate vs quinine, Outcome 8 Fever clearance time (hours).

Review: Artesunate versus quinine for treating severe malaria

Comparison: 1 Artesunate vs quinine

Outcome: 8 Fever clearance time (hours)



-100 -50 0 50 100
Favours artesunate Favours quinine

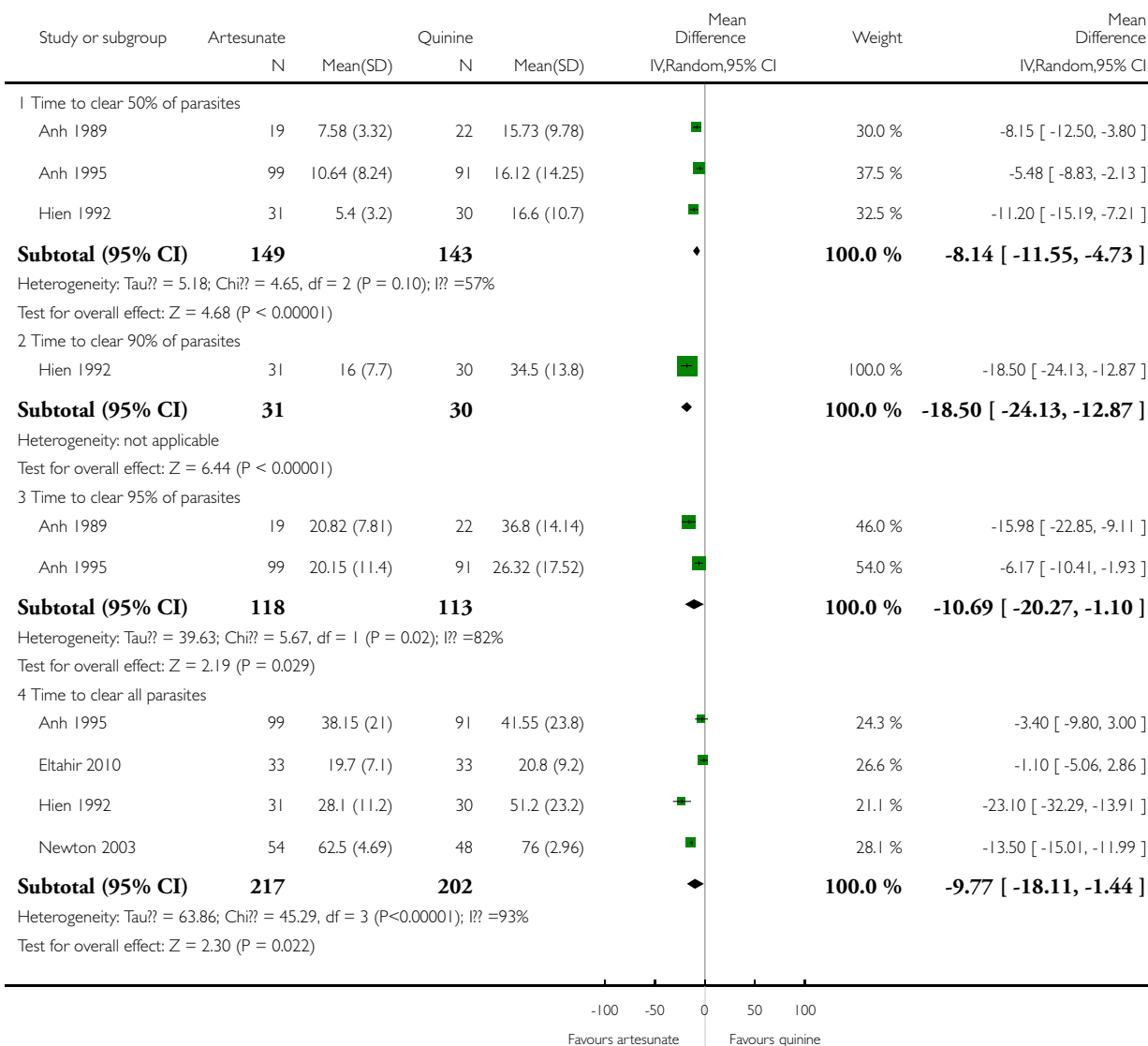
- (1) Axillary temperature was recorded every 6 h until 4 consecutive temperatures were < 37.5 °C
- (2) Vital signs were monitored every 15 mins for the first hour, then every 2 hours until 24 hours then every 6 hours until the axillary temp first dropped below 37.5 and remained below for 24 hours.
- (3) The axillary temperature was measured at 3 hour intervals until "fever clearance"

