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Pre-referral rectal artesunate for severe malaria (Review)

Okebe J, Eisenhut M

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Pre-referral rectal artesunate for severe malaria.
Cochrane Database of Systematic Reviews 2014, Issue 5. Art. No.: CD009964.
DOI: 10.1002/14651858.CD009964.pub2.

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[Intervention Review]

Pre-referral rectal artesunate for severe malaria

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Editorial group: Cochrane Infectious Diseases Group.
Publication status and date: Unchanged, published in Issue 8, 2014.

Citation: Okebe J, Eisenhut M. Pre-referral rectal artesunate for severe malaria. *Cochrane Database of Systematic Reviews* 2014, Issue 5. Art. No.: CD009964. DOI: 10.1002/14651858.CD009964.pub2.

ABSTRACT

Background

Severe or complicated malaria is a medical emergency and people die as a result of delays in starting treatment. Most patients need parenteral treatment, and in primary healthcare facilities, where intravenous therapy is not available but intramuscular injections can be given, intramuscular quinine, artesunate, and artemether have been used before transporting patients to hospital.

However, in rural settings with limited access to health care, intramuscular injections may also be unavailable. In these situations, rectal artesunate given prior to transfer to hospital by volunteers with little medical training, may be a feasible option.

Objectives

To evaluate the effects of pre-referral treatment with rectal artesunate on mortality and morbidity in people with severe malaria.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) published in The Cochrane Library; MEDLINE; EMBASE and LILACS up to 21 May 2014. We also searched the WHO clinical trial registry platform and the metaRegister of Controlled Trials (mRCT) for ongoing trials.

Selection criteria

Individual or cluster-randomized controlled trials comparing pre-referral rectal artesunate with placebo or injectable antimalarials in children and adults with severe malaria.

Data collection and analysis

Two authors independently screened titles and abstracts for potentially eligible trials, and extracted data from the included trials. Dichotomous outcomes were summarized using risk ratios (RR) and presented with 95% confidence intervals (95% CI). Where data allowed, we conducted subgroup analyses by age, trial region and whether participants were included in the trial analysis. We assessed the quality of evidence for the most important outcomes using the GRADE approach.

Main results

One trial met the inclusion criteria; a placebo-controlled trial of 17,826 children and adults living in rural villages in Ghana and Tanzania (Africa) and Bangladesh (Asia). Villagers with no previous medical training were trained to recognize the symptoms of severe malaria, administer rectal artesunate and refer patients to hospital. The trained villagers were supervised during the trial period. In the African sites only children aged 6 to 72 months were enrolled, whereas in Bangladesh, older children and adults were also enrolled.

In young children (aged 6 to 72 months) there were fewer deaths following rectal artesunate than with placebo (RR 0.74; 95% CI 0.59 to 0.93; one trial; 8050 participants; *moderate quality evidence*), while in older children and adults there were more deaths in those given rectal artesunate (RR 2.21; 95% CI 1.18 to 4.15; one trial; 4018 participants; *low quality evidence*).

In Africa, only 56% of participants reached a secondary healthcare facility within six hours compared to over 90% in Asia. There were no differences between the intervention and control groups in the proportion of participants reaching a healthcare facility within six hours (RR 0.99; 95% CI 0.98 to 1.01; 12,068 participants), or in the proportion with parasitaemia (RR 1.00; 95% CI 0.98 to 1.02; 17,826 participants), or with coma or convulsions on arrival (RR 1.01; 95% CI 0.90 to 1.14; 12,068 participants).

There are no existing trials that compare rectal versus intramuscular artesunate.

Authors' conclusions

In rural areas without access to injectable antimalarials rectal artesunate provided before transfer to a referral facility probably reduces mortality in severely ill young children compared to referral without treatment. However, the unexpected finding of possible higher mortality in older children and adults has to be taken into account in forming any national or local policies about pre-referral rectal artesunate.

