Artemisinin derivatives versus quinine for cerebral malaria in African children: a systematic review
Hmwe Hmwe Kyu & Eduardo Fernández

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; I²: 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.

Introduction
Malaria causes more than a million deaths worldwide each year, and over 90% of them occur in Africa. Plasmodium falciparum causes the most serious form of the disease. Cerebral malaria, which is the most life-threatening complication of P. falciparum malaria, is characterised by unrousable coma not attributable to any other cause. Even with correct treatment, the lethality rate among children with cerebral malaria approaches 20%. The recommended treatment for cerebral malaria is quinine by slow intravenous infusion. However, quinine has several drawbacks, including a short half-life, painful local reactions after intramuscular and intravenous administration and neurotoxicity. Permanent blindness with standard doses of quinine has been well documented. Furthermore, decreasing sensitivity to quinine has been reported in south-eastern Asia and the Amazon region, as well as in parts of Africa. Artemisinin derivatives, a relatively new group of antimalarials that produce a very rapid therapeutic response and are effective against multidrug-resistant P. falciparum, have been used increasingly over the past decade. Although resistance to artisiminin derivatives has been reported along the Thai–Cambodian border, it has not been detected anywhere else. 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, but no such toxic effects have been reported in humans.

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. However, in the second study the combined adverse outcome of either death or neurological sequelae was significantly less common in the arteether group. 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, arteether, artemotil, arteether, and artemef. 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 arteether 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. 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). 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). 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.

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 arteether/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 (I² = 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.

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 I² statistic (I² > 50% = substantial heterogeneity). 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 artemether and 2 arteether studies); to drop to ≥ 37.5 °C and remain there for at least 72 hours (1 arteether 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 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 arteether 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 arteether trials) and at the time of discharge (1 artemether and 4 arteether trials). This outcome was not assessed in 2 trials and was reported in various ways in the remaining studies (e.g. motor weakness, loss of neurological milestones, deafness, blindness, hallucinations, hemiparesis, 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...
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 artether 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 artether 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; I²: 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 artether (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 artether and arteether (RR: 0.94; 95% CI: 0.75–1.14) and overall artether and artether 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 artether 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 artether 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 1. Studies included in systematic review of RCTs comparing artemisinin derivatives with quinine for treating cerebral malaria in African children ≤ 15 years of age

