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Artemisinin Derivatives *Versus* Quinine for Severe Malaria in Children: *A Systematic Review and Meta-Analysis*

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RELEVANCE

In uncomplicated malaria, the WHO recommends Artemisinin-based combination therapy (ACT) (1) for infants and children. However, the Government of India recommends chloroquine for *P.vivax* and also *P.falciparum* in areas without resistance; ACT is advised only for confirmed *P.falciparum* in 117 districts with documented chloroquine resistance(2).

In contrast, the treatment of severe/complicated childhood malaria appears to be evolving. The 2005 IAP Guideline followed the National Malaria Programme and recommended quinine, suggesting artesunate/artemether as less preferred alternatives(3). In 2008, it was modified as quinine with tetracycline/doxycycline/clindamycin(4) in line with the WHO 2006 statement. The National Guideline 2009(2) suggests artesunate, quinine, artemether, in that order, contraindicating arteether and doxycycline in children. The WHO's 2010 Guideline(1) strongly recommends aresunate in adults with severe malaria, positioning quinine only as an alternative; however, it cites lack of evidence to frame a similar recommendation for children.

Despite appropriate therapy with parenteral quinine, the case fatality rate in severe malaria exceeds 20-30%. In addition, quinine administration requires hospital facilities for controlled infusion under close monitoring, owing to the risk of potentially serious (albeit treatable) side effects. Therefore alternate therapies are sought, to improve clinical outcomes and also simplify administration. Artemisinin derivatives appear to hold promise in this direction.

This systematic review of evidence addresses the question: "In children with severe/complicated malaria (*population*), do Artemisinin derivatives (*intervention*), improve clinical outcome in terms of mortality, clinical recovery, parasite clearance, adverse effects, etc (*outcome*), as compared to standard parenteral quinine therapy (*comparison*)?

CURRENT BEST EVIDENCE

A Medline search updated on 25 March 2010, with "*severe malaria*" and Limits: *Humans, Randomized Controlled Trial, Meta-Analysis, All Child (0-18 years)*, yielded 175 citations. A simultaneous Cochrane Library search for "*severe malaria*" in 'Record Title' listed 4 Cochrane reviews, 7 other systematic reviews and 98 clinical trials. Three relevant Cochrane reviews compared quinine with (*i*) artesunate(5), (*ii*) arteether(6) and (*iii*) artemisinin derivatives(7). The artesunate review(5) included one pediatric trial, but examined effects across all age groups together. The arteether review(6) examined only the intramuscular route, and the third review(7) was closed by the authors in 2009 in view of more recent reviews. Six of seven non-Cochrane reviews compared artesunate or artemether, but all were outdated. This necessitates a fresh systematic review to generate current best evidence.

From the literature search, 45 randomized trials were short-listed, but 42 excluded for the following reasons: (*i*) not RCT comparing artemisinin derivatives vs quinine (n=16), (*ii*)adult participants

(n=12), (*iii*) trials included children also, but presented data for adults and children together (n=3), (*iv*) outdated meta-analysis of trials (n=3), (*v*) trials compared different preparations/routes of Artemisinin without a quinine comparator (n=6), and (*vi*) severe malaria not defined as per standard criteria (n=2). Hand-searching of short-listed citations identified 7 additional trials; thus a total of 10 trials were included in this review.

Table I summarizes the trial characteristics. Two trials compared quinine with artesunate(8,9), six with artemether(10-15), and two with arteether(16,17). Four trials recruited only participants with cerebral malaria(10,11,13,14). The trials examined mortality, clinical outcomes (fever clearance time, coma recovery time, neurological sequelae), parasite clearance and some side effects.

Risk of bias (***Table II***) was low for three trials(11,12,14), moderate for another three(8,10,17) and high for four trials(9,13,15,16). Only one trial(11) provided a sample size calculation. None of the trials was blinded.

All the ten trials demonstrated comparable mortality between artemisinin derivatives and quinine; irrespective of the type of derivative, route of administration, type of severe malaria (cerebral or otherwise), or methodological quality of trial. Meta-analysis(**Figure I**) confirmed this for artemisinin derivatives individually and collectively (both random effects and fixed effect model). The trials together included a sample size sufficient for demonstrating a statistically significant mortality reduction, suggesting that the result is robust.

Seven trials reported fever clearance time, though three(8,11,12) presented data in a format that precluded meta-analysis; the remainder(9,15-17) showed comparable results between all three artemisinin derivatives and quinine. All trials reported coma recovery time, though three(8,11,12) could not be included in meta-analysis. Only one trial(13) suggested a favourable effect with artemether; the remainder showed no difference between groups. Likewise parasite clearance time was comparable between groups in five trials(8,9,11,12,17). Six trials(10,12-14,16,17) examined neurological sequelae at follow-up, and all showed comparable effect between artemisinin and quinine.

CRITICAL APPRAISAL

This is the first systematic review examining the scope of artemisinin derivatives for severe malaria in children. Despite several methodological strengths (multiple database search, hand-searching, methodo-logical grading, standard reporting format, meta-analysis, etc), one of its limitations was the inability to obtain separate pediatric data from trials(18-20) combining adult and pediatric data.

On the face of it, this systematic review appears to corroborate the WHO position that there is inadequate evidence favouring artemisinin derivatives in severe childhood malaria, suggesting the need for more RCTs(1). However, this may be an over-simplification, because although the review does not demonstrate superior efficacy of artemisinin derivatives, comparable effect across all outcomes suggests that either therapy could be equally efficacious. Given that quinine administration requires controlled infusion in a hospital setting, artemisinin could have an edge in terms of simpler administration and potentially greater safety (lower risk of quinine adverse events). Since treatment of severe malaria in the real-world setting is often presumptive (before confirmation of diagnosis), and urgent (required before transferring patients to hospital), unlike in randomized trials, Artemisinin may result in greater effectiveness, despite equivalent efficacy. This is especially important because neither the absence of *P.falciparum* on peripheral smear nor the presence of *P.vivax*, rule out severe malaria(2).

However, potentially better 'effectiveness' has to be counterbalanced against the possible risk of encouraging *Plasmodium* resistance through relatively unrestricted use of artemisinin derivatives. Thus a dichotomy between the interests of the individual child and the community could emerge over time. This suggests that a formal Health Technology Assessment rather than the simplistic decision models described earlier(2-4) is needed to make an informed choice.

TABLE I: CHARACTERISTICS OF INCLUDED TRIALS

Trial	Setting	Participants	Inclusion criteria	N (A/Q)	Administration	Outcomes
Artesunate						
Phuong, *et al.*(8)	Vietnam year NS	<15 y	PS + CF of severe malaria*	37/35	A = im[#] Q = iv*** + mefloquine po	Mortality FCT, CRT, PCT, LOS
Mohanty, *et al.*(9)	India 2000-02	Pediatric, but age NS	PS + CF of severe malaria*	40/40	A = iv[##] Q = iv***	Mortality, FCT, CRT, PCT, AE,
Artemether						
Murphy, *et al.*(10)	Kenya year NS	<12 y	PS + CF of cerebral malaria	83/78**	A = im[$] Q = iv***	Mortality, CRT, neurological sequelae
vanHensbroek, *et al*(11)	Gambia 1992-94	1-9 y	PS + CF of cerebral malaria	288/288	A = im[$] Q = im***	Mortality, FCT, CRT, PCT, AE
Taylor, *et al.*(12)	Malawi 1992-94	Pediatric, but age NS	PS + CF of severe malaria*	95/88	A = im[$] + Pyrisulpha Q = iv***	Mortality, FCT, CRT, PCT, AE, neurological sequelae
Ojuawo, *et al.*(13)	Nigeria year NS	2-6 y	PS + CF of cerebral malaria	18/19	A = im[$] Q = iv***	Mortality, FCT, CRT, PCT, neurological sequelae
Olumese, *et al.*(14)	Nigeria 1994-96	11mo-5y	PS + CF of cerebral malaria	54/59	A = im[$] Q = iv***	Mortality, FCT, CRT, PCT, AE, neurological sequelae
Huda, *et al.*(15)	India 2000-01	<14 y	PS + CF of s evere malaria*	23/23****	A = im[$$] Q = iv***	Mortality, FCT, CRT, PCT, neurological sequelae
Arteether						
Moyou-Somo, *et al.*(16)	Cameroon 1995-97	0-10y	PS + CF of severe malaria*	51/51	A = im[$] Q = iv***	Mortality, FCT, CRT, PCT, neurological sequelae
Thuma, *et al.*(17)	Zambia 1996-97	0-10y	PS + CF of severe malaria*	48/44	A = im[$] Q = iv***	Mortality, FCT, CRT, PCT, neurological sequelae