Analysis 1.9. Comparison 1 Artesunate vs quinine, Outcome 9 Parasite clearance time (hours).

Review: Artesunate versus quinine for treating severe malaria

Comparison: 1 Artesunate vs quinine

Outcome: 9 Parasite clearance time (hours)

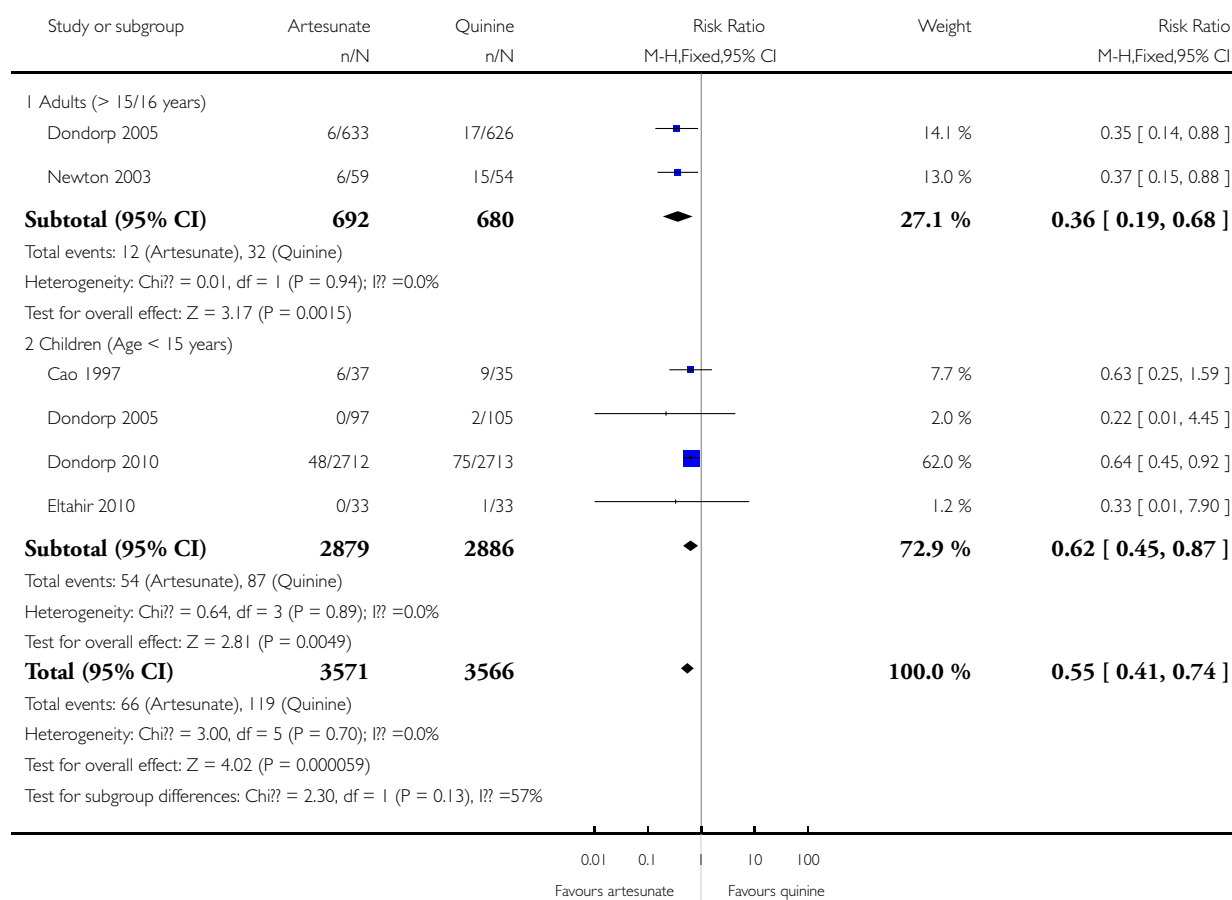


Analysis I.10. Comparison I Artesunate vs quinine, Outcome 10 Hypoglycaemia episodes: by age of participants.