<table>
<thead>
<tr>
<th>Study (country)</th>
<th>Participants</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aceng, 2005 (Uganda)</td>
<td>103 children (aged 6 months to 5 years) with cerebral malaria: seizures and unrousable coma lasting &gt; 30 minutes after seizures, <em>P. falciparum</em> in blood film and no other cause of coma</td>
<td>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.</td>
</tr>
<tr>
<td>Olumese, 1999 (Nigeria)</td>
<td>103 children (aged 11 months – 5 years) with cerebral malaria (WHO criteria)</td>
<td>Artemether: 3.2 mg/kg IM on day 1, then 1.6 mg/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.</td>
</tr>
<tr>
<td>Murphy, 1996 (Kenya)</td>
<td>200 children aged ≤ 12 years with cerebral malaria: unrousable coma (Blantyre score &lt; 2), <em>P. falciparum</em> parasitaemia with fever</td>
<td>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.</td>
</tr>
<tr>
<td>Ojuawo, 1998 (Nigeria)</td>
<td>37 children aged 2–6 years with cerebral malaria: unrousable coma, <em>P. falciparum</em> parasitaemia</td>
<td>Artemether: 3.2 mg/kg IM on day 1, then 1.6 mg/kg IM daily for 4 days. Quinine: 20 mg/kg IV over 2 h, then every 8 h until conscious, then O every 8 h to day 7.</td>
</tr>
<tr>
<td>Van Hensbroek, 1996 (Gambia)</td>
<td>576 children aged 1–9 years with cerebral malaria: Blantyre score ≤ 2 and asexual <em>P. falciparum</em> parasitaemia</td>
<td>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.</td>
</tr>
<tr>
<td>Taylor, 1998 (Malawi)</td>
<td>183 children admitted to paediatric ward with cerebral malaria: unrousable coma (Blantyre score ≤ 2) and asexual <em>P. falciparum</em> parasitaemia.</td>
<td>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.</td>
</tr>
<tr>
<td>Satti, 2002 (Sudan)</td>
<td>77 children aged 3 months to 15 years with cerebral malaria (WHO criteria)</td>
<td>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.</td>
</tr>
<tr>
<td>Thuma 2000 (Zambia)</td>
<td>95 children aged 0–10 years with cerebral malaria: asexual <em>P. falciparum</em> parasitaemia, Blantyre coma score ≤ 2 and no other cause for coma</td>
<td>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 0 10 mg/kg every 8 h.</td>
</tr>
<tr>
<td>Moyou-Somo 2001 (Cameroon)</td>
<td>106 children aged 0–10 years with cerebral malaria: asexual <em>P. falciparum</em> parasitaemia; Blantyre coma score ≤ 2, and no other cause of coma</td>
<td>Artemether: 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.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Trial</th>
<th>Randomization</th>
<th>Concealment</th>
<th>Blinding</th>
<th>Inclusion of randomized patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aceng 2005&lt;sup&gt;14,15&lt;/sup&gt;</td>
<td>A</td>
<td>A</td>
<td>Participants and microscopists</td>
<td>A</td>
</tr>
<tr>
<td>Murphy 1996&lt;sup&gt;20,21&lt;/sup&gt;</td>
<td>A</td>
<td>A</td>
<td>None</td>
<td>C</td>
</tr>
<tr>
<td>Ojuawo 1999&lt;sup&gt;19,16&lt;/sup&gt;</td>
<td>B</td>
<td>B</td>
<td>None</td>
<td>B</td>
</tr>
<tr>
<td>Olumese 1999&lt;sup&gt;19,16&lt;/sup&gt;</td>
<td>A</td>
<td>B</td>
<td>None</td>
<td>A</td>
</tr>
<tr>
<td>Taylor 1998&lt;sup&gt;23,24&lt;/sup&gt;</td>
<td>A</td>
<td>A</td>
<td>None</td>
<td>A</td>
</tr>
<tr>
<td>Van Hensbroek 1996&lt;sup&gt;22,25&lt;/sup&gt;</td>
<td>A</td>
<td>Microscopists and assessor of neurological sequelae</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>Satti 2002&lt;sup&gt;24,14&lt;/sup&gt;</td>
<td>B</td>
<td>B</td>
<td>None</td>
<td>B</td>
</tr>
<tr>
<td>Moyou-Somo 2001&lt;sup&gt;26,25&lt;/sup&gt;</td>
<td>A</td>
<td>B</td>
<td>None</td>
<td>A</td>
</tr>
<tr>
<td>Thuma 2000&lt;sup&gt;25,26&lt;/sup&gt;</td>
<td>A</td>
<td>A</td>
<td>Microscopists</td>
<td>A</td>
</tr>
</tbody>
</table>

A, adequate; B, unclear; C, inadequate; RCT, randomized controlled trial.
<sup>a</sup> Artemether versus quinine.
<sup>b</sup> 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 “neurological 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; I²: 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; I²: 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<sup>26</sup> (0/51 arteether versus 1/51 quinine; RR: 0.33; 95% CI: 0.01–8.00) and persistent hypoglycemia<sup>18</sup> (0/51 artemether...
versus 1/52 quinine; RR: 0.34; 95% CI: 0.01–8.15). The child with persistent hypoglycaemia 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; RR: 0.20; 95% CI: 0.02–1.70); QT prolongation on electrocardiogram (20/82 artemether versus 5/80 quinine; RR: 3.90; 95% CI: 1.54–9.89), and urticarial rash/vomiting (2/333 artemether versus 5/288 quinine; RR: 0.97; 95% CI: 0.33–2.75). Aceng et al. reported 82 adverse events in 36/48 artemether and 61 adverse events in 34/44 quinine patients25 (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 artemether 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 artemether 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 artemether studies (n = 194) because the small number of participants implies that...
Cerebral malaria in African children