A = Artemisinin derivative, AE = adverse events, CF = clinical features, CRT = coma recovery time, FCT = fever clearance time, im = intramuscular, iv = intravenous, LOS = length of stay in hospital, N = number of participants, NS = not specified, PCT = parasite clearance time, po = per oral, PS = peripheral smear showing asexual forms of Plasmodium falciparum, Pyri-sulpha = pyrimethamine-sulphadoxine, Q = Quinine; *Clinical features consistent with WHO categorisation of severe malaria; ** 200 were enrolled, but 161 analysed; *** Quinine dose 20 mg/kg loading followed by 10mg/kg 8 hourly until conscious for a total of seven days; **** 99 were enrolled, but 46 analysed; [#] Artesunate dose 3mg/kg followed by 2mg/kg at 12, 24, 48, 72 hr + mefloquine orally; [##]Artesunate dose 2.4 mg/kg loading followed by 1.2 mg/kg after six hours and once a day for five days; [$]Artemether/Arteether dose 3.2 mg/kg followed by 1.6 mg/kg for four days; [$$]Artemether dose 1.6 mg/kg bd followed by 1.6 mg/kg od for five days

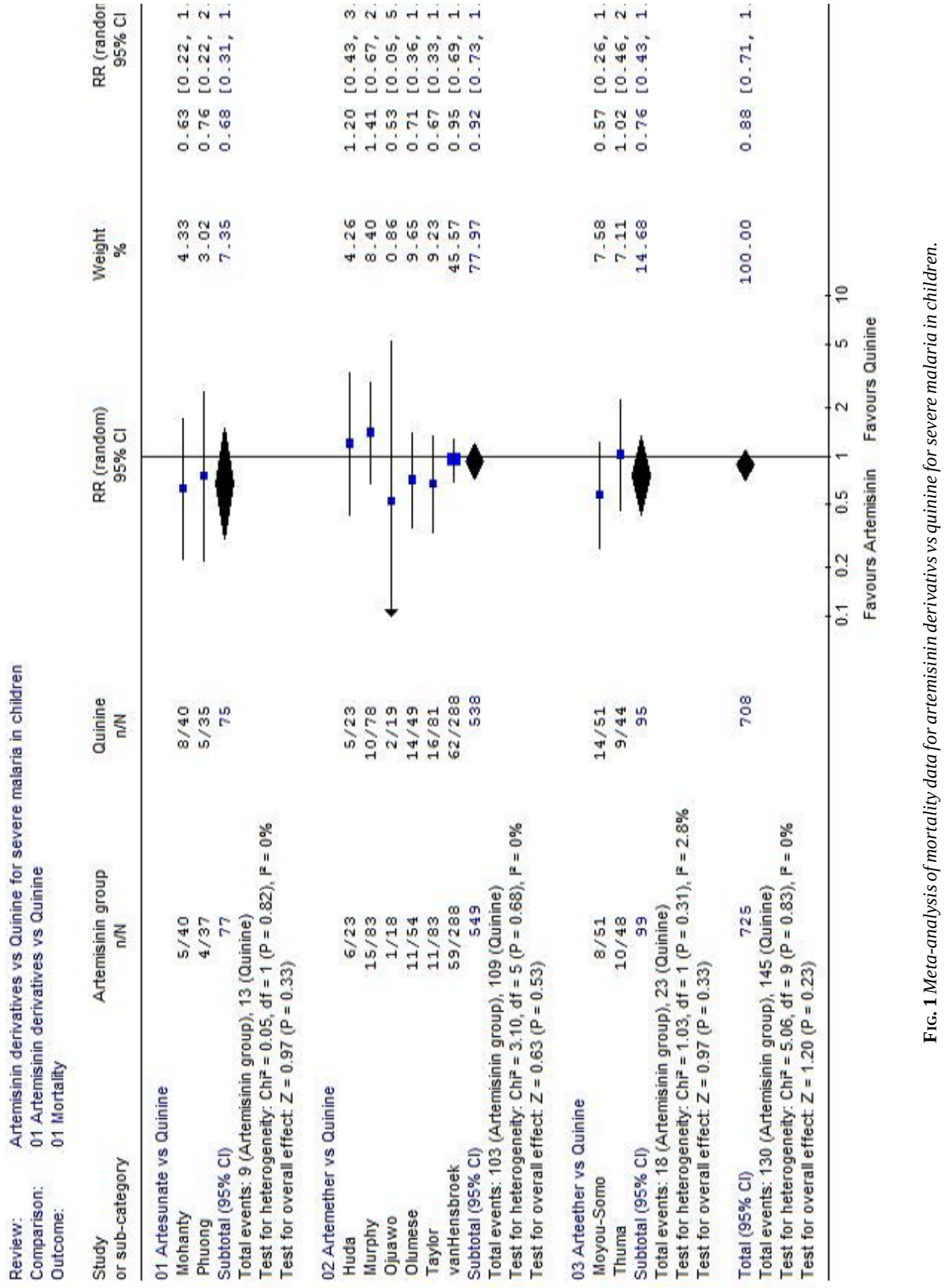

FIG. 1 *Meta-analysis of mortality data for artemisinin derivativs vs quinine for severe malaria in children.*

TABLE II: RISK OF BIAS AND OTHER DESIGN CHARACTERISTICS OF INCLUDED TRIALS (COCHRANE RISK OF BIAS TOOL)

Trial	Randomization	Allocation concealment	Blinding	Adequacy of outcome reporting	ITT analysis	Risk of Bias	Sample size	Ref
Phuong	Unclear	Adequate	Inadequate	Adequate	Yes	Moderate	Inadequate	8
Mohanty	Inadequate	Inadequate	Inadequate	Inadequate	No	High	Inadequate	9
