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Esu EB, Effa EE, Opie ON, Meremikwu MM

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[Intervention Review]

Artemether for severe malaria

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ABSTRACT

Background

In 2011 the World Health Organization (WHO) recommended parenteral artesunate in preference to quinine as first-line treatment for people with severe malaria. Prior to this recommendation many countries, particularly in Africa, had begun to use artemether, an alternative artemisinin derivative. This Cochrane Review evaluates intramuscular artemether compared with both quinine and artesunate.

Objectives

To assess the efficacy and safety of intramuscular artemether versus any other parenteral medication in the treatment of severe malaria in adults and children.

Search methods

We searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (the Cochrane Library), MEDLINE, Embase, and LILACS, ISI Web of Science, conference proceedings, and reference lists of articles. We also searched the WHO International Clinical Trial Registry Platform, ClinicalTrials.gov, and the metaRegister of Controlled Trials (mRCT) for ongoing trials up to 7 September 2018. We checked the reference lists of all studies identified by the search. We examined references listed in review articles and previously compiled bibliographies to look for eligible studies.

Selection criteria

Randomized controlled trials (RCTs) comparing intramuscular artemether with intravenous/intramuscular quinine or artesunate for treating severe malaria.

Data collection and analysis

The primary outcome was all-cause death. Two review authors independently screened each article by title and abstract, and examined potentially relevant studies for inclusion using an eligibility form. Two review authors independently extracted data and assessed risk of bias of included studies. We summarized dichotomous outcomes using risk ratios (RRs) and continuous outcomes using mean differences (MDs), and have presented both measures with 95% confidence intervals (CIs). Where appropriate, we combined data in meta-analyses and used the GRADE approach to summarize the certainty of the evidence.

Main results

We included 19 RCTs, enrolling 2874 adults and children with severe malaria, carried out in Africa (12 trials) and in Asia (7 trials).

Artemether versus quinine

For children, there is probably little or no difference in the risk of death between intramuscular artemether and quinine (RR 0.97, 95% CI 0.77 to 1.21; 13 trials, 1659 participants, moderate-certainty evidence). Coma resolution time may be about five hours shorter with artemether (MD −5.45, 95% CI −7.90 to −3.00; six trials, 358 participants, low-certainty evidence). Artemether may make little difference to neurological sequelae (RR 0.84, 95% CI 0.66 to 1.07; seven trials, 968 participants, low-certainty evidence). Compared to quinine, artemether probably shortens the parasite clearance time by about nine hours (MD −9.03, 95% CI −11.43 to −6.63; seven trials, 420 participants, moderate-certainty evidence), and may shorten the fever clearance time by about three hours (MD −3.73, 95% CI −6.55 to −0.92; eight trials, 457 participants, low-certainty evidence).

For adults, treatment with intramuscular artemether probably results in fewer deaths than treatment with quinine (RR 0.59, 95% CI 0.42 to 0.83; four trials, 716 participants, moderate-certainty evidence).

Artemether versus artesunate

Artemether and artesunate have not been directly compared in randomized trials in children.

For adults, mortality is probably higher with intramuscular artemether (RR 1.80, 95% CI 1.09 to 2.97; two trials, 494 participants, moderate-certainty evidence).

Authors' conclusions

Artemether appears to be more effective than quinine in children and adults. Artemether compared to artesunate has not been extensively studied, but in adults it appears inferior. These findings are consistent with the WHO recommendations that artesunate is the drug of choice, but artemether is acceptable when artesunate is not available.

16 September 2019

Up to date

All studies incorporated from most recent search

All published trials found in the last search (7 Sep, 2018) were included, and we did not identify any ongoing trials.

PLAIN LANGUAGE SUMMARY

Artemether injection for treating people with severe malaria

What is the aim of this review?

Injection of artesunate is recommended by the World Health Organization (WHO) for treating adults and children that have severe malaria as studies have shown that it results in fewer deaths compared to quinine treatment.

Artemether is an alternative artemisinin-based medicine but is only available as a pre-mixed oil-based solution for intramuscular injection. Artemether is now widely available and is used in many African countries, although it is not specifically recommended by the WHO. The aim of this review was to examine the effects of treating people that have severe malaria with artemether injected intramuscularly compared to treatment with other antimalarial medicines given intramuscularly or intravenously.

Key messages

Artemether may not be more effective than quinine at preventing deaths from severe malaria in children. However, in adults artemether is probably more effective than quinine at preventing deaths. With respect to other patient-oriented outcomes such as fever and parasite clearance time, artemether seems to be more effective than quinine in children and adults. For adults, artemether had a large effect on death compared to quinine but other outcomes were largely not reported or showed no significant difference. Artemether has not been compared to artesunate in children. Although there is a paucity of direct evidence comparing artemether with artesunate in adults, artemether probably increases the risk of death compared to artesunate. In settings where artesunate is not available, artemether remains a better alternative to quinine for the treatment of severe malaria.

What was studied in the review?

The review authors examined the available research that evaluated the effects of treating people that have severe malaria with artemether injected intramuscularly compared to treatment with other antimalarial medicines given intramuscularly or intravenously. Nineteen studies looked at the effects of treatment with intramuscular artemether on people with severe malaria compared to treatment with

other antimalarial medicines given intramuscularly or intravenously. These studies were undertaken in Africa (12 studies) and Asia (seven studies). This is an update of a 2014 Cochrane Review and includes a new trial from Central African Republic.

What are the main results of the review?

Artemether versus quinine

For children, intramuscular artemether is probably as good as quinine at preventing deaths from severe malaria (moderate-certainty evidence). Artemether may shorten time to coma resolution by about five hours (low-certainty evidence), and may reduce the number of children with signs of brain damage at the time of hospital discharge (low-certainty evidence).

In older children (> 15 years) and adults, treatment with artemether probably results in fewer deaths than quinine (moderate-certainty evidence).

Artemether versus artesunate

In adults, artemether performs worse than artesunate in terms of mortality (moderate-certainty evidence), but no trials have been conducted in young children.

How up to date is this review?

The review authors searched for studies up to 7 September 2018.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. 'Summary of findings' table 1

Artemether compared with quinine for treating children with severe malaria

Patient or population: children with severe malaria
Settings: malaria-endemic countries
Intervention: intramuscular artemether
Comparison: intravenous or intramuscular quinine

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Risk with quinine	Risk with artemether				
Death	**151 per 1000**	**147 per 1000** (116 to 183)	**RR 0.97** (0.77 to 1.21)	1659 (13 trials)	⊕⊕⊕⊖ MODERATE[a,b,c,d] Due to imprecision	Artemether probably makes little or no difference to death compared to quinine.
Coma resolution time	The mean coma resolution time ranged across control groups from **17.4 to 42.4 hours**	The mean coma resolution time in the intervention groups was **5.45 hours shorter** (7.90 to 3.00 shorter)	-	358 (6 trials)	⊕⊕⊖⊖ LOW[c,e,f,g] Due to risk of bias	Artemether may reduce coma resolution time compared to quinine.
Neurological sequelae at discharge	**220 per 1000**	**185 per 1000** (145 to 235)	**RR 0.84** (0.66 to 1.07)	968 (7 trials)	⊕⊕⊖⊖ LOW[a,b,c,h] Due to imprecision	Artemether may lead to fewer episodes of neurological sequelae. However, the effects of artemether vary and it is possible that artemether may lead to more neurological sequelae
Parasite clearance time	The mean parasite clearance time ranged across control groups from **22.4 to 61.25 hours**	The mean parasite clearance time in the intervention groups was **9.03 hours shorter** (11.43 to 6.63 shorter)	-	420 (7 trials)	⊕⊕⊕⊖ MODERATE[a,c,g,i] Due to inconsistency	Artemether probably reduces parasite clearance time compared to quinine.
Fever clearance time	The mean fever clearance time ranged across control groups from **18 to 61.25 hours**	The mean fever clearance time in the intervention groups was **3.73 shorter** (6.55 to 0.92 shorter)	-	457 (8 trials)	⊕⊕⊖⊖ LOW[c,j,k,l]	Artemether may reduce fever clearance time compared to quinine.

				Due to risk of bias and inconsistency	

*The **assumed risk** is the median control group risk across studies. 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).
Abbreviations: CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]No serious risk of bias: trials were variable in their risk of bias, but exclusion of the trials at high or unclear risk of selection bias did not change this result.
[b]No serious inconsistency: none of the individual trials found statistically significant effects, and there was no statistical heterogeneity between trials.
[c]No serious indirectness: trials were from West Africa, East Africa, Central Africa and one from India. All were in children with severe malaria (aged under 15 years), and most compared the standard dose of intramuscular artemether with the WHO recommended dose of intravenous quinine.
[d]Downgraded by 1 for serious imprecision: these trials, and the overall meta-analysis are underpowered to detect a difference or to prove equivalence.
[e]Downgraded by 2 for serious risk of bias: four of the six trials were at unclear risk of selection bias. When these four trials are excluded the result becomes non-significant.
[f]No serious inconsistency: statistically significant differences were only seen in two of the six trials. However, statistical heterogeneity between trials was low and the overall meta-analysis is statistically significant.
[g]No serious imprecision: the result is statistically significant and the overall meta-analysis is adequately powered to detect this effect.
[h]Downgraded by 2 for very serious imprecision: these trials, and the overall meta-analysis are underpowered to detect a difference or to prove equivalence. The 95% CI is very wide and includes clinically important differences and no effect.
[i]Downgraded by 1 for serious inconsistency: the mean difference in parasite clearance time ranged from a two hour increase with artemether to a 15 hour decrease.
[j]Downgraded by 1 for serious risk of bias: four of the seven trials were at unclear risk of selection bias. When these four trials are excluded the result becomes non-significant.
[k]Downgraded by 1 for serious inconsistency: the mean difference in fever clearance time ranged from a 25-hour increase with artemether to an 18-hour decrease.
[l]No serious imprecision: the overall meta-analysis is powered to detect this effect. The result is statistically significant but may not be clinically important.

Summary of findings 2. 'Summary of findings' table 2

Artemether compared with quinine for treating adults with severe malaria

Patient or population: adults with severe malaria
Settings: malaria-endemic countries
Intervention: intramuscular artemether
Comparison: intravenous or intramuscular quinine

Outcomes	Illustrative comparative risks* (95% CI)	Relative effect (95% CI)	Number of participants	Certainty of the evidence	Comments

	Risk with quinine	Risk with artemether		(trials)	(GRADE)	
Death	**208 per 1000**	**123 per 1000** (87 to 173)	**RR 0.59** (0.42 to 0.83)	716 (4 trials)	⊕⊕⊕⊖ MODERATE[a,b,c,d] Due to imprecision	Artemether probably reduces the risk of death compared to quinine.
Coma resolution time	-	-	Not pooled. Little difference.	657 (2 trials)	⊕⊕⊖⊖ LOW[a,e,f,g] Due to inconsistency and imprecision	Artemether may make little or no difference to coma resolution time compared to quinine.
Neurological sequelae at discharge	**4 per 1000**	**12 per 1000** (1 to 111)	**RR 2.92** (0.31 to 27.86)	560 (1 trial)	⊕⊕⊖⊖ LOW[g,h] Due to imprecision	Artemether may increase the risk of neurological sequelae compared to quinine. However, the effects vary and it is possible artemether decreases neurological sequelae.
Parasite clearance time	-	-	Not pooled. Little difference apparent.	716 (4 trials)	⊕⊕⊕⊖ MODERATE[a,c,f,i] Due to imprecision	Artemether probably makes no difference to parasite clearance time compared to quinine.
Fever clearance time	-	-	Not pooled. Little difference apparent.	716 (4 trials)	⊕⊕⊖⊖ LOW[a,c,f,j] Due to inconsistency and imprecision	Artemether may make little or no difference to parasite clearance time compared to quinine.

*The **assumed risk** is the median control group risk across studies. 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).
Abbreviations: **CI:** confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]No serious risk of bias: trials are generally well conducted and at low risk of bias.
[b]No serious inconsistency: statistically significant differences were only seen in one of the four trials. However, statistical heterogeneity between trials was low and the overall meta-analysis is statistically significant.

[c]No serious indirectness: all four trials compared intramuscular artemether with intravenous quinine in adults; two trials from Thailand, one each from Vietnam and Papua New Guinea
[d]Downgraded by 1 for serious imprecision: these trials, and the overall meta-analysis are very underpowered to detect a difference in mortality or to prove equivalence.
[e]Hien 1996 and Karbwang 1995 reported median coma time for artemether versus quinine (Hien 1996: 66 versus 48, P = 0.003; Karbwang 1995: 48 versus 48). Downgraded by 1 for inconsistency: one trial found a shorter median coma resolution time with quinine, and one trial found no difference.
[f]Downgraded by 1 for imprecision: the data could not be pooled.
[g]No serious risk of bias: this single trial was at low risk of bias.
[h]Downgraded by 2 for very serious imprecision: neurological sequelae in adults were uncommon. This trial is underpowered to detect or exclude clinically important differences.
[i]Two trials found no significant difference between parasite clearance time for artemether versus quinine (Karbwang 1992: mean 63.6 versus 61.6, P = 0.85; and Seaton 1998: median 48 versus 52, P = 0.381). Two other trials reported significantly shorter median parasite clearance times for artemether versus quinine (Hien 1996: 72 versus 90, P < 0.001 and Karbwang 1995: 54 versus 78, P = 0.007). No serious inconsistency: The two largest trials both found shorter median clearance times with artemether.
[j]Three trials reported median fever clearance time for artemether versus quinine (127 versus 90, P < 0.001; 32 versus 48, P = 0.034 and 79 versus 84, no significant difference) (Hien 1996, Seaton 1998 and Karbwang 1995). Karbwang 1992 reported mean fever clearance time and found a statistically significant reduction of about 30 hours with artemether. Downgraded by 1 for inconsistency: One trial found a shorter median fever clearance time with quinine, and two trials found a shorter time with artemether.

Summary of findings 3. 'Summary of findings' table 3

Artemether compared with artesunate for treating adults with severe malaria

Patient or population: adults with severe malaria
Settings: malaria-endemic countries
Intervention: intramuscular artemether
Comparison: intravenous or intramuscular artesunate

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Risk with artesunate	Risk with artemether				
Death	**87 per 1000**	**156 per 1000** (95 to 258)	**RR 1.80** (1.09 to 2.97)	494 (2 trials)	⊕⊕⊕⊖ MODERATE[a,b,c,d] Due to imprecision	Artemether probably increases the risk of death compared to artesunate.
Coma resolution time	-	-	Not pooled. No significant difference	494 (2 trials)	⊕⊕⊕⊖ MODERATE[a,c,e,f] Due to imprecision	Artemether probably makes little or no difference to coma resolution time compared to artesunate.
Neurological sequelae at discharge	-	-	-	0 (0 trials)	-	None of the studies looked at neurological sequelae in adults.

Parasite clearance time	-	-	Not pooled. No significant difference	494 (2 trials)	⊕⊕⊕⊖ MODERATE[a,c,f,g] Due to imprecision	Artemether probably makes little or no difference to parasite clearance time compared to artesunate.
Fever clearance time	-	-	Not pooled. No significant difference	494 (2 trials)	⊕⊕⊕⊖ MODERATE[a,c,f,h] Due to imprecision	Artemether probably makes little or no difference to fever clearance time compared to artesunate.

*The **assumed risk** is the median control group risk across studies. 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).
Abbreviations: **CI:** confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]No serious risk of bias: trials were generally well conducted and at low risk of bias.
[b]No serious inconsistency: there is no statistical heterogeneity.
[c]No serious indirectness: the two trials were conducted in Vietnam and Thailand and both compared intramuscular artemether with intravenous artesunate in adults.
[d]Downgraded by 1 for serious imprecision: these trials, and the overall meta-analysis are very underpowered to detect a difference in mortality or to prove equivalence.
[e]Phu 2010 and Vinh 1997 reported median coma resolution time for artemether versus artesunate (Phu 2010: 72 versus 60, P = 0.11; Vinh 1997: 47 (artemether) versus 30 (artesunate IM) versus 24 (artesunate IV). No serious inconsistency: Both trials suggest an advantage with artesunate although not statistically significant.
[f]Downgraded by 1 for serious imprecision: we could not pool these data as median data were presented for both trials.
[g]Phu 2010 and Vinh 1997 reported median parasite clearance time (Phu 2010: 72 versus 72, P = 0.97; Vinh 1997: 30 (artemether) versus 24 (artesunate IM) versus 24 (artesunate IV). No serious inconsistency: Both trials found no difference between treatments.
[h]Phu 2010 and Vinh 1997 reported median fever clearance time (Phu 2010: 108 versus 108, P = 0.27; Vinh 1997: 48 (artemether) versus 36 (artesunate IM) versus 30 (artesunate IV). No serious inconsistency: Both trials found no statistically significant difference between artemether and artesunate.

BACKGROUND

Description of the condition

Malaria is a febrile illness caused by *Plasmodium* parasites, which are transmitted to humans through the bite of infected female anopheline mosquitoes. Five species of *Plasmodium* cause this disease in humans, of which *Plasmodium falciparum* is the most common worldwide, and is responsible for almost all of the severe disease and deaths (WHO 2000; WHO 2008).

Severe malaria is diagnosed on the basis of a positive blood slide or antigen test for malaria, plus the presence of clinical or laboratory features of vital organ dysfunction. These include impaired consciousness, coma, convulsions, respiratory distress, shock (systolic blood pressure < 70 mmHg in adults, < 50 mmHg in children), jaundice, haemoglobinuria, hypoglycaemia, severe metabolic acidosis, and anaemia (WHO 2010). Cerebral malaria is one form of severe malaria, where the patient has some impairment of consciousness and cognition. This can vary from slight disorientation through to deep coma where the patient is unconscious and unrousable. Even with correct treatment cerebral malaria can cause a mortality rate of up to 20%, and a small proportion of people that survive infection can have persistent neurological sequelae (Jaffar 1997).

People living in malaria-endemic regions can develop a naturally acquired immunity to malaria through repeated exposure to the parasite over five to 10 years (Doolan 2009). This partial immunity is protective against the most severe forms of the disease, and as a consequence, in high transmission settings mortality from severe malaria is highest in young children and decreases with increasing age (WHO 2010).

Parenteral quinine used to be the standard treatment for severe malaria despite sporadic observations of resistance. Clinical and in vitro resistance to quinine has been observed in Southeast Asia, but not consistently in Africa (Wongsrichanalai 2002; Cui 2015). Artemisinin derivatives have become the keystone of malaria treatment and control (WHO 2015). They are effective at killing all asexual blood stages of *P falciparum* parasites, as well as disrupting sexual development, resulting in rapid clinical and parasitological cure and a reduction in malaria transmission rates (Tyagi 2018).

Evidence of resistance to artemisinin combination therapy has been reported for about a decade, initially in the Thai-Cambodia border region and now increasingly in Southeast Asia. Resistance has been characterized by delayed parasite clearance time in patients with uncomplicated and severe malaria (Ashley 2014; Hawkes 2014; Menard 2016)

The World Health Organization (WHO) strongly recommends parenteral artesunate as the drug of choice and artemether in preference to quinine for the treatment of severe malaria in adults and children, followed by a complete course of an effective artemisinin-based combination therapy (ACT) as soon as the patient can take oral medications (WHO 2015). The WHO based their recommendation of parenteral artesunate on evidence from two large multi-centre clinical trials that demonstrated the superiority of intravenous artesunate over the standard treatment, quinine (Dondorp 2005; Dondorp 2010). A Cochrane Review of available data concluded that treating people that have severe malaria with artesunate instead of quinine would reduce the risk of death by 39% in adults and 24% in children (Sinclair 2012).

Description of the intervention

Artesunate is only one of a number of antimalarials derived from artemisinin, which is extracted from the herb *Artemesia annua* and is the active ingredient in a Chinese herbal remedy for fever. Once ingested or injected, artemisinin derivatives undergo conversion to dihydroartemisinin, the active metabolite, which has a broad spectrum of activity against the blood stage asexual *Plasmodium* parasites (ter Kuile 1993; Navaratnam 2000). Artemisinin derivatives clear parasites from the peripheral blood quicker than other antimalarials, but only artesunate has been shown to impact mortality.

Unlike artesunate, artemether is poorly soluble in water and the parenteral formulation is only available as a pre-mixed oil-based solution for intramuscular injection (80 mg/mL for use in adults and 40 mg/mL for children). The standard dose is 3.2 mg/kg on admission followed by 1.6 mg/kg once daily until oral therapy is tolerated (WHO 2010). Peak plasma concentrations typically occur around six hours after intramuscular injection, but in severely ill children with poor peripheral perfusion, absorption can be highly erratic (Karbwang 1997; Murphy 1997; Mithwani 2004).

Conversely, artesunate is supplied as a dry powder for mixing with sodium bicarbonate prior to either intravenous or intramuscular injection (WHO 2010). The absorption of artesunate is more reliable compared with artemether, with peak plasma concentrations following intramuscular injection occurring at around one hour (Illet 2002; Nealon 2002; Hien 2004). These more favourable pharmacokinetic properties of artesunate moved research attention away from artemether; and artesunate now has a stronger evidence base and is the preferred therapy (WHO 2010; Sinclair 2012).

How the intervention might work

Deaths from severe malaria often occur between one and two days following hospital admission. Consequently, to be effective, antimalarial drugs need to achieve rapid therapeutic blood concentrations following administration. Artemisinins, especially artesunate and artemether, result in more rapid parasite clearance (being active on gametocytes (immature forms) and are safer and simpler to administer (ter Kuile 1993; Adjuik 2004). Artemether is a potent and rapidly acting blood schizonticide which is highly efficacious in treating complicated *P falciparum* malaria including cerebral malaria. The drug is given by intramuscular injection in the gluteal muscle. Its quick onset of action and high efficacy in bringing down the parasite load are the properties which make this drug a suitable therapeutic option against *P falciparum* infection. Artemether may be an excellent alternative for treatment of severe malaria and cerebral malaria in rural areas where facilities for intravenous administration may not yet be optimal and might increase the risk of infection.

Why it is important to do this review

A number of African countries incorporated intramuscular artemether into their national guidelines prior to the WHO recommendation for artesunate. Systematic reviews concluded that intramuscular artemisinin derivatives (including both artesunate and artemether) were not inferior to quinine in

preventing deaths from malaria, but were safer and easier to administer (McIntosh 2000; AQMSG 2001; Kyu 2009).

Following the WHO recommendation for artesunate as the preferred treatment for severe malaria, there is a need to re-evaluate the role of intramuscular artemether in the management of severe malaria in adults and children.

OBJECTIVES

To assess the efficacy and safety of intramuscular artemether versus any other parenteral medication in the treatment of severe malaria in adults and children.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs).

Types of participants

Adults and children (< 15 years of age) with severe malaria.

Types of interventions

Intervention

- Intramuscular artemether

Control

- Any other parenteral medication for the treatment of severe malaria

Types of outcome measures

Primary outcomes

- Death from any cause

Secondary outcomes

- Coma resolution time
- Neurological sequelae (such as blindness, deafness, hemiplegia and others)
- Time to hospital discharge
- Parasite clearance time
- Fever clearance time
- Need for blood transfusion
- Severe anaemia
- Adverse events (including hypoglycaemia, tinnitus, nausea, vomiting, haematological and cardiac-related adverse events)

Search methods for identification of studies

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

Electronic searches

Databases

We examined the following databases up to 7 September 2018 using the search terms detailed in Appendix 1: Cochrane Infectious Diseases Group Specialized Register; Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library; MEDLINE (PubMed); Embase, LILACS and ISI Web of Science. We also searched the WHO clinical trial registry platform, ClinicalTrials.gov and the metaRegister of Controlled Trials (mRCT) up to 7 September 2018 for ongoing trials using 'artemether', 'severe malaria', 'complicated malaria', 'artesunate', 'arteether', and 'child*' as search terms.

Searching other resources

Conference proceedings

We searched relevant proceedings of the following meetings for trial information: Multilateral Initiative on Malaria (MIM) Pan-African Malaria Conference; European Congress on Tropical Medicine and International Health; and American Society of Tropical Medicine and Hygiene (7 September 2018).

Researchers

We contacted researchers working in the field and the WHO for 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

Two review authors screened the abstract of each title obtained from the search for potentially relevant studies. We retrieved the corresponding full articles of these identified studies, and two review authors assessed inclusion by using an eligibility form. We independently screened each search result, assessed each article, and resolved any discrepancies between eligibility results through discussion. Also, we listed the excluded studies and the reasons for their exclusion.