Review: Artesunate versus quinine for treating severe malaria

Comparison: I Artesunate vs quinine

Outcome: 10 Hypoglycaemia episodes: by age of participants

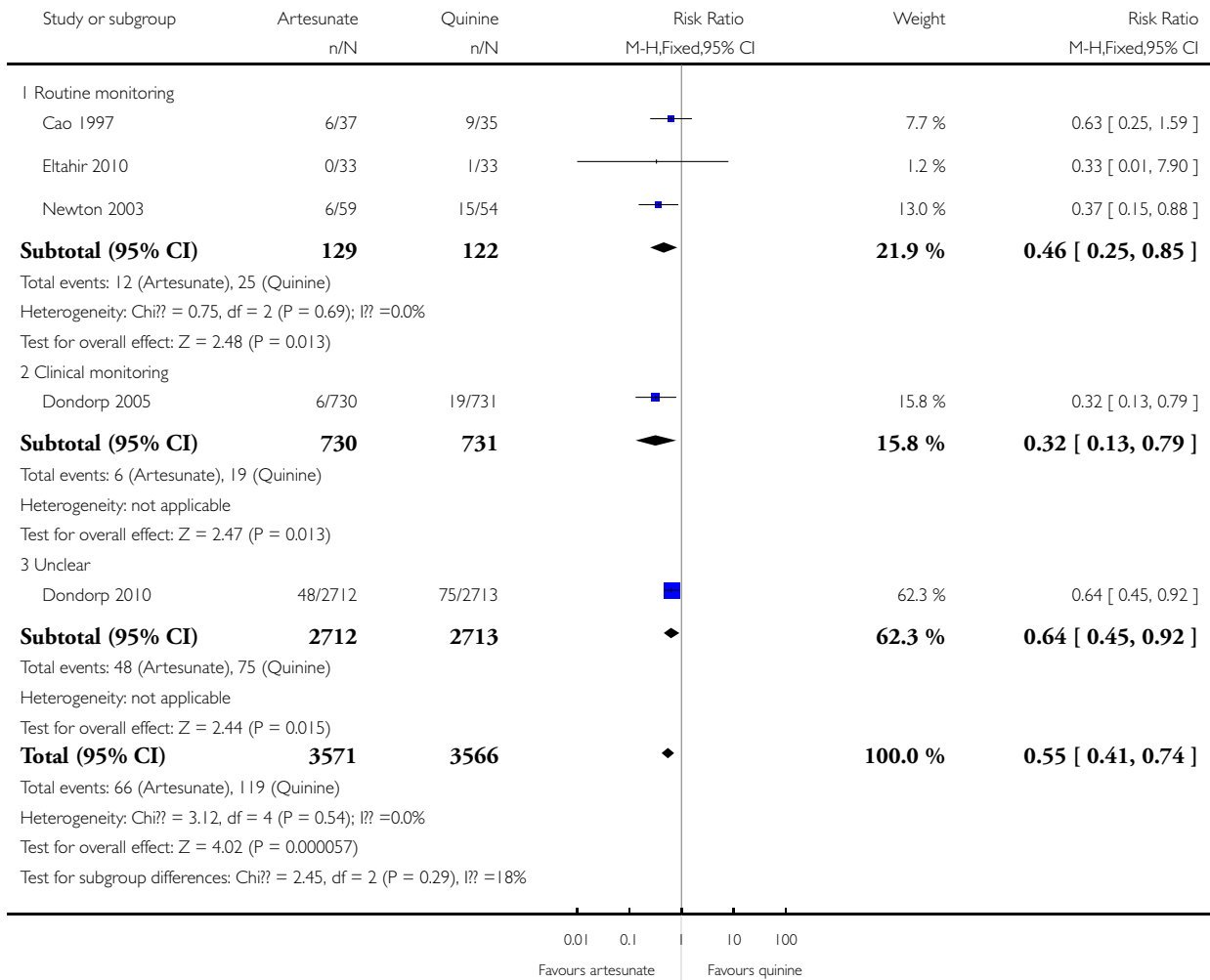


Analysis 1.11. Comparison 1 Artesunate vs quinine, Outcome 11 Hypoglycaemia episodes: by method of monitoring.

Review: Artesunate versus quinine for treating severe malaria

Comparison: 1 Artesunate vs quinine

Outcome: 11 Hypoglycaemia episodes: by method of monitoring



ADDITIONAL TABLES

Table 1. Search methods: detailed search strategy

Search set	CIDG SR ^a	CENTRAL	MEDLINE ^b	EMBASE ^b	LILACS ^b	ISI Web of Science
1	malaria	malaria	malaria	malaria	malaria	malaria
2	quinine	quinine	quinine	quinine	quinine	quinine
3	artesunate	quinimax	quinimax	quinimax	artesunate	artesunate
4	artemisinin*	CINCHONA ALKALOIDS	CINCHONA ALKALOIDS	CINCHONA-ALKALOID	artemisinin	arsumax
5	3 or 4	2 or 3 or 4	2 or 3 or 4	2 or 3 or 4	3 or 4	3 or 4
6	1 and 2 and 5	artesunate	artesunate	artesunate	1 and 2 and 5	1 and 2 and 5
7	-	arsumax	arsumax	arsumax	-	-
8	-	6 or 7	6 or 7	6 or 7	-	-
9	-	1 and 5 and 8	1 and 5 and 8	1 and 5 and 8	-	-
10	-	-	limit 9 to human	limit 9 to human	-	-

^aCochrane Infectious Diseases Group Specialized Register.

^bSearch terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Higgins 2008); upper case: MeSH or EMTREE heading; lower case: free text term.

Table 2. Definitions of outcome measures used in the review

Trial	Death	Neurological sequelae at discharge	Coma recovery time	Time to discharge	Fever clearance time	Parasite clearance time	Hypoglycaemia	Adverse effects
Anh 1989	Death	Not reported	Mean value (h) reported but not defined	Not reported	Not reported	Mean value (h) reported but not defined. Parasite counts every 8 h until 2 consecutive slides were negative and then every 24 h	Not reported	Not reported

Table 2. Definitions of outcome measures used in the review (Continued)