Murphy	Adequate	Adequate	Inadequate	Inadequate	No	Moderate	Inadequate	10
vanHensbroek	Adequate	Adequate	Inadequate	Adequate	Yes	Low	Adequate	11
Taylor	Adequate	Adequate	Inadequate	Adequate	No	Low	Inadequate	12
Ojuawo	Inadequate	Inadequate	Inadequate	Adequate	No	High	Inadequate	13
Olumese	Adequate	Adequate	Inadequate	Adequate	Yes	Low	Inadequate	14
Huda	Inadequate	Inadequate	Inadequate	Inadequate	No	High	Inadequate	15
Moyou-Somo	Adequate	Inadequate	Inadequate	Inadequate	No	High	Inadequate	16
Thuma	Adequate	Adequate	Inadequate	Inadequate	No	Moderate	Inadequate	17

ITT = intention-to-treat

EXTENDIBILITY

All the trials were conducted in developing countries, although mostly in Africa where the severity and outcome of malaria could be different from our country. However, the type of participants, clinical classification of severity, outcome parameters and overall results were similar between the Indian(9,15) and other trials. This suggests that the findings of this systematic review can be extended to our country in general.

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EURECA CONCLUSION IN THE INDIAN CONTEXT

- In children with severe malaria, Artemisinin derivatives result in similar mortality and clinical outcomes, as compared to parenteral quinine.
- Non-inferior efficacy could permit preferential use of Artemisinin, owing to simpler administration and potentially greater safety at the point-of-care, especially in field settings.

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