Data extraction and management

Two review authors independently extracted data from each study report onto a pre-designed data extraction form. We discussed any discrepancies with a third review author. We contacted the corresponding publication author in the case of unclear information or missing data. For each outcome we aimed to extract the number of participants randomized 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 baseline proportions of participants in the intervention and control arms in whom antipyretics were administered varied, we only included trials that reported fever clearance time and provided additional information about antipyretics use at baseline for participants in both intervention and control arm to avoid confounding in the summary estimate for fever clearance. Where there was significant difference between antipyretic use at baseline in intervention and control arms, we only reported fever clearance

time in a table. We defined cure rates in this review as time from first dose to first negative parasite reading for two consecutive readings.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias of each included study using Cochrane's 'Risk of bias' tool (Higgins 2011). We followed the guidance for making judgements on the risk of bias in six domains: sequence generation; allocation concealment; blinding (of participants, personnel and outcome assessors); incomplete outcome data; selective outcome reporting; and other risk of bias (such as the trial stopped early). We categorized these judgements as low risk of bias, high risk of bias, or unclear risk of bias.

Measures of treatment effect

We calculated results using risk ratios for dichotomous data, and mean difference values for continuous data, and have presented these effect estimates with 95% confidence intervals (CIs). We treated time-to-event outcomes as continuous data and accordingly mean difference calculated from mean time in intervention versus control groups. Where the data were not normally distributed and medians were reported, we excluded them from the meta-analysis and reported them in additional tables.

Unit of analysis issues

For multiple arm trials, we combined all relevant experimental intervention groups of the trial into a single group, and also combined all relevant control intervention groups into a single control group. For dichotomous outcomes, both the sample sizes and the numbers of people with events were added across groups. For continuous outcomes, we combined means and standard deviations using methods described in the *Cochrane Handbook for Systematic Reviews of Interventions*.

Dealing with missing data

We analysed data according to the intention-to-treat principle (all randomized participants should be analysed in the groups to which they were originally assigned). If there were discrepancies between the number randomized and the number analysed, we calculated the percentage loss to follow-up for each treatment group and reported this information.

However, if for some trials it was unclear whether there was loss to follow-up, we entered the number analysed into Review Manager 2014 whenever these figures were available. By attempting to carry out a complete case analysis, we avoided making assumptions about the outcomes of participants lost to follow-up. Where possible, we contacted authors for missing data.

Assessment of heterogeneity

We looked for statistical heterogeneity by inspecting the forest plots for overlapping CIs, applying the Chi^2 test ($P < 0.10$ considered statistically significant) and the I^2 statistic (I^2 value < 50% used to denote moderate levels of heterogeneity).

Assessment of reporting biases

Since asymmetry of funnel plots may result from publication bias, heterogeneity, or poor methodological quality (Sterne 2011), we planned to examine funnel plots using Review Manager 5 (RevMan 5) but found an insufficient number of trials to do this (Review Manager 2014).

Data synthesis

We analysed the data using RevMan 5 (Review Manager 2014). In the first instance, we applied a fixed-effect meta-analysis. However, if we detected moderate heterogeneity but still considered it appropriate to combine the trials, we then used a random-effects approach. Where heterogeneity was very high such that meta-analysis was not appropriate, we displayed the results in forest plots or tables but did not combine the results. Where data were only presented as medians and ranges, we have presented the results in tables.

For both dichotomous and continuous outcomes, optimal information size was calculated. The optimal information size (OIS) can be defined as the minimum amount of information needed in a meta-analysis to obtain reliable conclusions about an intervention. The optimal information size calculations were performed using a power calculator available at www.sealedenvelope.com/power. All calculations were performed for a power of 80% and an α error of 0.05 and the proportion in the control groups were taken from the median control group risk across trials. Also, a maximum 3% risk difference was chosen to represent equivalence (Table 1). For the continuous outcomes (coma resolution time, parasite clearance time, and fever clearance time) a six-hour time difference was chosen to represent a clinically important benefit (Table 2).

Certainty of the evidence

We assessed the certainty of the evidence following the GRADE approach and defined 'certainty' as an assessment of our confidence in the estimates of effect (Guyatt 2008). We rated each outcome as follows.

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect.
- Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

As all the included studies were RCTs the evidence for each outcome started as high certainty, but we would downgrade if there were valid reasons to do so within the following five categories: risk of bias; imprecision; inconsistency; indirectness; and publication bias (Balshem 2011). We summarized the certainty of the evidence for each outcome in a 'Summary of findings' table.

Subgroup analysis and investigation of heterogeneity

We grouped the analysis and results by children and adults. We reported results by whether the studies were carried out in Africa or in Asia. We examined whether loading dose or quinine influenced outcomes.

Sensitivity analysis

We conducted a sensitivity analysis to investigate the robustness of the results to the risk of bias components by including only trials

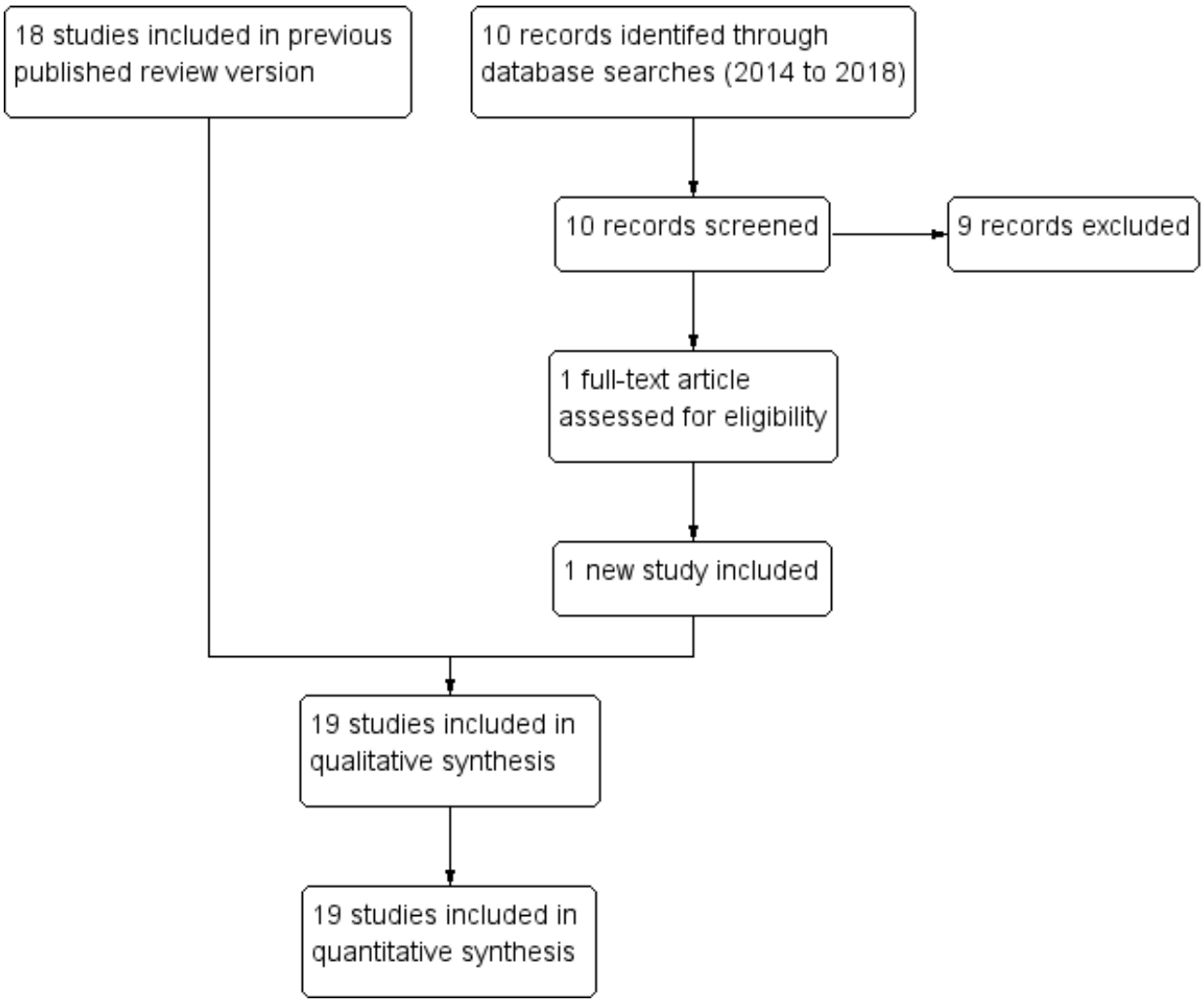
that concealed the allocation and had low incomplete outcome data (< 10%).

RESULTS

Description of studies

See the Characteristics of included studies section for details of the included trials.

Figure 1. PRISMA diagram.



In the previous version of this Cochrane Review, we identified 77 titles and abstracts from the electronic search of databases and 2 additional articles after contacting researchers and screening reference lists (Esu 2014). After we removed duplicates, 77 records remained. Of these, we obtained 35 potentially eligible articles. We identified 18 studies that fulfilled the selection criteria and reported on outcomes of interest.

For this review update, we identified 10 additional titles and abstracts from electronic searches of databases. There were 87 articles after we removed duplicates. Of these, there was only one potentially eligible article. This new study met the inclusion criteria (Bobossi-Serengbe 2015).

Results of the search

We conducted the literature search up to 7 September 2018 and identified 87 references (see Figure 1).

Included studies

In the previous version of this review, we included 18 RCTs, enrolling 2662 participants. Twelve trials enrolled children only (1447 participants aged between six months and 15 years), and six trials enrolled older children and adults (1215 participants aged between 13 and 79 years).

In this review update, we included one additional RCT enrolling 212 participants (children aged between six and 59 months) (Bobossi-Serengbe 2015).

Location

The trials in children were primarily conducted in Africa: Nigeria (five trials), Sudan (two trials), Central African Republic (one trial), the Gambia (one trial), Kenya (one trial), Malawi (one trial), and Mali (one trial); with only one trial from Asia (India).

Five adult trials were conducted in Asia: Vietnam (three trials), and Thailand (two trials); and one in Oceania; Papua New Guinea (one trial). We have attached a three-letter country code to each trial ID to aid forest plot interpretation.

Interventions

All 13 trials in children compared artemether with quinine. In most trials, artemether was given by intramuscular injection, with a loading dose of 3.2 mg/kg body weight followed by maintenance doses of 1.6 mg/kg for three to six days (see Table 3 for details). Only three trials followed this with oral therapy once tolerated (Murphy 1996; van Hensbroek 1996; Taylor 1998). For quinine, nine trials administered the WHO recommended loading dose of 20 mg/kg of intravenous or intramuscular quinine followed by a maintenance dose of 10 mg/kg. However, van Hensbroek 1996 administered the maintenance dose at 12-hourly intervals instead of eight-hour intervals (see Table 3).

In adults, four trials compared artemether with quinine (Karbwang 1992; Karbwang 1995; Hien 1996; Seaton 1998); and two trials compared artemether with artesunate (Vinh 1997; Phu 2010). Artemether was given intramuscularly over three to seven days with slight variations in dosing (see Table 4 and Table 5); and all four trials administered quinine at the WHO-recommended loading dose.

Supportive care

Twelve trials in children reported measurement of blood glucose on admission, but only nine trials reported any subsequent active monitoring for hypoglycaemia.

Only one trial in adults reported measuring blood glucose on admission and monitored hypoglycaemia up to 24 hours after admission (Hien 1996).

Outcome measures

Eighteen trials reported death, a measure of coma resolution, fever clearance and parasite clearance as outcomes. Eleven trials reported neurological sequelae at discharge. Only two trials reported duration of hospital stay (Aguwa 2010; Phu 2010); and two trials reported on the number of children requiring blood transfusions (Hien 1996; Olumese 1999). Twelve trials reported on adverse events including episodes of hypoglycaemia (Karbwang 1992; Walker 1993; Karbwang 1995; Hien 1996; Murphy 1996; van Hensbroek 1996; Seaton 1998; Adam 2002; Huda 2003; Minta 2005; Phu 2010; Bobossi-Serengbe 2015). We have listed the outcome definitions used in the included trials in Table 6.

Excluded studies

We excluded 14 trials and listed the reasons for their exclusion in the 'Characteristics of excluded studies' section.

Risk of bias in included studies

See Figure 2 for a summary of the 'Risk of bias' assessments. We have presented further details in the Characteristics of included studies tables.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included trial.

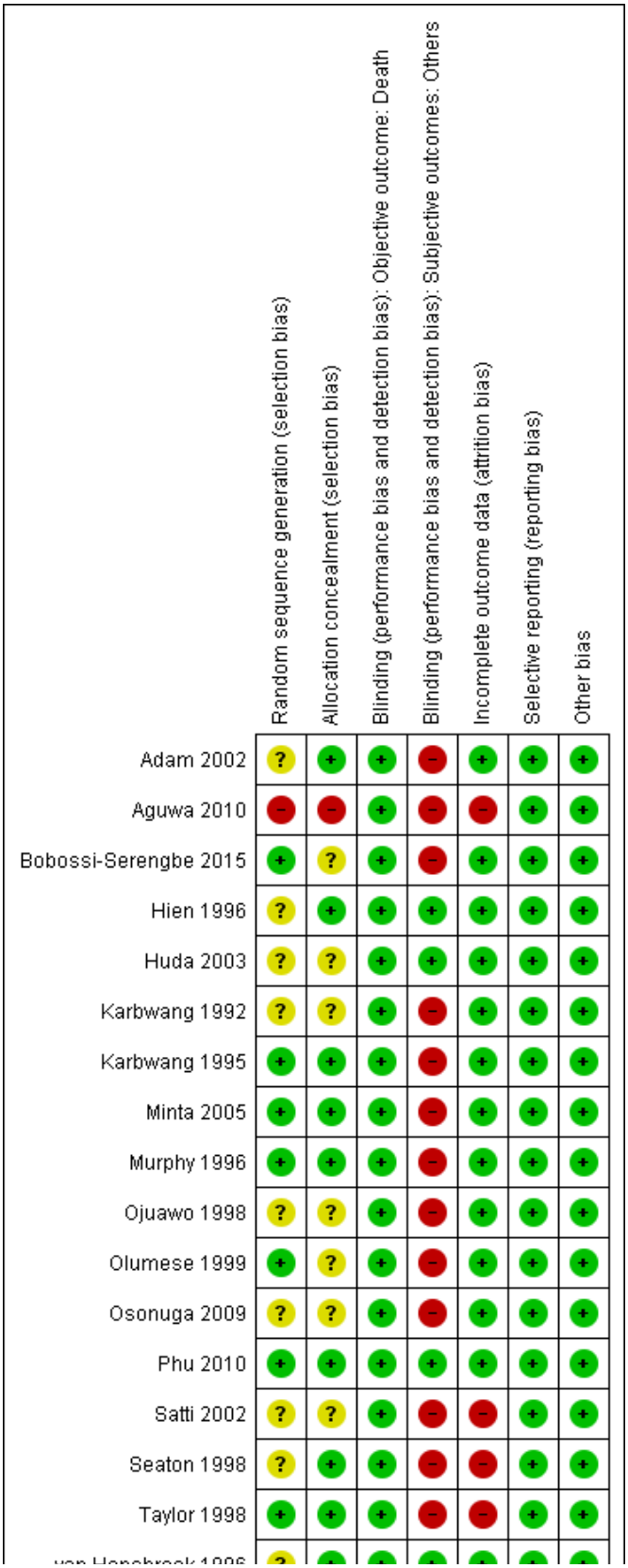
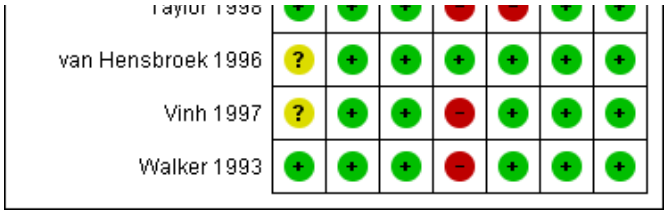


Figure 2. (Continued)



Allocation

Eight trials were at low risk of bias regarding the generation of allocation sequence while one trial was at high risk of bias (Aguwa 2010). Ten trials were at unclear risk of bias because review authors did not provide enough information to permit us to make a judgement.

Eleven trials were at low risk of bias regarding allocation concealment and the remaining trials provided insufficient information to make a judgement.

Blinding

In all trials except Hien 1996 and Phu 2010, investigators and participants were aware of treatment allocation. Participants were also not blind to the intervention as two different routes (intramuscular (artemether) and intravenous (quinine)) were used to administer the interventions. Blinding was unlikely to affect the assessment of the outcome 'death' in all trials. In one trial, microscopists were blinded to the intervention and clinical status of the patients (Huda 2003). The other subjective outcomes were thus at high risk of bias in all open included trials or at unclear risk of bias where trials did not provide information.

Incomplete outcome data

Fifteen trials reported no losses to follow-up. The remaining four trials reported over 10% attrition in either one or both trial arms (Seaton 1998; Taylor 1998; Satti 2002; Aguwa 2010). Two trials used the 'per protocol' number of participants as a denominator in the analysis (Seaton 1998; Taylor 1998). The other two trials used the number of participants randomized as the denominator in the analysis.

Selective reporting

We did not detect any evidence of selective outcome reporting based on comparison between the Methods section and results of the included studies.

Other potential sources of bias

We did not identify any other sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison** 'Summary of findings' table 1; **Summary of findings 2** 'Summary of findings' table 2; **Summary of findings 3** 'Summary of findings' table 3

Artemether versus quinine

Children

Twelve trials were conducted in children; 11 in Africa and one in Asia. All used loading doses of quinine.

Death

There was no overall difference in all-cause mortality between intramuscular artemether and intravenous quinine (RR 0.97, 95% CI 0.77 TO 1.21; 1659 participants, 13 trials, I^2 = 0%, Analysis 1.1). However, these 13 trials were too small to detect or exclude clinically important differences, and the overall meta-analysis remains significantly underpowered to prove equivalence (see Table 1 and Table 2). The current total sample size has adequate power to exclude effects as large as seven extra deaths per 100 patients. Adam 2002 reported death within 24 hours. There was no difference between intramuscular artemether and intravenous quinine (RR 0.35, 95% CI 0.02 to 8.10; 41 participants, 1 trial, Analysis 1.2).

Coma resolution time

The mean coma resolution time was about five hours shorter with artemether (26 hours) compared with quinine (30.55 hours) (MD −5.45 hours, 95% CI −7.90 to −3.00; 358 participants, 6 trials, I^2 = 0%, Analysis 1.3). The results were not statistically significant when a sensitivity analysis excluding studies with unclear allocation concealment was done (MD −5.53 hours, 95% CI −12.39 to 1.33; 95 participants, 2 trials, Analysis 3.3). In addition, three trials reported median time to coma resolution (see Table 7). Two trials found no overall difference (Murphy 1996; Taylor 1998); and one trial found the median time to be longer with artemether (26 hours versus 20 hours, P = 0.046, van Hensbroek 1996). Two other trials reported mean coma resolution time as mean (SD) but the data were not normally distributed and so we have reported this in an additional table (Table 7) (Minta 2005; Osonuga 2009).

Neurological sequelae

There was no statistically significant difference in the risk of neurological sequelae at hospital discharge between artemether (185 per 1000) and quinine (220 per 1000) (968 participants, 7 trials, I^2 = 1%, Analysis 1.4). Again these trials were too small to enable us to confidently detect or exclude what may be clinically important differences between treatments (see Table 1). The overall meta-analysis is adequately powered to exclude effects larger than eight additional sequelae per 100 patients.

Three trials continued to monitor patients with neurological sequelae after hospital discharge. Satti 2002 found no difference at day seven, Taylor 1998 found most sequelae had resolved and van Hensbroek 1996 found no difference at day 28 (Analysis 1.5).

Parasite clearance time

The mean parasite clearance time in children was approximately nine hours shorter with artemether (MD −9.03 hours, 95% CI −11.43 to −6.63; 420 participants, I^2 = 62%, 7 trials, Analysis 1.6). The results were similar after sensitivity analysis which excluded trials at

unclear or high risk of selection bias. The mean parasite clearance times for artemether and quinine were 36.25 and 43.18 hours respectively.

Three additional trials reported median parasite clearance time and all showed an overall benefit with artemether (see Table 7). Two trials expressed parasite clearance as the proportion of patients with parasite clearance at 72 hours and at seven days, with no overall differences between groups (see Analysis 1.7) (Ojuawo 1998; Bobossi-Serengbe 2015). The inconsistency may be due to trials differing with respect to the frequency with which they repeated malaria blood smears (see Table 6).

Fever clearance time

Eight trials reported mean fever clearance time with a statistically significant reduction of about three hours with artemether (MD −3.73 hours, 95% CI −6.55 to −0.92; 457 participants, 8 trials, I^2 = 83%, Analysis 1.8). The mean fever clearance times for artemether and quinine were 43.69 and 46.26 hours respectively. However, only two of the individual trials showed an overall difference between the groups. Three trials in children reported median fever clearance time and two trials found no overall difference between the two groups (see Table 7). There was high inconsistency due to opposing directions of effect. Also, the definitions of fever varied across the included trials. Six trials used a cut-off of body temperature less than 37.5 °C from initiation of treatment to define fever clearance (see Table 6).

Need for blood transfusion

One trial, Olumese 1999, reported on the number of patients requiring blood transfusions for severe malarial anaemia in both artemether and quinine arms (RR 1.27, 95% CI 0.62 to 2.59; 103 participants, 1 trial, I^2 = 0%, Analysis 1.9). No statistically significant difference was observed between both arms.

Adverse effects

Eight trials reported on the frequency of adverse events (Walker 1993; Murphy 1996; van Hensbroek 1996; Olumese 1999; Adam 2002; Huda 2003; Minta 2005; Bobossi-Serengbe 2015). Olumese 1999 and Huda 2003 reported no adverse events had occurred during the trial duration (see Table 8). One trial reported the absence of adverse events in the artemether arm (Minta 2005). No trial reported discontinuation of medication.

Only two trials reported episodes of hypoglycaemia (Analysis 1.10). Two trials reported the proportion of participants with QT prolongation (Minta 2005; Murphy 1996). There was significantly higher proportion of QT prolongation in the artemether arm (RR 3.10, 95% CI 1.33 to 7.19; 229 participants, 2 trials, I^2 = 52%, Analysis 1.11). Both trials varied in terms of the populations studied. Minta 2005 had fever (38 °C or more) as part of the inclusion criteria. In addition, all participants received a single dose of oral SP in addition to either IM artemether or IV quinine. Other adverse effects reported were local skin reaction at the injection site, abscess, urticarial rash, pruritus, supraventricular tachycardia, urinary tract infection, and haemoglobinuria. However, these trials were insufficiently powered to detect differences in adverse events. The trials had similar definitions of adverse events (included only adverse effects that could not be attributable to malaria).

Time to hospital discharge

None of the included trials reported time to discharge. One trial reported the proportion of patients that spent less than one week in hospital and found no significant difference between groups (see Table 7).

Adults

Four trials were conducted in adults: three in Asia and one in Oceania. All used loading doses of quinine.

Death

Artemether resulted in fewer deaths compared with quinine (RR 0.59, 95% CI 0.42 to 0.83; 716 participants, 4 trials, I^2 = 36%, Analysis 1.1) from trials conducted mostly in Asia.

Coma resolution time

Three trials reported a measure of coma resolution time. Hien 1996 reported median coma resolution time, which was shorter in the quinine arm. Karbwang 1995 found both arms to be comparable in terms of coma resolution time. The third trial, Karbwang 1992, reported mean coma resolution time but the data were incompletely reported (see Table 9).

Neurological sequelae

Only one trial reported neurological sequelae at discharge (Hien 1996). Four neurological sequelae were reported with no difference between groups (560 participants, 1 trial, Analysis 1.4).

Parasite clearance time

One trial reported mean parasite clearance time but showed no overall difference between artemether and quinine (26 participants, one trial, Analysis 1.6). Three other trials reported median parasite clearance time. Two trials reported a significantly shorter time to clearance of parasites with artemether (Karbwang 1995; Hien 1996; see Table 7). Seaton 1998 found no significant difference between artemether and quinine with respect to parasite clearance time.

Trials differed with respect to the frequency with which they repeated malaria blood smears (see Table 6).

Fever clearance time

Four trials reported a measure of fever clearance time. Karbwang 1992 reported mean fever clearance time and found an overall reduction of about 30 hours with artemether (MD −29.7 hours, 95% CI −54.14 to −5.26; 26 participants, 1 trial, Analysis 1.8). The other three trials in adults reported median fever clearance time; and two reported a statistically significant reduction in fever clearance time in favour of quinine and artemether respectively (Hien 1996; Seaton 1998). Karbwang 1995 found both groups were comparable (see Table 9).

