

# How does the efficacy and safety of artemisinin derivatives compare with quinine in the treatment of severe falciparum malaria in children?

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This review addresses the question: : How does the efficacy and safety of artemisinin derivatives compare with quinine in the treatment of severe falciparum malaria in children?

The WHO Pocketbook of Hospital Care for Children recommends quinine or artemisinin derivatives (artemether or artesunate) for the treatment of severe malaria. Quinine is recommended for most countries, except those in Southeast Asia and the Amazon basin. Whatever first-line therapy is used WHO now strongly recommends combination therapy; using an additional drug to which there is no resistance (sophadoxine-pyrimethamine, artemisinin-based combination therapy or clindamycin in combination with quinine). (Pocketbook chapter 6.2.1, page 141).

## INTRODUCTION

Malaria causes 850,000 child deaths every year [1]. The majority of malaria related morbidity and mortality is among children in Africa and Asia [4], where the parasite causes an estimated one billion episodes of fever [2]. In Africa one in five child deaths are due to malaria and the disease costs an estimated \$12 billion annually. [2, 3]. Despite vector control measures malaria is making a resurgence and resistance to first line therapies is an increasing problem [5, 6]. Child mortality from malaria continues to rise in sub-Saharan Africa [6-8] and has been predicted to continue to rise [9-11]. Artemisinin (qinghaosu) derivatives are a newly developed class of drug. These may be given orally, rectally, intravenously or intramuscularly. No resistance has yet been reported.

## METHODOLOGY

The Cochrane Database was searched for reviews and randomised trials and the Pubmed Clinical Queries tool was used to search 1966-2005 Medline database of the US National Library of Medicine using the search strategy (Artemisinin OR artemether OR artemotil OR artesunate OR arteminic acid OR dihydroartemisinin) AND (Quinine). This yielded 79 trials and 8 systematic reviews. » Run Search

Citations listed in retrieved trials were also hand searched and reviewed, yielding a further 5 trials and 3 systematic review. Of these 1 was not randomized, 1 was non-comparative and 3 compared artemisnins with an agent other than quinine. Papers were excluded if they were non-randomised or non-comparative, if they compared artemisinin derivatives with agents other than quinine, if their outcomes related to non-clinical endpoints such as biochemical or pharmacokinetic studies or resistance prevalence studies, were cost-effectiveness analyses, did not include children or were in a language other than English. These exclusion criteria applied to 50 trials and 3 systematic reviews, leaving a total of 32 papers for review, 29 of which were from the original search strategy and 3 from secondary references. Methodological quality of included articles was type 1b according to the criteria of the Oxford Centre for Evidence-Based Medicine [12] ([http://www.cebm.net/levels\\_of\\_evidence.asp](http://www.cebm.net/levels_of_evidence.asp)).

Primary outcomes assessed were mortality or adverse events (AEs). Secondary outcomes included fever clearance time (FCT), coma recovery time (CRT), neurological sequelae, parasite clearance time (PCT), 28-day cure rate and effect on gametocyte carriage. Heterogeneity among studies occurred in 6 domains: i) the use of different drug regimens, durations and modes of administration, ii) non-uniform methods of outcome reporting, iii) background prevalence of resistance at the study site, iv) the endemicity and seasonality of infections at the site, v) the degree of illness severity of patients studied and vi) age of study populations.

## RESULTS

### Mortality:

In adults with severe falciparum malaria, artemisinin derivatives reduce mortality compared with quinine. This was proved conclusively in trial of artesunate vs quinine involving 1461 people from Southeast Asia. The odds ratio for mortality for those receiving artesunate was 0.6 (95% CI 0.45-0.71),  $p=0.0002$ . Of the study participants, 202 (13.8%) were children younger than 15 years. When these children were analysed as a subgroup the resulting odds ratio was 0.43 (95% CI 0.13-1.42) [13].

Eleven other trials found no significant difference in mortality between artemisinin derivatives and quinine [14-24]. Two other studies [25, 26] described lower mortality in artemether group than quinine, but statistical significance was not reported.