Anh 1995	Death	Not reported	Mean value (h). Defined as time until consciousness regained. Glasgow Coma Scale measured every 12 h until regained consciousness	Not reported	Mean value (h) reported but not defined. Axillary temperature was recorded every 6 h until 4 consecutive temperatures were < 37.5 °C	Mean value (h) reported but not defined. Parasite count measured every 6 h until 3 consecutive blood smears were negative	Not reported	Not reported
Cao 1997	Death	Number survived with neurological sequelae. Case definition for neurological sequelae: abnormal neurological signs and/or symptoms at time of discharge from hospital that were not present before onset of the episode of malaria as reported by the child's parents. All children had a full neurological examination on admission and at discharge from hospital (personal communication from author)	Median value (h) reported. Defined as time (h) for Blantyre Coma Score to become 5/5. Coma score assessed every 4 h (or more frequently if critically ill) for the first 24 h, and then every 6 h until discharge	Median value (d) reported	Median value (h) reported. Defined as time until temperature first dropped to 37.5 °C or below and remained below this level for at least 24 h. Axillary temperature measured every 4 h (or more frequently if critically ill) for the first 24 h, and then every 6 h until discharge	Median value (h) reported but not defined. Parasite count measured every 4 h (or more frequently if critically ill) for the first 24 h, and then every 6 h until discharge. Once 2 successive peripheral blood films had revealed no <i>P. falciparum</i> , no further blood film was made unless indicated clinically	Blood glucose < 2.2 mmol/L. Blood glucose measured every 4 h for first 24 h and then every 6 h until discharge from hospital if indicated (coma, prostration, jaundice, or > 1 complication - personal communication from author)	Acute renal failure requiring dialysis, shock, convulsions, deterioration of coma score, gastrointestinal bleeding, anaemia requiring blood transfusion, chest infection, urinary tract infection, other infections, derangement of biochemical markers