PLAIN LANGUAGE SUMMARY

Rectal artesunate for treating people with suspected severe malaria before transfer to hospital

Cochrane Collaboration researchers conducted a review of the effects of pre-referral rectal artesunate for people with suspected severe malaria, living in rural areas without healthcare services. After searching for all relevant trials up to May 2014 they included only one randomized controlled trial. This trial was conducted at various sites across Ghana, Tanzania and Bangladesh, and enrolled 17,826 children and adults.

What is severe malaria and how might pre-referral rectal artesunate reduce deaths?

Severe malaria is a serious medical condition caused by infection with the *Plasmodium* parasite which typically causes vomiting, anaemia, fitting, coma, and death. It is treated by giving injections of antimalarial drugs, which need to be started as quickly as possible to reduce the risk of death and brain damage. In some rural areas where malaria is common, people have to travel for several hours to reach healthcare clinics and hospitals, and many die on the way. In these settings, people without formal healthcare education could be trained to give artesunate rectally to start treating malaria before transporting the patient to hospital.

What the research says

Only one trial evaluated rectal artesunate as pre-referral treatment. In the African sites only, children aged 6 to 72 months were included in the trial; while in the Asian trial site, older children and adults were included.

Young children in the African and Asian trial sites (aged 6 to 72 months) had fewer deaths with rectal artesunate than with placebo (*moderate quality evidence*). However, in Asia among older children and adults, there were more deaths in those that received rectal artesunate (*low quality evidence*).

In the African sites, 56% of children took longer than six hours to reach hospital whereas over 90% of people in the Asian site reached hospital within six hours.

The unexpected finding of more deaths with rectal artesunate in older children and adults should be taken into account when forming national and local policies about pre-referral treatment.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Pre-referral rectal artesunate compared to placebo for preventing deaths from severe malaria

Patient or population: Children and adults with severe malaria
Settings: Rural settings in Africa and Asia
Intervention: Rectal artesunate and referral for further care
Comparison: Placebo and referral for further care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Rectal Artesunate				
All cause mortality	Children aged 6 to 72 months		RR 0.74 (0.59 to 0.93)	8050 (1 study)	⊕⊕⊕◯ **moderate**[1,2,3,4]	
	41 per 1000	30 per 1000 (24 to 38)				
	Older children and adults		RR 2.21 (1.18 to 4.15)	4018 (1 study)	⊕⊕◯◯ **low**[1,5,6]	
	7 per 1000	15 per 1000 (8 to 29)				
Neurodisability	All age groups		RR 0.68 (0.35 to 1.30)	17,280 (1 study)	⊕⊕◯◯ **low**[1,7]	
	3 per 1000	2 per 1000 (1 to 4)				

*The **assumed risk** is the control group risk from the single included study. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the control group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] No serious risk of bias: Allocation was concealed and trial participants and staff were blinded to treatment allocation.
[2] Downgraded by 1 for serious inconsistency: In both Africa and Asia there was a trend towards benefit with rectal artesunate in this age group. However in Africa, where most of the deaths occurred, and where almost half of participants failed to reach secondary care within six hours, the magnitude of the effect was smaller and did not reach statistical significance (RR 0.81; 95% CI 0.63 to 1.04).
[3] No serious indirectness: Children aged 6 to 72 months were recruited from community settings in Tanzania, Ghana and Bangladesh.
[4] No serious imprecision: The overall result reached statistical significance and was adequately powered to detect this effect.
[5] Downgraded by 1 for serious indirectness: Older children and adults were only recruited from community settings in Bangladesh. This result may not easily be generalized to elsewhere.
[6] Downgraded by 1 for serious imprecision: There were very few deaths in this group, and the trial was underpowered to detect this effect.
[7] Downgraded by 1 for serious imprecision: Too few events, wide confidence interval, single site.

BACKGROUND

Description of the condition

Malaria remains an important global health challenge. In 2009 approximately 225 million clinical cases and 781,000 malaria-related deaths occurred worldwide (WHO 2010a). The greatest burden of disease occurs in sub-Saharan Africa where the highest risk is in children below the age of five years (WHO 2010a). The dominant parasite species *Plasmodium falciparum* accounts for over 95% of cases.

Severe or complicated malaria is characterized by signs of vital organ dysfunction, and prompt and effective drug treatment is required to prevent severe neurological deficit and death (WHO 2010b). Patients are often unable to take drugs by mouth because of repeated vomiting or a reduced level of consciousness, and parenteral treatment with either intravenous (IV) or intramuscular (IM) injections is preferred.

Description of the intervention

Artesunate and artemether are antimalarial compounds derived from the herb *Artemisia annua*. Once administered these artemisinin-derivatives are rapidly converted to the active metabolite dihydroartemisinin, which has been shown to rapidly clear malaria parasites from the peripheral blood (German 2008). Artemisinin-derivatives now form the backbone of the global malaria treatment strategy where they are used orally in artemisinin-based combinations for uncomplicated malaria, or as injections for severe malaria (WHO 2010b).

Artesunate is the recommended first line treatment for severe malaria worldwide (WHO 2010b), and when given by intravenous or intramuscular injection has been shown to reduce deaths in both children and adults compared to the older alternative quinine (Dondorp 2005; Dondorp 2010). This effect has been consistent across all published randomized trials, and the most recent Cochrane review of artesunate versus quinine concluded that further studies comparing these two drugs parenterally are probably unnecessary (Sinclair 2012).

In hospital-based studies artesunate also appears to be reliably absorbed and effective when administered rectally. A systematic review (Karunajeewa 2007) identified two studies directly comparing rectal artesunate with parenteral alternatives (Barnes 2004; Karunajeewa 2006). These two studies were conducted in hospital settings, enrolled a total of 268 participants, and both reported a reduction in parasitaemia as the primary outcome. Neither were powered to look at mortality and only one patient died (after rectal treatment). Rectal artesunate was associated with superior reductions in parasitaemia at 12 and 24 hours compared to parenteral quinine (Barnes 2004) and intramuscular artemether (Karunajeewa 2006). The review found no studies directly comparing rectal artesunate with parenteral artesunate.

A more recent review of pharmacokinetic data concluded that rectal artesunate had similar characteristics to oral administration but with a slightly shorter time to maximum plasma concentration (T_{max}) (Morris 2011). Rectal artesunate has the advantage of not having a first pass effect through the liver so bioavailability after administration is high (Morris 2011). The rate of absorption in children is modified by the body temperature, with higher absorption positively correlated with rising body temperature (Karunajeewa 2004). The volume of distribution is also influenced by body weight which in this context is a proxy for age (Karunajeewa 2004; Stepniewska 2009).

How the intervention might work

The risk of death from severe malaria is greatest within the first 24 hours of onset of illness (Marsh 1995). Treatment should therefore start as soon as possible in such patients, preferably before the referral process is completed. Ideally the drug should be given intravenously although current recommendations allow for intramuscular or rectal administration where this is not possible or available (WHO 2010b).

In most malaria endemic countries injectable formulations of artesunate and quinine and the necessary skill to give them are mainly concentrated in large healthcare facilities. The transit time to these facilities is often prolonged due to long distances and a lack of adequate transport. The resulting delays in accessing treatment could account for the high mortality associated with the disease (Marsh 1995). Indeed, results of verbal autopsy studies have demonstrated that the majority of patients with severe malaria never reached the hospital (Kamugisha 2007; Kaatano 2009; Mudenda 2011). Addressing this situation requires improvements in the initial emergency response package for identifying and treating cases of suspected severe malaria. Specifically, this would involve the use of effective drugs in formulations that can be easily administered by healthcare staff at the point of first contact, taking into account the level of skill available at such points. In this context artesunate suppositories offer a distinct potential advantage as a means of initiating treatment of severe malaria as they are easy to administer by individuals with minimal training (Tozan 2010).

Why it is important to do this review

The exact role of rectal artesunate in the management of malaria has remained the subject of discussion. While rectal artesunate provides a pragmatic solution for early treatment, its effects on mortality and morbidity are less clear. Furthermore, the rectal route of treatment may not be universally acceptable (Inthavilay 2010). Studies on the effects of rectal artesunate have mainly been conducted in hospitals (Awad 2003; Barnes 2004) and are difficult

to generalize to rural settings where a pre-referral intervention is needed. A trial by Gomes and colleagues (Gomes 2009) evaluated the effects of a single dose rectal artesunate administered before referral on death and permanent disability and the trial was designed to address some of these questions (Gomes 2011). This trial's findings were used to inform recommendations (WHO 2010b). However, the results of this trial and the subsequent recommendation of rectal artesunate as pre-referral treatment in severe malaria has been the subject of criticism. Notably, Hirji and Premji reported limitations in the design, implementation, analysis and interpretation of the trial data (Hirji 2011); while others questioned the ethics of using a placebo control group in patients considered to be critically ill (Bello 2009).

These concerns indicated a real interest in this field and make this review timely. Given the importance of early intervention for the outcomes of severe malaria it is vital that we have a concise summary of the available evidence regarding the use of rectal artesunate at an important early stage in the management of severe malaria.

OBJECTIVES

To evaluate the effects of pre-referral treatment with rectal artesunate on mortality and morbidity in people with severe malaria.

METHODS

Criteria for considering studies for this review

Types of studies

Individual and cluster-randomized controlled trials.

Types of participants

Children and adults with any of the features of severe malaria as defined by the World Health Organization (WHO 2000). We also considered trials where additional criteria such as inability to swallow oral drugs or need for hospitalization was used to define entry into the study.

Types of interventions

Comparison 1: Artesunate given rectally before referral to a healthcare facility versus placebo.

Comparison 2: Artesunate given rectally before referral to a healthcare facility versus intramuscular or intravenous injections of an antimalarial drug.

Types of outcome measures

Primary outcomes

- All cause mortality.

Secondary outcomes

- Neurodisability defined as any neurological deficit persisting beyond the acute phase of illness.
- Proportion of patients with severe malaria reaching a secondary healthcare facility.
- Proportion of patients with parasitaemia on admission in the secondary healthcare facility.
- Average parasite count per group on admission in the secondary healthcare facility.
- Time to presentation at healthcare facility.

Search methods for identification of studies

We searched for all relevant trials regardless of language or publication status (published, unpublished, in press and in progress).

Electronic searches

The search specialist at the editorial base searched the following databases up to May 2014 using search terms detailed in Appendix 1: Cochrane Central Register of Controlled Trials (CENTRAL) published in The Cochrane Library; MEDLINE; EMBASE and LILACS. We also searched the WHO clinical trial registry platform and the metaRegister of Controlled Trials (mRCT) for ongoing trials.

Searching other resources

We checked the reference lists of included studies identified from the above mentioned methods.

Data collection and analysis

Selection of studies

The review authors (JO and ME) independently screened titles and abstracts of the search results for potentially eligible trials. Following agreement on what trials need further review we retrieved the full text of these articles and applied the eligibility criteria as above mentioned. Trials that did not meet the criteria were excluded and the reasons for exclusion were summarized in the "Characteristics of excluded studies" table.