A meta-analysis based on individual patient data comparing mortality using intramuscular artemether and intravenous quinine showed odds ratio 0.80 (95%CI 0.62-1.02),  $p=0.08$ . When Asian adults were analysed, odds ratio (OR) was 0.59 (95%CI 0.35-1.01),  $p=0.012$  suggesting an important clinical benefit [27]. It is possible that geographic differences exist and this may be a function of higher quinine resistance in Southeast Asia, though other factors cannot be excluded. In a global meta-analysis reported by geographic region, adults from Southeast Asia had lower mortality with artemether (40% reduction) that trended towards statistical significance, OR 0.38 (95%CI 0.14-1.02), but among African children there was no difference, OR 1.01 (95%CI 0.73-1.40) [28]. Another meta-analysis conducted across Africa also showed no difference in mortality [29].

In only a single trial [30] was higher mortality found among patients treated with artemether compared with those treated with quinine ( $p<0.05$ ). This study of Kenyan children with cerebral malaria found that those with respiratory distress had higher and earlier mortality if given artemether ( $p<0.05$ ). It was postulated children with acidosis may have absorbed intramuscular artemether poorly. Concern was also raised about the consequences of rapid breakdown of parasites in the face of already severe illness. It is known, however, that respiratory distress is an independent risk factor for mortality in severe malaria [31] so distinguishing a drug effect from underlying disease effect is difficult.

Importantly, the higher mortality in the artemether group that was apparent in the intention to treat analysis was confounded by many patients who did not in fact have cerebral malaria, and after their exclusion the difference was not significant. The concerning findings of higher mortality in the artemether group are likely confounded by these multiple and interacting factors.

A systematic review of studies of adults and children was conducted in 2000 [32]. Results were reported individually for the various artemisinin derivatives. Compared with quinine, mortality with artemisinin had an OR of 0.68 (95%CI 0.28-1.65). For artemether OR 0.72 (95%CI 0.57-0.91), however, excluding two studies which raised methodological concerns regarding allocation concealment resulted in OR 0.79 (95%CI 0.59-1.05). For artesunate the OR was 0.35 (95%CI 0.20-0.61). For all artemisinin derivatives combined, OR 0.61 (95%CI 0.46-0.82), giving a relative risk reduction (RRR) of 48% and number needed to treat of 25. Most of the studies in this meta-analysis used artemether. When only cases of cerebral malaria were studied, combining all artemisinin derivatives gave OR 0.63 (95%CI 0.44-0.88) and RRR 31%. Excluding studies with inadequate allocation concealment however, gave OR 0.78 (95%CI 0.55-1.10) [32].

**Summary:** Compared with quinine, artesunate reduces mortality in adults with severe malaria, especially in Southeast Asia. Children in Southeast Asia are likely to have a similar benefit, but this has not yet been shown in African children. A definitive large scale multi-centre study of IV artesunate in African children is required. Rectal artesunate has been suggested for treatment of severe malaria in remote settings. No trial has shown this approach to be inferior to quinine.

#### **Adverse Events:**

Data regarding adverse events were not uniformly collected. The frequency of serious AEs was small in most studies and no statistical inferences can be drawn.[9, 14-17, 19-22, 25, 26, 30, 33-39] A meta-analysis found quinine to be associated with more frequent episodes of hypoglycaemia, but statistical significance was not stated [27]. A systematic review of all

studies to 2000 claimed all AEs were mild and none led to discontinuation of treatment [32].

AEs reported included hypoglycaemia, pruritis and urticaria, tinnitus and dizziness. Prolongation of the QT-interval on the electrocardiograph was reported but no clinically relevant dysrhythmias occurred. All these events were reported more frequently in patients treated with quinine but occurred with artemisinin derivatives also. Local pain at the site intramuscular injection occurred only with quinine. No tenesmus was reported in rectally administered medication. Artemisinins did not lead to neurological toxicity, though in one study more seizures occurred in artemether treated patients [40].

**Summary:** Mild AE occurred with both treatments. Overall both treatments were well tolerated. Uniformly collected data in large studies with adequate power are needed.

#### **Secondary outcomes:**

##### **Fever Clearance Time:**

Although widely reported as a surrogate for efficacy, fever clearance time (FCT) is of doubtful clinical significance[40-42]. Most studies found no difference in FCT [9, 14-20, 22-25, 27, 30, 39, 43], though in some [21, 29, 33-36] but not all [26] FCT was shorter with artemisinin.

##### **Coma Recovery Time:**

Heterogeneity exists among studies in the definition of CRT and many studies did not use standardized scales [44]. Most studies found no difference in CRT between artemisinin derivatives and quinine [13-16, 18, 20, 21, 23, 25, 27, 29, 30, 32, 36, 43]. CRT was significantly faster with artemisinin derivatives in some studies [22, 24, 26, 33] and faster with quinine in another [17]. Current evidence does not suggest an advantage to artemisinin derivatives over quinine in terms of coma recovery time.

##### **Neurological sequelae:**

Concern was first raised about neurotoxicity of artemisinin derivatives in animal studies [45, 46]. Their safety in humans has repeatedly been demonstrated [47]. No significant difference in residual neurological deficits between those treated with artemisinin derivatives and quinine has been demonstrated [13, 15-17, 20, 21, 23, 24, 30, 32]. Two meta-analyses, one of which was an individual patient data analysis [27], suggested no significant difference in neurological outcome [27, 29]. Some papers showed prolonged coma and more seizures in artemether treated patients [32] but almost all neurological defects that were followed over months resolved with time. There is no clear advantage of artemisinin derivatives over quinine in terms of improved neurological outcomes. Artemisinin derivatives do not cause neurotoxicity in children.

##### **Parasite Clearance Time:**

PCT is widely used as a marker of antimalarial efficacy. It is widely accepted that artemisinin derivatives clear parasitaemia faster than other antimalarial agents [6, 38] but this does not correlate with clinical recovery [16, 24, 30, 48]. The clinical significance of PCT has therefore been questioned [17, 21, 22, 40, 48, 49]. PCT has several definitions so comparing results across studies is difficult. In 13 studies artemisinin derivatives did clear parasitaemia significantly faster than quinine [9, 17, 19, 21, 22, 24, 27, 29, 30, 32-37, 39] but this was not the case in other studies [14-16, 18, 20, 23, 25, 26, 43].

##### **28-day Cure Rate and Recrudescence:**

The cure rate (absence of parasitaemia or clinical symptoms) depends not only on the initial drug used but also on adjunctive long-acting antimalarial drugs [32, 50]. There was heterogeneity

among studies in the adjunctive drugs used (eg sulfadoxine-pyrimethamine, mefloquine, tetracycline) and often different adjuncts were used in the two treatment arms. Although many studies reported a 28-day cure rate, this should not be interpreted as reflecting differences between artemisinin derivatives and quinine in isolation of other agents. Cure rate depends on multiple factors, including background quinine resistance, initial parasite load and host immune factors. Several papers addressed cure [18, 20, 32, 35, 38] and recrudescence [9, 15, 16, 25, 34, 37, 39], but patient numbers in these studies were small and no definitive conclusion can be drawn in this review.

#### Gametocytaemia:

The last stage in the life cycle of *P. falciparum* is the development of gametocytes (sexual forms) in the blood which are taken up by a mosquito and are required for transmissibility [6]. Gametocytes are more likely to occur when treatment failure results in recrudescence, which can occur if the initial parasite burden is high or with drug resistance [6, 51]. Antimalarial drugs differ in their effect on gametocyte carriage [6, 40] and those that reduce gametocytes may reduce disease transmission [52], the public health impact will depend on local transmission rates [50]. In a study of 5193 patients of which 3241 were children, artemisinin derivatives markedly reduced gametocyte carriage compared with quinine. The relative risk of gametocytaemia after a treatment course with quinine compared with artemisinin derivatives was 6.8 (95%CI 3.1-15.1),  $p < 0.0001$  [51]. The same study also reported that after widespread introduction of artemisinin derivatives in 1994, there was a sudden reduction in malaria incidence by nearly half [51]. Similar and more detailed findings have been documented in adults [52-54]

#### SUMMARY

Artemisinin derivatives are highly effective, safe and well tolerated in the treatment of malaria in children. All studies confirm that artemisinins, given intravenously, orally or rectally were at least as effective as quinine for severe or cerebral malaria. Recrudescence and the development of drug resistance are risks if these agents are used as monotherapy, therefore dual formulations are important. Rectal administration is very useful in remote areas with inadequate access to medical facilities. Artemisinins lead to a reduction in transmission in Southeast Asia. Large scale multi-centre studies in African children are currently being undertaken [55] to definitively determine the impact of these agents on mortality.

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