Table 2. Definitions of outcome measures used in the review (Continued)

Dondorp 2005	Death	Neurological sequelae at discharge from hospital	Not reported	Median value (d) reported	Not reported	Not reported	Blood glucose < 2.2 mmol/L. Blood glucose checked in all patients on admission and then monitored on clinical indication	Not reported
Dondorp 2010	Death	Severe neurological complications (initially assessed at discharge from hospital but the protocol was changed after 11% of patients had been enrolled, so that children who had not fully recovered at discharge were assessed 28 days after enrollment)	Not reported	Median value (d) reported	Not reported	Not reported	Not reported	Not reported
Eltahir 2010	Death	Not reported	Mean value measured from administration of first antimalarial until the Glasgow coma score reached 15. Vital signs and coma scale were monitored every 15 mins for	Not reported	Mean value measured from administration of first antimalarial until the axillary temp first dropped below 37.5 and remained below for 24 hours	Mean value measured from administration of the first antimalarial until the first of two sequential negative blood films. Blood films were taken every 4 hours	Blood glucose levels were measured every 6 hours.	Not reported

Table 2. Definitions of outcome measures used in the review (Continued)

			the first hour, then every 2 hours until 24 hours then every 6 hours					
Hien 1992	Death	Not reported	Mean, median, and mode values reported in hours. Defined as time to regain full consciousness (Glasgow Coma Scale of 15/15). Glasgow Coma Scale measured at 3-h intervals until full recovery of consciousness, and at 6-h intervals thereafter	Not reported	Mean value (h) reported. Defined as time (h) until "fever clearance". The axillary temperature was measured at 3-h intervals until "fever clearance", and at 6-h intervals thereafter	Mean value (h) reported but not defined. Parasite counts performed every 4 h for 12 h, then every 6 h until 3 consecutive films were negative	Not reported	None reported
Newton 2003	Death	Not reported	Median value (h) reported. Defined as time to reach a Glasgow Coma Scale of 15 in those participants with a score < 11/15 on admission. Glasgow Coma Scale measured every 15 min for first h, at 2 h, and then every 2 h until 12 h, every 4 h from	Not reported	Median value (h) reported. Defined as time until the axillary temperature first dropped below 37.5 °C and remained below that level for 24 h. Axillary temperature measured every 15 min for the first h, at 2 h, and then every 2 h until 12	Median value (h) reported. Defined as time to a 50% reduction in parasite density. Parasite counts were measured at 0, 1, 2, 4, 6, 8, 10, 12, 16, 20, and 24 h, and then every 6 h until 6 h after parasite clearance	Plasma glucose less than or equal to 2.2 mmol/L. Plasma glucose measured at 0, 4, 8, 12, 16, 20, and 24 h and then every 6 h	Seizures, bleeding and sepsis after admission, pulmonary oedema, oliguria, time in intensive care unit

Table 2. Definitions of outcome measures used in the review (Continued)

		12 to 24 h, and every 6 h from 24 h until the score reached 15	h, every 4 h from 12 to 24 h, and every 6 h from 24 h until fever cleared
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Table 3. Time-to-event data: medians, ranges, and modes

