Research

Artemisinin derivatives versus quinine for cerebral malaria in African children: a systematic review

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Objective To summarize the existing evidence on the efficacy of artemether and arteether, two artemisinin derivatives, versus quinine for treating cerebral malaria in children.

Methods We searched the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE and the http://clinicaltrials.gov web site. We also checked the reference lists of existing systematic reviews and of all trials identified by the above methods. We searched exclusively for randomized controlled trials (RCTs) comparing artemether/arteether with quinine for treating cerebral malaria in children. Two independent reviewers assessed study eligibility and trial quality and extracted the data.

Findings Nine RCTs were included in the analysis, and all were from Africa. Five had adequate allocation concealment. Seven trials compared artemether with quinine (1220 children), and two compared arteether with quinine (194 children). No statistically significant difference was found between artemisinin derivatives and quinine in preventing mortality (relative risk, RR: 0.91; 95% confidence interval, CI: 0.73–1.14; I^2: 0%). The quality of the evidence, as assessed by the Grade evidence profile, was moderate. The only serious adverse event was seen in a patient in the quinine group who developed fatal black water fever.

Conclusion Artemisinin derivatives are not inferior to quinine in preventing death in children with cerebral malaria.

Une traduction en français de ce résumé figure à la fin de l'article. Al final del artículo se facilita una traducción al español. الترجمة العربية لهذه الخلاصة في نهاية النص الكامل لهذه المقالة.

Introduction

Malaria causes more than one million deaths worldwide each year, and over 90% of them occur in Africa.[1] *Plasmodium falciparum* causes the most serious form of the disease.[2] Cerebral malaria, which is the most life-threatening complication of *P. falciparum* malaria, is characterised by unrousable coma not attributable to any other cause.[2] Even with correct treatment, the lethality rate among children with cerebral malaria approaches 20%.[3]

The recommended treatment for cerebral malaria is quinine by slow intravenous infusion.[4] However, quinine has several drawbacks, including a short half-life, painful local reactions after intramuscular and intravenous administration[5] and neurotoxicity.[5,6] Permanent blindness with standard doses of quinine has been well documented.[6] Furthermore, decreasing sensitivity to quinine has been reported in south-eastern Asia and the Amazon region,[7] as well as in parts of Africa.[8]

Artemisinin derivatives, a relatively new group of antimalarials that produce a very rapid therapeutic response and are effective against multidrugresistant *P. falciparum*, have been used increasingly over the past decade.[9] Although resistance to artimisinin derivatives has been reported along the Thai–Cambodian border,[10] it has not been detected anywhere else.[9] The neurotoxic effects of artemisinin derivatives have been observed in pre-clinical animal studies at doses about 10 times higher than those used for human treatment,[11] but no such toxic effects have been reported in humans.[12]

One Cochrane systematic review has compared arteether with quinine for the treatment of children with cerebral malaria, and another meta-analysis has compared artemether with quinine in adults and children with severe *P. falciparum* malaria. In the first study, no statistically significant difference was found in the number of deaths or other outcomes, such as coma recovery time, parasite clearance time and fever clearance time.[13] However, in the second study the combined adverse outcome of either death or neurological sequelae was significantly less common in the artemether group.[12]

After the meta-analysis mentioned above, new clinical trials in which artemether has been compared with quinine for the treatment of cerebral malaria in children have been carried out. Although *P. falciparum* malaria is linked to high mortality in children and cerebral malaria is its most life threatening complication, very few systematic reviews on the treatment of children with cerebral malaria have been performed. Previous systematic reviews have compared either artemether or arteether with quinine, yet it makes sense to summarize their efficacy in a single review because both drugs are oil soluble artemisinin derivatives. If these drugs are as efficacious as quinine in preventing death in children, they are preferable to quinine for the following reasons: (i) their side-effects are fewer and (ii) the Thai–Cambodian border is the only place where resistance to them has been reported, whereas resistance to quinine has been observed in several parts of the world.

The objective of this review is to summarize the existing evidence surrounding the efficacy of artemisinin derivatives (artemether and arteether) versus quinine for the treatment of cerebral malaria in children. It will address the following question. "How efficacious are artemisinin derivatives compared with quinine for the treatment of cerebral malaria in children?"

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Methods

Search strategy

We searched the following databases exclusively for randomized controlled trials (RCTs): Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 1, 2008); MEDLINE (1966 to May 2008) and EMBASE (1980 to May 2008). We used the following search terms: malaria, quinine, quinimax, cinchona alkaloids, artemisinin, artemether, artemotil, arteether, and artecef. We also searched the http://clinicaltrials.gov web site for completed and ongoing trials. We contacted individual researchers working in the field and attempted to identify all relevant trials regardless of language or publication status (published or unpublished). We checked the reference lists of existing systematic reviews and of all trials identified by the above methods.

Inclusion criteria

We searched exclusively for RCTs that compared artemether or arteether (any route of administration) with quinine (any route of administration) for the treatment of children ≤ 15 years of age with cerebral malaria.

Outcome measures

The primary outcome measure was mortality at hospital. Secondary outcome measures were the time elapsed before recovery from coma, fever clearance time, parasite clearance time, neurological sequelae and adverse events.

Study selection

After screening the abstracts of all trials identified by the search strategy, the authors obtained full papers of potentially relevant trials and independently used an eligibility form to apply the inclusion criteria to the papers. Disagreements were resolved through discussion and consensus.

Assessment of methodological quality

The authors independently assessed the methodological quality of selected trials according to the Cochrane Infectious Diseases Group guidelines.[14] The following aspects of study design were assessed: (i) generation of the allocation sequence, (ii) allocation concealment, (iii) blinding (participant/provider/outcome assessor), and (iv) inclusion of all randomized patients in the analysis.

The generation of the allocation sequence and concealment were classified as follows: "adequate", if the method used for treatment allocation was mentioned and the allocation sequences were unpredictable (e.g. computer-generated random numbers, table of random numbers); "unclear", if the trial was randomized but no method was described; inadequate, if sequences were predictable (e.g alternative allocation).[15] Allocation concealment was classified as "adequate" if participants and the investigators who recruited them could not anticipate the assignment (e.g. central randomization; sequentially-numbered, opaque, sealed envelopes); unclear, if the method used was not mentioned; "inadequate", if participants and those enrolling them in the study could predict the next assignment (e.g. an open allocation schedule, unsealed or non-opaque envelopes).[15] Inclusion of all randomized participants in the analysis was categorized as "adequate" (if ≥ 90%), "inadequate" (if < 90%) or "unclear" (if the number of children randomized or analysed was not described). Disagreements were resolved by consensus.