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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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Trial</th>
<th>Artemether</th>
<th>Quinine</th>
<th>P-value in original trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coma recovery time in hours, median (IQR)</td>
<td>Taylor, 1998&lt;sup&gt;23&lt;/sup&gt;</td>
<td>18 (8–30)</td>
<td>20 (10–54)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td></td>
<td>Murphy, 1996&lt;sup&gt;20&lt;/sup&gt;</td>
<td>12 (2.80–96)</td>
<td>13 (2.83–96)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td></td>
<td>Van Hensbroek, 1996&lt;sup&gt;22&lt;/sup&gt;</td>
<td>26 (15–48)</td>
<td>20 (12–43)</td>
<td>0.05</td>
</tr>
<tr>
<td>Parasite clearance time in hours, median (IQR)</td>
<td>Taylor, 1998&lt;sup&gt;23&lt;/sup&gt;</td>
<td>32 (25–36)</td>
<td>40 (32–48)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Murphy, 1996&lt;sup&gt;20&lt;/sup&gt;</td>
<td>39.5 (24–45)</td>
<td>48.0 (37–56)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Van Hensbroek, 1996&lt;sup&gt;22&lt;/sup&gt;</td>
<td>48 (36–60)</td>
<td>60 (48–72)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Fever clearance time in hours, median (IQR)</td>
<td>Taylor, 1998&lt;sup&gt;23&lt;/sup&gt;</td>
<td>31 (24–52)</td>
<td>45 (33–60)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td></td>
<td>Murphy, 1996&lt;sup&gt;20&lt;/sup&gt;</td>
<td>32 (4–86)</td>
<td>32 (4–96)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td></td>
<td>Van Hensbroek, 1996&lt;sup&gt;22&lt;/sup&gt;</td>
<td>30 (16–48)</td>
<td>33 (12–60)</td>
<td>0.80</td>
</tr>
</tbody>
</table>

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 arteether studies that reported coma recovery time in means and standard deviations showed a shorter coma recovery time in the arteether 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<sup>28</sup> and standard deviations from interquartile ranges<sup>29</sup> for the remaining 3 studies, which we then incorporated into our meta-analysis. When the results of the 7 arteether studies were pooled together, the weighted mean difference in coma recovery time between the arteether 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 arteether and quinine groups (Fig. 4, Fig. 5). However, when the studies in which means were estimated from medians<sup>28</sup> and standard deviations from interquartile ranges<sup>29</sup> 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 arteether 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 arteetherin 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 arteetherin derivatives are not inferior to quinine in preventing death in children with cerebral malaria.

Acknowledgement

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Competing interests: None declared.
Résumé
Efficacité comparée de dérivés de l’artémisine 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’artémisine, par rapport à celle de la quinine, dans le traitement du paludisme cérébral chez l’enfant.


Résultats Neuf essais contrôlés randomisés, tous réalisés en Afrique, ont été pris en compte dans l’analyse. Pour cinq de ces essais, l’affectation des traitements était correctement dissimulée. Sept comparèrent 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’artémisine 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 bilio-hémoglobinurique fatale, a été observé chez un patient appartenant au groupe sous quinine.

Conclusion Les dérivés de l’artémisine ne sont pas inférieurs à la quinine dans la prévention de la mortalité chez les enfants atteints de paludisme cérébral.
Cerebral malaria in African children

References


10. WHO. Resistance to artemisinin derivatives along the Thai–Cambodian border. Wkly Epidemiol Rec 2007;82:360. PMID:17330387


Effect of Antimalarials on the Risk of Neurological Sequelae

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Artemisinin drugs</th>
<th>Quinine</th>
<th>RR (fixed)</th>
<th>Weight</th>
<th>RR (fixed)</th>
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<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI</td>
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<td>95% CI</td>
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<tr>
<td>01 Artemether</td>
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<tr>
<td>Aceng</td>
<td>45/71</td>
<td>42/55.00(24.30)</td>
<td>12.98</td>
<td>0.80</td>
<td>-13.06, 11.46</td>
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<tr>
<td>Olumese</td>
<td>35/40.00(22.80)</td>
<td>37/41.00(12.00)</td>
<td>16.23</td>
<td>2.50</td>
<td>-8.47, 13.47</td>
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<tr>
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<td>114</td>
<td>16.23</td>
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<td>Test for heterogeneity: Chi² = 3.60, df = 5 (P = 0.61), I² = 0%</td>
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<td>Test for overall effect: Z = 0.70 (P = 0.48)</td>
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<tr>
<td>02 Arte-ether</td>
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<tr>
<td>Moyou</td>
<td>43/46.30(28.50)</td>
<td>37/40.70(19.90)</td>
<td>17.80</td>
<td>5.60</td>
<td>-4.87, 16.07</td>
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<td>Thuma</td>
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<td>71</td>
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<td>Test for overall effect: Z = 0.33 (P = 0.74)</td>
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<td>95</td>
<td>14.34</td>
<td>4.00</td>
<td>-15.67, 7.67</td>
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</table>

RCT, randomized controlled trial; SD, standard deviation; WMD, weighed mean difference.