Outcome	Trial	Artesunate	Quinine	Comparative results reported in article
Coma recovery time (h): median (range), number	Hien 1992	35 (5 to 453); mode = 17; mean = 68.9	48 (7 to 144), mode = 43; mean = 58.1	'Not significantly different'
	Cao 1997	42 (4 to 228), n = 10	31 (4 to 66), n = 2	-
	Newton 2003	17 (1 to 125), n = 16	18 (1 to 188), n = 16	'P = 0.6'
	Eltahir 2010	mean = 8.1 (SD not given), n = 4	mean = 9.1, (SD not given), n = 5	'P=0.4'
Time to localise pain (h) : median (IQR), number	Dondorp 2010	12 (6 to 24), n = 698	12 (6 to 24), n = 726	'Hazard Ratio 0.87 (0.78-0.98), P = 0.0093'
Time to speak (h/days): median (IQR), number	Dondorp 2005	1 day (0.2 to 0.35), n = 730	1 day (0.2 to 0.21), n = 731	'P = 0.73'
	Dondorp 2010	20 hrs (8 to 42), n = 664	18 hrs (11 to 36), n = 695	'Hazard Ratio 0.88 (0.79-0.99), P = 0.016'
Time to hospital discharge (d): median (range/IQR), number	Cao 1997	8 (5 to 20), n = 33	8 (5 to 24), n = 29	'P = 0.99'
	Dondorp 2005	5 (0 to 54), n = 623	5 (0 to 45), n = 567	'P = 0.20'
	Dondorp 2010	3 (IQR 2 to 5), n = 2478	3 (IQR 2 to 5) n = 2412	'P = 0.059'
Fever clearance time (until first below 37.5 °C) (h): median (range), number	Cao 1997	4 (4 to 198), n = 35	8 (0 to 96), n = 35	'P = 0.17'
	Newton 2003	11 (1 to 83), n = 42	13 (1 to 184), n = 42	'P = 0.2'
Fever clearance time (until remains below 37.5 °C for 24 h) (h): median (range), number	Cao 1997	84 (4 to 198), n = 35	81 (0 to 246), n = 30	'P = 0.62'
	Newton 2003	41 (3 to 138), n = 32	65 (12 to 383), n = 27	'P = 0.2'

Table 3. Time-to-event data: medians, ranges, and modes (Continued)

Time to parasite clearance of 50% (h): median (range), number	Cao 1997	5.7 (2.0 to 15.3), n = 35	13.2 (2.4 to 103.0), n = 32	'P < 0.0001'
	Newton 2003	9.1 (0.3 to 37.2), n = 56	8.0 (0.2 to 46.0), n = 49	'P = 0.3'
Time to parasite clearance of 90% (h): median (range), number	Cao 1997	12.0 (3.7 to 35.0), n=35	27.7 (7.5 to 107.0), n=32	'P < 0.0001'
	Newton 2003	20.5 (2.8 to 50.11), n=54	24.7 (0.9 to 67.7), n=48	'P = 0.08'
Time to parasite clearance of 100% (h): median (range), number	Cao 1997	36.0 (16.0 to 126.0), n=34	84.0 (12.0 to 240.0), n=32	'P < 0.0001'

Table 4. Adverse event reporting

Study ID	Additional comments on adverse events
Anh 1989	No comment on adverse events
Anh 1995	No comment on adverse events
Cao 1997	'All 3 drug regimens were well tolerated, and no patient had to discontinue treatment because of adverse effects.' This study also conducted some cardiac monitoring on a non-randomised subset of patients and does not report any significant differences between groups
Dondorp 2005	'With the exception of hypoglycaemia there were no serious adverse effects that could be attributed to either treatment.'
Dondorp 2010	'We detected no severe adverse effects that could be attributed directly to drug toxicity. Although one patient treated with artesunate developed a mild urticarial rash, no severe type 1 hypersensitivity reactions were recorded.'
Eltahir 2010	'Following quinine infusion, 12 patients developed tinnitus and one hypoglycaemia. Abdominal pain and nausea were observed in three and four patients in artesunate and quinine groups, respectively.'
Hien 1992	No comment on adverse events
Newton 2003	'Patients treated with quinine consistently developed cinchonism and had a significantly higher frequency of hypoglycemia. One patient had a probable adverse reaction to artesunate. This patient presented with parasitaemia of 31%, a plasma lactate level of 14.5 mmol/L, and a serum bilirubin level of 23 mg/dL and developed a widespread erythematous urticarial rash 17 h after treatment with intravenous artesunate was initiated.'