Data extraction

Before data extraction, we pilot tested a data abstraction form and modified it. We then independently used the form to extract the following information: ethical approval, participants (informed consent, mean/median age, sex, diagnostic criteria, baseline coma score, duration of coma, parasite counts), methods (randomization, allocation concealment, blinding, inclusion of all randomized patients in the analysis or not, how drop-outs were dealt with), intervention (type, frequency and duration of treatment, dose and route of administration, duration of follow-up), outcome and potential conflict of interest. For each outcome, we extracted the number of children randomized and the number analysed in each treatment group. For binary outcomes, we recorded the number of children having the event and the number assessed in each treatment group. For continuous outcomes, we extracted means and standard deviations or medians and interquartile ranges for each treatment group, as well as the numbers assessed in each group. Disagreements between reviewers were resolved by discussion.

Measuring inter-rater agreement

We used Cohen's (unweighted) kappa coefficient (κ) for measuring agreement between reviewers. The κ for abstract screening was 0.78, for full text eligibility, 0.82; for allocation concealment, 0.90; for blinding of outcome assessor, 0.87; and for inclusion of all randomized patients in the analysis, 0.73.

Data analysis

We analysed the data with Review Manager 4.2 (RevMan 4.2, The Cochrane Collaboration, Oxford, United Kingdom) using relative risk (RR) for dichotomous data, weighted mean difference for continuous data and 95% confidence intervals (CIs).

We performed an analysis according to the values reported by the original authors, followed by an intention to treat analysis. If the outcomes of excluded children were given in the original article, we used this information in our intention to treat analysis. If the outcomes were not given, we assumed that all missing subjects on artemether/arteether treatment were dead and that all those on quinine treatment were alive. This extreme case analysis was performed to avoid favouring the intervention drugs if they were not as efficacious as quinine for cerebral malaria. We used fixed effects modelling in all analyses because most of the studies included few participants and the pooled result for the primary outcome showed little heterogeneity ($I^2 = 0\%$).

We constructed a funnel plot to look for evidence of publication bias. The funnel plot is asymmetric, but asymmetry can be a chance finding when fewer than 10 studies are included in the scatter plot.[16]

To test the robustness of the findings, we performed two sensitivity analyses. They were limited to studies with adequate allocation concealment and studies in which the route of administration in the treatment group was intramuscular.

We looked for statistical heterogeneity by inspecting forest plots for overlapping CIs and by using the I^2 statistic ($I^2 > 50\% =$ substantial heterogeneity).[17] The potential sources of heterogeneity for the primary outcome measure were prespecified in

the protocol. They included different diagnostic criteria, different outcome measurement criteria, type of allocation concealment, level of blinding, severity of disease, drug sensitivity or resistance patterns based on country of origin, use of additional antimalarials and route of treatment administration.

Description of studies

We identified 176 studies through our literature search. Abstract screening yielded 19 articles that potentially met our inclusion criteria, and 10 of them were excluded during the full article review (Fig. 1). This resulted in only nine articles being included in this study.

The 7 artemether trials and the 2 arteether trials that met our inclusion criteria comprised a total of 1220 and 194 children, respectively. All studies were conducted in Africa (Cameroon, the Gambia, Kenya, Malawi, Nigeria, the Sudan, Uganda and Zambia). The characteristics of the participants, the diagnostic criteria for cerebral malaria and the interventions conducted in each study are described in Table 1.

Outcome measures

In all 9 trials, death was reported as a primary outcome. The definitions of secondary outcomes applied in the studies varied, as shown below.

Coma recovery time:

From the initiation of treatment, the time it took for the child to regain consciousness (4 artemether studies) or to achieve a Blantyre Coma Score of 5 (1 artemether and 2 arteether studies). No definition was given in the remaining studies. The coma recovery time was reported as means and standard deviations in 6 trials and as medians and interquartile ranges in 3 trials.

Fever clearance time:

From the initiation of treatment, the time taken for the body temperature to drop to < 37.5 °C and remain there for at least 48 hours (1 artemether study); to drop to ≤ 37.5 °C and remain there for at least 24 hours (1 arteether and 2 arteether studies); to drop to ≤ 37.5 °C and remain there for at least 72 hours (1 artemether study) and to drop to < 38 °C and remain there for at least 24 hours (1 artemether study). Of these 6 studies, one specified the body temperature as being axillary

Fig. 1. **Identification of studies included in systematic review of RCTs comparing artemisinin derivatives with quinine for treating cerebral malaria in African children ≤ 15 years of age**
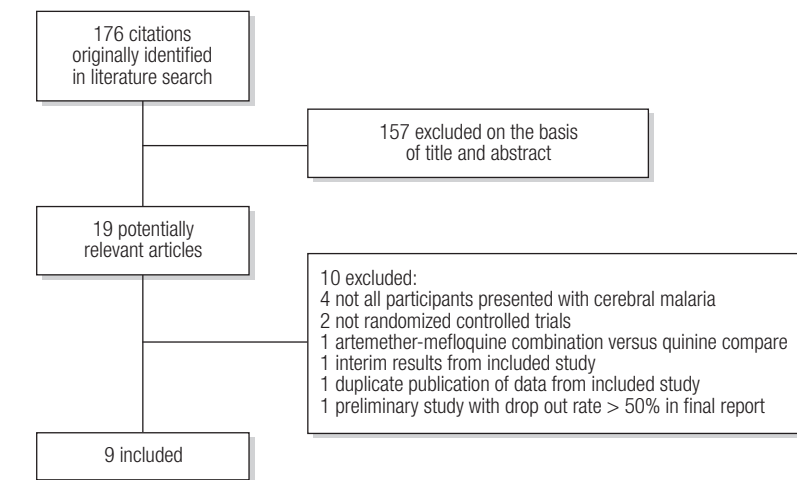
RCT, randomized controlled trial.

and another as rectal or axillary, but the rest gave no indication. The fever clearance time was reported as means and standard deviations in 6 trials and as medians and interquartile ranges in 3 trials.

Parasite clearance time:

From the initiation of treatment, the time it took to obtain two consecutive negative thick blood smear results (2 artemether studies); to obtain the first negative blood smear result (1 artemether study); to obtain the first negative blood smear result with no positive smears in the following 24 hours (1 arteether study); and to obtain the first of two consecutive negative thick smear results without subsequent positive smears until day 7 (1 artemether study). No definition was given in 3 studies. The parasite clearance time was reported as means and standard deviations in 5 trials and as medians and interquartile ranges in 3 trials. In the remaining study, the outcome was parasite clearance on day 7 (dichotomous end point, i.e. whether 2 consecutive thick blood films done with a 12-hour interval between them were negative or not).