Data extraction and management

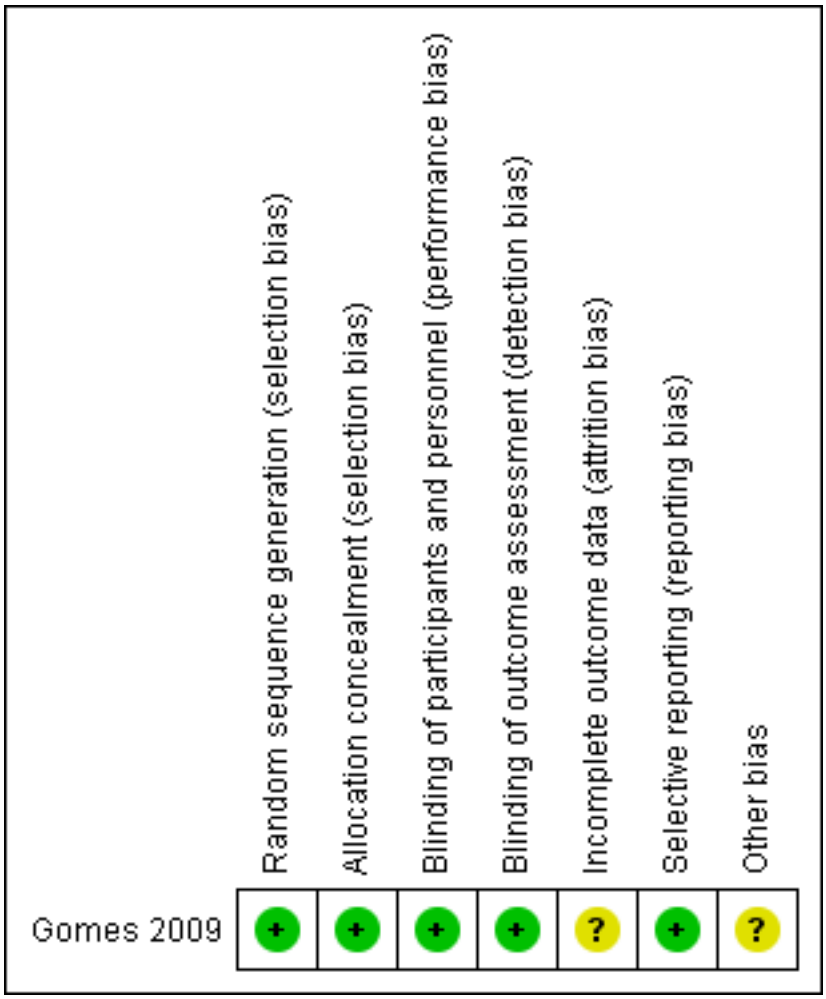
JO and ME extracted data from the included trials and JO entered these in the table of Characteristics of included studies. JO resolved differences in the data by discussion with ME.
We extracted the following information:

- Start and end dates, location and details of the trial design.
- Background of the trial sites: malaria endemicity; available healthcare services; distance to healthcare facilities when stated.
- Eligibility (inclusion and exclusion) criteria of the participants, including the sample size and ages.
- Details about the interventions: type and dose of suppositories used.
- The type and cadre of staff administering the treatment.
- The method used for the diagnosis of severe malaria.
- The methods used for ruling out diseases other than malaria.
- For each outcome we noted the number of participants analyzed for each group as well as attrition. For dichotomous outcomes we also recorded the number of participants that experienced the event. For count data we planned to extract the number of events per group and the total person time at risk in each group (where feasible).

Assessment of risk of bias in included studies

JO and ME independently assessed the risk of bias in the included trial using the Cochrane Collaboration's risk of bias tool (Higgins 2011). We included the following assessment categories: sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and "other bias" (such as clustering). We assigned judgements as either "yes" (low risk of bias), "no" (high risk of bias) or "unclear". We resolved differences through discussion and reaching consensus, and summarized the results of the assessment in Figure 1.

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for the included trial.



Measures of treatment effect

We used risk ratios (RR) to measure treatment effects for dichotomous outcomes (death from all causes; presence of neurodisability; percentage reaching hospital; percentage with parasitaemia). We presented count data as rate ratios because we could not analyze them as continuous data (average parasite count per group as these were presented as categories). All measures were presented with 95% confidence intervals (CIs). We performed subgroup analysis for dichotomous outcomes by age and region (Africa versus Asia).

Unit of analysis issues

The unit of analysis was individuals and we analyzed the data accordingly using methods described previously (Higgins 2011).