Table 5. Summary of cost-effectiveness studies

	Lubell 2009	Lubell 2011
Location(s)	Asia	Sub-Saharan Africa
Population	Mostly adults (86%)	Children
Type of analysis	Cost-effectiveness	Cost-effectiveness
Perspective taken	Provider	Provider
Main cost categories	Drug cost (but not administration costs) Inpatient care cost	Drugs Fluids Laboratories Hotel
Currency	USD	USD
Price year	2008	2009
Sensitivity analysis?	Yes	Yes
Time horizon	Immediate	Immediate
Total cost per treatment episode artesunate vs. quinine	\$43.0 vs. \$32.4	\$66.5 vs. \$63.5
Number needed to treat	13	41
Incremental cost per death averted	\$135.6	\$123
Incremental cost per DALY averted	Not calculated	\$3.8

WHAT'S NEW

Last assessed as up-to-date: 31 January 2011.

Date	Event	Description
10 May 2012	New search has been performed	updated with economic evaluation
10 May 2012	New citation required but conclusions have not changed	Economic evaluation conducted by new author (R. Isba) and added to the review

HISTORY

Protocol first published: Issue 2, 2006

Review first published: Issue 4, 2007

Date	Event	Description
12 April 2011	Amended	Dates corrected (review assessed as up-to-date is 31 January 2011, not 2010 as previously stated)
16 February 2011	New citation required and conclusions have changed	Two new trials of artesunate versus quinine in African children have been added
28 November 2010	New search has been performed	Major update. New Search November 2010. David Sinclair has joined the author team and become contact author, and Katharine Jones has stepped down from the author team
30 July 2009	New search has been performed	New search conducted; no new trials for inclusion. Contact person changed
5 August 2008	Amended	Converted to new review format with minor editing.

CONTRIBUTIONS OF AUTHORS

Katharine Jones and Sarah Donegan assessed the eligibility and methodological quality of trials, extracted and analysed data, and completed the first published version of the review. David Sinclair replaced Katharine Jones for the 2011 update of this review. David Lalloo contributed to the design and writing of the review. Rachel Isba designed and conducted the economic commentary.

DECLARATIONS OF INTEREST

Dr David Lalloo was part of the data and safety monitoring committee for the two Dondorp trials. This committee is independent, does not run or gain anything from the trial, and has a main role of protecting participants.

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK.
- University of Liverpool, UK.

External sources

- Department for International Development (DFID), UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

2007, Issue 4 (first review version): We removed the requirement for all participants to fulfil the WHO definition for severe malaria (Gilles 2000) in view of the large number of participants this would have excluded from the review as the largest included trial used a clinical case definition.

We changed the intervention from “parenteral artesunate” to “intravenous, intramuscular, or rectal artesunate” to clarify that trials using artesunate suppositories would be included in the review.

We subgrouped “neurological sequelae” into “neurological sequelae at discharge” and “neurological sequelae at day 28”.

We added a number of sensitivity analyses post-hoc after noting significant variation in study design across trials.

We presented data for hypoglycaemia in a forest plot rather than a table as stated in the protocol to reflect the clinical importance of this outcome.

INDEX TERMS

Medical Subject Headings (MeSH)

Antimalarials [administration & dosage; *therapeutic use]; Artemisinins [administration & dosage; *therapeutic use]; Injections, Intramuscular; Injections, Intravenous; Malaria [*drug therapy; mortality]; Quinine [administration & dosage; *therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans