Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial

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Summary

Background Severe malaria is a major cause of childhood death and often the main reason for paediatric hospital admission in sub-Saharan Africa. Quinine is still the established treatment of choice, although evidence from Asia suggests that artesunate is associated with a lower mortality. We compared parenteral treatment with either artesunate or quinine in African children with severe malaria.

Methods This open-label, randomised trial was undertaken in 11 centres in nine African countries. Children (<15 years) with severe falciparum malaria were randomly assigned to parenteral artesunate or parenteral quinine. Randomisation was in blocks of 20, with study numbers corresponding to treatment allocations kept inside opaque sealed paper envelopes. The trial was open label at each site, and none of the investigators or trialists, apart from for the trial statistician, had access to the summaries of treatment allocations. The primary outcome measure was in-hospital mortality, analysed by intention to treat. This trial is registered, number ISRCTN50258054.

Findings 5425 children were enrolled; 2712 were assigned to artesunate and 2713 to quinine. All patients were analysed for the primary outcome. 230 (8·5%) patients assigned to artesunate treatment died compared with 297 (10·9%) assigned to quinine treatment (odds ratio [OR] stratified for study site 0·75, 95% CI 0·63–0·90; relative reduction 22·5%, 95% CI 8·1–36·9; p=0·0022). Incidence of neurological sequelae did not differ significantly between groups, but the development of coma (65/1832 [3·5%] with artesunate vs 91/1768 [5·1%] with quinine; OR 0·69 95% CI 0·49–0·95; p=0·0231), convulsions (224/2712 [8·3%] vs 273/2713 [10·1%]; OR 0·80, 0·66–0·97; p=0199), and deterioration of the coma score (166/2712 [6·1%] vs 208/2713 [7·7%]; OR 0·78, 0·64–0·97; p=0·0245) were all significantly less frequent in artesunate recipients than in quinine recipients. Post-treatment hypoglycaemia was also less frequent in patients assigned to artesunate than in those assigned to quinine (48/2712 [1·8%] vs 75/2713 [2·8%]; OR 0·63, 0·43–0·91; p=0·0134). Artesunate was well tolerated, with no serious drug-related adverse effects.

Interpretation Artesunate substantially reduces mortality in African children with severe malaria. These data, together with a meta-analysis of all trials comparing artesunate and quinine, strongly suggest that parenteral artesunate should replace quinine as the treatment of choice for severe falciparum malaria worldwide.

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Introduction

Falciparum malaria is a major contributor to child mortality in Africa and one of the main causes of paediatric hospital admission across sub-Saharan Africa. Many deaths occur in or near the home, but for children who are admitted to hospital with severe malaria and receive parenteral antimalarial treatment, about one in six will die.[1,2] From the time of its introduction to European medicine in the 1630s until the deployment of parenteral chloroquine in the 1950s, quinine was the mainstay of severe malaria treatment. Resistance to chloroquine emerged in southeast Asia and then spread to Africa at the end of the 1970s. Quinine then resumed its primary role in the treatment of severe malaria. Parenteral quinine

has a narrow therapeutic ratio.[1–3] Intravenous quinine administration needs a constant rate infusion with dosing three times a day. Intramuscular administration is painful, and can cause sterile abscesses and predispose to lethal tetanus.[4] Although blindness and deafness may follow self poisoning, these side-effects are rare in severe malaria; however, quinine-induced hyperinsulinaemic hypoglycaemia is a particular problem in patient management, especially in pregnant women.[1,2,5]

The primacy of quinine in the treatment of severe malaria has been challenged by the introduction of artemisinin derivatives. The first comparative clinical trials were done with intramuscular artemether—a lipophilic derivative of dihydroartemisinin. Artemether proved safer

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For more about **AQUAMAT** see
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Panel 1: Modified criteria for severe falciparum malaria

At least one of:

- Plasma base excess less than –3·3 mmol/L
- Glasgow coma scale less than 11 of 15, or Blantyre coma scale less than 3 of 5 in preverbal children
- Haemoglobin less than 50 g/L and parasitaemia greater than 100 000 parasites per μL
- Blood urea greater than 10 mmol/L
- Compensated shock (capillary refill ≥3 s or temperature gradient on legs, but no hypotension)
- Decompensated shock; systolic blood pressure less than 70 mm Hg and cool peripheries
- Asexual parasitaemia more than 10%
- Visible jaundice and more than 100 000 parasites per μL
- Plasma glucose less than 3 mmol/L
- Respiratory distress, defined as costal indrawing, use of accessory muscles, nasal alar flaring, deep breathing, or severe tachypnoea

and easier to use than quinine, but did not improve overall survival in an individual patient data meta-analysis[6] of 1919 randomised patients. In a prospectively defined subgroup analysis, artemether reduced mortality significantly in southeast Asian adults, but not in African children. A large multicentre randomised trial (South East Asian Quinine Artesunate Malaria Trial [SEAQUAMAT]),[7] which compared intravenous artesunate with quinine in Asian patients (mainly adults) with severe malaria was then undertaken. It was stopped after enrolment of 1461 patients because of a substantial survival benefit in favour of artesunate. In a meta-analysis of the SEAQUAMAT study and earlier, smaller randomised trials,[7] artesunate reduced the mortality of severe malaria in Asian patients from 23·1% to 14·2%, a relative reduction of 38·6%. The treatment was also highly cost effective.[8] In 2006, WHO changed its guidelines to recommend artesunate for severe malaria in adults.[9]

The treatment effect in the SEAQUAMAT trial was similar in adults and the 202 children enrolled, but perceived differences in the natural history and drug susceptibility of severe falciparum malaria in African children compared with Asian patients left uncertainty about the optimum treatment for this important patient group. Expert opinion regarded parenteral quinine as a satisfactory treatment, and research priorities focused on improving other aspects of the care of the sick child. Nowadays quinine remains by far the most widely used treatment of severe malaria in Africa. We undertook a large multicentre randomised trial (African Quinine Artesunate Malaria Trial [AQUAMAT]) that compared parenteral treatment with either artesunate or quinine in African children with severe malaria.