The definitions of fever varied across the included trials. Three trials used a cut-off of body temperature less than 37.5 °C from initiation of treatment to define fever clearance (see Table 6).

Need for blood transfusion

One trial reported on the number of patients requiring blood transfusions for severe malarial anaemia in both artemether and

quinine arms (Hien 1996). No overall difference was observed between both arms (560 participants, one trial, Analysis 1.9).

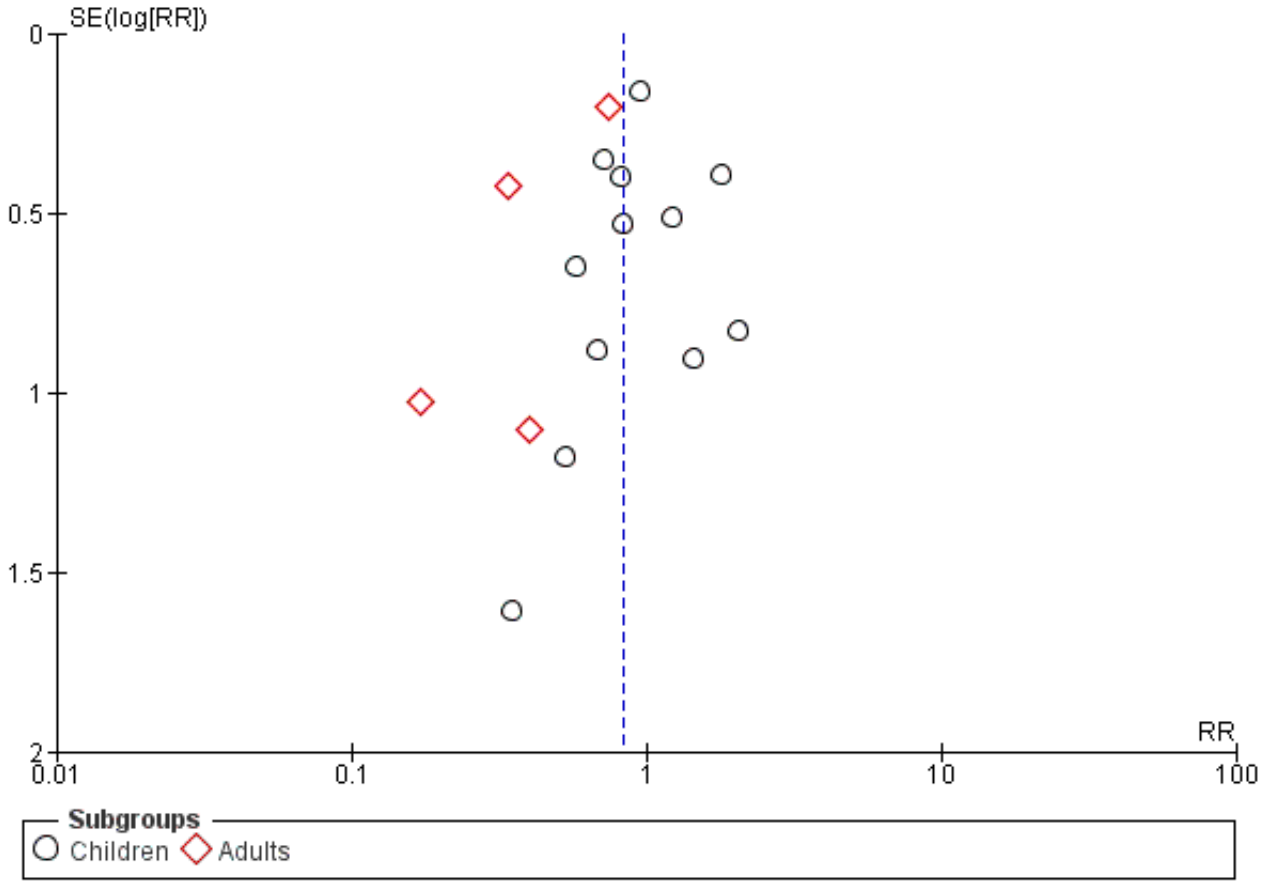
Adverse events

One trial reported episodes of hypoglycaemia (Analysis 1.10). Other adverse effects reported were abscess, induration at injection site, leg discomfort, chest infection and gastrointestinal bleeding. However, these trials were insufficiently powered to detect differences in adverse events. The trials had similar definitions of adverse events (included only adverse effects that could not be attributable to malaria).

Publication bias

We constructed a funnel plot for trials that reported death (Figure 3). Visual examination suggested the funnel plot is asymmetric due to the absence of smaller trials at the base. Asymmetry in the funnel plot could result from possible selection bias where smaller studies reporting greater treatment benefit for the experimental group were published (publication bias). The gap in the bottom corner of the graph suggests that smaller studies without statistically significant effects remain unpublished (Higgins 2011).

Figure 3. Funnel plot of comparison: 1 Artemether versus quinine, outcome: 1.1 Death.



Artemether versus artesunate

Adults

Two trials, both from Asia, were conducted in adults.

Death

Only two trials directly compared intramuscular artemether and intravenous artesunate. Overall, the risk of all-cause mortality was higher following treatment with artemether (RR 1.80, 95% CI 1.09 to 2.97; 494 participants, 2 trials, Analysis 2.1). However, both trials were too small to detect or exclude clinically important differences, and the overall meta-analysis remains significantly underpowered to prove superiority (see Table 1 and Table 2).

Coma resolution time

Two trials reported median coma resolution times. Both trials reported a shorter coma resolution time with artesunate. However, these differences were not statistically significant (Table 10).

Parasite clearance time

Two trials found no overall difference in median parasite clearance time (Vinh 1997; Phu 2010).

Fever clearance time

Phu 2010 found no statistically significant difference in median fever clearance time between intramuscular artemether and intravenous artesunate. The additional small trial found a benefit

in favour of artesunate although this was not statistically significant (Vinh 1997).

Need for blood transfusion

Phu 2010 found no difference between treatments with respect to the need for blood transfusion in adult severe malaria patients (370 participants, one trial, Analysis 2.2).

Adverse effects

Only Phu 2010 reported adverse events. Overall, the risk of hypoglycaemia was higher in adults treated with intramuscular artemether compared with artesunate (RR 1.70, 95% CI 0.40 to 7.24; 370 participants, 1 trial, Analysis 2.3).

DISCUSSION

We present the main results of the review alongside a GRADE appraisal of the certainty of evidence in the 'Summary of findings' tables (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3).

Summary of main results

We included 19 RCTs, enrolling 2874 children and adults with severe malaria. Twelve trials were conducted in Africa and seven trials were undertaken in Asia.

Artemether versus quinine

For children (trials mostly conducted in Africa), there is probably little or no difference in the risk of death between intramuscular artemether and quinine (moderate-certainty evidence). Artemether may shorten the coma recovery time by about five hours (low-certainty evidence), and makes little difference in the number of children with subsequent neurological sequelae (low-certainty evidence). Artemether probably shortens the parasite clearance time by about nine hours (moderate-certainty evidence), and may shorten the fever clearance time by about three hours (low-certainty evidence).

For older children (> 15 years) and adults in Asia, artemether probably reduces deaths compared with quinine (moderate-certainty evidence), but larger trials are required to have full confidence in this finding.

Artemether versus artesunate

Artemether and artesunate have only been compared in two trials in adults from Asia, and mortality is probably higher with intramuscular artemether (moderate-certainty evidence) but larger trials are required to have confidence in this finding.

Overall completeness and applicability of evidence

Although 16 trials directly compared artemether versus quinine, none were adequately powered to detect clinically important differences. The total number of participants included in these trials (2375 participants) remains far short of the 7429 participants included in trials of artesunate versus quinine (Sinclair 2012). The majority of data comparing artemether and quinine were from trials conducted in sub-Saharan Africa where artemether is most widely used.

The two trials directly comparing artemether and artesunate were conducted in adults in Asia, and the results are therefore poorly applicable to children in Africa.

Artemether is prone to erratic and partial absorption and takes longer to achieve peak plasma concentrations, as demonstrated in animal and human studies (Murphy 1997; Hien 2004; Mithwani 2004). These pharmacokinetic attributes make artemether that is injected intramuscularly less readily available in the human body and may explain the difference in outcomes between artesunate and intramuscular artemether we have observed in this review.

Certainty of the evidence

We assessed the certainty of the evidence using the GRADE approach and have presented it in three 'Summary of findings' tables (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3).

The evidence of equivalence between intramuscular artemether and intravenous quinine in children is of moderate certainty due to the small sample sizes of the included trials and the overall lack of power to fully exclude clinically important differences.

Similarly, we downgraded the certainty of the evidence for reductions in mortality in adults treated with artemether compared with quinine, and artesunate compared with artemether, to moderate certainty due to imprecision. Larger trials are needed to have full confidence in these effects.

Potential biases in the review process

Our search strategy was comprehensive, and was without restrictions based on language, date of publication or publication status. We found several studies which mostly had small sample sizes and thus even the overall meta-analysis was underpowered for several review outcomes. There was also a lack of direct evidence comparing artemether with artesunate. The findings of the funnel plot for death (Artemether versus quinine: Figure 3) may suggest publication bias. However, asymmetry in the funnel plot may also be due to other reasons, such as poor methodological quality in smaller studies leading to spuriously inflated effects, true heterogeneity in the treatment effect, sampling variation, or chance (Higgins 2011).

Agreements and disagreements with other studies or reviews

Some meta-analyses and systematic reviews have evaluated the efficacy of artemether compared to quinine in treating severe malaria in children and adults. The earliest study was a meta-analysis of randomized controlled trials (Pittler 1999).

Pittler 1999 found no difference in deaths between intramuscular artemether and parenteral quinine in adults and children although there were fewer adverse effects associated with the administration of intramuscular artemether. AQMSG 2001 reported significantly fewer deaths and neurological sequelae with artemether compared to quinine. PrayGod 2008 found no difference in deaths, parasite clearance time, fever clearance time and neurological sequelae among children between artemether and quinine. However, the study found coma resolution time in children was faster with artemether compared to quinine.

Another systematic review concluded that artemether was not inferior to quinine for preventing death from cerebral malaria in children (Kyu 2009). After the meta-analyses and systematic reviews mentioned above, new clinical trials in which artemether has been compared with quinine and artesunate for the treatment of severe malaria in Africa and Asia have been published. However, no studies have compared artemether to artesunate in African children. These new studies are included in this Cochrane Review.

AUTHORS' CONCLUSIONS

Implications for practice

Although there is a paucity of direct evidence comparing artemether with artesunate, artemether is probably less effective than artesunate at preventing deaths from severe malaria. In circumstances where artesunate is not available, artemether is an alternative to quinine. Since 2015, the World Health Organization recommends intravenous or intramuscular artesunate over quinine for the treatment of severe malaria in adults and children. Artemether is also recommended in preference to quinine for the treatment of severe malaria where artesunate is not available.

Implications for research

Larger, adequately powered clinical trials are necessary for conclusive evidence on the relative effects of artemether. However, additional studies are unlikely given the current treatment recommendations.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Adam 2002

Methods	Trial design: open label RCT

Adam 2002 *(Continued)*

	Trial dates: November 2001 to January 2002
Participants	Number of participants: 41 children enrolled Inclusion criteria: children with severe malaria (age range not stated); cerebral malaria; repeated convulsions; severe anaemia with haemoglobin < 5g/dL; hyperparasitaemia (parasite count > 100,000 rings/µL); or combinations of these criteria. Exclusion criteria: none stated

Interventions	• Intramuscular artemether (Kunming Pharmaceuticals; China)
	  * Loading dose of 3.2 mg/kg on day 1...
	  * ...followed by 1.6 mg/kg once daily for the following 4 days
	• Intravenous quinine
	  * Loading dose of 20 mg/kg of quinine dihydrochloride in 10 mL/kg 5% dextrose over 4 hours...
	  * ...followed by 10 mg/kg of quinine dihydrochloride in 10 mL/kg 5% dextrose solution over 4 hours, every 8 hours for at least 72 hours...
	  * ...followed by oral quinine (for 7 days as soon as patient could tolerate).

Outcomes	Outcomes included in the review: • Death • Coma resolution time • Parasite clearance time • Fever clearance time • Episodes of hypoglycaemia Outcomes not included in the review: • Gametocyte carriage • Recrudescence
Notes	Location: Outpatient clinic in New Halfa, Eastern Sudan Transmission: "meso-endemic" Funding: none stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Each child was randomized". No further details provided.
Allocation concealment (selection bias)	Low risk	"Envelopes containing the assigned treatment were opened sequentially at the time when each patient was recruited to the study".
Blinding (performance bias and detection bias) Objective outcome: Death	Low risk	Described as open-label. However, lack of blinding is unlikely to bias an objective outcome like death.
Blinding (performance bias and detection bias) Subjective outcomes: Others	High risk	An open-label trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up were reported.

Adam 2002 *(Continued)*

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

Aguwa 2010

Methods	Trial design: RCT Trial dates: July to October 2007
Participants	Number of participants: 90 children enrolled Inclusion criteria: children between 6 months and 12 years of age presenting with fever (> 37.5 °C) and *P falciparum* infection with 1 or more general danger signs of severe or complicated malaria based on the WHO criteria for severe malaria. Exclusion criteria: serious concomitant illness (for example, sickle cell anaemia, HIV, tuberculosis and other chronic diseases); severe malnutrition; known hypersensitivity to 1 of the trial drugs.

Interventions	• Intramuscular artemether (Paluther; May and Baker)
	  * Loading dose of 3.2 mg/kg on admission...
	  * ...followed by 1.6 mg/kg once daily for 2 days.
	• Intravenous or intramuscular quinine (Quinimax; Sanofi)
	  * Loading dose 20 mg salt/kg body weight on admission...
	  * ...followed by 10 mg/kg every 8 hours; the infusion rate did not exceed 5 mg salt/kg per hour

Outcomes	Outcomes included in the review: • Death • Proportion of children recovered from coma on day 3 • Proportion of children discharged by day 7 • Proportion of children with fever clearance on day 3 and day 14 • Proportion of children with parasite clearance on day 3 and day 14 Outcomes not included in the review: • Hospital bed-days
Notes	Location: Federal Medical Centre, Birnin Kudu, Jigawa State of Nigeria Transmission: stable perennial transmission Funding: none stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"Patients were assigned to receive quinine if the last digit of their hospital identification number was odd and to receive artemether if the last digit of their hospital identification number was even or zero".
Allocation concealment (selection bias)	High risk	Trial authors did not describe any methods of allocation concealment, and this would not be possible using this randomization method.

Aguwa 2010 *(Continued)*

Blinding (performance bias and detection bias) Objective outcome: Death	Low risk	No blinding was described. However, lack of blinding is unlikely to bias an objective outcome like death.
Blinding (performance bias and detection bias) Subjective outcomes: Others	High risk	No blinding is described, and blinding would not be feasible.
Incomplete outcome data (attrition bias) All outcomes	High risk	Losses to follow-up at day 14 were > 10% in both trial arms.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	No other bias identified.

Bobossi-Serengbe 2015

Methods	Trial design: randomized trial Trial dates: June to August 2010
Participants	Number of participants: 212 hospitalized children Inclusion criteria: children between 6 and 59 months with clinical signs of severe malaria; *P falciparum* infection; and informed consent from parents or guardians. Exclusion criteria: children with known hypersensitivity to quinine.

Interventions	• Intramuscular artemether
	  * Loading dose of 2 mg/kg on admission at 12 hour intervals...
	  * ...followed by 2 mg/kg once daily for 2 days.
	• Intravenous quinine
	  * Loading dose 10 mg salt/kg body weight on admission...
	  * ...followed by 10 mg/kg every 4 hours for 3 days...
	  * ...then oral quinine continued until the 7th day.

Outcomes	Outcomes included in the review: • Death • Proportion with parasitaemia on day 3 and day 7 • Adverse events Outcomes not included in the review: none
Notes	Location: Bangui Pediatric Complex, Bangui, Central African Republic Transmission: stable perennial transmission Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement

Bobossi-Serengbe 2015 *(Continued)*

Random sequence generation (selection bias)	Low risk	Web-based block randomization used.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) Objective outcome: Death	Low risk	Not stated. However, lack of blinding is unlikely to bias an objective outcome like death.
Blinding (performance bias and detection bias) Subjective outcomes: Others	High risk	No blinding is described, and blinding would not be feasible as the route of administration is different for artemether and quinine.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up reported.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	No other bias identified.

Hien 1996

Methods	Trial design: double-blind RCT Trial dates: not stated

Participants	Number of participants: 560 adults aged 15 to 79 years enrolled
	Inclusion criteria: patients were included in the trial if they:
	• (or an accompanying relative) gave informed consent;
	• had asexual forms of *P falciparum* on a peripheral-blood smear;
	• were older than 14 years;
	• were not in the first trimester of pregnancy;
	• were not intravenous drug users;
	• had received less than 3 g of quinine or 2 doses of artemisinin or a derivative in the previous 48 hours;
	• and had 1 or more of the following:
	  * a score on the Glasgow Coma Scale of less than 11 (indicating cerebral malaria);
	  * anaemia (hematocrit, 20 percent), with a parasite count exceeding 100,000 parasites/mm^3 on a peripheral blood smear;
	  * jaundice (serum bilirubin, 2.5 mg/dL (50 mmol per litre)), with a parasite count of more than 100,000 parasites/mm^3 on a peripheral blood smear;
	  * renal impairment (urine output, 400 mL per 24 hours; and serum creatinine, 3 mg/dL (250 mmol/L));
	  * hypoglycaemia (blood glucose, 40 mg/dL (2.2 mmol/L));
	  * hyperparasitaemia (10% parasitaemia);
	  * systolic blood pressure below 80 mmHg with cool extremities (indicating shock).
	Exclusion criteria: none stated

Hien 1996 *(Continued)*

Interventions	• Intramuscular artemether (Kunming Pharmaceutical)
	  * Loading dose of 4 mg/kg...
	  * ...followed by 2 mg/kg 8-hourly for a minimum of 3 days...
	  * ...followed by either a single oral dose of 15 mg of mefloquine or oral dose of 10 mg quinine sulphate for up to 4 days.
	• Intramuscular quinine
	  * Loading dose of 20 mg/kg...
	  * ...followed by 10 mg/kg per kilogram 8-hourly...
	  * ...followed by either a single oral dose of 15 mg/kg mefloquine or oral dose of 10 mg/kg quinine sulphate for up to 4 days

Outcomes	Outcomes included in the review: • Death • Coma resolution time • Neurological sequelae • Fever clearance time • Parasite clearance time • Hypoglycaemia • Need for blood transfusion • Adverse effects Outcomes not included in the review: • Duration of parenteral antimalarial treatment • Time for plasma lactate level to fall below 2.5 mmol/L
Notes	Location: Special Research Ward, Centre for Tropical Diseases, Ho Chi Minh City, Vietnam Transmission: not stated Funding: Wellcome Trust

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Trial authors provided no information on methods of sequence generation.
Allocation concealment (selection bias)	Low risk	"The drugs for each patient were placed in a coded sealed envelope and the envelopes were randomized in blocks of 20. Once a patient was enrolled in the study the envelope was opened".
Blinding (performance bias and detection bias) Objective outcome: Death	Low risk	"To maintain blinding, a separate team of nurses, who were not otherwise involved with the care of the study patients, drew up and gave the injections. The drugs were kept in an opaque packet in a locked cabinet during the study". Both interventions were administered by intramuscular injection so blinding was feasible.
Blinding (performance bias and detection bias) Subjective outcomes: Others	Low risk	"To maintain blinding, a separate team of nurses, who were not otherwise involved with the care of the study patients, drew up and gave the injections. The drugs were kept in an opaque packet in a locked cabinet during the study". Both interventions were administered by intramuscular injection so blinding was feasible.

Hien 1996 *(Continued)*

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

Huda 2003

Methods	Trial design: open RCT Trial dates: April 2000 to July 2001

Participants	Number: 46 children aged 6 months to 12 years enrolled
	
	Inclusion criteria:
	
	• Asexual forms of *P falciparum* from peripheral blood smear;
	• 1 or more clinical manifestations of severe malaria present which included:
	  * cerebral malaria;
	  * severe anaemia (haemoglobin < 5 g/dL or hematocrit < 15%);
	  * metabolic abnormalities (hypoglycaemia: plasma glucose < 40 mg/dL or < 2.2 mmol/L);
	  * algid malaria (associated with peripheral circulatory failure or shock);
	  * blackwater fever;
	  * renal failure;
	  * spontaneous bleeding (thrombocytopenia, DIC);
	  * pulmonary oedema;
	  * jaundice.
	
	Exclusion criteria:
	
	• History of having received artemether/quinine within 24 hours preceding admission.
	• Severe protein energy malnutrition.
	• Clinical/laboratory evidence of other significant illness not attributable to severe malaria.

Interventions	• Intramuscular artemether
	  * Loading dose of 1.6 mg/kg twice a day on admission...
	  * ...followed by 1.6 mg/kg once a day for 5 days.
	• Intravenous quinine
	  * Loading dose of 20 mg/kg...
	  * ...followed by 10 mg/kg every 8 hours by infusion...
	  * ...followed by oral quinine sulphate once the patient was conscious, for a total period of 7 days.
	
	Supportive therapy was given to all patients.

Outcomes	Outcomes included in the review: • Death • Parasite clearance time • Fever resolution time • Coma recovery Outcomes not included in the review: none

Huda 2003 *(Continued)*

Notes	Location: Inpatient Unit of Department of Pediatrics, and Parasitology laboratory, Department of Microbiology, Uttar Pradesh, India Transmission: unknown Funding: none stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Trial authors provided no information on methods of sequence generation.
Allocation concealment (selection bias)	Unclear risk	Trial authors provided no information on allocation concealment.
Blinding (performance bias and detection bias) Objective outcome: Death	Low risk	An open-label trial is unlikely to bias an objective outcome like death.
Blinding (performance bias and detection bias) Subjective outcomes: Others	Low risk	"The slides for malarial parasites were transported to the parasitology laboratory where the person examining the slides was unaware of the clinical status of the patient and also the treatment assignment group".
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up were recorded.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	No other bias identified.

Karbwang 1992

Methods	Trial design: RCT Trial dates: May to December 1991
Participants	Number of participants: 26 adults aged 15 to 45 years enrolled Inclusion criteria: patients with severe *P falciparum* malaria (WHO definition) with no history of antimalarials within 24 hours prior to admission, aged between 15 to 45 years and weighed 45 to 60 kg Exclusion criteria: none stated

Interventions	• Intramuscular artemether (Arthermin®)
	  * Loading dose of 160 mg...
	  * ...followed by 80 mg once daily for 6 days
	• Intravenous quinine
	  * Loading dose of 20 mg/kg...
	  * ...followed by 10 mg/kg 8-hourly for 7 days...
	  * ...followed by quinine sulphate tablets as soon as oral medication was possible.

Karbwang 1992 *(Continued)*

Outcomes	Outcomes included in the review: • Death • Coma resolution time • Neurological sequelae • Fever clearance time • Parasite clearance time • Adverse effects Outcomes not included in the review: • Survival rate • Cause of death
Notes	Location: Prapokklao Hospital, Chantaburi, Thailand Transmission: not stated Funding: support from United Medical Ltd., Bangkok (provided artemether)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The patients were randomized to receive either quinine or artemether".
Allocation concealment (selection bias)	Unclear risk	Trial authors provided no information on allocation concealment.
Blinding (performance bias and detection bias) Objective outcome: Death	Low risk	Trial authors provided no information on blinding. However, lack of blinding is unlikely to bias an objective outcome like death.
Blinding (performance bias and detection bias) Subjective outcomes: Others	High risk	Trial authors provided no information on blinding, however it may not be feasible due to different routes of administration for both interventions.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up reported.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	No other bias identified.

Karbwang 1995

Methods	Trial design: RCT Trial dates:1992 to 1994
Participants	Number of participants: 102 adults aged between 15 and 55 years enrolled

Karbwang 1995 *(Continued)*

	Inclusion criteria: male and non-pregnant female patients with severe *P falciparum* malaria (WHO definition) with no history of antimalarial treatment within 24 hours before admission aged 15 to 65 years and weighing 45 to 75 kg Exclusion criteria: patients with concurrent diseases were excluded

Interventions	• Intramuscular artemether
	  * Loading dose of 160 mg...
	  * ...followed by 80 mg once daily for 6 days.
	• Intravenous quinine
	  * Loading dose of 20 mg/kg...
	  * ...followed by 10 mg/kg 8-hourly for 7 days...
	  * ...followed by quinine sulphate tablets as soon as oral medication was possible.

Outcomes	Outcomes included in the review: • Death • Coma resolution time • Neurological sequelae • Fever clearance time • Parasite clearance time • Adverse effects Outcomes not included in the review: • Survival rate
Notes	Location: Prapokklao Hospital, Chantaburi, Thailand Transmission: not stated Funding: UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomization at WHO Office.
Allocation concealment (selection bias)	Low risk	"Each treatment was enclosed in a sealed envelope, which was opened only after the physician in charge had decided to recruit the patient into the study".
Blinding (performance bias and detection bias) Objective outcome: Death	Low risk	Trial authors provided no information on blinding. However, lack of blinding is unlikely to bias an objective outcome like death.
Blinding (performance bias and detection bias) Subjective outcomes: Others	High risk	Trial authors provided no information on blinding; however it might not have been feasible due to different routes of administration for both interventions.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up about 5%.

Karbwang 1995 *(Continued)*

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

Minta 2005

Methods	Trial design: open RCT Trial dates: June 1993 to February 1994 and June 1994 to December 1994
Participants	Number of participants: 67 children aged 3 months to 15 years enrolled Inclusion criteria: fever (core temperature ≥ 38 °C); positive blood smear for *P falciparum* with ≥ 0.1% of parasitized erythrocytes; 1 major criterion or 2 minor criteria for severe malaria cases (WHO criteria); and parental consent Exclusion criteria: children with infection who had been treated within 24 hours with quinine or intramuscular injection were not eligible.

Interventions	• Intramuscular artemether (Paluther)
	  * Loading dose of 3.2 mg/kg on admission (2 times)...
	  * ...followed by 1.6 mg/kg once daily for 4 days.
	• Intravenous quinine
	  * Loading dose of 20 mg/kg on admission...
	  * ...followed by 10 mg/kg every 8 hours until oral drug administration was possible (10 mg/kg every 8 hours).

Outcomes	Outcomes included in the review: • Death • Coma resolution time • Fever clearance • Parasite clearance • Adverse events Outcomes not included in the review: • Recrudescence
Notes	Location: Gabriel Touré's Hospital, Mali Transmission: unknown Funding: Rhône-Poulenc Rorer Doma (France)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomization by clinical monitor.
Allocation concealment (selection bias)	Low risk	Opaque envelopes used to conceal allocation.

Minta 2005 *(Continued)*

Blinding (performance bias and detection bias) Objective outcome: Death	Low risk	An open-label trial is unlikely to bias an objective outcome like death. No blinding is described, and blinding would not be feasible.
Blinding (performance bias and detection bias) Subjective outcomes: Others	High risk	An open-label trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up reported.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	No other bias identified.

Murphy 1996

Methods	Trial design: open RCT Trial dates: not stated
Participants	Number: 160 children aged 5 months to 12 years enrolled Inclusion criteria: children were admitted to the trial if they had *P falciparum* asexual parasitaemia; were comatose; and parental consent was obtained. Exclusion criteria: children were excluded if there was evidence of a pre-existing neurological deficit; head injury; or history of recent treatment with antimalarial drugs other than chloroquine.

Interventions	• Intramuscular artemether (Paluther, Rhône-Poulenc)
	  * Loading dose of 3.2 mg/kg...
	  * ...followed by 1.6 mg/kg once daily; at least 3 doses of artemether were given...
	  * ...followed by sulphadoxine-pyrimethamine if parasitaemia had cleared and the child could drink. Otherwise artemether was continued for a total of 5 days (4 maintenance doses)
	• Intravenous quinine (Laboratoires Renaudin, Paris)
	  * Loading dose of 20 mg/kg infused over 4 hours...
	  * ...followed by 10 mg/kg every 8 hours with dose given over 2 hours. At least 3 doses of parenteral quinine were given, and continued until the child was able to drink and parasitaemia had cleared...
	  * ...then a single dose of sulphadoxine-pyrimethamine (sulphadoxine 25 mg/kg, pyrimethamine 1.25 mg/kg) given orally or intramuscularly.

Outcomes	Outcomes included in the review: • Time to death • Coma resolution • Neurological sequelae • Fever clearance • Parasite clearance • Adverse effects Outcomes not included in the review: • Mortality with respiratory distress

Murphy 1996 *(Continued)*

Notes	Location: Kenya Medical Research Institute (KEMRI) Coastal Research Unit, Kilifi district hospital, Kenya. Transmission: unknown Funding: • KEMRI • UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) • The Wellcome Trust

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centrally-coded unique trial numbers.
Allocation concealment (selection bias)	Low risk	Sealed envelopes prepared by the clinical monitor.
Blinding (performance bias and detection bias) Objective outcome: Death	Low risk	An open-label trial is unlikely to bias an objective outcome like death.
Blinding (performance bias and detection bias) Subjective outcomes: Others	High risk	An open-label trial. Blinding unlikely as artemether and quinine were given by 2 different routes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	40 patients (14 from artemether arm and 26 from quinine arm) excluded (mostly for not meeting inclusion criteria).
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	No other bias identified.

Ojuawo 1998

Methods	Trial design: RCT Trial dates: not stated
Participants	Number of participants: 37 children enrolled (age range not stated) Inclusion criteria: Children with unrousable coma, asexual forms of *P falciparum* parasitaemia and no other identifiable cause of coma. Exclusion criteria: none stated

Interventions	• Intramuscular artemether
	  * Loading dose of 3.2 mg/kg on admission...
	  * ...followed by 1.6 mg/kg 12 hours later...
	  * ...then 1.6 mg/kg once daily for 2 days

Ojuawo 1998 *(Continued)*

	• Intravenous quinine
	  * Loading dose of 10 mg/kg infused over 2 hours...
	  * ...followed by 10 mg/kg every 8 hours until patient regained consciousness
	  * ...then switched to oral dose for a total of 7 days

Outcomes	Outcomes included in the review: • Death • Coma resolution time • Neurologic sequelae • Fever clearance time • Percentage of children with parasites clearance at days 3 and 7 Outcomes not included in the review: none
Notes	Location: University of Ilorin Teaching Hospital, Nigeria Transmission: unknown Funding: none stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomly assigned to either of the two treatment modalities".
Allocation concealment (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement.
Blinding (performance bias and detection bias) Objective outcome: Death	Low risk	Unlikely to be biased whether blinding was done or not.
Blinding (performance bias and detection bias) Subjective outcomes: Others	High risk	No information about blinding provided by trial authors. Blinding unlikely as artemether and quinine were given by 2 different routes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up recorded.
Selective reporting (reporting bias)	Low risk	Most relevant outcomes reported.
Other bias	Low risk	No other bias identified.

Olumese 1999

Methods	Trial design: open label RCT Trial dates: not stated
Participants	Number of participants: 103 children aged 11 months to 5 years enrolled

Olumese 1999 *(Continued)*

	Inclusion criteria: Children aged 6 months to 5 years satisfying the WHO criteria for cerebral malaria, viz. unrousable coma lasting more than 30 minutes (with or without convulsions) with the presence of peripheral *P falciparum* parasitaemia were included in the trial. Exclusion criteria: none stated

Interventions	• Intramuscular artemether
	  * Loading dose of 3.2 mg/kg on admission...
	  * ...followed by 1.6 mg/kg once daily for 4 days
	• Intravenous quinine (Lemquine®)
	  * Loading dose of 20 mg/kg infused over 4 hours...
	  * ...followed by 10 mg/kg infused over 2 hours given every 8 hours until the patient is conscious and oral quinine continued at 10 mg/kg orally every 8 hours to complete a total of 21 doses or 7 days
	
	Loading dose quinine was omitted in patients with a positive history of quinine or mefloquine ingestion in the preceding 24 hours before hospital presentation.

Outcomes	Outcomes included in the review: • Death • Parasite clearance time • Fever clearance time • Survival and neurological symptoms • Coma recovery time • Neurological deficits • Blood transfusions Outcomes not included in the review: • Time to full ambulation
Notes	Location: Emergency Paediatric ward, University College Hospital, Ibadan, Nigeria Transmission: unknown Funding: World Bank/UNDP/WHO special fund for Research and Training in Tropical Diseases (TDR)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated allocation.
Allocation concealment (selection bias)	Unclear risk	Methods not described by trial authors.
Blinding (performance bias and detection bias) Objective outcome: Death	Low risk	Unlikely to be biased whether blinding was done or not.
Blinding (performance bias and detection bias) Subjective outcomes: Others	High risk	No information of blinding reported by authors. Blinding unlikely as artemether and quinine were given by 2 different routes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up recorded.

Olumese 1999 *(Continued)*

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

Osonuga 2009

Methods	Trial design: RCT Trial dates: not stated
Participants	Number: 32 children aged 1 to 12 years enrolled Inclusion criteria: children aged 1 to 12 years, with fever (temperature > 37.5 °C), presence of convulsion, vomiting, hypoglycaemia, anaemia and headache. Informed consent obtained from the parents and guardians. Assurance that patients will be resident within catchments of trial for follow-up. Absence of concomitant illness such as bronchopneumonia, typhoid, meningitis, urinary tract infection. Exclusion criteria: history of blood transfusion in the last 2 months, presence of concomitant illness, history of previous allergy to quinine and artemether.

Interventions	• Intramuscular artemether (Rhône-Poulence, Rorer France)
	  * Loading dose of 1.6 mg/kg twice on day 0...
	  * ...followed by 1.6 mg/kg once daily for the next 4 days
	• Intravenous quinine (Evans)
	  * Loading dose of 10 mg/kg infused over 4 hours...
	  * ...followed by 10 mg/kg given at 8-hour intervals and oral quinine (10 mg/kg body weight, 8-hour intervals) as soon as the patient's condition allowed.
	
	Treatment with quinine was for a total of 7 days.

Outcomes	Outcomes included in the review: • Coma resolution time • Fever clearance time • Parasite clearance time Outcomes not included in the review: none
Notes	Location: Overcomers Specialist Clinic Ileshan and General Hospital Ikenne, Nigeria Transmission: unknown Funding: none stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The children were randomly allocated into 2 treatment groups; treatment Q and A for quinine and artemether respectively".
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment provided by trial authors.
Blinding (performance bias and detection bias)	Low risk	Unlikely to be biased whether blinding was done or not.

Osonuga 2009 *(Continued)*
Objective outcome: Death

Blinding (performance bias and detection bias) Subjective outcomes: Others	High risk	No information of blinding reported by authors. Blinding unlikely as artemether and quinine were given by 2 different routes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition about 6% and not likely to affect outcomes.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting. Authors have published 3 outcomes in 3 different publications from the same trial.
Other bias	Low risk	No other bias identified.

Phu 2010

Methods	Trial design: double-blind RCT Trial dates: May 1996 to June 2003
Participants	Number of participants: 370 adults aged between 15 and 77 years enrolled Inclusion criteria: peripheral blood smears had asexual forms of *P falciparum* and had at least 1 of the following severe complications: • cerebral malaria (Glasgow Coma Score was less than 11); • renal acute failure (oliguria and serum creatinine > 250 µmol/L); • jaundice (total serum bilirubin > 50 µmol/L) with a parasite count of more than 100,000/µL or with serum creatinine > 250 µmol/L; • hypoglycaemia (blood glucose < 2.2 mmol/L); • anaemia (haematocrit < 20%) with a parasite count of more than 100,000/µL; • hyperparasitaemia (parasite count > 500,000/µL); • hyperlactataemia (plasma lactate > 4 mmol/L); • metabolic acidosis (standard base excess ≥ 5 mmol/L, base deficit < 10 mmol/L); • shock (systolic blood pressure < 80 mmHg with cool extremities). Exclusion criteria: patients were not included if they were < 14 years, were pregnant in the first trimester, were known intravenous drug abusers, had received more than 3 g of quinine or 2 doses of any artemisinin derivatives in the previous 48 hours before admission, had a past history of allergy to any artemisinin derivatives, or if known to be HIV positive.

Interventions	• Intramuscular artemether (Kunming Pharmaceutical Company, Kunming, China)
	  * Loading dose of 3.2 mg/kg...
	  * ...followed by 1.6 mg/kg daily for at least 2 days.
	• Intramuscular artesunate (Guilin No 2 Pharmaceutical Factory, Guangxi, China)
	  * Loading dose of 2.4 mg/kg on admission...
	  * ...followed by 1.2 mg/kg once daily for at least 2 days...
	  * ...followed by 2 mg/kg of oral artesunate to complete a total of 7 days.

Outcomes	Outcomes included in the review: • Death • Coma resolution time • Time to discharge

Phu 2010 *(Continued)*

- Fever clearance time
- Parasite clearance time
- Episodes of hypoglycaemia
- Adverse effects

Outcomes not included in the review:

- Time to drinking
- Time to eating
- Time to sitting
- Time to standing
- Time to walking

Notes	Location: Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam Transmission: not stated Funding: Wellcome Trust, UK

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomization was generated from random number tables".
Allocation concealment (selection bias)	Low risk	"Labels with the name of drug for each patient were put in coded sealed opaque envelopes, and the envelopes were randomized in blocks of 20. Once a patient was enrolled in the study the envelope was opened".
Blinding (performance bias and detection bias) Objective outcome: Death	Low risk	"An independent team of nurses, not otherwise involved in the study or responsible for the care of these patients, open the envelope, randomized the patient and prepared the injection. Neither the treating physicians, study doctors and nurses, or patients knew which anti-malarial drugs was administered".
Blinding (performance bias and detection bias) Subjective outcomes: Others	Low risk	"An independent team of nurses, not otherwise involved in the study or responsible for the care of these patients, open the envelope, randomized the patient and prepared the injection. Neither the treating physicians, study doctors and nurses, or patients knew which anti-malarial drugs was administered".
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up recorded.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	No other bias identified.

Satti 2002

Methods	Trial design: RCT Trial dates: May 1995 to June 1996

Satti 2002 *(Continued)*

Participants	Number: 77 children enrolled aged 3 months to 15 years Inclusion criteria: children who satisfied the WHO criteria for diagnosis of cerebral malaria (such as unrousable coma for at least 30 minutes following convulsions, positive blood film for malaria, exclusion of other causes of encephalopathy); and informed consent by parent or guardian. Exclusion criteria: concomitant acute illness such as pneumonia, meningitis or acute renal failure and any contraindication to IM injection.

Interventions	• Intramuscular artemether
	  * Loading dose of 1.6 mg/kg, repeated after 12 hours...
	  * ...followed by 1.6 mg/kg once daily for 4 days.
	• Intravenous quinine
	  * Loading dose of 10 mg/kg...
	  * ...followed by 10 mg/kg repeated every 8 hours and changed to oral dose when patient was able to drink.
	
	Treatment with quinine was for a total of 7 days.

Outcomes	Outcomes included in the review: • Death • Coma resolution time • Neurological sequelae • Fever clearance time • Parasite clearance time Outcomes not included in the review: • 28th-day cure rate
Notes	Location: Khartoum Children's Emergency Hospital and Ahmed Gasim Specialist Hospital for Children, Sudan Transmission: unknown Funding: • Danish Development Agency (DANIDA) • German Academic Exchange Service (DAAD)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The cases were randomly allocated into two groups".
Allocation concealment (selection bias)	Unclear risk	No information provided by trial authors about allocation concealment.
Blinding (performance bias and detection bias) Objective outcome: Death	Low risk	Unlikely to be biased whether blinding was done or not.
Blinding (performance bias and detection bias) Subjective outcomes: Others	High risk	No information of blinding reported by authors. Blinding unlikely as artemether and quinine were given by 2 different routes.

Satti 2002 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	More than 10% of participants in each arm dropped out before day 28.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	No other bias identified.

Seaton 1998

Methods	Trial design: open-label RCT Trial dates: June 1992 to May 1995
Participants	Number: 33 adults aged above 12 years Inclusion criteria: blood smear showed asexual forms of *P falciparum*; in addition to fulfilling 1 or more of the WHO criteria for severe or complicated malaria. Exclusion criteria: patients under the age of 12 years, pregnant women, those who had received parenteral antimalarial treatment prior to admission and those with a co-existent bacterial, viral, fungal or mixed malarial infection.

Interventions	• Intramuscular artemether (Rhone-Poulenc Rorer)
	  * Loading dose of 3.2 mg/kg...
	  * ...followed by 1.6 mg/kg once daily for 4 days.
	• Intravenous quinine (Medipharma)
	  * Loading dose of 20 mg/kg...
	  * ...followed by 10 mg/kg 8-hourly and patients able to tolerate oral medication were switched to oral quinine after 48 hours to complete a total of 7 days.

Outcomes	Outcomes included in the review: • Death • Coma resolution time • Fever clearance time • Parasite clearance time • Episodes of hypoglycaemia • Adverse effects Outcomes not included in the review: none
Notes	Location: Port Moresby General Hospital, Papua New Guinea Transmission: seasonal/sporadic Funding: • UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) • Colt Foundation • Wellcome Trust

Risk of bias

Bias	Authors' judgement	Support for judgement

Seaton 1998 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Patients were randomly assigned to treatment with quinine or artemether.
Allocation concealment (selection bias)	Low risk	Envelopes containing the assigned treatment were opened sequentially when a patient was recruited.
Blinding (performance bias and detection bias) Objective outcome: Death	Low risk	Unlikely to be biased whether blinding was done or not.
Blinding (performance bias and detection bias) Subjective outcomes: Others	High risk	No information of blinding reported by authors. Blinding unlikely as artemether and quinine were given by 2 different routes.
Incomplete outcome data (attrition bias) All outcomes	High risk	Differential proportion of withdrawals from both arms (25% versus 10%).
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	No other bias identified.

Taylor 1998

Methods	Trial design: open label RCT Trial dates: January 1992 to June 1994
Participants	Number: 183 children enrolled (age range not stated) Inclusion criteria: children with asexual forms of *P falciparum* detected in a peripheral blood smear, and a Blantyre Coma Score ≤ 2, and if no other cause of fever or altered consciousness could be discovered. Exclusion criteria: none stated

Interventions	• Intramuscular artemether
	  * Loading dose of 3.2 mg/kg on admission...
	  * ...followed by 1.6 mg/kg once daily; a minimum of 3 doses were given...
	  * ...then oral sulphadoxine-pyrimethamine (approximately 25 mg/kg sulphadoxine and 1.25 mg/kg pyrimethamine) if parasitaemia had cleared and the patient was fully conscious.
	• Intravenous quinine
	  * Loading dose of 20 mg/kg infused over 4 hours...
	  * ...followed by 10 mg/kg infused over 2 hours at 8-hour intervals. After a minimum of 3 intravenous quinine doses, oral quinine given in 10 mg/kg doses at 8-hour intervals if the patient was able to drink...
	  * ...then oral sulphadoxine-pyrimethamine (same as above).

Outcomes	Outcomes included in the review: • Death • Coma resolution time • Neurological sequelae • Fever clearance time

Taylor 1998 *(Continued)*

	• Parasite clearance time Outcomes not included in the review: • Recurrent parasitaemia • Reticulocyte response
Notes	Location: Paediatric ward at the Queen Elizabeth Central Hospital, Malawi Transmission: unknown Funding: UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomization.
Allocation concealment (selection bias)	Low risk	"Randomized treatment assignments were prepared in blocks of ten by the sponsoring agency. Following initial stabilization, diagnosis and examination, a sealed envelope containing the treatment group was opened, and the patient was allocated to treatment".
Blinding (performance bias and detection bias) Objective outcome: Death	Low risk	An open-label trial is unlikely to bias an objective outcome like death.
Blinding (performance bias and detection bias) Subjective outcomes: Others	High risk	An open-label trial.
Incomplete outcome data (attrition bias) All outcomes	High risk	Differential proportion of withdrawals from both arms (13% versus 8%).
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	No other bias identified.

van Hensbroek 1996

Methods	Trial design: open-label trial Trial dates: 1992 to 1994
Participants	Number: 576 children aged 1 to 9 years enrolled Inclusion criteria: unconscious children 1 to 9 years of age with a Blantyre coma score of 2 or less, asexual forms of *P falciparum* identified on a thick blood film, and a parent or guardian gave informed consent.

van Hensbroek 1996 *(Continued)*

	Exclusion criteria: patients with diseases other than malaria at the time of admission and those who recovered consciousness immediately after correction of hypoglycaemia or within 1 hour if they were convulsing on admission. Patients treated with quinine before admission.

Interventions	• Intramuscular artemether (Paluther, Rhone-Poulenc)
	  * Loading dose of 3.2 mg/kg on admission...
	  * ...followed by daily doses of 1.6 mg/kg for 3 days.
	• Intravenous quinine (Rotexmedica, Germany)
	  * Loading dose of 20 mg/kg...
	  * ...followed by 10 mg/kg every 12 hours...
	  * ...then oral quinine (once patient was able to swallow) for a total of 5 days.
	
	An oral dose of approximately 1.25 mg/kg pyrimethamine and 25 mg/kg sulfadoxine was given to both arms to reduce recrudescence (in the 2nd and 3rd years of the trial).

Outcomes	Outcomes included in the review: • Death • Coma resolution time • Neurological sequelae at discharge • Neurological sequelae at 28 days • Fever clearance time • Parasite clearance time • Adverse effects Outcomes not included in the review: • Residal neurological sequelae (5 months' follow-up) • 28th day cure rate
Notes	Location: Royal Victoria Hospital and Sibanor Health Centre, Banjul, Gambia Transmission: unknown Funding: • UNDP/World Bank/WHO special programme for research and training in tropical diseases (TDR) • The Netherlands Foundation for the Advancement of Tropical Research • The Ter Meulen Foundation • The Medical Research Council

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Trial authors do not provide details of sequence generation.
Allocation concealment (selection bias)	Low risk	"The treatment code for each child was stored in a sealed envelope that was opened after the admission procedure was completed and parental consent had been obtained".
Blinding (performance bias and detection bias) Objective outcome: Death	Low risk	An open-label trial is unlikely to bias an objective outcome like death.
Blinding (performance bias and detection bias)	Low risk	"Each blood film was examined by two independent observers who were unaware of the treatment code".

van Hensbroek 1996 *(Continued)*

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

Vinh 1997

Methods	Trial design: open RCT Trial dates: March 1992 to September 1994
Participants	Number: 124 adults aged between 16 and 66 years Inclusion criteria: 15 years of age or older, with clinical symptoms and signs of malaria and the presence of asexual forms of *P falciparum* in their peripheral blood. In addition, having at least 1 of the following signs: • unrousable coma (Glasgow Coma Score < 3); • hypoglycaemia (blood glucose < 2.2 mmol/L (40 mg %); • acute renal failure (plasma creatinine > 265.2 µmol/L (3 mg %) with or without oliguria); • jaundice (total bilirubin > 51.3 mol/L (3 mg %)) with parasitaemia > 100,000/µL or with plasma creatinine >1.5 mg %; • anaemia (haematocrit < 20%) with parasitaemia > 100,000/µL; • shock (systolic arterial pressure < 80 mmHg with a thready pulse and cold clammy extremities); • hyperparasitaemia >500,000/µL. Exclusion criteria: patients were excluded from the trial if prior treatment with more than 3 g of quinine or 2 doses of artemisinin or a derivative had been recorded by the peripheral health care worker. Pregnant patients in the first trimester, and patients with concomitant diseases (such as active tuberculosis, bacterial meningitis), or mixed infections with *P vivax* were also excluded from the trial.

Interventions	• Intramuscular artemether (Kunming Pharmaceutical, Yunnan, China)
	  * Loading dose of 200 mg...
	  * ...followed by 100 mg once daily for 3 days.
	• Intramuscular artesunate (Guilin No. 2 Pharmaceutical Factory, Guangxi, China)
	  * Loading dose of 120 mg...
	  * ...followed by 60 mg once daily for 3 days.
	• Intravenous artesunate (Guilin No. 2 Pharmaceutical Factory, Guangxi, China)
	  * Loading dose of 120 mg...
	  * ...followed by 60 mg once daily for 3 days.
	
	All patients received 750 mg mefloquine (Lariam®, Roche) as a single dose after regaining consciousness or at day 4.

Outcomes	Outcomes included in the review: • Death • Coma resolution time • Fever clearance time

Vinh 1997 *(Continued)*

	• Parasite clearance time Outcomes not included in the review: • Fatality rate
Notes	Location: Tan Phu Regional Hospital, Vietnam Transmission: endemic Funding: Roche Asian Research Foundation, Hong Kong

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Trial authors do not provide details about random sequence generation.
Allocation concealment (selection bias)	Low risk	"When a patient fulfilled the enrolment criteria, a sealed envelope containing the code for the treatment regimen was opened to allocate him/her to one of the following 4 treatment groups".
Blinding (performance bias and detection bias) Objective outcome: Death	Low risk	Described as open-label. However, lack of blinding is unlikely to bias an objective outcome like death.
Blinding (performance bias and detection bias) Subjective outcomes: Others	High risk	An open-label trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up were reported.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	No other bias identified.