Dealing with missing data

We performed intention-to-treat analyses by including all outcome data available in the article, irrespective of whether the participants completed the trial or not.

Assessment of heterogeneity

We assessed for statistical heterogeneity between subgroups by visually inspecting the forest plots for overlapping confidence intervals, applying the Chi^2 test (where a P value < 0.10 is considered

statistically significant), and by using the I^2 statistic (with values > 40% representing moderate heterogeneity, > 60% substantial heterogeneity, and > 80% considerable heterogeneity).

Assessment of reporting biases

We assessed if trial outcomes were reported for all randomized participants by comparing the proportions of those with outcomes against the number enrolled in each trial arm. Where this was not the case, we checked to see if there was an explanation for the difference.

Data synthesis

JO analyzed the data using (Review Manager (RevMan) 2012) software and applied a fixed-effect model. Because we only included one trial we could not do meta-analyses however, effect sizes were calculated for all outcomes. We assessed the quality of evidence for the most important outcomes using the GRADE approach, and presented the judgements in a Summary of Findings table.

Subgroup analysis and investigation of heterogeneity

Where statistical heterogeneity was observed we investigated the influence of trial characteristics with subgroup analysis by age (6 to 72 months versus > 72 months), trial region (Africa or Asia) and whether the participants were included in the trial analysis or not.