Methods

Study design

This was a multicentre, open-label trial in children admitted to hospital with severe malaria, undertaken between Oct 3, 2005, and July 14, 2010. 11 centres in nine countries (Mozambique, The Gambia, Ghana, Kenya, Tanzania, Nigeria, Uganda, Rwanda, and Democratic Republic of the Congo) in Africa participated. The study was coordinated by the Mahidol-Oxford Tropical Medicine Research Unit in Bangkok, Thailand, which provided logistic support and data management. All clinicians were familiarised with the severe malaria criteria for enrolment (panel 1). Most children were managed on general paediatric wards. Children younger than 15 years were included if they had a positive rapid diagnostic test for *Plasmodium falciparum* lactate dehydrogenase (Optimal, Diamed, Cressier, Switzerland) and, in the admitting physician's clinical opinion, they had severe malaria, and they or their attendant relative or guardian gave fully informed written consent. Patients were not included if there was a convincing history of full treatment with parenteral quinine or an artemisinin derivative for more than 24 h before admission. Age criteria varied slightly between sites at the request of the respective ethics review boards (webappendix p 13). In Mozambique, adults were also studied but were analysed separately and will be reported elsewhere.

The trial protocol was reviewed and approved by each site's ethics review board, and by the Oxford Tropical
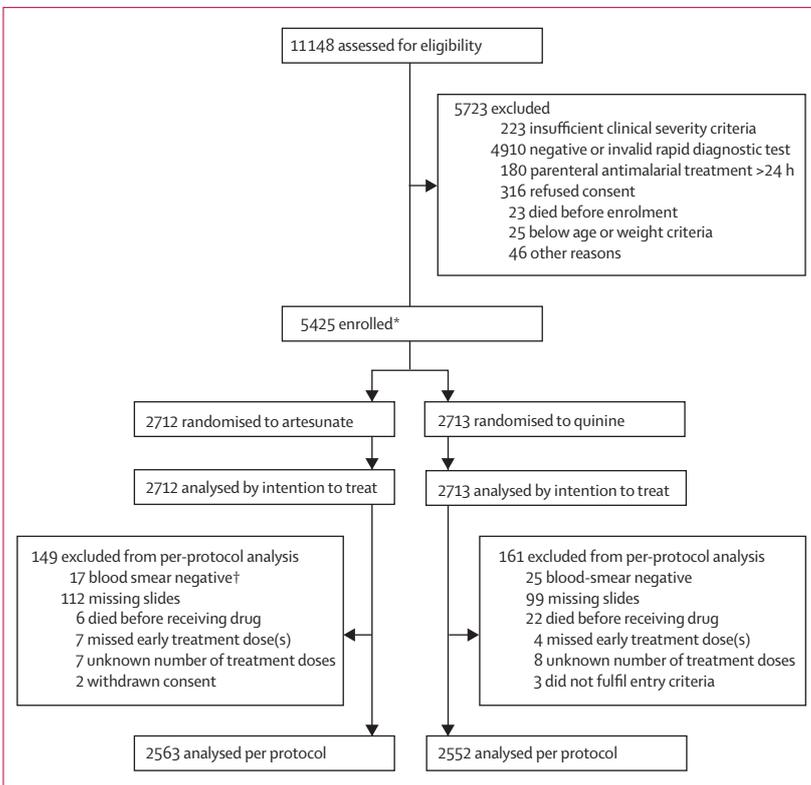

Figure 1: Trial profile
*663 in Beira, 442 in Kilifi, 436 in Kumasi, 921 in Muheza, 540 in Korogwe, 502 in Banjul, 450 in Ilorin, 386 in Rwanda, 663 in Mbarara, and 422 in Kinshasa. †Two patients also had other criteria.

	Quinine (N=2713)	Artesunate (N=2712)
Female sex	1295 (48%)	1315 (48%)
Age (years)	2·9 (1·7–4·3)	2·8 (1·6–4·2)
Fever before enrolment (days)	3 (2–4)	3 (2–4)
Coma before enrolment (h)	5·0 (2·5–10)	5·0 (2·0–9·5)
Pretreatment with antimalarials		
None	1270 (47%)	1281 (47%)
Ineffective*	371 (14%)	387 (15%)
Effective*	959 (37%)	938 (36%)
Complications on admission		
Coma†	945 (35%)	880 (32%)
Convulsions	879 (32%)	811 (30%)
Jaundice	59 (2%)	55 (2%)
Severe anaemia (haemoglobin <50 g/L)	692 (29%)	737 (30%)
Shock	339 (12%)	323 (12%)
Decompensated shock	88 (35%)	90 (39%)
Severe acidosis (BE <−8 mmol/L)	975 (43%)	1009 (44%)
Hypoglycaemia (<3 mmol/L)	278 (10%)	277 (10%)
Respiratory distress‡	428 (16%)	439 (16%)
Severe prostration§	1668 (61%)	1683 (62%)
Blackwater fever	116 (4%)	121 (4%)
Hyperparasitaemia (>10%)	573 (24%)	584 (25%)
Clinical examination		
Weight (kg)	12·6 (4·6)	12·4 (4·8)
Temperature (°C)	38·0 (1·1)	38·0 (1·1)
Blood pressure (mm Hg)		
Systolic	95 (16)	95 (16)
Diastolic	56 (14)	56 (14)
Coma depth (total N, median [IQR])		
Blantyre coma score	1704, 4 (2–5)	1713, 4 (2–5)
Glasgow coma score	1005, 11 (8–15)	999, 11 (8–15)
Comorbidity		
Immune compromised (from history)	49 (2%)	45 (2%)
Severe malnutrition	43 (2%)	54 (2%)
		(Continues in next column)

	Quinine (N=2713)	Artesunate (N=2712)
(Continued from previous column)		
Suspected pneumonia	226 (8%)	227 (8%)
Confirmed by radiograph	29 (13%)	29 (13%)
Clinical sepsis	355 (13%)	302 (11%)
Confirmed by culture	33 (9%)	32 (11%)
Suspected meningitis	166 (6%)	169 (6%)
Confirmed meningitis	3 (2%)	6 (4%)
Other significant comorbidities	71 (3%)	80 (3%)
Laboratory assessments		
Parasitaemia (parasites per µL; geometric mean, range)	49110 (0–1858880)	47922 (0–1494640)
Sodium (mmol/L)	132 (6·5)	131 (6·5)
Potassium (mmol/L)	4·1 (0·9)	4·1 (0·9)
Chloride (mmol/L)	105 (10)	105 (10)
Blood urea nitrogen (mmol/L)	6·1 (4·9)	6·1 (4·6)
Haemoglobin (g/L)	70 (31)	68 (29)
pH	7·36 (0·14)	7·36 (0·14)
$PaCO_2$ (mm Hg)	28·2 (10·1)	27·9 (9·1)
HCO_3 (mmol/L)	16·6 (5·7)	16·6 (5·6)
Plasma BE (mmol/L)	−8·6 (7·3)	−8·5 (7·3)
Anion gap (mmol/L)	17·2 (5·0)	17·0 (4·9)

Data are number (%), median (IQR), or mean (SD), unless otherwise indicated. BE=base excess . $PaCO_2$=partial pressure of carbon dioxide. HCO_3=bicarbonate. *See webappendix p 12 for classification of categories. †Depth of coma was assessed either by Blantyre coma score (for preverbal children, n=3417) or Glasgow coma scale (n=2004). ‡Respiratory distress was defined as costal indrawing, use of accessory muscles, nasal alar flaring, deep breathing, or severe tachypnoea. §Severe prostration was defined as inability to breastfeed for children younger than 6 months or inability to sit for older children.

Table 1: Baseline characteristics in the two treatment groups

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Research Ethics Committee. Permission to investigate HIV status was obtained only from some ethics review boards.

Randomisation and masking

Eligible patients were randomly assigned to treatment with either intravenous or intramuscular artesunate or quinine. Each centre had a policy of using one route of administration. Randomisation was done by people unrelated to the study and provided to the study sites in blocks of 20. Study numbers were kept inside opaque sealed paper envelopes. After full informed written consent was obtained, the next envelope, which contained a unique study box number, was opened by the study physician or nurse. Then the corresponding numbered sealed box was opened. This box contained the study drug, case record form (labelled with the unique study number), and all disposables needed for drug administration and blood sampling. Treatment was started immediately. All other
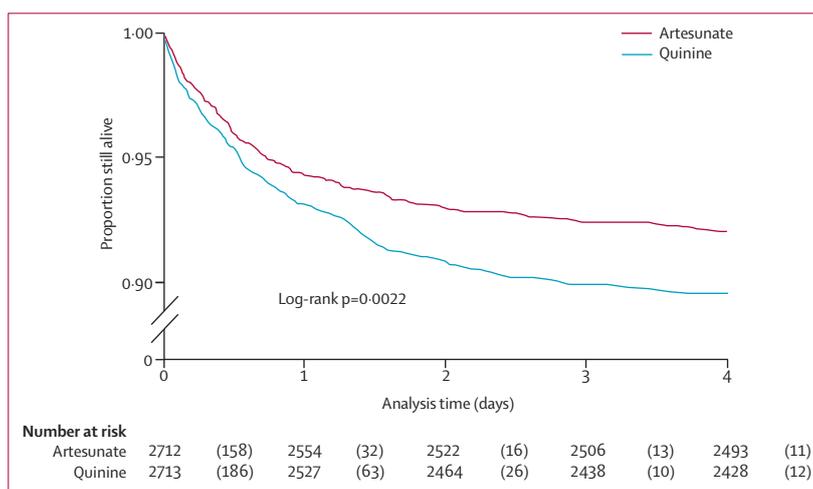

Figure 2: Kaplan-Meier curves comparing survival in African children with severe falciparum malaria treated with either parenteral artesunate or quinine
The numbers in parentheses are the deaths during the indicated time. In eight patients the exact time of death during the night was missing and was estimated as 2359 h.

Number at risk

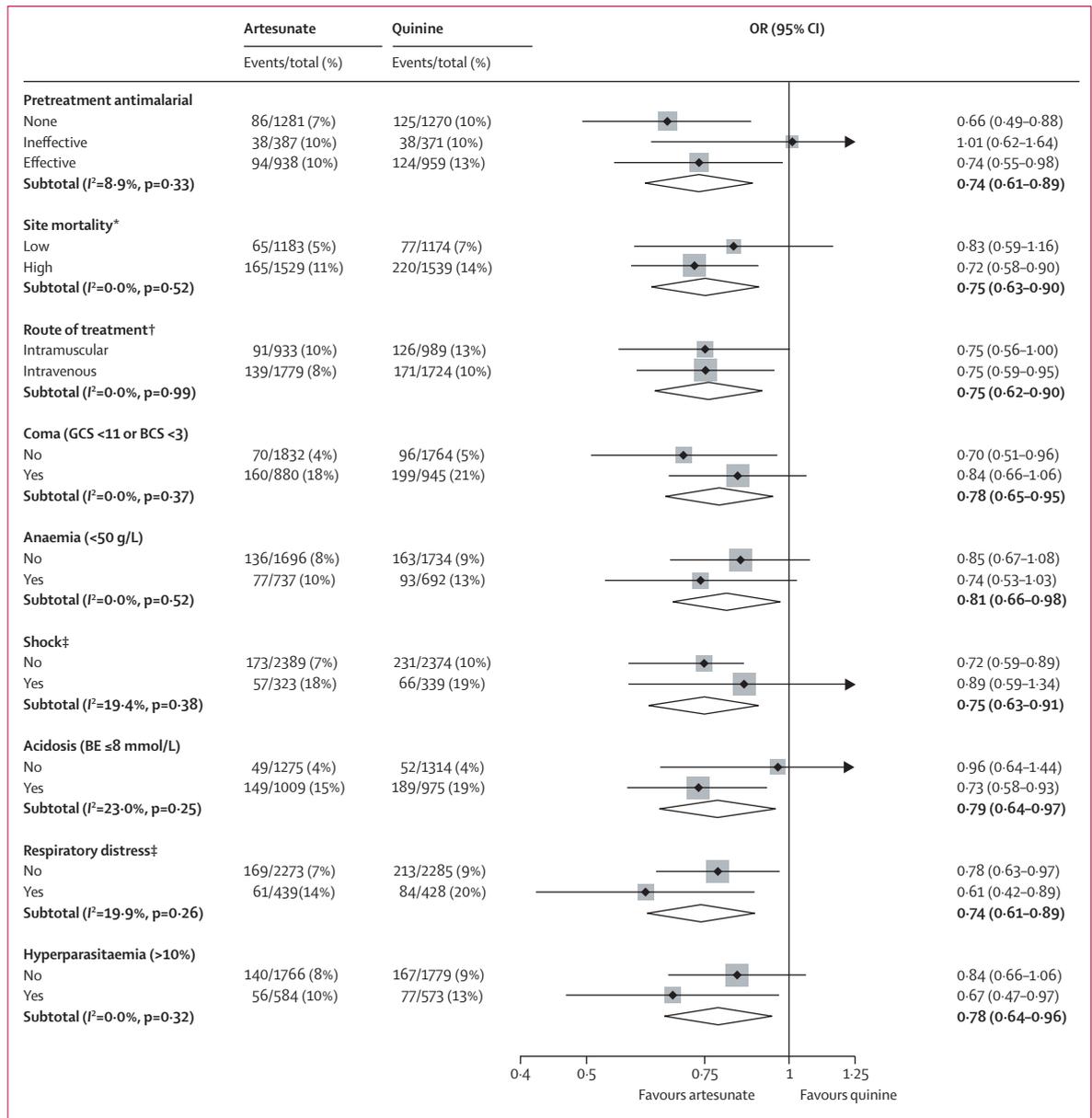|									
Artesunate	2712	(158)	2554	(32)	2522	(16)	2506	(13)	2493	(11)
Quinine	2713	(186)	2527	(63)	2464	(26)	2438	(10)	2428	(12)

See **Online** for webappendix

Figure 3: Treatment effect in protocol-specified subgroups

The forest plot shows odds ratios and 95% CIs. The size of the squares is proportional to the size, and therefore weight, of the subgroup. The diamonds show the combined differences. The efficacy of antimalarial pretreatment was classified before study unblinding (webappendix p 12). Hyperparasitaemia means greater than 10% of red cells parasitised. OR=odds ratio. GCS=Glasgow coma scale. BCS=Blantyre coma scale. BE=base excess. *Site mortality classified as low if the site mortality rate was lower than the overall study mortality rate, and high if the site mortality rate was higher than the overall study mortality rate. †Classified according to centre policy (ten sites); classified according to individual data (one site). ‡Decompensated or compensated shock. I^2 denotes the percentage of total variation across subgroups resulting from heterogeneity rather than chance, with the p value of significance.

aspects of supportive treatment, based on WHO guidelines, were unaffected by the trial.[1,2,9]

Although the trial was open label at each site, none of the investigators or trialists, apart from for the trial statistician (TEP), had access to the summaries of treatment allocations. When notes or case record forms were reviewed, all study drug details were removed to preserve masking. All case reviews and laboratory assessments were done blinded to treatment allocation, which was not revealed until the database was locked at the end of the trial.

Procedures

Artesunate (Guilin Pharmaceutical Factory, Guangxi, China) was given in a dose of 2·4 mg/kg on admission, at 12 h, at 24 h, and thereafter once daily until oral medication

could be taken reliably. The contents of each 60 mg vial were dissolved initially in 1 mL 5% sodium bicarbonate (provided with the drug) and then diluted with 5% dextrose before injection either as a bolus into an indwelling intravenous cannula, or administration by deep intramuscular injection to the anterior thigh. Quinine dihydrochloride (Indus Pharma, Karachi, Pakistan) was given in a 20 mg salt per kg loading dose infused over 4 h (in 5–10 mL/kg of 5% dextrose), followed by a 10 mg salt per kg infusion over 2–8 h three times daily until starting oral therapy. For intramuscular treatment the doses were the same as for intravenous treatment; quinine was diluted in normal saline to a concentration of 60 mg/mL, and injected into the anterior thigh. The loading dose was given as a split dose into each thigh.

When the patient was able to take tablets, but after a minimum of 24 h of parenteral treatment, oral artemether-lumefantrine (Coartem, Novartis, Basel, Switzerland) in a full standard dose (1·5/9 mg/kg twice daily for 3 days with milk or fat) was given to complete the treatment.

A 1 mL blood sample was taken for immediate haematocrit and biochemical analyses with the EC8+ card for a handheld blood analyser (i-STAT, Abbott Laboratories, Abbott Park, IL, USA). This device produced an immediate printed paper report with time of day, which was kept with the case record form. Haemoglobin was reported with the i-STAT result or, when not available, calculated from the measured haematocrit (n=146).[10] Thick and thin blood smears were prepared for later malaria parasite counting at the Bangkok reference laboratory. In 109 cases no count was available from the reference laboratory, so the parasitaemia reported by the study site was used. Children were discharged from hospital at the discretion of the physician, and a discharge assessment was completed. Children who had not made a full neurological recovery by discharge were followed up at regular intervals for 12 months or until full recovery. Full neurological assessments were completed at every visit. Training in neurological assessment was provided to all sites by a specialist paediatric neurologist (MO) to ensure uniformity.

Trial sites were monitored regularly by Family Health International, Nairobi, Kenya. Investigators provided reports every 2 weeks to the coordinating centre in Bangkok and met every year to review study progress. Drug content and quality were checked in ampoules taken randomly from the purchase lots (webappendix p 7). The data and safety monitoring committee made three interim analyses during the trial. Adequacy of randomisation was assessed by checking by centre that randomisation was balanced according to baseline variables, and by allocation time to assess whether the expected random variations were observed.

Study outcomes

The analysis was undertaken according to a prespecified analytical plan. The primary outcome measure was in-hospital mortality compared between treatments on an intention-to-treat basis. Secondary outcome measures were the incidence of severe neurological complications

	Quinine (n/N, %)	Artesunate (n/N, %)	OR (95% CI)	p value
Mortality, ITT analysis	297/2713 (10·9%)	230/2712 (8·5%)	0·75 (0·63–0·90)	0·0022
Mortality, per-protocol analysis	260/2552 (10·2%)	208/2563 (8·1%)	0·78 (0·64–0·94)	0·0099
Death or sequelae at 28 days	316/2695 (11·7%)	253/2689 (9·4%)	0·78 (0·65–0·93)	0·0056
Malaria-attributable mortality*	288/2704 (10·7%)	223/2705 (8·2%)	0·75 (0·63–0·91)	0·0025
Mortality in strictly defined severe malaria†	291/2338 (12·4%)	226/2280 (9·9%)	0·77 (0·64–0·93)	0·0055
Case fatality in HIV-positive children‡	19/61 (31%)	16/64 (25%)	0·74 (0·33–1·62)	0·45
Development of coma§	91/1768 (5·1%)	65/1832 (3·5%)	0·69 (0·49–0·95)	0·0231
Deterioration of coma score	208/2713 (7·7%)	166/2712 (6·1%)	0·78 (0·64–0·97)	0·0245
Convulsions developing or persisting >6 h after admission	273/2713 (10·1%)	224/2712 (8·3%)	0·80 (0·66–0·97)	0·0199
Hypoglycaemia	75/2713 (2·8%)	48/2712 (1·8%)	0·63 (0·43–0·91)	0·0134
Severe anaemia (<50 g/L) after admission§	98/1734 (5·7%)	78/1696 (4·6%)	0·81 (0·59–1·11)	0·18
Blackwater fever§	18/2597 (0·7%)	30/2591 (1·2%)	1·69 (0·94–3·05)	0·076

ITT=intention to treat. *The likelihood that malaria contributed to or directly caused the death was assessed by an independent endpoint review committee blinded to the treatment allocation. †As defined in panel 1. ‡HIV status was assessed only in Beira, Muheza, and Kilifi (n=2095). §Development of coma, anaemia, and blackwater fever was assessed only in patients without these disorders on admission.

Table 2: Mortality and complications according to treatment group
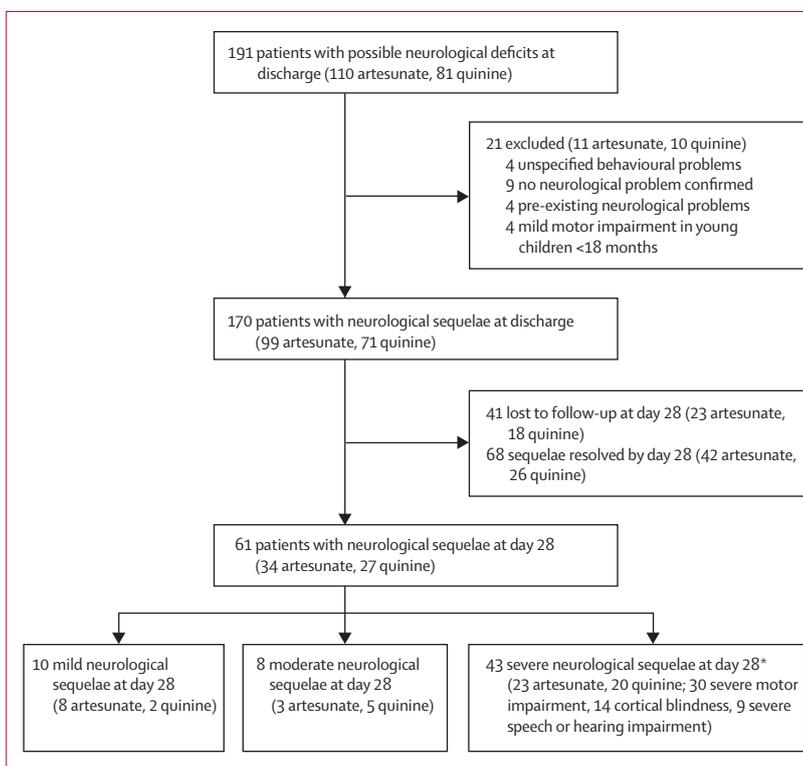

Figure 4: Neurological sequelae at discharge and after 28 days (range 3–8 weeks) in children with severe falciparum malaria
*Some patients had severe impairment in more than one domain.

	Quinine (median, IQR)	N	Artesunate (median, IQR)	N	HR (95% CI)	p value
Time to discharge (days)	3·0 (2·0–5·0)	2412	3·0 (2·0–5·0)	2478	1·04 (0·99–1·10)	0·059
Time to eat (h)	12 (2–24)	2269	9 (0–24)	2358	0·99 (0·93–1·06)	0·74
Time to sit unsupported (h)	22 (6–44)	2312	18 (6–42)	2373	1·02 (0·95–1·08)	0·60
Time to localise pain (h)*	12 (6–24)	726	12 (6–24)	698	0·87 (0·78–0·98)	0·0093
Time to speak (h)*	18 (11–36)	695	20 (8–42)	664	0·88 (0·79–0·99)	0·016

*Time to localise pain and time to speak was assessed only for surviving patients with coma on admission (Blantyre coma scale <3 or Glasgow coma scale <11).

Table 3: Recovery times in surviving patients according to treatment group

(assessed at 28 days, range 3–8 weeks) and a combined outcome measure of death and severe persistent neurological sequelae. Initially, neurological outcomes were assessed only at discharge from hospital, but this procedure led to substantial overestimation of neurological deficit, especially in young children. The protocol was therefore changed in April, 2007, (after 11% of patients had been enrolled) so that children who had not yet fully recovered at discharge were assessed 28 days after enrolment, and active follow-up was instituted. Outcome measures were also assessed per protocol, excluding patients not fulfilling the entry criteria, those with a negative or missing admission blood slide for *P falciparum*, those dying before receiving the study drug, and those missing a study drug dose on the first day of treatment. Subgroup analyses included stratification into two predefined groups: those who fulfilled the criteria for severe malaria[1,2,11] and those who did not. In sites at which testing was approved, the HIV status of participants was assessed after obtaining a separate informed consent, and the outcomes in HIV-1 infected patients with malaria were compared according to treatment allocation.

Two committees were formed to provide independent expert assessment and classification of outcomes before study unblinding. A neurological outcome committee, comprising two experienced paediatricians (both with neurological expertise and experience of working in Africa) and one clinical malariologist, graded neurological sequelae. These sequelae were assessed in four domains: motor function, visual function, hearing, and speech, and also whether the child had developed epilepsy. Sequelae persisting at follow-up were graded as mild, moderate, or severe in each domain according to the extent of functional impairment (webappendix p 5). The overall grade was combined. If there were sequelae in more than one functional domain the grade was increased. The relation of sequelae to severe malaria was assessed taking into account any pre-existing comorbidity. A separate endpoint review committee, comprising one paediatrician with malaria experience and one clinical malariologist, identified cases in which a pathological change other than malaria or its acute complications was likely to be the main cause of death.

Statistical analysis

Inclusion of more than 5306 children with severe malaria was needed to show, with 80% power and 95% confidence, a 25% reduction in mortality from 8% to 6%. This calculation was based on an estimated severe malaria mortality of 16% with about half the enrolled patients anticipated to fulfil the criteria for severe malaria. Patient data and outcomes were provided to an independent data and safety monitoring committee, who reviewed the trial yearly.

For binary outcomes, the odds ratios (ORs) between treatment groups, stratified by study site, were estimated by the Mantel-Haenszel method. Heterogeneity between sites was examined with the Breslow-Day test. In Rwanda, the two small sites run by the same investigators were pooled. Time to event outcomes were compared with the log-rank test, and hazard ratios (HRs) were estimated by a Cox proportional hazard model, stratified by site. Statistical analyses were done with Stata (version 11.1).

This trial is registered, number ISRCTN50258054.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. We recorded no major differences in baseline characteristics between the two treatment groups (table 1). 5425 patients were recruited (figure 1), of whom 527 (9·7%) died. 230 of 2712 (8·5%) patients given artesunate died versus 297 of 2713 (10·9%) given quinine (relative risk 0·78, 95% CI 0·66–0·91; OR 0·75, 0·63–0·90, in favour of artesunate; p=0·0022). This represents a relative reduction in mortality of 22·5% (95% CI 8·1–36·9%) and corresponds to an overall number needed to treat to prevent one death of 41 (95% CI 25–112). We recorded no heterogeneity between study sites (p=0·99). Eight patients (five artesunate, three quinine) were taken from hospital against advice and could not be followed up further. They were censored in the survival analysis at the time of discharge. The survival analysis (figure 2) for overall mortality during admission by antimalarial treatment gives the same result as the Mantel-Haenszel analysis (HR stratified by study site 0·76, 95% CI 0·64–0·91; p=0·0022). Mantel-Haenszel analysis of the predefined subgroups showed no evidence of any differences in odds ratios between subgroups (figure 3), and these results were confirmed by Cox regression (data not shown).

The per-protocol analysis excluded patients who died rapidly before receiving antimalarial treatment (six artesunate, 22 quinine; p=0·0023), patients with incomplete initial antimalarial treatment with the study drug, and those with negative or missing blood slides for
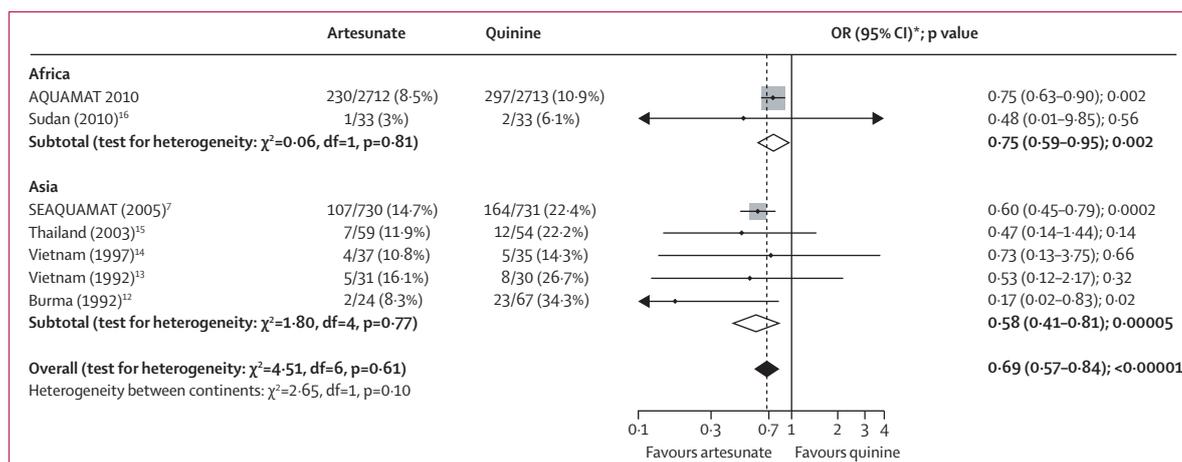
Figure 5: Meta-analysis of all randomised controlled trials that have compared mortality of severe malaria in patients treated with parenteral artesunate versus parenteral quinine[12-16]

The solid vertical line represents equality of the two groups; the dashed line is the overall treatment difference. The horizontal lines and the width of the diamonds show the CIs for the odds ratios. The size of the squares is proportional to the size, and therefore weight, of the trial. OR=odds ratio. *99% CIs for totals.

P falciparum (figure 1), but these omissions did not substantially affect the result (table 2). The endpoint review committee identified 16 children (seven artesunate, nine quinine) in whom death was unlikely to be related to severe malaria. Omission of these cases from the analysis also had no effect on the magnitude of the survival benefit with artesunate (table 2 and webappendix p 3). In 4618 children fulfilling strict criteria for severe malaria (panel 1), mortality was 9·9% (226/2280) with artesunate and 12·4% (291/2338) with quinine (OR 0·77, 95% CI 0·64–0·93; p=0·0055). Eight fatal cases (five quinine, three artesunate) did not have an accurate time of death recorded. In the remainder, 345 of 519 deaths occurred within the first 24 h after admission, of which 158 of 2709 (5·8%) were assigned to artesunate treatment and 187 of 2708 (6·9%) to quinine treatment (OR 0·84, 95% CI 0·67–1·04, p=0·109). Of the 174 of 519 deaths that occurred more than 24 h after admission, 69 of 2551 (2·7%) patients were treated with artesunate and 105 of 2521 (4·2%) with quinine (OR 0·63, 0·47–0·87, p=0·004). HIV serology was assessed routinely in Beira, Muheza, and Kilifi. Of 2095 patients tested, 125 (6%) were positive (64 artesunate, 61 quinine). Mortality in these patients was high (table 2).

497 children (224 artesunate, 273 quinine) had convulsions that either developed after admission, irrespective of duration, or were present on admission and persisted for more than 6 h, and 156 patients (65 artesunate, 91 quinine) developed coma or had a deterioration of their coma score after starting antimalarial treatment (table 2). The development of coma, deterioration in coma score, and convulsions all occurred more frequently in patients who received quinine than in those who received artesunate (table 2). In the 4898 survivors, 170 (99 artesunate, 71 quinine) had not yet made full neurological recoveries at discharge (figure 4). Of these patients, 129 (76 artesunate, 53 quinine) were followed up between 3 and 8 weeks after

enrolment. At this first follow-up assessment 68 (53%) had recovered fully, 18 (14%; 11 artesunate, seven quinine) were mildly or moderately impaired, and 43 (33%; 20 quinine, 23 artesunate) had severe neurological deficits. The overall incidence of any persistent neurological sequelae in assessed survivors at 28 days after cerebral malaria was 3·2% (24/706 artesunate, 23/737 quinine) and of severe neurological sequelae was 2·3% (17/706 artesunate, 17/737 quinine). We recorded no difference between the treatment groups. Of the 14 patients with any neurological sequelae who did not have cerebral malaria initially (ten artesunate, four quinine), seven had multiple convulsions (three quinine, four artesunate) and all had severe prostration on admission.

We detected no severe adverse effects that could be attributed directly to drug toxicity. Although one patient treated with artesunate developed a mild urticarial rash, no severe type 1 hypersensitivity reactions were recorded. Another patient treated with artesunate developed peripheral gangrene of toes and fingers, which was attributed to the disease and not the drug. One patient given quinine developed severe stridor after administration of ampicillin, and died. This death was attributed to ampicillin rather than quinine. Hypoglycaemia after starting antimalarial treatment was significantly less frequent in patients who received artesunate than in those who received quinine (table 2). Blackwater fever was rare in both groups (table 2).

Blood transfusions were given to 1487/2712 (55%) patients assigned to artesunate and 1495/2713 (55%) assigned to quinine. A fluid bolus at the start of treatment was given to 589/2712 (22%) patients assigned to artesunate and 596/2713 (22%) assigned to quinine. 3259 (60%) children received antibiotics (1606 artesunate, 1653 quinine; p=0·20).

In cerebral malaria survivors, the time from randomisation until the child was able to localise a

painful stimulus or was able to speak was slightly longer overall in patients treated with artesunate than in those given quinine when compared by survival analysis (table 3). The times to eat or to sit unsupported did not differ between treatment groups (table 3).

The content of artesunate in all ampoules tested was within the pharmaceutical content limits of 10% of the stated active ingredient. All tested vials of quinine contained between 105% and 112% of the stated content (webappendix p 7).

In a meta-analysis of all severe malaria trials that have compared survival after parenteral artesunate with that after parenteral quinine, the overall OR was 0·69 (0·57–0·84; p<0·00001) in favour of artesunate (figure 5). We noted no significant heterogeneity between the results generated in Africa and Asia (figure 5).

Discussion

This large multicentre trial shows that artesunate substantially reduces the overall mortality of African children diagnosed with severe malaria. We recorded little heterogeneity between treatment centres in the benefit associated with artesunate, suggesting that the findings are robust. Before this trial, concerns had been raised that artesunate might not be better than quinine in African children, whereas it clearly was in Asian patients. The concerns arose because of perceived differences in pathology and the prevalence of more quinine-susceptible malaria parasites, and because in the earlier SEAQUAMAT trial undertaken in Asia,[7] the survival curves did not separate clearly until 48 h after starting treatment, whereas most deaths in African children occurred before this time. Fortunately these concerns were not substantiated. More than 7000 severely ill patients have now been included in randomised comparisons of parenteral artesunate and quinine (figure 5). Compared with parenteral quinine, artesunate reduced the mortality of severe malaria in African children by 22·5%, and in Asian patients by 38·6%.[7] These studies together comprise nearly 80% of all patients ever enrolled in randomised controlled trials of patients admitted with severe malaria, and they provide definitive evidence that artesunate is the most effective available treatment for severe malaria, and that it is safe (panel 2).

This multicentre trial was open label because the substantial differences in the parenteral formulations of the two drugs prevented adequate concealment. Although individual trial site investigators knew the individual treatment allocations, all the other clinical and laboratory investigators were masked to the parenteral treatments given. The similarity of results across the different trial sites suggests that significant bias was unlikely. The great strength of this trial is its unprecedented size, its consistency both internally and with previous studies, and therefore the confidence that health-care workers throughout the tropical world can have in its result.

Artesunate prevented death from severe malaria, but not at the expense of an increase in neurological sequelae. Indeed, the overall incidence of confirmed persistent severe sequelae after severe malaria was low.[17] Initially the assessment of neurological deficit was made at discharge from hospital, but many children, especially in the younger age group, had not made a full neurological recovery at discharge. Subsequently, assessments were made 4 weeks later, by which time about half the apparent deficits had resolved fully.

This life-saving benefit of artesunate compared with quinine in severe malaria has to derive from its greater intrinsic parasiticidal activity. The principal pharmacodynamic advantage of artesunate is that it has a much broader stage-specificity of action than does quinine.[18] The artemisinins kill circulating ring-stage parasites before they can mature,[19,20] which reduces sequestration of infected erythrocytes in the venules and capillaries of vital organs and thereby prevents potentially lethal microvascular obstruction.[21–23] The large and consistent reduction in mortality associated with artesunate, and the consistent finding that mortality reduction is greatest in hyperparasitaemia,[7] lends support to the central quantitative role of parasitised erythrocyte sequestration in the pathology of malaria.

The benefits of parenteral artesunate compared with quinine were greater than the benefits of intramuscular artemether reported in previous trials.[6,7] In a double-blind trial[24] comparing artesunate and artemether in 370 Vietnamese adults with severe falciparum malaria, 13 patients died in the artesunate group (7%) and 24 in the artemether group (13%). Taken together, these different study results suggest that the live-saving benefit compared with quinine provided by artesunate is roughly twice that provided by artemether. Artesunate and artemether have similar pharmacodynamic properties in vitro, so the most likely explanation for their different

efficacies in vivo is the substantial difference in their pharmacokinetic properties. Parenteral artemether is an oil-based formulation given only by intramuscular injection. Absorption is slow and erratic, whereas the water-soluble hemisuccinate artesunate is absorbed rapidly and reliably after intramuscular injection and can be given intravenously.[25–30] Thus the pharmacodynamic advantage of artemether over quinine might have been offset by its poor absorption kinetics. In summary, in the treatment of severe falciparum malaria, it seems that artesunate is better than artemether, which in turn is better than quinine.

The benefits of artesunate (and artemether) compared with quinine were greater in patients from southeast Asia than in African children,[6,7] although the studies were not large enough to show this difference reliably. There are several possible explanations for this finding. African children usually have some background immunity that assists the therapeutic response, and in particular accelerates circulating parasite clearance.[31] This effect hastens recovery and could reduce the therapeutic advantage of artesunate. The greater quinine susceptibility of P falciparum in Africa is often proposed as contributing to improved therapeutic responses, but the differences are not large, and are unlikely to have a major effect in vivo. Incorrect diagnosis is likely to be a major contributory factor; severe malaria is overdiagnosed in African children, and sepsis is underdiagnosed.[32] Febrile sick children with positive malaria blood smears are usually diagnosed initially as having severe malaria, but the specificity of a positive blood smear is poor in settings in which a high proportion of all children are parasitaemic. Septicaemia and pneumonia are especially difficult to differentiate clinically from severe malaria. Sepsis and severe malaria also commonly coexist in African children.[32] Prompt and appropriate treatment of sepsis should further reduce the mortality of severely ill children with malaria parasitaemia.

Parenteral artesunate is simple to administer, is safe, and reduces mortality substantially compared with quinine. No serious adverse effects were identified in this large study or in previous large studies.[7,24,33] By contrast, intramuscular quinine is locally toxic[4] (because of its acidity), and intravenous quinine needs a carefully rate-controlled infusion and continuous or three times daily administration to avoid dangerous hypotension.[9] Importantly, quinine is associated with potentially serious hypoglycaemia.[1,2,5] In this trial, 22 children died before receiving quinine compared with only six who died before receiving artesunate. This finding is probably indicative of the difficulties in administering parenteral quinine promptly and safely. Any delay in treating severe infection will increase mortality.[33] The ease and safety of parenteral artesunate are important practical advantages. Artesunate is more expensive to buy, but quinine is more expensive to administer. A major factor restricting the deployment of artesunate has been unavailability of a product satisfying international good manufacturing standards. The most widely used product, assessed in this study, does not yet have this certification, which has prevented deployment in some countries.[34–39] This barrier must be overcome speedily so that parenteral artesunate can be deployed in malaria-endemic areas to save lives.

Artesunate should now become the treatment of choice for severe malaria for children and adults worldwide. Malaria causes an estimated 800 000 deaths every year in African children.[40] Severe malaria is often the most common admission diagnosis in febrile children, so a change in treatment policy from quinine to artesunate has the potential to save thousands of children's lives every year. If 4 million African children with severe malaria every year were to receive prompt treatment with parenteral artesunate instead of quinine, and the benefits were similar to those recorded in this trial, then approximately 100 000 lives might be saved per year.

Contributors
The coordinating committee designed the study. All investigators in the trial sites undertook the trial, with support from the team in Bangkok. All investigators and the coordinating committee reviewed and discussed the trial results. The writing committee did the data analysis and prepared the report.

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Conflicts of interest

NJW is co-chairman and OAM is a member of the WHO antimalarial treatment guidelines committee. JD was Temporary Adviser for WHO Model List of Essential Medicines for Children in 2007–08. All other authors declare that they have no conflicts of interest.

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