Walker 1993

Methods	Trial design: open RCT Trial dates: not stated
Participants	Number: 54 children aged 1 to 5 years enrolled Inclusion criteria: patients were admitted if they satisfied the strict WHO definition of cerebral malaria. Exclusion criteria: none stated

Interventions	• Intramuscular artemether
	  * Loading dose of 3.2 mg/kg on admission...
	  * ...followed by 1.6 mg/kg for 4 days.

Walker 1993 *(Continued)*

- Intravenous quinine
  * Loading dose of 20 mg/kg infused over 4 hours on admission...
  * ...followed by 10 mg/kg every 8 hours until patient regained consciousness...
  * ...then oral medication was continued at 10 mg/kg, every 8 hours for a total of 7 days.

Outcomes	Outcomes included in the review: • Death • Coma resolution time • Neurological sequelae • Fever clearance time • Parasite clearance time • Adverse effects Outcomes not included in the review: • Time to sit unaided • Time to drink • Discharge packed cell volume • Mortality rate • 28th-day cure rate • Parasite recrudescence
Notes	Location: University College Hospital, Ibadan, Nigeria Transmission: unknown Funding: World Bank/UNDP/WHO Special Fund for Research and Training in Tropical Diseases (TDR)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers used.
Allocation concealment (selection bias)	Low risk	"Each child was then assigned a random number from a list prepared by an independent collaborator and thus allocated at random to receive either intramuscular artemether or intravenous quinine".
Blinding (performance bias and detection bias) Objective outcome: Death	Low risk	An open-label trial is unlikely to bias an objective outcome like death.
Blinding (performance bias and detection bias) Subjective outcomes: Others	High risk	"This was a randomized, open, controlled study in which no attempt was made to 'blind' the investigators, as the test drug and the control drug were given by 2 different routes".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 patient excluded from fever clearance time outcome assessment because of urinary tract infection.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	No other bias identified.

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

Study	Reason for exclusion
Aceng 2005	Intervention was rectal artemisinin.
Bhattacharya 1997	Not an RCT.
Bunnag 1992	Drug-resistant malaria not severe malaria.
Dunyo 2011	Uncomplicated malaria.
Falade 2007	Comparison not parenteral treatment.
Fargier 1999	Not an RCT.
Karbwang 1994	Comparison not parenteral treatment.
Karunajeewa 2006	Not an RCT.
Myint 1987	Not an RCT.
Osonuga 2006	No desired review outcomes.
Reham 2012	Patients not randomly selected (non-probability consecutive sampling used).
Rehman 2013	Design is a case-control prospective study.
Shwe 1988	Not an RCT.
Shwe 1992	Participants in the artemether arm also received single dose of mefloquine.
White 1992	Participants not randomized.

Abbreviations: RCT: randomized controlled trial.

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

Danis 1996

Methods	Multicentre trial
Participants	Information not available
Interventions	Information not available
Outcomes	Information not available
Notes	Information not available

Faiz 2001

Methods	RCT

Faiz 2001 *(Continued)*

Participants	105 adults enrolled
Interventions	Information not available
Outcomes	Information not available
Notes	Information not available

Abbreviations: RCT: randomized controlled trial.

DATA AND ANALYSES

Comparison 1. Artemether versus quinine

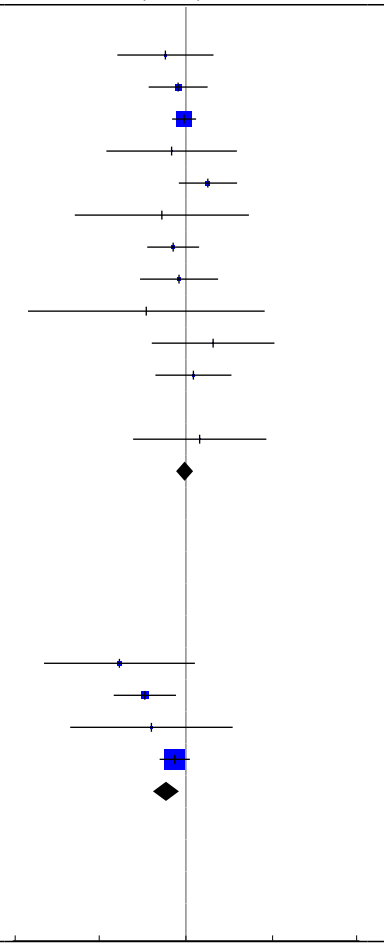
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	17		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Children	13	1659	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.77, 1.21]
1.2 Adults	4	716	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.42, 0.83]
2 Death: Time since admission to hospital	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Death within 24 hours	1	41	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.02, 8.10]
3 Coma resolution time (hours)	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Children	6	358	Mean Difference (IV, Fixed, 95% CI)	-5.45 [-7.90, -1.00]
4 Neurological sequelae at discharge	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Children	7	968	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.66, 1.07]
4.2 Adults	1	560	Risk Ratio (M-H, Fixed, 95% CI)	2.92 [0.31, 27.86]
5 Neurological sequelae at follow-up	2	566	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.49, 1.38]
5.1 Day 7	1	134	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.27, 2.14]
5.2 Day 28	1	432	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.46, 1.53]
6 Parasite clearance time	8	446	Mean Difference (IV, Fixed, 95% CI)	-8.82 [-11.20, -6.45]
6.1 Children	7	420	Mean Difference (IV, Fixed, 95% CI)	-9.03 [-11.43, -6.63]
6.2 Adults	1	26	Mean Difference (IV, Fixed, 95% CI)	1.70 [-15.56, 18.96]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Proportion with parasite clearance	2	498	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.91, 1.00]
7.1 At 72 hours	2	249	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.84, 1.02]
7.2 At 7 days	2	249	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.95, 1.02]
8 Fever clearance time (hours)	9		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 Children	8	457	Mean Difference (IV, Fixed, 95% CI)	-3.73 [-6.55, -0.92]
8.2 Adults	1	26	Mean Difference (IV, Fixed, 95% CI)	-29.70 [-54.14, -5.26]
9 Need for blood transfusion	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Children	1	103	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.62, 2.59]
9.2 Adults	1	560	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.73, 1.29]
10 Episodes of hypoglycaemia	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Children	2	617	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.44, 1.05]
10.2 Adults	1	560	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.30, 0.64]
11 Adverse events	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 QT prolongation	2	229	Risk Ratio (M-H, Fixed, 95% CI)	3.10 [1.33, 7.19]
11.2 Local skin reactions	1	576	Risk Ratio (M-H, Fixed, 95% CI)	0.12 [0.03, 0.50]
11.3 Abscess	2	1136	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.04, 0.90]
11.4 Urticarial rash	1	576	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.15]
11.5 Supraventricular tachycardia	1	54	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.01, 4.59]
11.6 Pruritus	1	67	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.13]
11.7 Urinary tract infection	1	54	Risk Ratio (M-H, Fixed, 95% CI)	3.46 [0.15, 81.36]
11.8 Induration at injection site	1	33	Risk Ratio (M-H, Fixed, 95% CI)	15.44 [0.94, 253.49]
11.9 Leg discomfort	1	560	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.22, 2.16]
11.10 Chest infection	1	560	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.81, 1.53]
11.11 GI bleeding	1	560	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.52, 1.20]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.12 Haemoglobinuria	1	212	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.00, 1.56]

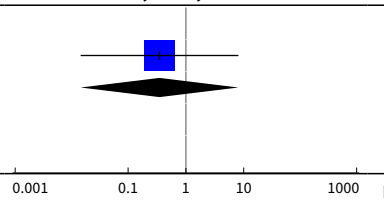
Analysis 1.1. Comparison 1 Artemether versus quinine, Outcome 1 Death.

Study or subgroup	Artemether n/N	Quinine n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Children					
Walker 1993	3/25	6/29		4.43%	0.58[0.16,2.08]
Taylor 1998	10/83	12/81		9.68%	0.81[0.37,1.78]
van Hensbroek 1996	59/288	62/288		49.39%	0.95[0.69,1.31]
Satti 2002	2/38	3/39		2.36%	0.68[0.12,3.87]
Murphy 1996	18/89	8/71		7.09%	1.79[0.83,3.89]
Ojuawo 1998	1/18	2/19		1.55%	0.53[0.05,5.33]
Olumese 1999	11/54	14/49		11.69%	0.71[0.36,1.42]
Huda 2003	5/23	6/23		4.78%	0.83[0.3,2.35]
Adam 2002	0/20	1/21		1.17%	0.35[0.02,8.1]
Minta 2005	4/33	2/34		1.57%	2.06[0.4,10.5]
Aguwa 2010	7/44	6/46		4.67%	1.22[0.44,3.35]
Osonuga 2009	0/16	0/16			Not estimable
Bobossi-Serengbe 2015	3/108	2/104		1.62%	1.44[0.25,8.47]
Subtotal (95% CI)	**839**	**820**		**100%**	**0.97[0.77,1.21]**
Total events: 123 (Artemether), 124 (Quinine)					
Heterogeneity: Tau^2=0; Chi^2=6.16, df=11(P=0.86); I^2=0%					
Test for overall effect: Z=0.3(P=0.76)					
1.1.2 Adults					
Karbwang 1992	1/14	5/12		7.26%	0.17[0.02,1.27]
Karbwang 1995	6/47	19/50		24.82%	0.34[0.15,0.77]
Seaton 1998	1/15	3/18		3.68%	0.4[0.05,3.46]
Hien 1996	36/284	47/276		64.25%	0.74[0.5,1.11]
Subtotal (95% CI)	**360**	**356**		**100%**	**0.59[0.42,0.83]**
Total events: 44 (Artemether), 74 (Quinine)					
Heterogeneity: Tau^2=0; Chi^2=4.66, df=3(P=0.2); I^2=35.63%					
Test for overall effect: Z=3.02(P=0)					
Test for subgroup differences: Chi^2=5.55, df=1 (P=0.02), I^2=81.99%					



Analysis 1.2. Comparison 1 Artemether versus quinine, Outcome 2 Death: Time since admission to hospital.

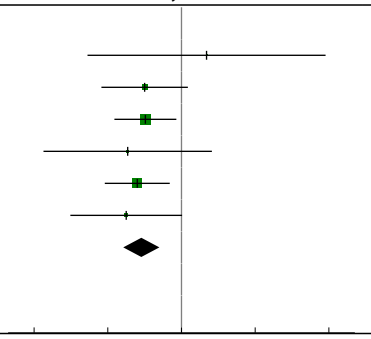
Study or subgroup	Artemether n/N	Quinine n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Death within 24 hours					
Adam 2002	0/20	1/21		100%	0.35[0.02,8.1]
Subtotal (95% CI)	**20**	**21**		**100%**	**0.35[0.02,8.1]**
Total events: 0 (Artemether), 1 (Quinine)					
Heterogeneity: Not applicable					



Study or subgroup	Artemether n/N	Quinine n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Z=0.66(P=0.51)					

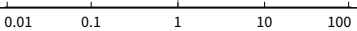
Analysis 1.3. Comparison 1 Artemether versus quinine, Outcome 3 Coma resolution time (hours).

Study or subgroup	Artemether N	Artemether Mean(SD)	Quinine N	Quinine Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.3.1 Children							
Walker 1993	25	40.1 (30.7)	29	36.7 (29.6)		2.31%	3.4[-12.75,19.55]
Satti 2002	38	21 (11)	39	26 (15)		17.5%	-5[-10.86,0.86]
Ojuawo 1998	18	12.5 (5.8)	19	17.4 (7.2)		34.09%	-4.9[-9.1,-0.7]
Olumese 1999	54	35.1 (27.1)	49	42.4 (31.6)		4.61%	-7.3[-18.72,4.12]
Huda 2003	23	34.8 (8.2)	23	40.8 (7)		31.01%	-6[-10.41,-1.59]
Adam 2002	20	12.5 (5.2)	21	20 (16.9)		10.48%	-7.5[-15.08,0.08]
Subtotal * **	**178**		**180**			**100%**	**-5.45[-7.9,-3]**
Heterogeneity: Tau^2=0; Chi^2=1.68, df=5(P=0.89); I^2=0%							
Test for overall effect: Z=4.35(P<0.0001)							



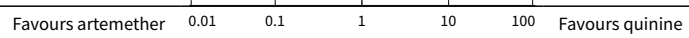
Analysis 1.4. Comparison 1 Artemether versus quinine, Outcome 4 Neurological sequelae at discharge.

Study or subgroup	Artemether n/N	Quinine n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 Children					
Walker 1993	3/22	2/23		1.83%	1.57[0.29,8.51]
van Hensbroek 1996	48/229	57/226		53.67%	0.83[0.59,1.16]
Taylor 1998	16/74	10/68		9.75%	1.47[0.72,3.02]
Satti 2002	2/38	1/39		0.92%	2.05[0.19,21.71]
Murphy 1996	16/71	25/63		24.78%	0.57[0.33,0.96]
Ojuawo 1998	2/18	2/19		1.82%	1.06[0.17,6.72]
Olumese 1999	5/43	7/35		7.22%	0.58[0.2,1.67]
Subtotal (95% CI)	**495**	**473**		**100%**	**0.84[0.66,1.07]**
Total events: 92 (Artemether), 104 (Quinine)					
Heterogeneity: Tau^2=0; Chi^2=6.05, df=6(P=0.42); I^2=0.76%					
Test for overall effect: Z=1.39(P=0.16)					
1.4.2 Adults					
Hien 1996	3/284	1/276		100%	2.92[0.31,27.86]
Subtotal (95% CI)	**284**	**276**		**100%**	**2.92[0.31,27.86]**
Total events: 3 (Artemether), 1 (Quinine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.93(P=0.35)					
Test for subgroup differences: Chi^2=1.16, df=1 (P=0.28), I^2=13.5%					



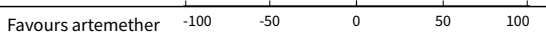
Analysis 1.5. Comparison 1 Artemether versus quinine, Outcome 5 Neurological sequelae at follow-up.

Study or subgroup	Artemether n/N	Quinine n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.5.1 Day 7					
Murphy 1996	6/71	7/63		25.93%	0.76[0.27,2.14]
Subtotal (95% CI)	**71**	**63**		**25.93%**	**0.76[0.27,2.14]**
Total events: 6 (Artemether), 7 (Quinine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.52(P=0.6)					
1.5.2 Day 28					
van Hensbroek 1996	18/218	21/214		74.07%	0.84[0.46,1.53]
Subtotal (95% CI)	**218**	**214**		**74.07%**	**0.84[0.46,1.53]**
Total events: 18 (Artemether), 21 (Quinine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.56(P=0.57)					
Total (95% CI)	**289**	**277**		**100%**	**0.82[0.49,1.38]**
Total events: 24 (Artemether), 28 (Quinine)					
Heterogeneity: Tau^2=0; Chi^2=0.03, df=1(P=0.87); I^2=0%					
Test for overall effect: Z=0.75(P=0.46)					
Test for subgroup differences: Chi^2=0.03, df=1 (P=0.87), I^2=0%					



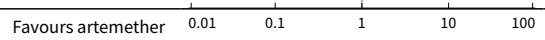
Analysis 1.6. Comparison 1 Artemether versus quinine, Outcome 6 Parasite clearance time.

Study or subgroup	Artemether N	Artemether Mean(SD)	Quinine N	Quinine Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.6.1 Children							
Walker 1993	25	39.3 (28)	29	37.2 (21.2)		3.14%	2.1[-11.32,15.52]
Satti 2002	38	36 (18)	39	41 (12)		12.03%	-5[-11.85,1.85]
Olumese 1999	54	44.5 (26.6)	49	42 (22.8)		6.2%	2.5[-7.04,12.04]
Huda 2003	23	40.9 (8.4)	23	51.9 (1.2)		46.97%	-11[-14.47,-7.53]
Adam 2002	20	16 (9.2)	21	22.4 (11.5)		13.98%	-6.4[-12.76,-0.04]
Minta 2005	33	45.5 (20)	34	61.3 (20)		6.17%	-15.73[-25.29,-6.17]
Osonuga 2009	16	31.5 (14.5)	16	46.5 (6)		9.61%	-15[-22.67,-7.33]
Subtotal ***	**209**		**211**			**98.1%**	**-9.03[-11.43,-6.63]**
Heterogeneity: Tau^2=0; Chi^2=15.69, df=6(P=0.02); I^2=61.76%							
Test for overall effect: Z=7.37(P<0.0001)							
1.6.2 Adults							
Karbwang 1992	14	63.3 (30)	12	61.6 (12.6)		1.9%	1.7[-15.56,18.96]
Subtotal ***	**14**		**12**			**1.9%**	**1.7[-15.56,18.96]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.19(P=0.85)							
Total ***	**223**		**223**			**100%**	**-8.82[-11.2,-6.45]**
Heterogeneity: Tau^2=0; Chi^2=17.15, df=7(P=0.02); I^2=59.18%							
Test for overall effect: Z=7.28(P<0.0001)							
Test for subgroup differences: Chi^2=1.46, df=1 (P=0.23), I^2=31.32%							



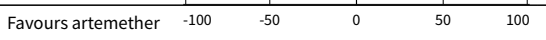
Analysis 1.7. Comparison 1 Artemether versus quinine, Outcome 7 Proportion with parasite clearance.

Study or subgroup	Artemether n/N	Quinine n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.7.1 At 72 hours					
Ojuawo 1998	15/18	18/19		7.41%	0.88[0.7,1.11]
Bobossi-Serengbe 2015	90/108	93/104		40.11%	0.93[0.84,1.04]
Subtotal (95% CI)	**126**	**123**		**47.52%**	**0.92[0.84,1.02]**
Total events: 105 (Artemether), 111 (Quinine)					
Heterogeneity: Tau^2=0; Chi^2=0.2, df=1(P=0.66); I^2=0%					
Test for overall effect: Z=1.59(P=0.11)					
1.7.2 At 7 days					
Ojuawo 1998	15/18	18/19		7.41%	0.88[0.7,1.11]
Bobossi-Serengbe 2015	108/108	104/104		45.06%	1[0.98,1.02]
Subtotal (95% CI)	**126**	**123**		**52.48%**	**0.98[0.95,1.02]**
Total events: 123 (Artemether), 122 (Quinine)					
Heterogeneity: Tau^2=0; Chi^2=4.23, df=1(P=0.04); I^2=76.35%					
Test for overall effect: Z=0.96(P=0.34)					
Total (95% CI)	**252**	**246**		**100%**	**0.95[0.91,1]**
Total events: 228 (Artemether), 233 (Quinine)					
Heterogeneity: Tau^2=0; Chi^2=25.47, df=3(P<0.0001); I^2=88.22%					
Test for overall effect: Z=1.84(P=0.07)					
Test for subgroup differences: Chi^2=1.39, df=1 (P=0.24), I^2=27.81%					

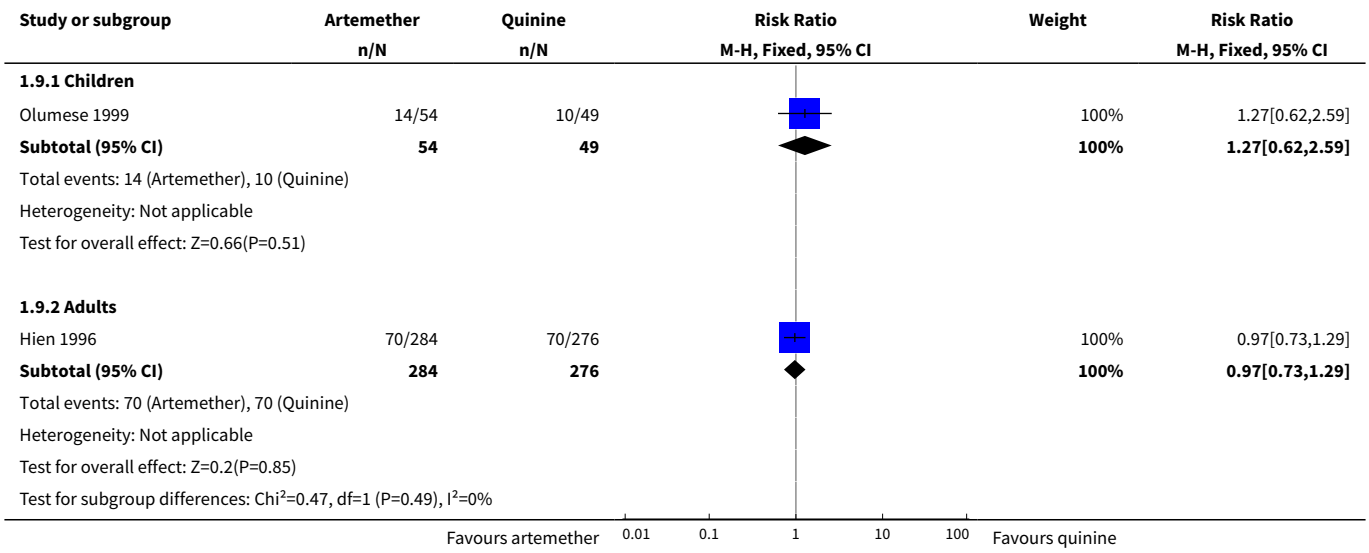


Analysis 1.8. Comparison 1 Artemether versus quinine, Outcome 8 Fever clearance time (hours).

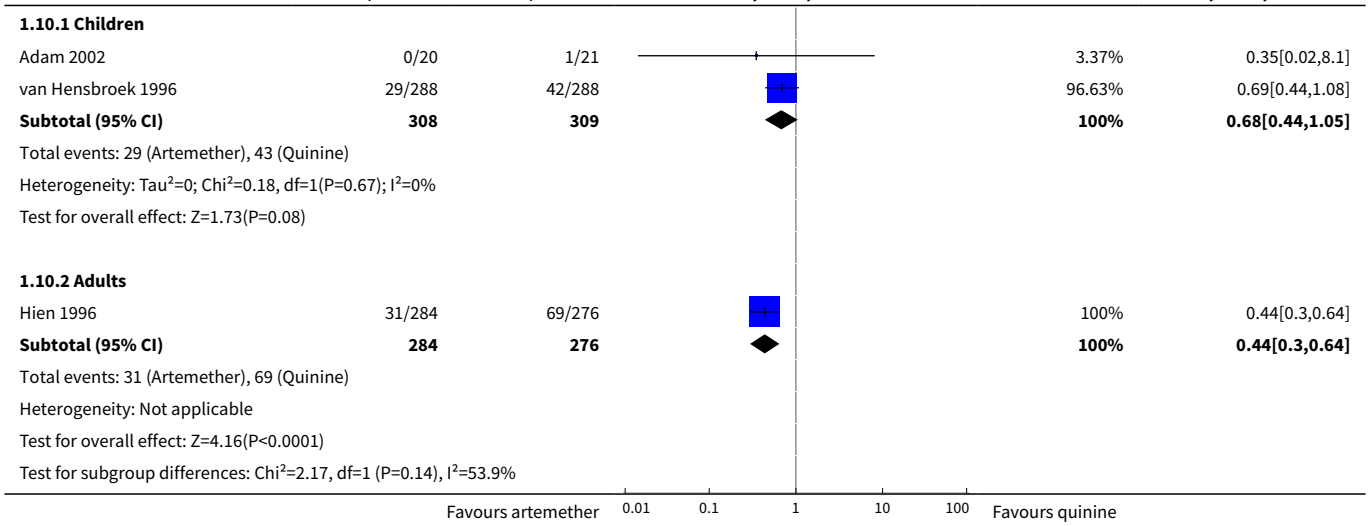
Study or subgroup	Artemether N	Artemether Mean(SD)	Quinine N	Quinine Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.8.1 Children							
Walker 1993	25	46.7 (20)	29	57.8 (27.3)		4.94%	-11.1[-23.76,1.56]
Satti 2002	38	31 (13)	39	36 (18)		16.16%	-5[-12,2]
Ojuawo 1998	18	34.7 (12.7)	19	53.3 (16.6)		8.78%	-18.6[-28.09,-9.11]
Olumese 1999	54	44.6 (26.6)	49	51.3 (25.6)		7.78%	-6.7[-16.79,3.39]
Huda 2003	23	44.5 (7.7)	23	45.9 (7.2)		42.66%	-1.4[-5.71,2.91]
Adam 2002	20	30.5 (20.9)	21	18 (8.2)		8.24%	12.5[2.7,22.3]
Minta 2005	33	45.5 (20)	34	61.3 (20)		8.65%	-15.73[-25.29,-6.17]
Osonuga 2009	16	72 (27.7)	16	46.5 (20.5)		2.78%	25.5[8.62,42.38]
Subtotal ***	**227**		**230**			**100%**	**-3.73[-6.55,-0.92]**
Heterogeneity: Tau^2=0; Chi^2=40.41, df=7(P<0.0001); I^2=82.68%							
Test for overall effect: Z=2.6(P=0.01)							
1.8.2 Adults							
Karbwang 1992	14	64.3 (27.8)	12	94 (34.7)		100%	-29.7[-54.14,-5.26]
Subtotal ***	**14**		**12**			**100%**	**-29.7[-54.14,-5.26]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.38(P=0.02)							
Test for subgroup differences: Chi^2=4.28, df=1 (P=0.04), I^2=76.63%							



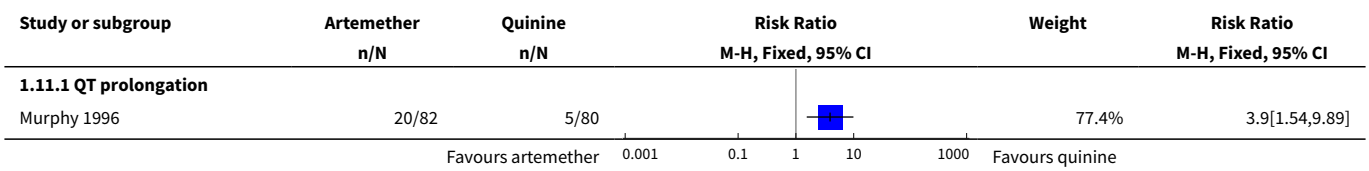
Analysis 1.9. Comparison 1 Artemether versus quinine, Outcome 9 Need for blood transfusion.



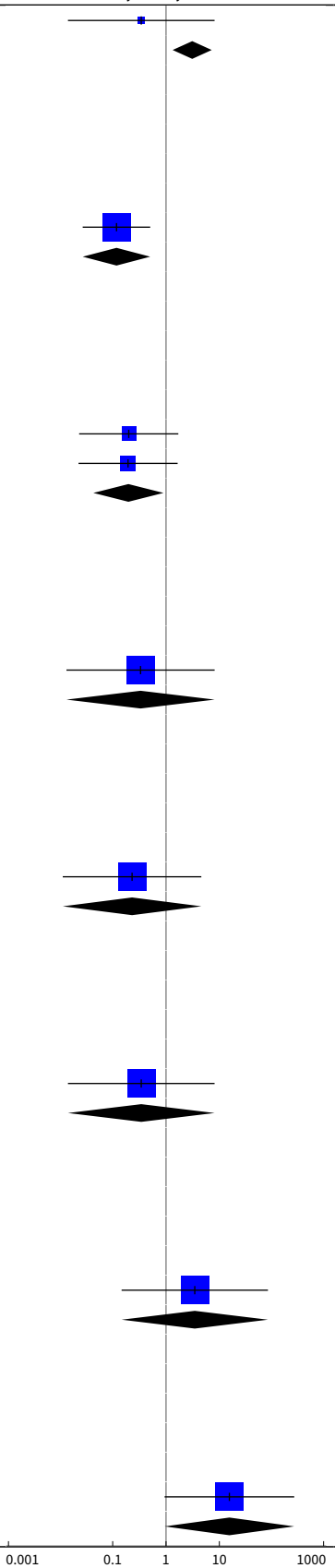
Analysis 1.10. Comparison 1 Artemether versus quinine, Outcome 10 Episodes of hypoglycaemia.

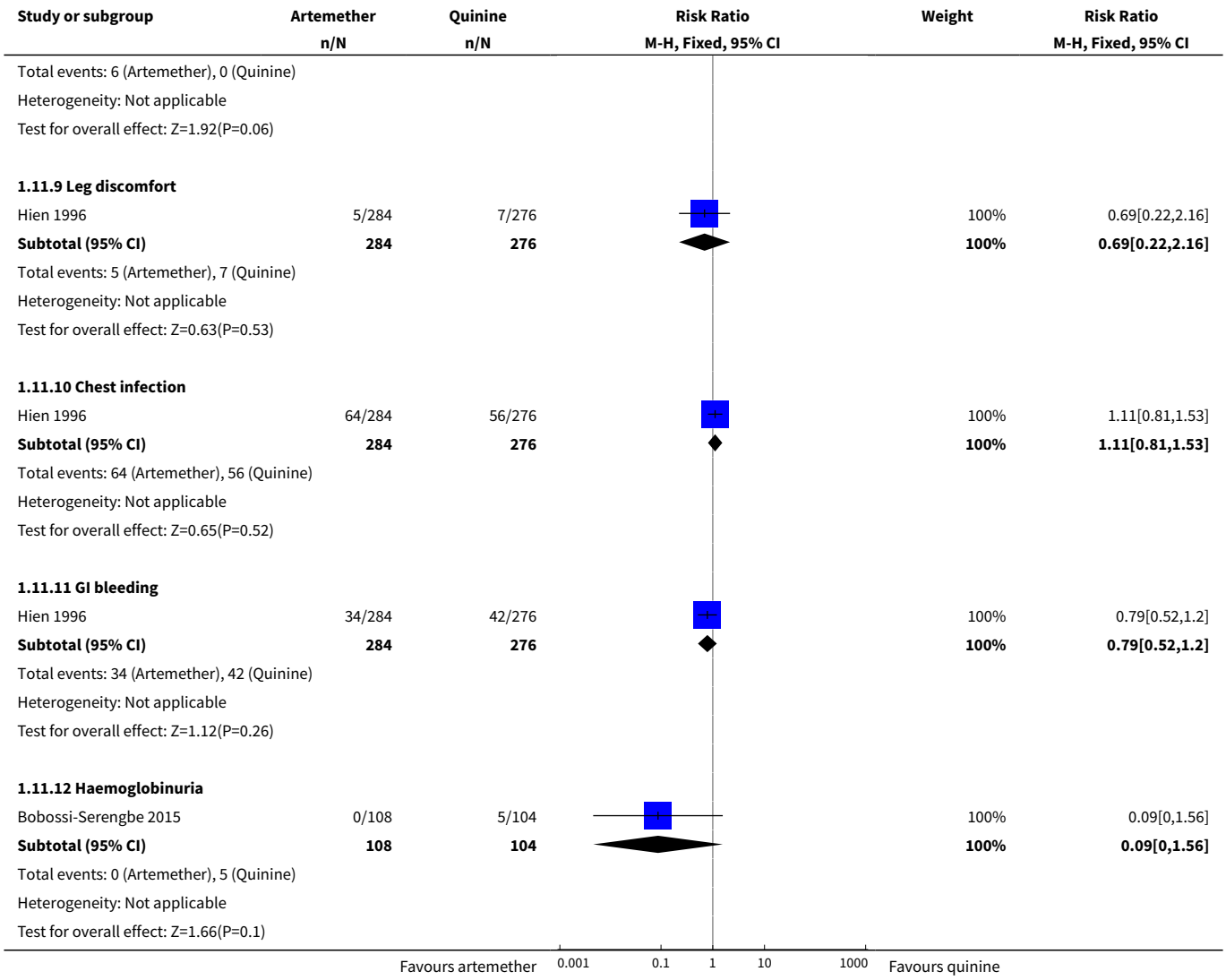


Analysis 1.11. Comparison 1 Artemether versus quinine, Outcome 11 Adverse events.



Study or subgroup	Artemether n/N	Quinine n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Minta 2005	0/33	1/34		22.6%	0.34[0.01,8.13]
Subtotal (95% CI)	**115**	**114**		**100%**	**3.1[1.33,7.19]**
Total events: 20 (Artemether), 6 (Quinine)					
Heterogeneity: Tau^2=0; Chi^2=2.09, df=1(P=0.15); I^2=52.21%					
Test for overall effect: Z=2.63(P=0.01)					
1.11.2 Local skin reactions					
van Hensbroek 1996	2/288	17/288		100%	0.12[0.03,0.5]
Subtotal (95% CI)	**288**	**288**		**100%**	**0.12[0.03,0.5]**
Total events: 2 (Artemether), 17 (Quinine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.88(P=0)					
1.11.3 Abscess					
van Hensbroek 1996	1/288	5/288		49.65%	0.2[0.02,1.7]
Hien 1996	1/284	5/276		50.35%	0.19[0.02,1.65]
Subtotal (95% CI)	**572**	**564**		**100%**	**0.2[0.04,0.9]**
Total events: 2 (Artemether), 10 (Quinine)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.99); I^2=0%					
Test for overall effect: Z=2.1(P=0.04)					
1.11.4 Urticarial rash					
van Hensbroek 1996	0/288	1/288		100%	0.33[0.01,8.15]
Subtotal (95% CI)	**288**	**288**		**100%**	**0.33[0.01,8.15]**
Total events: 0 (Artemether), 1 (Quinine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.67(P=0.5)					
1.11.5 Supraventricular tachycardia					
Walker 1993	0/25	2/29		100%	0.23[0.01,4.59]
Subtotal (95% CI)	**25**	**29**		**100%**	**0.23[0.01,4.59]**
Total events: 0 (Artemether), 2 (Quinine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.96(P=0.34)					
1.11.6 Pruritus					
Minta 2005	0/33	1/34		100%	0.34[0.01,8.13]
Subtotal (95% CI)	**33**	**34**		**100%**	**0.34[0.01,8.13]**
Total events: 0 (Artemether), 1 (Quinine)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.66(P=0.51)					
1.11.7 Urinary tract infection					
Walker 1993	1/25	0/29		100%	3.46[0.15,81.36]
Subtotal (95% CI)	**25**	**29**		**100%**	**3.46[0.15,81.36]**
Total events: 1 (Artemether), 0 (Quinine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.77(P=0.44)					
1.11.8 Induration at injection site					
Seaton 1998	6/15	0/18		100%	15.44[0.94,253.49]
Subtotal (95% CI)	**15**	**18**		**100%**	**15.44[0.94,253.49]**





Comparison 2. Artemether versus artesunate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Adults	2	494	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [1.09, 2.97]
2 Need for blood transfusion	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Adults	1	370	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.78, 1.32]
3 Episodes of hypoglycaemia	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

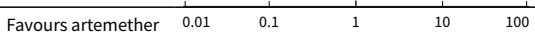
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Spontaneous bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 Artemether versus artesunate, Outcome 1 Death.

Study or subgroup	Artemether n/N	Artesunate n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Adults					
Vinh 1997	5/22	5/49		15.21%	2.23[0.72,6.92]
Vinh 1997	5/23	5/30		21.31%	1.3[0.43,3.97]
Phu 2010	24/184	13/186		63.48%	1.87[0.98,3.55]
Subtotal (95% CI)	**229**	**265**		**100%**	**1.8[1.09,2.97]**
Total events: 34 (Artemether), 23 (Artesunate)					
Heterogeneity: Tau^2=0; Chi^2=0.47, df=2(P=0.79); I^2=0%					
Test for overall effect: Z=2.31(P=0.02)					

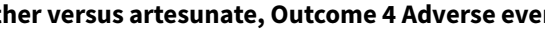
Analysis 2.2. Comparison 2 Artemether versus artesunate, Outcome 2 Need for blood transfusion.

Study or subgroup	Artemether n/N	Artesunate n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.2.1 Adults					
Phu 2010	69/184	69/186		100%	1.01[0.78,1.32]
Subtotal (95% CI)	**184**	**186**		**100%**	**1.01[0.78,1.32]**
Total events: 69 (Artemether), 69 (Artesunate)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.08(P=0.94)					



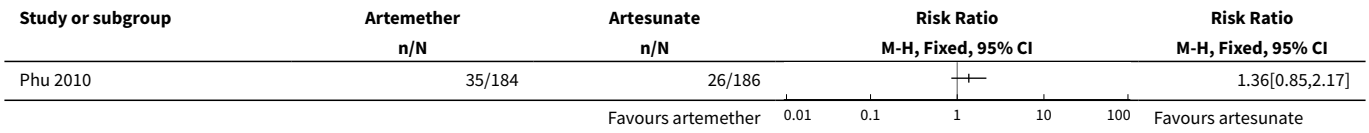
Analysis 2.3. Comparison 2 Artemether versus artesunate, Outcome 3 Episodes of hypoglycaemia.

Study or subgroup	Artemether n/N	Artesunate n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Phu 2010	5/184	3/186		1.7[0.4,7.24]



Analysis 2.4. Comparison 2 Artemether versus artesunate, Outcome 4 Adverse events.

Study or subgroup	Artemether n/N	Artesunate n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
2.4.1 Spontaneous bleeding				

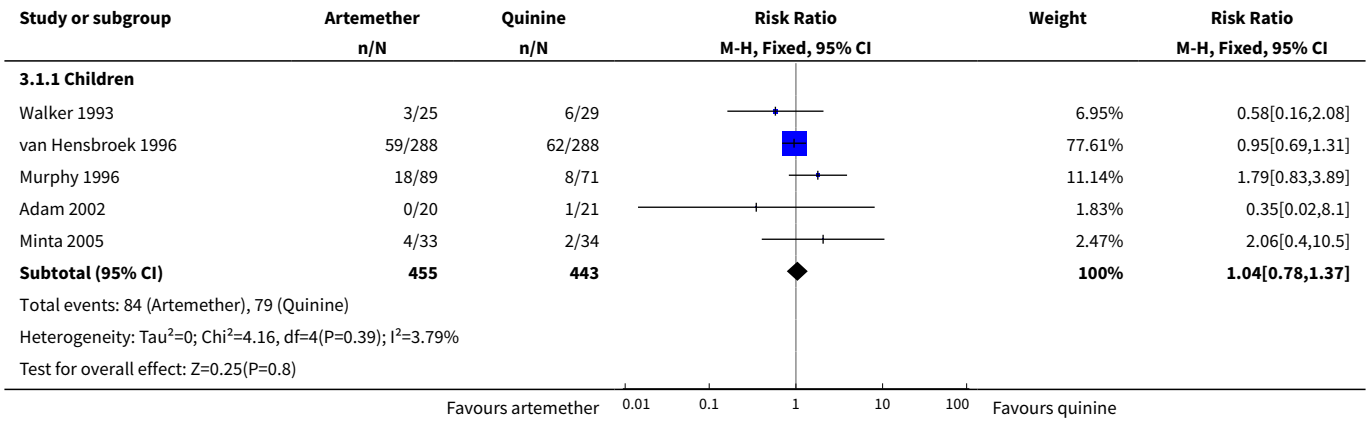


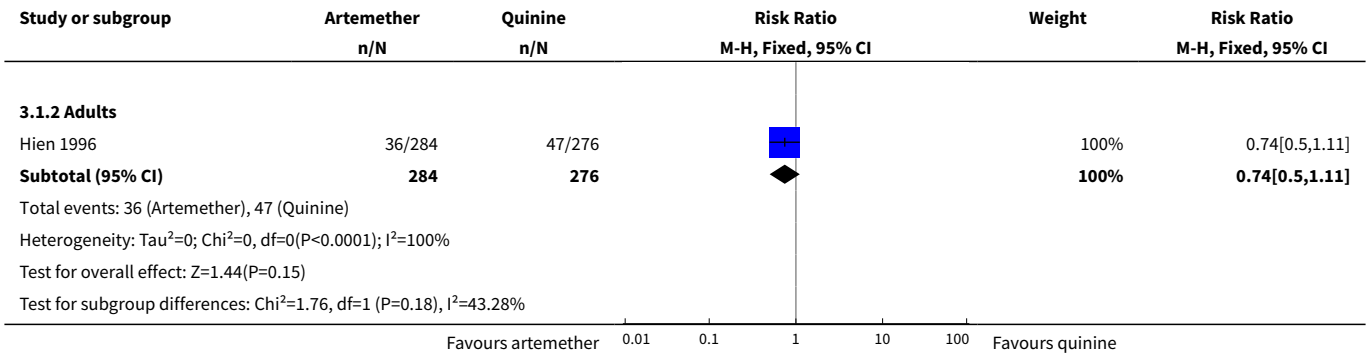
Comparison 3. Artemether versus quinine (sensitivity analysis)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Children	5	898	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.78, 1.37]
1.2 Adults	1	560	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.50, 1.11]
2 Death: Time since admission to hospital	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Death within 24 hours	1	41	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.02, 8.10]
3 Coma resolution time (hours)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Children	2	95	Mean Difference (IV, Fixed, 95% CI)	-5.53 [-12.39, 1.33]
4 Neurological sequelae at discharge	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Children	3	634	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.58, 1.01]
4.2 Adults	1	560	Risk Ratio (M-H, Fixed, 95% CI)	2.92 [0.31, 27.86]
5 Neurological sequelae at follow-up	2	566	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.49, 1.38]
5.1 Day 7	1	134	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.27, 2.14]
5.2 Day 28	1	432	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.46, 1.53]
6 Parasite clearance time	3	162	Mean Difference (IV, Fixed, 95% CI)	-7.73 [-12.65, -2.80]
6.1 Children	3	162	Mean Difference (IV, Fixed, 95% CI)	-7.73 [-12.65, -2.80]
7 Fever clearance time (hours)	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 Children	3	162	Mean Difference (IV, Fixed, 95% CI)	-4.03 [-10.05, 1.99]
8 Need for blood transfusion	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Adults	1	560	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.73, 1.29]

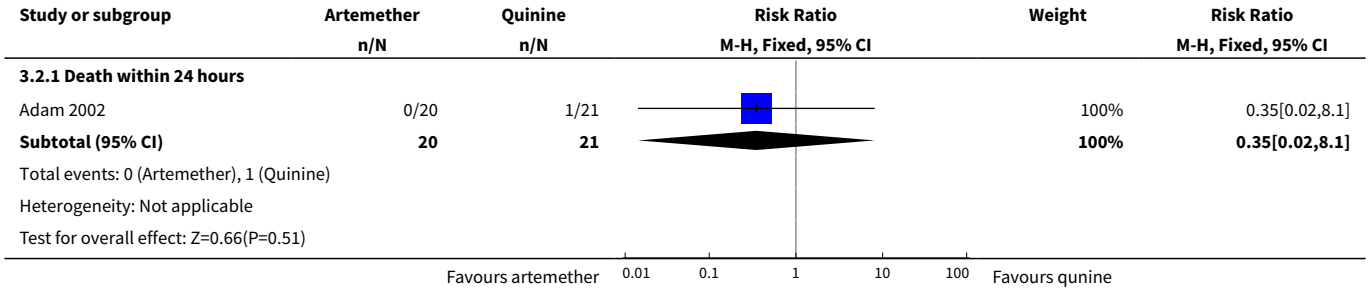
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9 Episodes of hypoglycaemia	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Children	2	617	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.44, 1.05]
9.2 Adults	1	560	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.30, 0.64]
10 Adverse events	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 QT prolongation	2	229	Risk Ratio (M-H, Fixed, 95% CI)	3.10 [1.33, 7.19]
10.2 Local skin reactions	1	576	Risk Ratio (M-H, Fixed, 95% CI)	0.12 [0.03, 0.50]
10.3 Abscess	2	1136	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.04, 0.90]
10.4 Urticarial rash	1	576	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.15]
10.5 Supraventricular tachycardia	1	54	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.01, 4.59]
10.6 Pruritus	1	67	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.13]
10.7 Urinary tract infection	1	54	Risk Ratio (M-H, Fixed, 95% CI)	3.46 [0.15, 81.36]
10.8 Induration at injection site	1	33	Risk Ratio (M-H, Fixed, 95% CI)	15.44 [0.94, 253.49]
10.9 Leg discomfort	1	560	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.22, 2.16]
10.10 Chest infection	1	560	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.81, 1.53]
10.11 GI bleeding	1	560	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.52, 1.20]
10.12 Haemoglobinuria	1	212	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.00, 1.56]

Analysis 3.1. Comparison 3 Artemether versus quinine (sensitivity analysis), Outcome 1 Death.

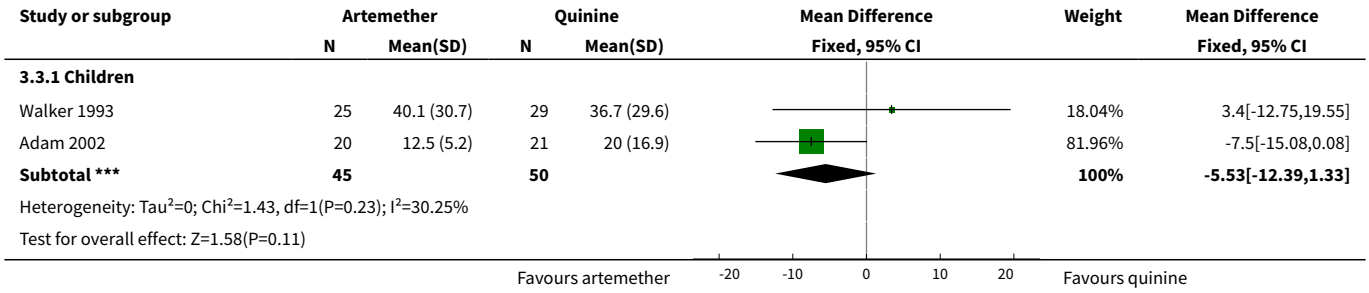




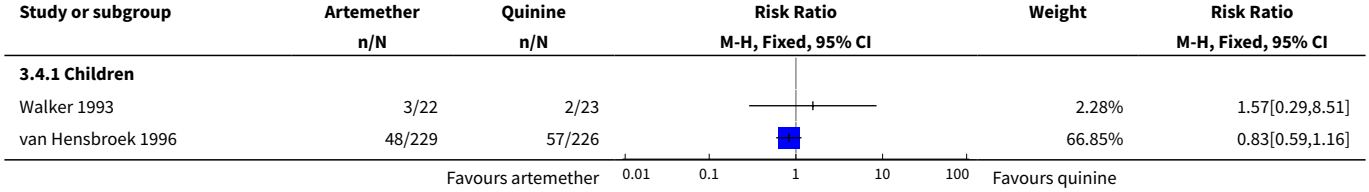
Analysis 3.2. Comparison 3 Artemether versus quinine (sensitivity analysis), Outcome 2 Death: Time since admission to hospital.

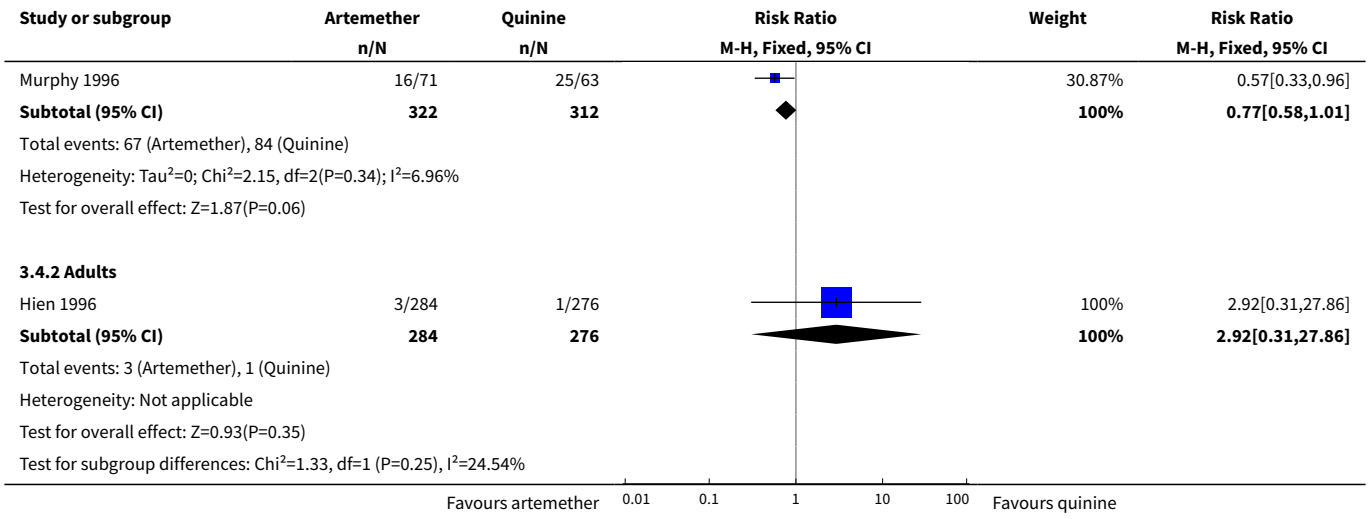


Analysis 3.3. Comparison 3 Artemether versus quinine (sensitivity analysis), Outcome 3 Coma resolution time (hours).

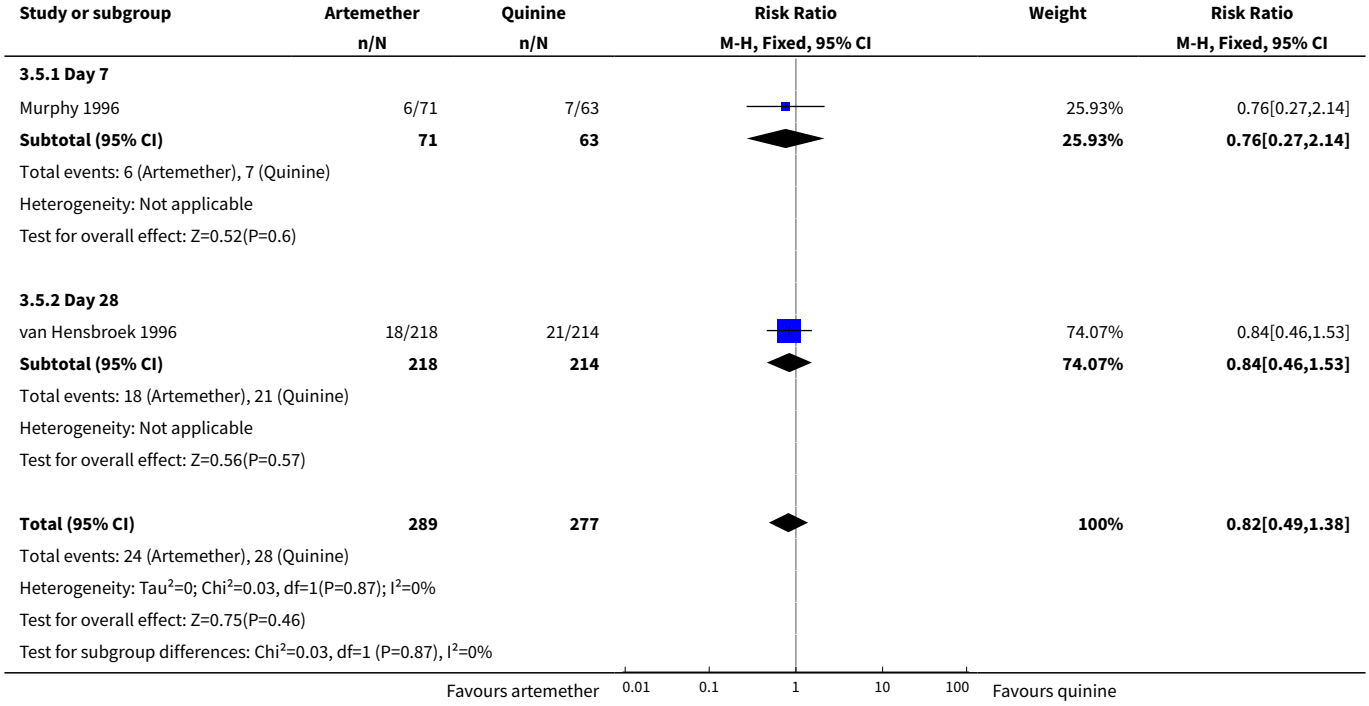


Analysis 3.4. Comparison 3 Artemether versus quinine (sensitivity analysis), Outcome 4 Neurological sequelae at discharge.

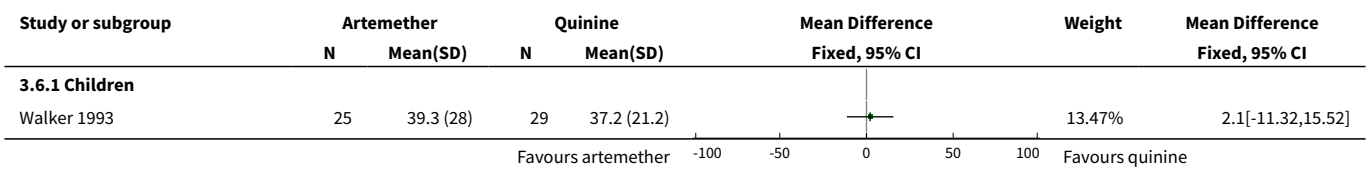




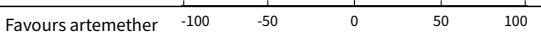
Analysis 3.5. Comparison 3 Artemether versus quinine (sensitivity analysis), Outcome 5 Neurological sequelae at follow-up.



Analysis 3.6. Comparison 3 Artemether versus quinine (sensitivity analysis), Outcome 6 Parasite clearance time.

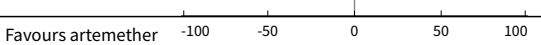


Study or subgroup	Artemether N	Artemether Mean(SD)	Quinine N	Quinine Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Adam 2002	20	16 (9.2)	21	22.4 (11.5)		60.02%	-6.4[-12.76,-0.04]
Minta 2005	33	45.5 (20)	34	61.3 (20)		26.51%	-15.73[-25.29,-6.17]
Subtotal ***	**78**		**84**			**100%**	**-7.73[-12.65,-2.8]**
Heterogeneity: Tau^2=0; Chi^2=4.92, df=2(P=0.09); I^2=59.33%							
Test for overall effect: Z=3.08(P=0)							
Total ***	**78**		**84**			**100%**	**-7.73[-12.65,-2.8]**
Heterogeneity: Tau^2=0; Chi^2=4.92, df=2(P=0.09); I^2=59.33%							
Test for overall effect: Z=3.08(P=0)							



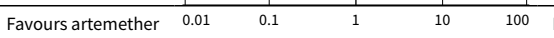
Analysis 3.7. Comparison 3 Artemether versus quinine (sensitivity analysis), Outcome 7 Fever clearance time (hours).

Study or subgroup	Artemether N	Artemether Mean(SD)	Quinine N	Quinine Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.7.1 Children							
Walker 1993	25	46.7 (20)	29	57.8 (27.3)		22.62%	-11.1[-23.76,1.56]
Adam 2002	20	30.5 (20.9)	21	18 (8.2)		37.75%	12.5[2.7,22.3]
Minta 2005	33	45.5 (20)	34	61.3 (20)		39.63%	-15.73[-25.29,-6.17]
Subtotal ***	**78**		**84**			**100%**	**-4.03[-10.05,1.99]**
Heterogeneity: Tau^2=0; Chi^2=17.87, df=2(P=0); I^2=88.81%							
Test for overall effect: Z=1.31(P=0.19)							



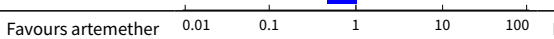
Analysis 3.8. Comparison 3 Artemether versus quinine (sensitivity analysis), Outcome 8 Need for blood transfusion.

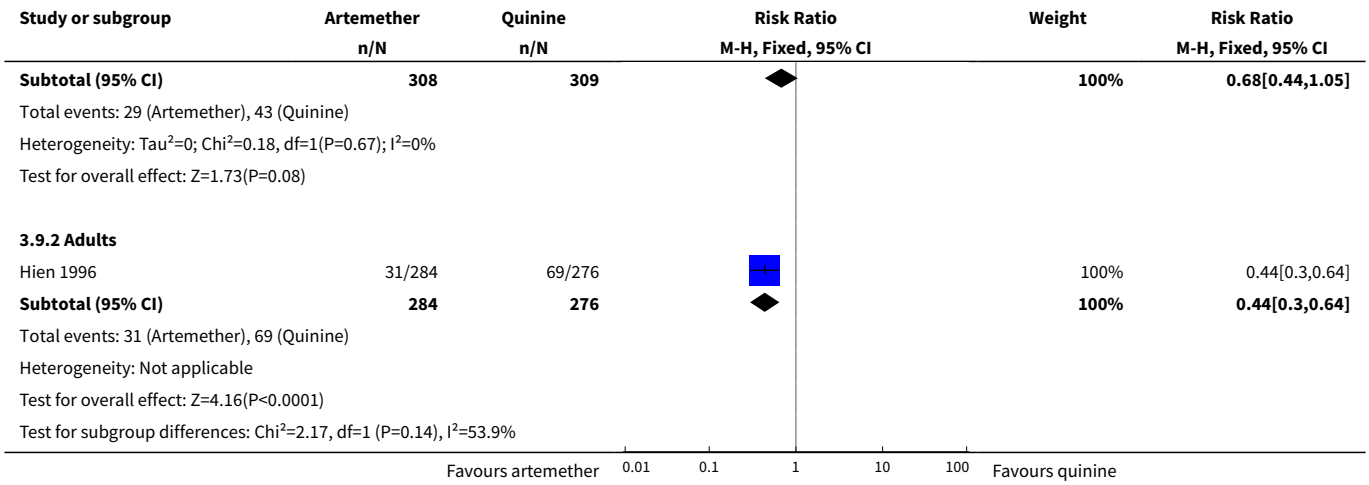
Study or subgroup	Artemether n/N	Quinine n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.8.1 Adults					
Hien 1996	70/284	70/276		100%	0.97[0.73,1.29]
Subtotal (95% CI)	**284**	**276**		**100%**	**0.97[0.73,1.29]**
Total events: 70 (Artemether), 70 (Quinine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.2(P=0.85)					



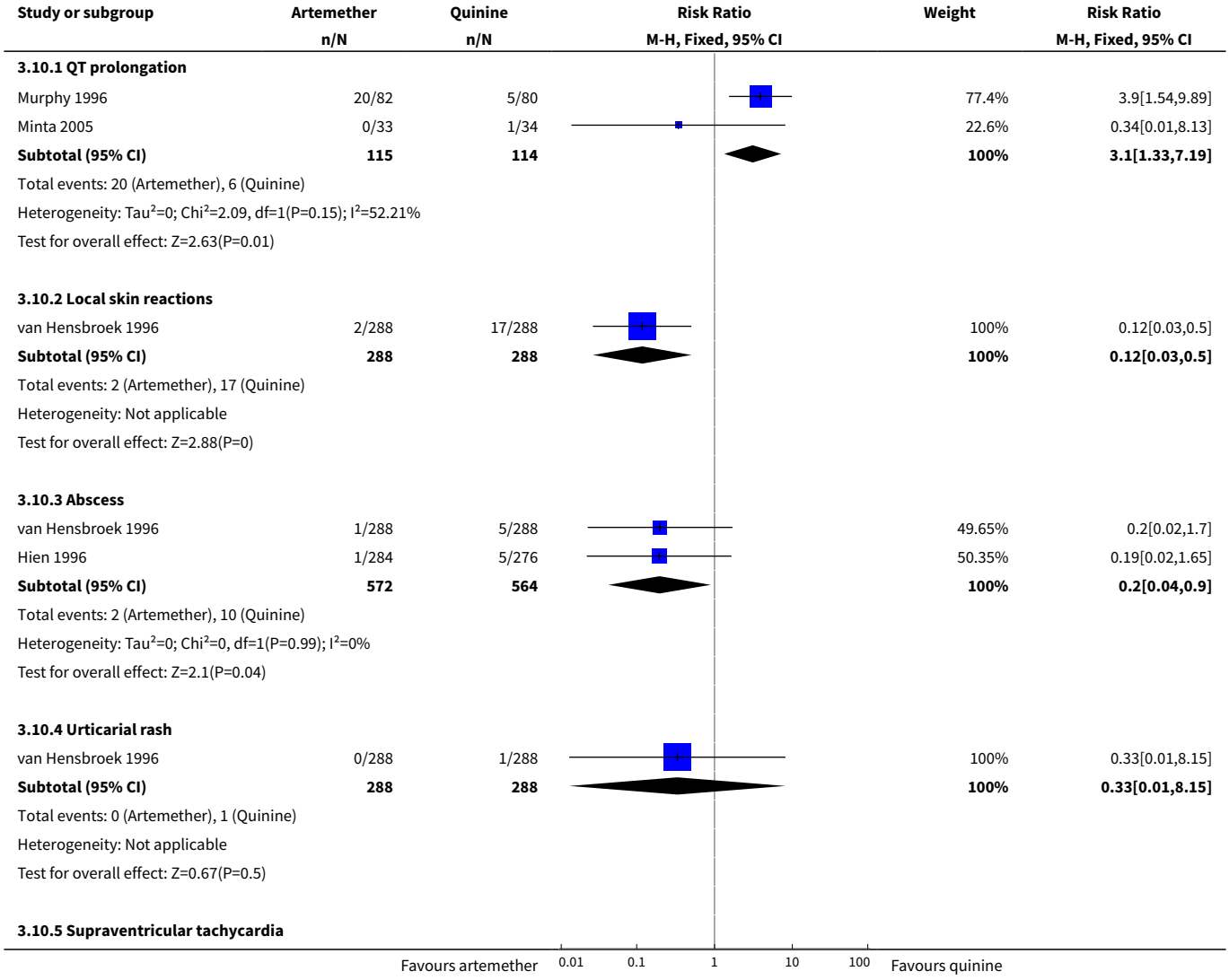
Analysis 3.9. Comparison 3 Artemether versus quinine (sensitivity analysis), Outcome 9 Episodes of hypoglycaemia.

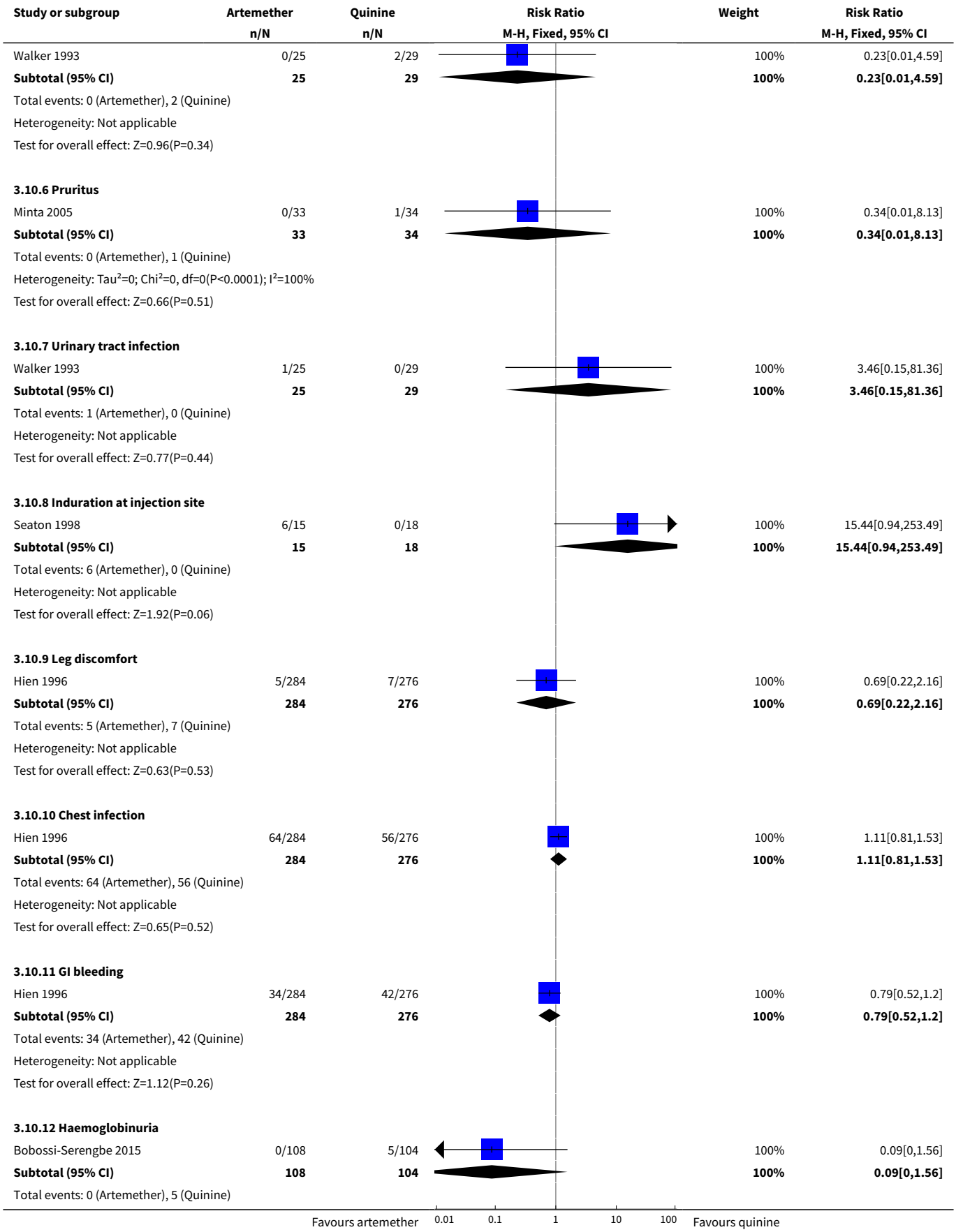
Study or subgroup	Artemether n/N	Quinine n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.9.1 Children					
Adam 2002	0/20	1/21		3.37%	0.35[0.02,8.1]
van Hensbroek 1996	29/288	42/288		96.63%	0.69[0.44,1.08]

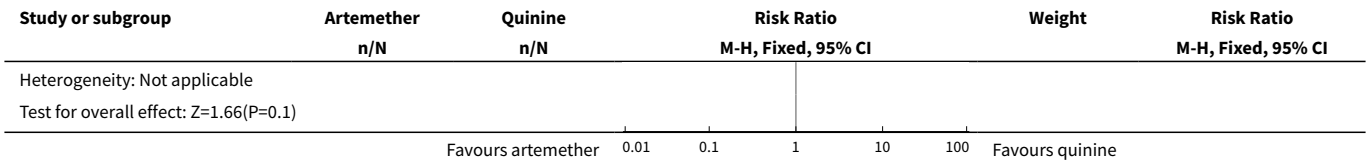




Analysis 3.10. Comparison 3 Artemether versus quinine (sensitivity analysis), Outcome 10 Adverse events.



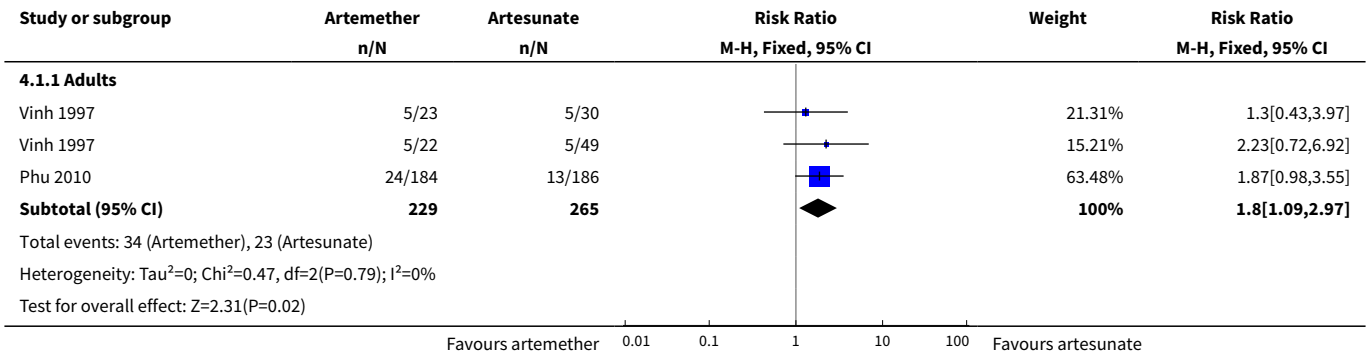




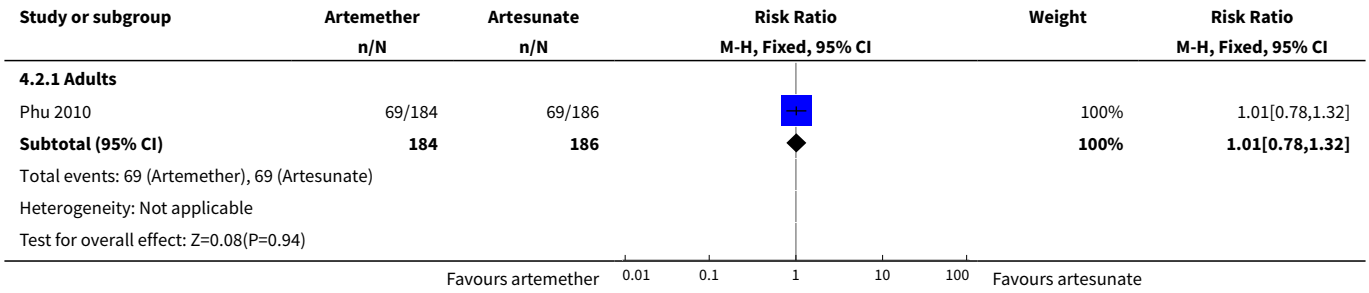
Comparison 4. Artemether versus artesunate (sensitivity analysis)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Adults	2	494	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [1.09, 2.97]
2 Need for blood transfusion	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Adults	1	370	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.78, 1.32]
3 Episodes of hypoglycaemia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Spontaneous bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

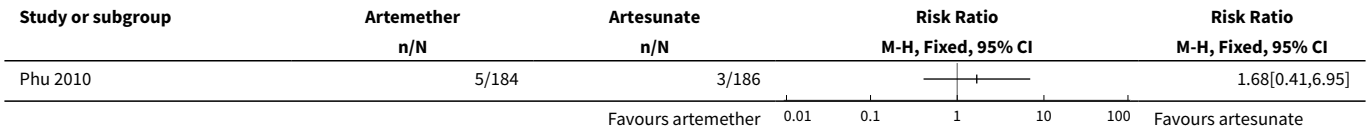
Analysis 4.1. Comparison 4 Artemether versus artesunate (sensitivity analysis), Outcome 1 Death.



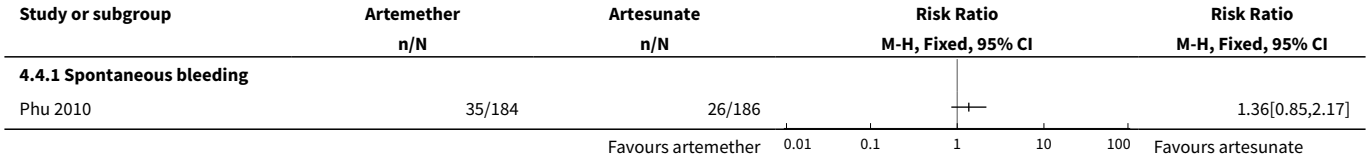
Analysis 4.2. Comparison 4 Artemether versus artesunate (sensitivity analysis), Outcome 2 Need for blood transfusion.



Analysis 4.3. Comparison 4 Artemether versus artesunate (sensitivity analysis), Outcome 3 Episodes of hypoglycaemia.



Analysis 4.4. Comparison 4 Artemether versus artesunate (sensitivity analysis), Outcome 4 Adverse events.



ADDITIONAL TABLES

Table 1. Optimal information size calculations; dichotomous outcomes

Outcome	Type of test	Proportion in control group[a]	Proportion in Intervention group	Estimated RR	Total sample size[b,c]
Death	Superiority	0.15	0.12	0.80	4068
	Equivalence	0.15	0.12 to 0.18[d]	-	5956
Neurological sequelae	Superiority	0.25	0.20	0.80	2184
	Equivalence	0.25	0.22 to 0.28[d]	-	8760

[a]The proportion in the control group is taken from the median control group risk across trials.
[b]These calculation were performed using a power calculator available at www.sealedenvelope.com/power
[c]All calculations were performed for a power of 80% and an α error of 0.05.
[d]A maximum 3% risk difference was chosen to represent equivalence.

Table 2. Optimal information size calculations; continuous outcomes

Outcome	Type of test	Mean in control group[a]	Mean in Intervention group[b]	SD of outcome	Total sample size[c,d]
Coma resolution time	Superiority	25	19	20	350
	Equivalence	25	19 to 31	20	382
Parasite clearance time	Superiority	42	36	20	350
	Equivalence	42	36 to 48	20	382
Fever clearance time	Superiority	48	42	20	350
	Equivalence	48	36 to 54	20	382

[a]The mean in the control group is taken from the median control group across studies.
[b]A six-hour time difference was chosen to represent a clinically important benefit.
[c]These calculations were performed using a power calculator available at: www.sealedenvelope.com/power
[d]All calculation were performed for a power of 80% and an α error of 0.05.