Neurological sequelae were assessed on recovery (2 artemether trials) and at the time of discharge (1 arteether and 4 artemether trials). This outcome was not assessed in 2 trials and was reported it in various ways in the remaining studies (e.g. motor weakness, loss of neurological milestones, deaf-

ness, blindness, hallucinations, hemi-paresis, hypertonia, mental retardation, monoparesis, quadraparesis and speech impairment).

Methodological quality of included studies

Table 2 presents the methodological quality of included studies. Of the 7 artemether studies, 5 had adequately generated the allocation sequence and 4 had adequately concealed treatment allocation. In all 7 trials investigators were aware of the treatment allocation. Participants were blinded to it in only 1 trial, microscopists in 2 trials and those who assessed the neurological sequelae in 1 trial. Both arteether studies had adequately generated the allocation sequence and 1 study had adequately concealed it. Investigators and participants were aware of treatment allocation in both arteether studies. Microscopists were blinded in 1 study.

Results

Death

In seven comparisons of artemether with quinine, no significant difference in the risk of death was detected. Furthermore, the pooled meta-analysis did not show a statistically significant difference between artemether and quinine (RR: 0.95; 95% CI: 0.74–1.20; n = 1220) (Fig. 2). In the sensitivity analyses, when we omitted studies with unclear allocation concealment, the RR

Table 1. **Studies included in systematic review of RCTs comparing artemisinin derivatives with quinine for treating cerebral malaria in African children ≤ 15 years of age**

Study (country)	Participants	Intervention
Aceng, 2005 (Uganda)[18]	103 children (aged 6 months to 5 years) with cerebral malaria: seizures and unarousable coma lasting > 30 minutes after seizures, *P. falciparum* in blood film and no other cause of coma	Artemether: for children ≤ 8.9 kg, 40 mg R immediately, then 40 mg daily; for 9–18.9 kg, 80 mg R immediately, then 40 mg daily; for 19–27.9 kg, 120 mg R immediately, then 80 mg daily, all for 7 days. Quinine: 20 mg/kg IV, then 10 mg/kg IV every 8 h until conscious, then 10 mg/kg O every 8 h for 7 days.
Olumese, 1999 (Nigeria)[19]	103 children (aged 11 months – 5 years) with cerebral malaria (WHO criteria)	Artemether: 3.2mg/kg IM on day 1, then 1.6mg/kg IM daily for next 4 days. Quinine: 20 mg/kg IV, then 10 mg/kg IV every 8 h until conscious, then O to complete 21 doses.
Murphy, 1996 (Kenya)[20]	200 children aged ≤ 12 years with cerebral malaria: unrousable coma (Blantyre score < 2), *P. falciparum* parasitaemia with fever	Artemether: 3.2 mg/kg IM loading dose, then 1.6 mg/kg IM daily for 4 days. Quinine: 20 mg/kg IV, then 10 mg/kg IV every 8 h for at least 3 doses, then O when able to drink.
Ojuawo, 1998 (Nigeria)[21]	37 children aged 2–6 years with cerebral malaria: unrousable coma, *P. falciparum* in blood film and no other cause of coma	Artemether: 3.2 mg/kg IM, then 1.6 mg/kg IM every 12 h for 3 days. Quinine: 10 mg/kg IV over 2 h, then every 8 h until conscious, then O every 8 h to day 7.
Van Hensbroek, 1996 (Gambia)[22]	576 children aged 1–9 years with cerebral malaria: Blantyre score ≤ 2 and asexual *P. falciparum* parasitaemia	Artemether: 3.2 mg/kg IM on day 1, then 1.6 mg/kg IM daily for 4 days. Quinine: 20 mg/kg IM, then 10 mg/kg IM every 12 h for 5 days, then O when able to swallow.
Taylor, 1998 (Malawi)[23]	183 children admitted to paediatric ward with cerebral malaria: unrousable coma (Blantyre score ≤ 2) and asexual *P. falciparum* parasitaemia.	Artemether: 3.2 mg/kg IM, then 1.6 mg/kg IM daily. Quinine: 20 mg/kg IV, then 10 mg/kg IV every 8 h, then 10 mg/kg O every 8 h when able to drink.
Satti, 2002 (Sudan)[24]	77 children aged 3 months to 15 years with cerebral malaria (WHO criteria)	Artemether: 1.6 mg/kg IM, repeated after 12 h and then daily for 4 days. Quinine: 10 mg/kg IV every 8 h, then 10 mg/kg O 3 times daily for 7 days.
Thuma 2000 (Zambia)[25]	95 children aged 0–10 years with cerebral malaria: asexual *P. falciparum* parasitaemia, Blantyre coma score ≤ 2 and no other cause for coma	Artemether: 3.2 mg/kg IM loading dose, then 1.6 mg/kg IM daily for next 4 days. Quinine for 7 days: 20 mg/kg IV loading dose, then 10 mg/kg IV every 8 h, followed by O 10 mg/kg every 8 h.
Moyou-Somo 2001 (Cameroon)[26]	106 children aged 0–10 years with cerebral malaria: asexual *P. falciparum* parasitaemia; Blantyre coma score ≤ 2, and no other cause of coma	Arteether: 3.2 mg/kg IM the first day, then 1.6 mg/kg IM the next 4 days. Quinine for 7 days: 20 mg/kg IV loading dose, then 10 mg/kg IV every 8 h, followed by 10 mg/kg O every 8 h.

IM, intramuscularly; IV, intravenously; O, orally; *P. falciparum*, *Plasmodium falciparum*; R, rectally; RCT, randomized controlled trial.

increased slightly, from 0.95 to 0.98 (95% CI: 0.75–1.27). We got a similar result (RR: 0.98; 95% CI: 0.76–1.25) when we only included studies in which intramuscular artemether was used.

In the two comparisons of arteether versus quinine, the pooled meta-analysis showed no significant difference between the two treatments in terms of the risk of death from cerebral malaria (RR: 0.75; 95% CI: 0.43–1.30; n = 194) (Fig. 2).

Pooled analysis of the results of all artemether and arteether comparisons with quinine indicated no significant difference between the results obtained in the two treatment groups, with little heterogeneity between studies (RR: 0.91; 95% CI: 0.73–1.14; I^2: 0%)

(Fig. 2). A sensitivity analysis done by limiting the meta-analysis to studies with adequate allocation concealment (RR: 0.98; 95% CI: 0.77–1.26) and studies using intramuscular artemether or arteether (RR: 0.94; 95% CI: 0.75–1.17) showed that the overall estimated RR is fairly stable irrespective of the study quality and route of administration of the intervention drugs.

The pooled RRs from the intention to treat analysis showed no significant difference between the results obtained with artemether and quinine (RR: 1.07; 95% CI: 0.85–1.35) and overall artemether and arteether comparisons with quinine (RR: 1.00; 95% CI: 0.81–1.24), and thus enhancing the robustness of the findings.

Time to coma recovery, fever clearance and parasite clearance

The pooled result from 4 trials showed a significantly shorter coma recovery time in the artemether group than in the quinine group (Fig. 3) but no significant difference in fever clearance time (Fig. 4). The pooled results from 3 trials showed no significant difference between the artemether and quinine groups in parasite clearance time (Fig. 5, available at: http://www.who.int/bulletin/volumes/87/12/08-060327/en/index.html). The remaining 3 artemether studies, which reported all outcomes in medians and interquartile ranges, showed that parasite clearance time was significantly shorter in the

Table 2. **Methodological quality assessment for studies included in systematic review of RCTs comparing artemisinin derivatives with quinine for treating cerebral malaria in African children ≤ 15 years of age**

Trial	Randomization	Concealment	Blinding	Inclusion of randomized patients
Aceng 2005[18,a]	A	A	Participants and microscopists	A
Murphy 1996[20,a]	A	A	None	C
Ojuawo 1998[21,a]	B	B	None	B
Olumese 1999[19,a]	A	B	None	A
Taylor 1998[23,a]	A	A	None	A
Van Hensbroek 1996[22,a]	A	A	Microscopists and assessor of neurological sequelae	A
Satti 2002[24,a]	B	B	None	B
Moyou-Somo 2001[26,b]	A	B	None	A
Thuma 2000[25,b]	A	A	Microscopists	A

A, adequate; B, unclear; C, inadequate; RCT, randomized controlled trial.
[a] Artemether versus quinine.
[b] Arteether versus quinine.

artemether group than in the quinine group ($P < 0.001$) (Table 3). No significant difference in coma recovery time, fever clearance time or parasite clearance time was noted between the arteether and quinine groups (Fig. 3, Fig. 4 and Fig. 5).

Neurological sequelae

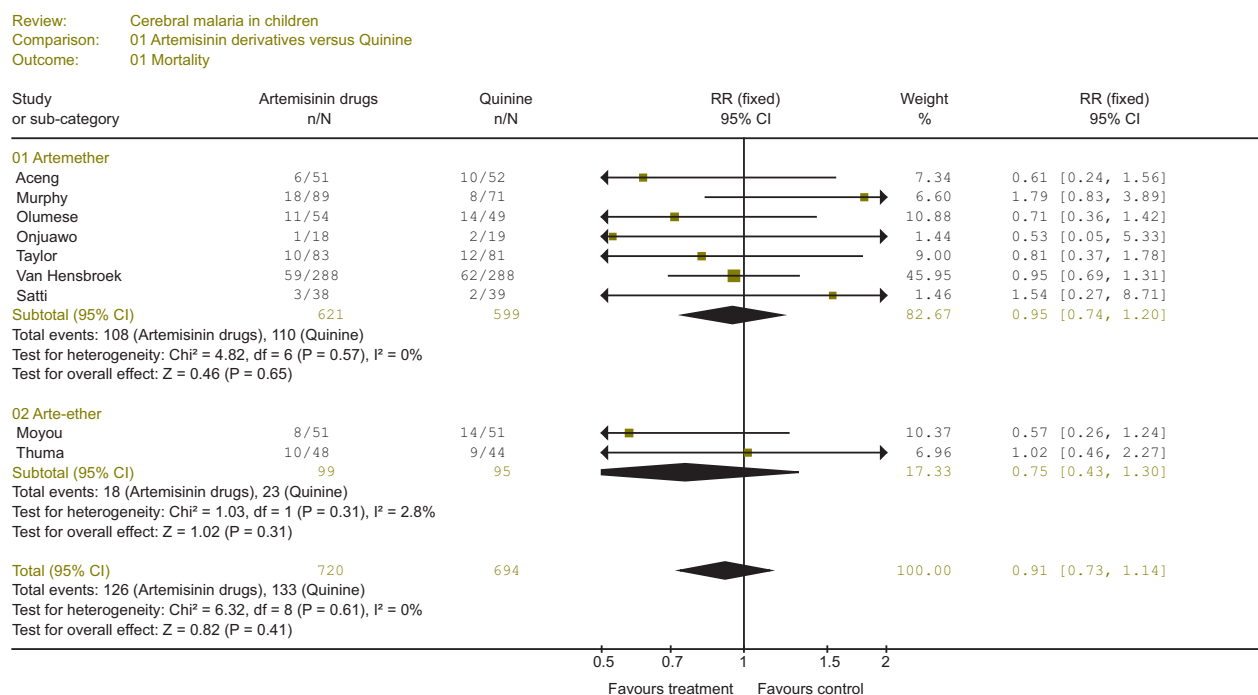Neurological sequelae at recovery or discharge were pooled together as "neu-rological sequelae at recovery" using the number of cerebral malaria survivors as the denominator. There was no evidence of a difference in the risk of neurological sequelae between artemether and quinine based on 6 studies (RR: 0.92; 95% CI: 0.72–1.17; I^2: 0%); arteether and quinine based on 1 study (RR: 1.08; 95% CI: 0.60–1.96), and overall comparisons of artemether and arteether with quinine (RR: 0.94; 95% CI: 0.75–1.17; I^2: 0%)

(Fig. 6, available at: http://www.who.int/bulletin/volumes/87/12/08-060327/en/index.html).

Adverse effects

Different adverse effects were reported across studies. Among the serious ones were fatal black water fever[26] (0/51 arteether versus 1/51 quinine; RR: 0.33; 95% CI: 0.01–8.00) and persistent hypoglycemia[18] (0/51 artemether

Fig. 2. **Forest plot of results of RCTs comparing artemisinin derivatives with quinine for treating cerebral malaria in African children ≤ 15 years of age: mortality**

Review: Cerebral malaria in children
Comparison: 01 Artemisinin derivatives versus Quinine
Outcome: 01 Mortality

Study or sub-category	Artemisinin drugs n/N	Quinine n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI
01 Artemether					
Aceng	6/51	10/52		7.34	0.61 [0.24, 1.56]
Murphy	18/89	8/71		6.60	1.79 [0.83, 3.89]
Olumese	11/54	14/49		10.88	0.71 [0.36, 1.42]
Onjuawo	1/18	2/19		1.44	0.53 [0.05, 5.33]
Taylor	10/83	12/81		9.00	0.81 [0.37, 1.78]
Van Hensbroek	59/288	62/288		45.95	0.95 [0.69, 1.31]
Satti	3/38	2/39		1.46	1.54 [0.27, 8.71]
Subtotal (95% CI)	621	599		82.67	0.95 [0.74, 1.20]
Total events: 108 (Artemisinin drugs), 110 (Quinine)					
Test for heterogeneity: Chi² = 4.82, df = 6 (P = 0.57), I² = 0%					
Test for overall effect: Z = 0.46 (P = 0.65)					
02 Arte-ether					
Moyou	8/51	14/51		10.37	0.57 [0.26, 1.24]
Thuma	10/48	9/44		6.96	1.02 [0.46, 2.27]
Subtotal (95% CI)	99	95		17.33	0.75 [0.43, 1.30]
Total events: 18 (Artemisinin drugs), 23 (Quinine)					
Test for heterogeneity: Chi² = 1.03, df = 1 (P = 0.31), I² = 2.8%					
Test for overall effect: Z = 1.02 (P = 0.31)					
Total (95% CI)	720	694		100.00	0.91 [0.73, 1.14]
Total events: 126 (Artemisinin drugs), 133 (Quinine)					
Test for heterogeneity: Chi² = 6.32, df = 8 (P = 0.61), I² = 0%					
Test for overall effect: Z = 0.82 (P = 0.41)					

0.5   0.7   1   1.5   2
Favours treatment   Favours control

RCT, randomized controlled trial; RR, relative risk.
Image produced using Review Manager 4.2 (RevMan 4.2, The Cochrane Collaboration, Oxford, United Kingdom).
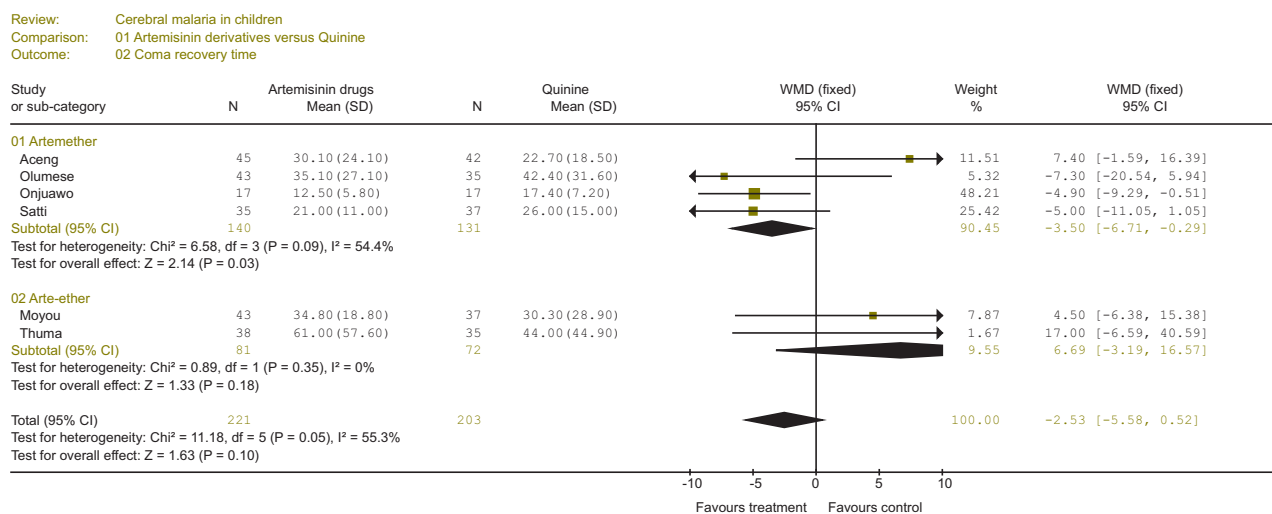
Fig. 3. **Forest plot of results of RCTs comparing artemisinin derivatives with quinine for treating cerebral malaria in African children ≤ 15 years of age: coma recovery time**

Review: Cerebral malaria in children
Comparison: 01 Artemisinin derivatives versus Quinine
Outcome: 02 Coma recovery time

Study or sub-category	Artemisinin drugs N	Mean (SD)	Quinine N	Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Artemether							
Aceng	45	30.10(24.10)	42	22.70(18.50)		11.51	7.40 [-1.59, 16.39]
Olumese	43	35.10(27.10)	35	42.40(31.60)		5.32	-7.30 [-20.54, 5.94]
Onjuawo	17	12.50(5.80)	17	17.40(7.20)		48.21	-4.90 [-9.29, -0.51]
Satti	35	21.00(11.00)	37	26.00(15.00)		25.42	-5.00 [-11.05, 1.05]
Subtotal (95% CI)	140		131			90.45	-3.50 [-6.71, -0.29]
Test for heterogeneity: Chi² = 6.58, df = 3 (P = 0.09), I² = 54.4%							
Test for overall effect: Z = 2.14 (P = 0.03)							
02 Arte-ether							
Moyou	43	34.80(18.80)	37	30.30(28.90)		7.87	4.50 [-6.38, 15.38]
Thuma	38	61.00(57.60)	35	44.00(44.90)		1.67	17.00 [-6.59, 40.59]
Subtotal (95% CI)	81		72			9.55	6.69 [-3.19, 16.57]
Test for heterogeneity: Chi² = 0.89, df = 1 (P = 0.35), I² = 0%							
Test for overall effect: Z = 1.33 (P = 0.18)							
Total (95% CI)	221		203			100.00	-2.53 [-5.58, 0.52]
Test for heterogeneity: Chi² = 11.18, df = 5 (P = 0.05), I² = 55.3%							
Test for overall effect: Z = 1.63 (P = 0.10)							

-10   -5   0   5   10
Favours treatment   Favours control

RCT, randomized controlled trial; SD, standard deviation; WMD, weighted mean difference.
Image produced using Review Manager 4.2 (RevMan 4.2, The Cochrane Collaboration, Oxford, United Kingdom).

versus 1/52 quinine; RR: 0.34; 95% CI: 0.01–8.15). The child with persistent hypoglycemia had poor liver function before starting treatment.[18] Other adverse events included injection abscess requiring incision and drainage (1/288 artemether versus 5/288 quinine;[22] RR: 0.20; 95% CI: 0.02–1.70); QT prolongation on electrocardiogram (20/82 artemether versus 5/80 quinine;[20] RR: 3.90; 95% CI: 1.54–9.89), and urticarial rash/vomiting (2/333 artemether versus 4/330 quinine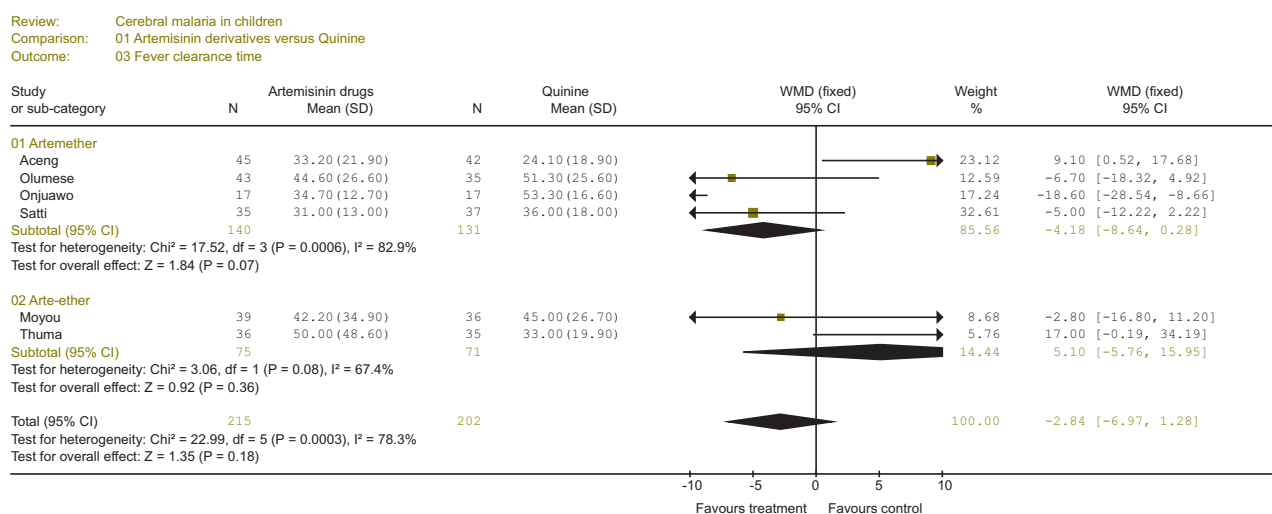;[18,22] RR: 0.53; 95% CI: 0.12–2.41). Thuma et al. reported 82 adverse events in 36/48 arteether and 61 adverse events in 34/44 quinine patients[25] (RR: 0.97; 95% CI: 0.77–1.22).

Discussion

This review showed no statistically significant difference between artemisinin derivatives and quinine in preventing death in children with cerebral malaria. Sensitivity analyses and intention to treat analyses, separately for artemether studies as well as for all artemether and arteether studies, were quite consistent and confirmed the robustness of this result. The evidence for the pooled RR of death for children treated with artemisinin derivatives versus quinine was of moderate quality, based on the Grade evidence profile[27]. When artemether and arteether studies were assessed separately, the quality of the evidence for the pooled estimate of death was rated as moderate in artemether studies (*n* = 1220) and as low in arteether studies (*n* = 194) because the small number of participants implies that

Fig. 4. **Forest plot of results of RCTs comparing artemisinin derivatives with quinine for treating cerebral malaria in African children ≤ 15 years of age: fever clearance time**

Review: Cerebral malaria in children
Comparison: 01 Artemisinin derivatives versus Quinine
Outcome: 03 Fever clearance time

Study or sub-category	Artemisinin drugs N	Mean (SD)	Quinine N	Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Artemether							
Aceng	45	33.20(21.90)	42	24.10(18.90)		23.12	9.10 [0.52, 17.68]
Olumese	43	44.60(26.60)	35	51.30(25.60)		12.59	-6.70 [-18.32, 4.92]
Onjuawo	17	34.70(12.70)	17	53.30(16.60)		17.24	-18.60 [-28.54, -8.66]
Satti	35	31.00(13.00)	37	36.00(18.00)		32.61	-5.00 [-12.22, 2.22]
Subtotal (95% CI)	140		131			85.56	-4.18 [-8.64, 0.28]
Test for heterogeneity: Chi² = 17.52, df = 3 (P = 0.0006), I² = 82.9%							
Test for overall effect: Z = 1.84 (P = 0.07)							
02 Arte-ether							
Moyou	39	42.20(34.90)	36	45.00(26.70)		8.68	-2.80 [-16.80, 11.20]
Thuma	36	50.00(48.60)	35	33.00(19.90)		5.76	17.00 [-0.19, 34.19]
Subtotal (95% CI)	75		71			14.44	5.10 [-5.76, 15.95]
Test for heterogeneity: Chi² = 3.06, df = 1 (P = 0.08), I² = 67.4%							
Test for overall effect: Z = 0.92 (P = 0.36)							
Total (95% CI)	215		202			100.00	-2.84 [-6.97, 1.28]
Test for heterogeneity: Chi² = 22.99, df = 5 (P = 0.0003), I² = 78.3%							
Test for overall effect: Z = 1.35 (P = 0.18)							

-10   -5   0   5   10
Favours treatment   Favours control

RCT, randomized controlled trial; SD, standard deviation; WMD, weighted mean difference.
Image produced using Review Manager 4.2 (RevMan 4.2, The Cochrane Collaboration, Oxford, United Kingdom).

Table 3. **Time to recovery from coma, parasite clearance and fever clearance in studies included in systematic review of RCTs comparing artemether with quinine for treating cerebral malaria in African children ≤ 15 years of age**

Outcome	Trial	Artemether	Quinine	P-value in original trials
Coma recovery time in hours, median (IQR)	Taylor, 1998[23]	18 (8–30) *n* = 73	20 (10–54) *n* = 69	> 0.05
	Murphy, 1996[20]	12 (2.80–96) *n* = 71	13 (2.83–96) *n* = 63	> 0.05
	Van Hensbroek, 1996[22]	26 (15–48) *n* = 223	20 (12–43) *n* = 221	0.05
Parasite clearance time in hours, median (IQR)	Taylor, 1998[23]	32 (25–36) *n* = 73	40 (32–48) *n* = 69	< 0.001
	Murphy, 1996[20]	39.5 (24–45) *n* = 71	48.0 (37–56) *n* = 63	< 0.001
	Van Hensbroek, 1996[22]	48 (36–60) *n* = 229	60 (48–72) *n* = 226	< 0.001
Fever clearance time in hours, median (IQR)	Taylor, 1998[23]	31 (24–52) *n* = 73	45 (33–60) *n* = 69	< 0.05
	Murphy, 1996[20]	32 (4–86) *n* = 71	32 (4–96) *n* = 63	> 0.05
	Van Hensbroek, 1996[22]	30 (16–48) *n* = 229	33 (12–60) *n* = 226	0.80

IQR, interquartile range; RCT, randomized controlled trial.

meta-analyses may have insufficient power to detect significant differences in the arteether group.

Meta-analysis of 4 artemether studies that reported coma recovery time in means and standard deviations showed a shorter coma recovery time in the artemether group (weighted mean difference: −3.50; 95% CI: −6.71 to −0.29) (Fig. 3). For the purposes of sensitivity analysis, we estimated means from medians[28] and standard deviations from interquartile ranges[29] for the remaining 3 studies, which we then incorporated into our meta-analysis. When the results of the 7 artemether studies were pooled together, the weighted mean difference in coma recovery time between the artemether and quinine groups was no longer significant (weighted mean difference: −0.26; 95% CI: −2.70 to 2.18).

For studies that reported the results in means and standard deviations for fever clearance time and parasite clearance time, meta-analysis showed

no significant difference between the artemether and quinine groups (Fig. 4, Fig. 5). However, when the studies in which means were estimated from medians[28] and standard deviations from interquartile ranges[29] were included in the analyses, both fever clearance time (weighted mean difference: −5.83; 95% CI: −8.84 to −2.82) and parasite clearance time (weighted mean difference: −8.83; 95% CI: −10.75 to −6.90) were significantly shorter in the artemether group than in the quinine group. These inconsistencies may be attributable to differences in quinine sensitivity patterns in the study areas. Conversely, the pooled RR for the secondary outcome, neurological sequelae, revealed the lack of a significant difference between artemisinin derivatives and quinine, with little heterogeneity among studies (Fig. 6).

Conclusion

Despite the fact that methodological limitations of the studies in this review

downgrade the quality of the evidence, findings for death, the primary outcome, were consistent across all analyses. This suggests that artemisinin derivatives are not inferior to quinine in preventing death in children with cerebral malaria. ■

Résumé

Efficacité comparée de dérivés de l'artémisinine et de la quinine contre le paludisme cérébral chez les enfants africains : revue systématique

Objectif Récapituler les éléments existants sur l'efficacité de l'artéméther et de l'artééther, deux dérivés de l'artémisinine, par rapport à celle de la quinine, dans le traitement du paludisme cérébral chez l'enfant.

Méthodes Nous avons effectué une recherche dans le Registre central Cochrane des essais contrôlés et dans MEDLINE et EMBASE, ainsi que sur le site Internet http://clinicaltrials.gov. Nous avons aussi examiné les listes de références des revues systématiques existantes et de tous les essais identifiés par les méthodes ci-dessus. Nous avons recherché exclusivement des essais contrôlés randomisés (ECT) comparant l'artéméther ou l'artééther à la quinine dans le traitement du paludisme cérébral chez l'enfant. Deux examinateurs indépendants ont évalué l'admissibilité des études et la qualité des essais, puis ont extrait les données.

Résultats Neuf essais contrôlés randomisés, tous réalisés en Afrique, ont été pris en compte dans l'analyse. Pour cinq de ces essais, l'affectations des traitements était correctement dissimulée. Sept comparaient l'artéméther à la quinine (1220 enfants), tandis que deux autres comparaient l'artééther à la quinine (194 enfants). Aucune différence statistiquement significative n'a été relevée entre les dérivés de l'artémisinine et la quinine dans la prévention de la mortalité (risque relatif, RR : 0,91 ; intervalle de confiance à 95 %, IC : 0,73-1,14 ; I² : 0 %). D'après l'évaluation GRADE des profils de données probantes, la qualité des éléments était moyenne. Le seul effet indésirable grave, une fièvre bilieuse hémoglobinurique fatale, a été observé chez un patient appartenant au groupe sous quinine.

Conclusion Les dérivés de l'artémisinine ne sont pas inférieurs à la quinine dans la prévention de la mortalité chez les enfants atteints de paludisme cérébral.

Resumen

Revisión sistemática de comparación de los derivados de la artemisinina y la quinina como tratamientos de la malaria cerebral en niños africanos

Objetivo Obtener una sinopsis de los datos probatorios existentes sobre la eficacia del artemetero y el arteéter, dos derivados de la artemisinina, frente a la quinina como tratamiento de la malaria cerebral en los niños.

Métodos Realizamos búsquedas en el Registro Central Cochrane de Ensayos Controlados y en MEDLINE, EMBASE y el sitio web http://clinicaltrials.gov. Examinamos también las listas de referencias de revisiones sistemáticas ya existentes y de todos los ensayos localizados según se ha señalado. Buscamos exclusivamente los ensayos controlados aleatorizados (ECT) en que se habían comparado el artemetero/arteéter y la quinina como tratamientos de la malaria cerebral infantil. Dos revisores independientes evaluaron la idoneidad para el estudio y la calidad de los ensayos y extrajeron los datos.

Resultados Se analizaron en total nueve ECT, todos ellos correspondientes a África. En cinco de los ensayos se había ocultado adecuadamente la asignación del tratamiento. En siete se habían comparado artemetero y la quinina (1220 niños), y en los otros dos el arteéter y la quinina (194 niños). No se observó ninguna diferencia estadísticamente significativa entre los derivados de la artemisinina y la quinina en lo referente a la prevención de la mortalidad (riesgo relativo, RR: 0,91; intervalo de confianza del 95%: 0,73–1,14; I²: 0%). La calidad de los datos probatorios, según el perfil del grado de evidencia, fue moderada. El único evento adverso grave fue el observado en un paciente tratado con quinina que desarrolló un cuadro mortal de paludismo hemoglobinúrico.

Conclusión Los derivados de la artemisinina no son inferiores a la quinina como medio de prevención de la mortalidad en los niños con malaria cerebral.

ملخص

مقارنة بين مشتقات الأرتيميزينين والكينين في معالجة الملاريا الدماغية للأطفال الأفريقيين: مراجعة منهجية

الغرض: تلخيص البيّنات المتوفرة حول نجاعة دوائي أرتيميثر و أرتيثر، وهما من مشتقات الأرتيميزينين، مقارنة بالكينين في معالجة الملاريا الدماغية لدى الأطفال.

الطريقة: أجرى الباحثون بحثاً في السجل المركزي لمكتبة كوكران للتجارب ذات الشواهد، في موقع الإنترنت لخط استرجاع النشريات الطبية (ميدلاين) MEDLINE, EMASE وموقع http://clinicaltrials.gov. كما دققوا قوائم المراجع للمراجعات المنهجية الموجودة وجميع التجارب المحددة بالطرق السابقة. وأجروا بحثاً مقتصراً على التجارب المعشاة ذات الشواهد للمقارنة بين دوائي أرتيميثر/أرتيثر وبين الكينين في معالجة الملاريا الدماغية لدى الأطفال. وقام مراجعان مستقلان بتقييم صلاحية الدراسة وجودة التجربة واستخلصا البيانات.