Table 3. Characteristics of trials comparing artemether and quinine in children

Trial ID	Year of study	Age limits	Quinine dosing schedule			Artemether dosing schedule		
			Loading dose	Maintainance	Follow-on therapy	Loading dose	Maintainance	Follow-on therapy
Adam 2002	2002	'Children'	20 mg/kg IV	10 mg/kg IV every 8 hours for 72 hours	Oral quinine for 7 days	3.2 mg/kg IM	1.6 mg/kg IM once daily for 4 days	None
Aguwa 2010	2007	6 months to 12 years	20 mg/kg IV or IM	10 mg/kg IV/IM every 8 hours	None	3.2 mg/kg IM	1.6 mg/kg IM once daily for 2 days	None
Bo-bossi-Serengbe 2015	2010	6 to 59 months	10 mg/kg IV	10 mg/kg IV every 4 hours	Oral quinine for 7 days	2 mg/kg IM twice daily	2 mg/kg IM once daily for 2 days	None
Huda 2003	2001	< 14 years	20 mg/kg IV	10 mg/kg IV every 8 hours	Quinine to complete 7 days	1.6 mg/kg IM twice daily	1.6 mg/kg IM once daily for 5 days	None
Minta 2005	2004	3 months to 15 years	20 mg/kg IV	10 mg/kg IV every 8 hours	Quinine 10 mg/kg every 8 hours	3.2 mg/kg IM twice daily	1.6 mg/kg IM once daily for 4 days	None
Murphy 1996	1996	5 months to 12 years	20 mg/kg IV	10 mg/kg IV every 8 hours	SP once	3.2 mg/kg IM	1.6 mg/kg IM once daily for 4 days	SP once
Ojuawo 1998	1998	Mean age about 4 years	10 mg/kg IV	10 mg/kg IV every 8 hours	Quinine to complete 7 days	3.2 mg/kg IM	1.6 mg/kg IM 12 hrs later, then once daily for 2 days	None
Olumese 1999	1999	11 months to 5 years	20mg/kg IV	10mg/kg IV every 8 hours	Quinine to complete 7 days	3.2 mg/kg IM	1.6 mg/kg IM once daily for 4 days	None
Osonuga 2009	2009	1 to 12 years	10 mg/kg IV	10 mg/kg IV every 8 hours	Quinine to complete 7 days	1.6 mg/kg IM twice daily	1.6 mg/kg IM once daily for 4 days	None
Satti 2002	1996	3 months to 15 years	10 mg/kg IV	10 mg/kg IV every 8 hours	Quinine to complete 7 days	1.6 mg/kg IM twice daily	1.6 mg/kg IM once daily for 4 days	None
Taylor 1998	1994	Mean age of 3 years	20 mg/kg IV	10 mg/kg IV every 8 hours for at least 2 doses	SP once	3.2 mg/kg IM	1.6 mg/kg IM once daily for 2 days at least	SP once
van Hens-broek 1996	1994	1 to 9 years	20 mg/kg IV	10 mg/kg IV every 12 hours	Quinine to complete 5 days	3.2 mg/kg IM	1.6 mg/kg IM once daily for 3 days	SP once[a]

Table 3. Characteristics of trials comparing artemether and quinine in children *(Continued)*

Walker 1993	1993	1 to 5 years	20 mg/kg IV	10 mg/kg IV every 8 hours	Quinine to complete 7 days	3.2 mg/kg IM	1.6 mg/kg IM once daily for 4 days	None

Abbreviations: IM = intramuscular; IV = intravenous; SP = sulphadoxine-pyrimethamine.
[a]Only in the second and third years of the study.

Table 4. Characteristics of trials comparing artemether and quinine in adults

Trial ID	Year of study	Age limits	Quinine dosing schedule			Artemether dosing schedule		
			Loading dose	Maintainance	Follow-on therapy	Loading dose	Maintainance	Follow-on therapy
Hien 1996	1996	15 to 79 years	20 mg/kg IM	10 mg/kg IM every 8 hours	Quinine or mefloquine to complete 7 days	4 mg/kg IM	2 mg/kg IM once daily for 4 days	Quinine or mefloquine to complete 7 days
Karbwang 1992	1991	15 to 45 years	20 mg/kg IV	10 mg/kg every 8 hours for 7 days	Quinine to complete 7 days	160 mg IM	80 mg IM once daily for 6 days	None
Karbwang 1995	1994	15 to 55 years	20 mg/kg IV	10 mg/kg every 8 hours for 7 days	Quinine to complete 7 days	160 mg IM	80 mg IM once daily for 6 days	None
Seaton 1998	1995	> 12 years	20 mg/kg IV	10 mg/kg IV every 8 hours	Quinine to complete 7 days	3.2 mg/kg IM	1.6 mg/kg IM once daily for 4 days	None

Abbreviations: IM = intramuscular; IV = intravenous.

Table 5. Characteristics of studies comparing artemether and artesunate in adults

Trial ID	Year of study	Age limits	Artemether dosing schedule			Artesunate dosing schedule		
			Loading dose	Maintainance	Follow-on therapy	Loading dose	Maintainance	Follow-on therapy
Phu 2010	2003	15 to 77 years	3.2 mg/kg IM	1.6 mg/kg IM daily	None	2.4 mg/kg IM	1.2 mg/kg IM once daily	2 mg/kg of artesunate to complete 7 days

Table 5. Characteristics of studies comparing artemether and artesunate in adults *(Continued)*

Vinh 1997	1994	15 to 66 years	200 mg IM	100 mg IM once daily for 3 days	Mefloquine once	120 mg IM or IV	60 mg IM or IV once daily for 3 days	Mefloquine once

Abbreviations: IM = intramuscular; IV = intravenous.

Table 6. Definitions of outcome measures used in the review

Trial ID	Coma resolution time	Fever clearance time	Parasite clearance time	Hypoglycaemia
Adam 2002	Mean value (h) reported and defined as a Blantyre coma score of 5 recorded for at least 24 hours	Mean value (h) reported and defined as the time after which the temperature remained normal (axillary temperature < 37.5 °C)	Mean value (h) reported and defined as the time passed from admission and start of treatment until 2 consecutive negative smears. Blood films repeated every 8 hours.	Number of episodes (n/N) reported but not defined
Aguwa 2010	Proportions with coma resolution on D3 reported but not defined	Proportions with fever clearance on D3 and D14 reported and defined as body temperature ≤ 37.5 °C after commencement of treatment	Proportions with parasite clearance on D3 and D14. Parasite clearance was taken as adequate clinical and parasitological response (ACPR) at days 3 and 14. Parasite count taken on D0, D3 and D14.	Not reported
Bobossi-Serengbe 2015	Not reported	Not reported	Proportions with parasite clearance on D3 and D7 reported but not defined.	Not reported
Hien 1996	Median value (h) reported and defined as the time to reach a score of 15 on the Glasgow Coma Scale	Median value (h) reported but not defined.	Median value (h) reported and defined as the time passed from admission and start of treatment until 3 consecutive negative blood smears. Blood films repeated every 4 hours for the first 24 hours and then every 6 hours.	Number of episodes (n/N) reported but not defined
Huda 2003	Glasgow coma scale was used in grading the level of consciousness of the patients every 8 hours	Mean value (h) reported and defined as time to clearance of fever	Mean value (h) reported but not defined	Not reported
Karbwang 1992	Unclear if values reported are means or medians (h)	Mean value (h) reported and defined as time for the temperature to fall below 37.5 °C and remain that value for 72 hours	Mean value (h) reported and defined as the time for the parasite count to fall below the level of microscopic detection (thick film)	Not reported
Karbwang 1995	Median value (h) reported and defined as the time taken for the patients to recover completely from unconciousness	Mean value (h) reported and defined as time for the temperature to fall below 37.5 °C and remain that value for 72 hours	Median value (h) reported and defined as the time taken for parasite count to fall below the level of microscopic detection (thick film)	Not reported
Minta 2005	Mean value (h) reported and defined as the time to normalization of consciousness	Mean value (h) reported but not defined	Mean value (h) reported and defined as time till negative parasitaemia result	Not reported
Murphy 1996	Median value (h) reported but not described	Median value (h) reported but not described	Median value (h) reported but not described. Every 4 hours until clearance	Not reported
Ojuawo 1998	Mean value (h) reported and defined as the interval between on-	Mean value (h) reported and defined as the interval between the onset of ther-	Defined as: 2 successive thick blood films done at 12 hours interval are	Not reported

Table 6. Definitions of outcome measures used in the review *(Continued)*

	set of therapy and the attainment of full consciousness	apy and the time the body temperature is ≤ 37 °C and remained so	negative for asexual forms of *Plasmodium* species	
Olumese 1999	Mean value (h) reported and defined as time to regain full consciousness	Mean value (h) reported and defined as the time for temperature to fall below 37.5 °C and remain so for at least 48 hours	Mean value (h) reported and defined as the time from start of drug administration to the first of 2 consecutive negative thick smears remaining negative until day 7	Not reported
Osonuga 2009	Mean value (h) reported and defined as time to attainment of a Blantyre score of 5 for at least 24 hours from initiation of treatment	Mean value (h) reported but not defined	Mean value (h) reported but not defined. Thick and thin film done on D0 and repeated on Days 3, 7 and 14	Not reported
Phu 2010	Median value (h) reported and defined as time to Glasgow Coma Score of 15.	Median value (h) reported and defined as the time for temperature to fall below 37.5 °C and remain so	Median value (h) reported and defined as the time to clear all parasites	Number of episodes (n/N) reported but not defined
Satti 2002	Mean value (h) reported and defined as time to regaining consciousness	Mean value (h) reported and defined as the time for temperature to fall below 37.5 °C	Mean value (h) reported and defined as time to clear parasites measured every 6 hours till clearance	Not reported
Seaton 1998	Median value (h) reported but not defined	Median value (h) reported and defined as a temperature < 37.5 °C on 2 successive readings	Median value (h) reported and defined as the time at which the blood films were negative for *P falciparum* for at least 8 hours	Number of episodes (n/N) reported but not defined
Taylor 1998	Median value (h) reported and defined as time required for a child to achieve a Blantyre Coma Score of 5	Median value (h) reported and defined as the time at which the rectal or axillary temperature dropped below 37.5 °C and remained < 37.5 °C for 24 consecutive hours	Median value (h) reported and defined as the time at which the first of 2 negative (0 parasites/200 WBC) thick blood films was prepared. Every 4 hours till clearance	Not reported
van Hensbroek 1996	Median value (h) reported and defined as time to regain full consciousness	Median value (h) reported and defined as time needed for the rectal temperature to fall below 38.0 °C for at least 24 hours	Median value (h) reported and defined as time needed for all parasites to clear relative to parasite density at admission and assessed every 12 hours till clearance	Number of episodes (n/N) reported and defined as a blood glucose level below 40 mg/dL (2.2 mmol/L)
Vinh 1997	Median value (h) reported and defined as time to regain full consciousness	Median value (h) reported and defined as time for axillary temperature to fall – and remain for ≥ 24 hours – to 37.5 °C or lower	Median value (h) reported and defined as time to clear parasites	Not reported
Walker 1993	Mean value (h) reported but not defined	Mean value (h) reported	Mean value (h) reported and defined as the time for parasitaemia to be cleared and to remain so up to Day 7. Assessed every 6 hours during	Not reported

Table 6. Definitions of outcome measures used in the review *(Continued)*

	period of coma and then every 12 hours.

Abbreviations: WBC = white blood cell.

Table 7. Additional data: Artemether versus quinine in children

Pre-specified outcome	Trial reported outcome	Trial	No. of participants	Artemether	Quinine	Comparative results reported in article
Coma resolution time (hours)	Median (IQR)	Murphy 1996	160	12 (2.8 to 96)	13 (2.8 to 96)	Not significantly different
	Median (IQR)	van Hensbroek 1996	576	26 (15 to 48)	20 (12 to 43)	P = 0.046
	Median (IQR)	Taylor 1998	164	18 (8 to 30)	20 (10 to 54)	Not significantly different
	Coma recovery (%) on Day 3	Aguwa 2010	90	15.9%	21.4%	RR = 0.763 (95% CI 0.065 to 9.015)
	Mean (SD)	Osonuga 2009	32	4.5 (13.05)	9 (24.59)	P = 0.523
	Mean (SD)	Minta 2005	67	30.57 (29.02)	25.15 (31.62)	P = 0.53
Time to hospital discharge	% spending less than one week in hospital	Aguwa 2010	90	61.76%	71.74%	P = 0.829
Fever clearance (hours)	Median (IQR)	Murphy 1996	160	32 (4 to 86)	32 (4 to 96)	Not significantly different
		van Hensbroek 1996	576	30 (16 to 48)	33 (12-60)	P = 0.8
		Taylor 1998	164	31 (24 to 52)	45 (33 to 60)	"Significant"
	Fever clearance (%) on Day 3	Aguwa 2010	90	90.0%	87.7%	P = 0.753
Parasite clearance (hours)	Median (IQR)	Murphy 1996	160	39.5 (24 to 45)	48 (37 to 56)	P < 0.001
		van Hensbroek 1996	576	48 (36 to 60)	60 (48 to 72)	P < 0.001
		Taylor 1998	164	32 (25 to 36)	40 (32 to 48)	'significant'

Table 7. Additional data: Artemether versus quinine in children *(Continued)*

	Parasite clearance (%) on Day 3	Aguwa 2010	90	99.0% n = 44	96.8% n = 46	P = 0.422
Needing blood transfusion	-	van Hensbroek 1996	-	-	-	"The two groups were similar in terms of the need for blood transfusions,and the incidence of secondary bacterial infections (data not shown)."

Abbreviations: IQR = interquartile range.

Table 8. Adverse event monitoring and reporting

Study ID	Sample size	Clinical symptoms monitoring	Biochemistry	Haematological	Electrocardiogram	Additional comments on adverse events
Adam 2002	41	Not reported	Not reported	Not reported	Not reported	"Neurological deficits were not observed in any patient during the follow-up period"
Aguwa 2010	90	Not reported	Not reported	Not reported	Not reported	None
Hien 1996	560	Clinical assessment every 4 hours for the first 24 hours and 6-hourly afterwards	Blood glucose, lactate and cytokine levels measured 4, 8, 12 and 24 hours after admission	Full blood count (FBC) on admission	Pre-treatment and 12 hours after initiation of treatment on Day 0, 4 hours after last dose and at discharge	None
Huda 2003	46	Lumbar puncture Chest x-ray on day 0	Blood Glucose, Renal Function Test, Liver Function Test and Serum Electrolyte on Days 0 and 3	FBC on Days 0 and 3	Day 0	"No serious side effects of either of the drugs were observed in our study..... Closer and more frequent monitoring and larger sample size would have probably revealed more subtle adverse drug effects."
Karbwang 1992	26	Clinical evaluation daily for at least 7 days Lumbar puncture Chest x-ray on day 0	Biochemistry on Days 0, 2, 4 and 7	FBC on Days 0, 2, 4 and 7	On admission for all patients; then once daily and every 6 hours for quinine and artemether	"The side effects in the quinine group were dizziness and vertigo. No side effects were detected with artemether".

Table 8. Adverse event monitoring and reporting *(Continued)*

					patients respectively	
Karbwang 1995	102	Clinical evaluation on admission and twice daily for at least 7 days Lumbar puncture Chest x-ray on day 0	Biochemistry on Days 0, 2, 4 and 7	FBC on Days 0, 2, 4 and 7	On admission for all patients; then once daily and every 6 hours for quinine and artemether patients respectively	QTc prolongation and tinnitus were the major adverse events in Quinine arm. Mild transient pain at injection site for approximately 15 mins after artemether treatment.
Minta 2005	67	Clinical examination daily on Days 1 to 7, and 14	Blood glucose on Days 1, 2, 3, 5, 7 and 14 Urea and Serum electrolyte, transaminases, phosphatases on Days 1, 3, 5, 7 and 14	FBC on Days 1, 3, 5, 7 and 14	Once daily on Days 1, 3, 5, 7 and 14	None
Murphy 1996	160	Clinical assessment on admission, then at 6-, then 12-hour intervals till discharge	Blood glucose, urea, electrolytes, blood gases and when clinically indicated	FBC on Day 0 and when clinically indicated Blood cultures on Day 0	On admission and at 6, 24, 30, 48 and 54 hours	None
Ojuawo 1998	37	Clinical assessment on Day 0	Urea and electrolyte Blood sugar and liver function test on Day 0	FBC on Day 0	None	None
Olumese 1999	103	Clinical assessments on Days 0, 3, 7, 14, 28	Blood glucose, urea and creatinine, electrolytes on Days 0, 3, 7, 14, 28	WBC count on Days 0, 3, 7, 14, 28	None	"No adverse reactions to the two drugs were recorded during the study".
Osonuga 2009	32	Clinical examination on Days 0 to 7 and 14	None	None	None	None
Phu 2010	370	Clinical examination on admission Chest x-ray on admission Lumbar puncture	Blood urea nitrogen, serum creatinine, aspartate aminotransferase, alanine transaminase, plasma lactate	FBC on admission	None	None
Satti 2002	77	Clinical evaluation on admission and every six hours on Days 0 to 4, and	Blood glucose, serum creatinine, serum aspartate,	WBC, haemoglobin on Days 0 and 3	None	None

Table 8. Adverse event monitoring and reporting *(Continued)*

		then once daily on Days 14, 21 and 28	aminotransferase on Day 0			
Seaton 1998	33	Chest X-ray on admission	Renal and liver function tests on admission, Days 3 and 7	FBC on Days 0, 3 and 7	None	None
Taylor 1998	183	CSF collected on admission	Blood glucose, Blood pH, on Day 0 (every four hours for the first 24 hours	Haematocrit every 8 hours FBC, urea, and electrolytes on Days 0, 3, 7 and 28	On admission, 6, 48, 54 and 96 hours	"Of the initial 127 patients on whom serial electrocardiographic tracings were made, more patients in the quinine group showed prolongation of the corrected QT intervals after treatment, but the differences were not statistically or clinically significant." "There were no significant differences between the two treatment groups in terms of adverse effects associated with antimalarial treatment (i.e. new signs and symptoms which develop within seven days of the start of treatment)."
van Hensbroek 1996	576	Clinical examination on Day 0 Lumbar puncture on admission	Blood glucose on admission, after 4 hours and 12 hours	PCV, haemoglobin, Blood culture on Day 0	None	None
Vinh 1997	124	Clinical examination on admission	Blood glucose, serum creatinine, serum bilirubin on admission	FBC on admission	None	None
Walker 1993	54	Clinical examination twice daily Spinal taps	Urea and Electrolyte, on days 3, 7, 14, 28	PCV on days 3, 7, 14, 28	On admission, at 4 and 6 hours	None

Abbreviations: CSF: cerebrospinal fluid; FBC: full blood count; PCV: packed cell volume; WBC: white blood cells

Table 9. Additional data: Artemether versus quinine in adults

Pre-specified outcome	Trial reported outcome	Trial	No. of participants	Artemether	Quinine	Comparative results reported in article
Coma resolution time (hours)	Median (IQR)	Hien 1996	560	66 (30 to 132)	48 (20 to 84)	P = 0.003
	Median (range)	Karbwang 1995	97	48 (6 to 144)	48 (6 to 144)	Not significantly different

Table 9. Additional data: Artemether versus quinine in adults *(Continued)*

Fever clearance (hours)	Median (IQR)	Hien 1996	560	127 (60 to 216)	90 (54 to 144)	< 0.001
	Median (range)	Seaton 1998	33	32 (20 to 112)	48 (28 to 88)	P = 0.034
	Median (range)	Karbwang 1995	97	79 (16 to 147)	84 (36 to 144)	Not significantly different
Parasite clearance (hours)	Median (IQR)	Hien 1996	560	72 (54 to 102)	90 (66 to 108)	< 0.001
	Median (range)	Seaton 1998	33	48(4 to 72)	52 (12 to112)	P = 0.381
	Median (range)	Karbwang 1995	97	54 (30 to 164)	78 (18 to 168)	P = 0.007

Abbreviations: IQR = interquartile range.

Table 10. Additional data: Artemether versus artesunate in adults

Pre-specified outcome	Trial reported outcome	Trial	Number of participants	Artemether	Artesunate IM	Artesunate IV	Comparative results reported in article
Coma resolution time (hours)	Median (range)	Phu 2010	370	72 (2 to 2232) n = 184	60 (4 to 2136), n = 186	-	P = 0.11
	Median (95% CI)	Vinh 1997	124	47 (31 to 63)	30 (18 to 42)	24 (4 to 44)	-
Fever clearance (hours)	Median (range)	Phu 2010	370	108 (0 to 888) n = 184	108 (0 to 888), n = 186	-	P = 0.27
	Median (95% CI)	Vinh 1997	124	48 (38 to 58)	36 (30 to 42)	30 (18 to 42)	-
Parasite clearance (hours)	Median (range)	Phu 2010	370	72 (2 to 204)	72 (7 to 330)	-	P = 0.97
	Median (95% CI)	Vinh 1997	124	30 (26 to 34)	24 (15 to 33)	24 (15 to 33)	Not statistically significant

Abbreviations: CI: confidence interval; IM: intramuscular; IV: intravenous.

APPENDICES

Appendix 1. Search strategy

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	Embase[b]	LILACS[b]	ISI Web of Science
1	malaria	Malaria ti, ab, MeSH	Malaria ti, ab, MeSH	Malaria ti, ab, Emtree	malaria	malaria
2	artemether	Artemether ti, ab	Artemether ti, ab	Artemether ti, ab, Emtree	artemether	artemether
3	Artemisinin*	Artemisinin* ti, ab	Artemisinin* ti, ab	Artemisinin* ti, ab	Artemisinin*	Artemisinin*
4	intramus-cular	Intramuscular ti, ab	Intramuscular ti, ab	Intramuscular ti, ab	intramus-cular	intramuscular
5	parenteral	Injections, Intra-muscular [MeSH]	Injections, Intra-muscular [MeSH]	Intramuscular drug ad-ministration [Emtree]	parenteral	parenteral
6	2 or 3	Parenteral ti, ab	Parenteral ti, ab	Parenteral drug adminis-tration [Emtree]	2 or 3	2 or 3
7	4 or 5	2 or 3	2 or 3	2 or 3	4 or 5	4 or 5
8	1 and 5 and 7	4 or 5 or 6	4 or 5 or 6	4 or 5 or 6	1 and 5 and 7	1 and 5 and 7
9	-	1 and 7 and 8	1 and 7 and 8	1 and 7 and 8	-	Randomised clinical trial*
10	-	-	-	-	-	8 and 9

[a]Cochrane Infectious Diseases Group Specialized Register.
[b]Search terms used in combination with the search strategy for retrieving trials developed by the Cochrane Collaboration (Lefebvre 2011).

WHAT'S NEW

Date	Event	Description
13 June 2019	New citation required but conclusions have not changed	This is an update of a Cochrane Review. The conclusions remain the same as the last published version (Esu 2014)
13 June 2019	New search has been performed	We updated the literature search to 7 September 2018 and included one new study.

CONTRIBUTIONS OF AUTHORS

Ekpereonne Esu (EE) and Emmanuel E Effa (EEE) identified and extracted data from eligible trials for this review. EE entered data into Review Manager 5 (Review Manager 2014). EEE and EE performed 'Risk of bias' assessments and analysed data. EE prepared the 'Summary of findings' tables and the first draft of the review. All authors read, gave input to all sections, and approved the final version.

DECLARATIONS OF INTEREST

EE has no known conflicts of interest.
EEE has no known conflicts of interest.
OO has no known conflicts of interest.
MM has no known conflicts of interest.

SOURCES OF SUPPORT

Internal sources

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

External sources

- Department for International Development, UK.

  Project number: 300342-104

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol, we specified that we would include only trials in children (aged < 15 years) (Esu 2013). However, we amended the inclusion criteria to include trials in adults and children.

We planned to explore data by drug regimen, type of severe malaria (cerebral versus non-cerebral malaria), time since admission to hospital, length of follow-up, and geographical region, but data were insufficient.

Dr Amirhaobu Uwaoma stepped down from the review author team.

INDEX TERMS

Medical Subject Headings (MeSH)

Africa; Age Factors; Antimalarials [*administration & dosage] [adverse effects]; Artemether [*administration & dosage] [adverse effects]; Artesunate [administration & dosage] [adverse effects]; Asia; Coma [drug therapy]; Fever [drug therapy]; Injections, Intramuscular [mortality]; Malaria, Cerebral [drug therapy] [mortality]; Malaria, Falciparum [*drug therapy] [mortality]; Oceania; Quinine [administration & dosage] [adverse effects]; Randomized Controlled Trials as Topic; Treatment Outcome

MeSH check words

Adolescent; Adult; Child; Child, Preschool; Humans; Infant