الموجودات: أُدرجت تسع تجارب معشاة ذات شواهد في التحليل، وجميعهم كانوا من أفريقيا. خمس من التجارب كانت طريقة إخفاء توزيع الأدوية لديها كافية. وأجرت سبع تجارب مقارنة بين الأرتيميثر والكينين (في 1220 طفلاً)، بينما قارنت تجربتان بين الأرتيثر والكينين (في 194 طفلاً). ولم يكتشف اختلاف ذو مدلول إحصائي بين مشتقات الأرتيميزينين والكينين في توقي الوفاة (الاختطار النسبي: 0.91؛ وفاصلة الثقة 95%: 0.73 – 1.14: /²، 0%). وكانت جودة البينة متوسطة، وذلك حسب تقييم مرتسم درجة البيّنة. ولوحظ حدث ضار وحيد شديد الخطورة في مريض من مجموعة العلاج بالكينين وظهرت عليه حمى الماء الأسود القاتلة.

الاستنتاج: مشتقات الأرتيميزينين ليست أقل فعالية من الكينين في توقي الوفاة بين الأطفال المصابين بالملاريا بالدماغية.
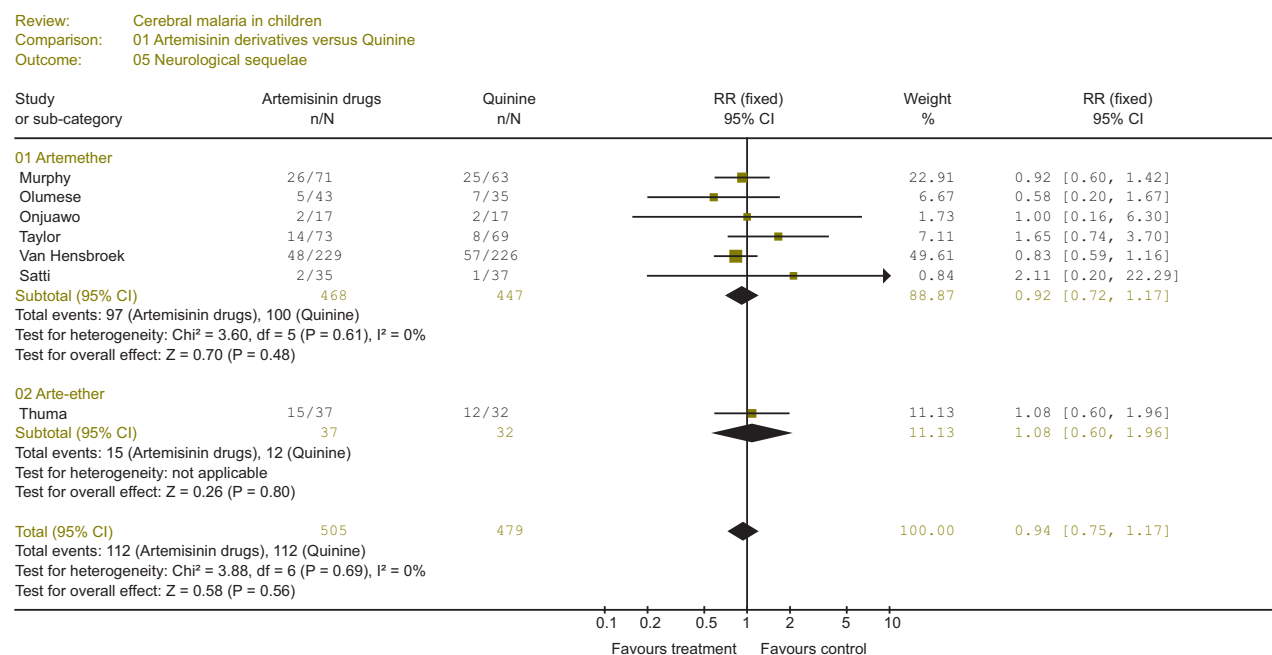
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Fig. 5. **Forest plot of results of RCTs comparing artemisinin derivatives with quinine for treating cerebral malaria in African children ≤ 15 years of age: parasite clearance time**

Review: Cerebral malaria in children
Comparison: 01 Artemisinin derivatives versus Quinine
Outcome: 04 Parasite clearance time
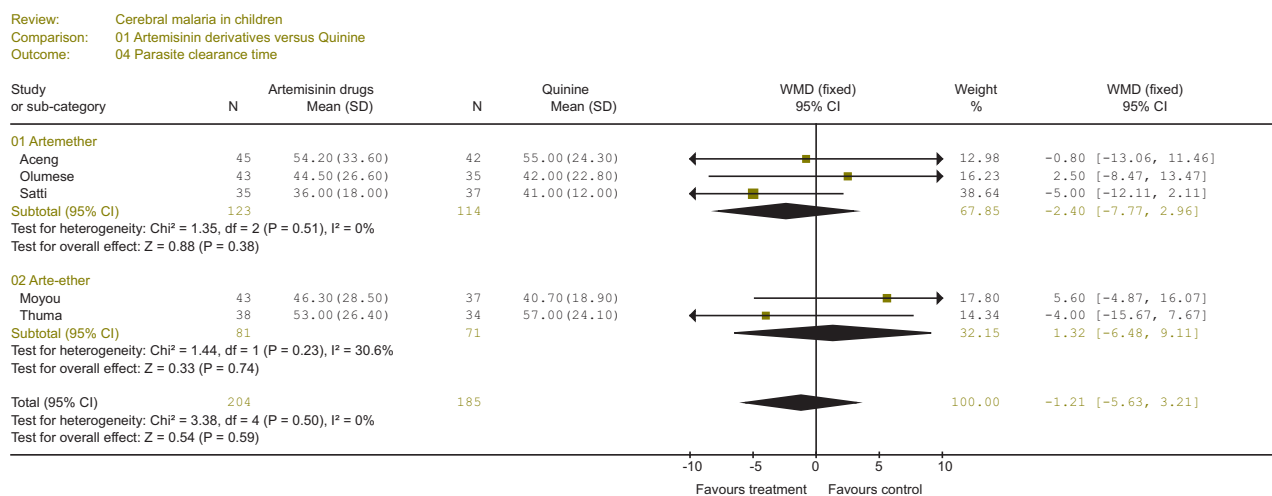
RCT, randomized controlled trial; SD, standard deviation; WMD, weighed mean difference.
Image produced using Review Manager 4.2 (RevMan 4.2, The Cochrane Collaboration, Oxford, United Kingdom).

Fig. 6. **Forest plot of results of RCTs comparing artemisinin derivatives with quinine for treating cerebral malaria in African children ≤ 15 years of age: neurological sequelae**

Review: Cerebral malaria in children
Comparison: 01 Artemisinin derivatives versus Quinine
Outcome: 05 Neurological sequelae

RCT, randomized controlled trial; RR, relative risk.
Image produced using Review Manager 4.2 (RevMan 4.2, The Cochrane Collaboration, Oxford, United Kingdom).