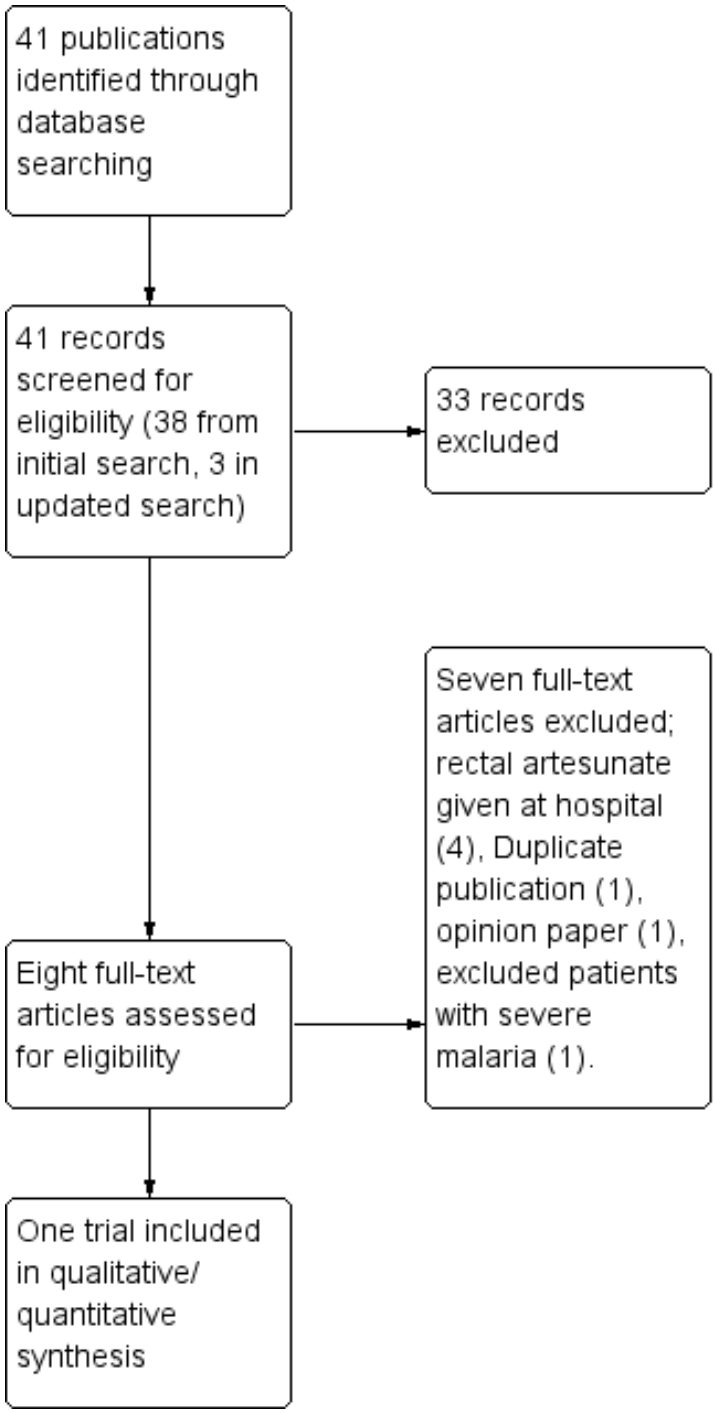
RESULTS

Description of studies

Results of the search

The search identified 38 potentially relevant publications of which only one was eligible (Gomes 2009). We excluded thirty articles after reviewing the titles and abstracts, and a further seven publications were excluded with reasons after we reviewed the full text (Figure 2). We did not find any trial that evaluated our second comparison.

Figure 2. Search results and article selection.



Included studies

The trial by Gomes and colleagues (Gomes 2009) was a community-based individually randomized placebo-controlled trial involving 291 villages in three countries with different levels of malaria transmission: Bangladesh (149 villages) with a low unstable transmission and two African countries, Ghana and Tanzania (142 villages), with high transmission. A total of 17,826 children and adults with suspected severe malaria were randomized to receive either a single artesunate suppository (n = 8954) or placebo (n = 8872). The trial report focused on 12,068 participants (6072 artesunate; 5996 placebo); 5758 (32.3%) participants were excluded from the primary analysis because they had either received an antimalarial injection around the time of randomization (n = 1110) or were retrospectively observed to have a negative blood smear at the time of randomization (n = 4648).

Trial participants were categorized as children aged 6 to 72 months (67%, n = 8050), or older children and adults (aged over 72 months). Only children aged between 6 and 72 months were recruited at the African sites and made up 75% of the total in this group (Table 1). Children aged 6 to 72 months received 100 mg artesunate while the rest received 400 mg artesunate rectally and all were subsequently referred to a healthcare facility (clinic or hospital). Mortality was assessed at the healthcare facility and during home visits carried out 7 to 30 (median 14) days after randomization (Characteristics of included studies).

Excluded studies

Of the seven excluded articles four were trials that gave artesunate to participants in hospital (Barnes 2004; Aceng 2005; Karunajeewa 2006; Gomes 2010), one was a secondary publication based on Barnes 2004, one was an opinion paper addressing ethical issues with using placebo as control group in the included trial (Kitua 2010) and one trial excluded participants with severe malaria (Krishna 2001).

Risk of bias in included studies

The risk of bias assessment relates to the one included trial (Gomes 2009).

Allocation

Participants were allocated to either the intervention or control groups by making use of consecutively numbered treatment boxes. A computer was used to generate the allocation sequence by means of block-randomization.

Blinding

All trial staff were blinded to the treatment allocation until the endpoints were finalized.

Incomplete outcome data

The trial authors described their analysis to be an "intention to treat" analysis. However, results were presented for 12,068 (68%) participants and 5758 (32%) randomized participants were excluded from the analysis because either the blood slide collected on enrolment and read at the referral hospital was negative (4648 participants) or they had received an injection with an antimalarial shortly before randomization (1110 participants).

Selective reporting

The trial authors did not report all pre-specified outcomes as per the protocol in the trial registry however, there was no evidence from the data that they were excluded. The risk of selective outcome reporting in the published report of the trial was low.

Other potential sources of bias

Most of the children aged between 6 and 72 months were recruited from sites in Africa while all older children and adult participants were from the sites in Bangladesh. Mortality and presentation at a healthcare facility were quite different between the African and Asian sites and this could have been due to differences in the distance to, or the quality of, care at these referral facilities (Table 1). One of the African sites with 1020 (16.9%) trial participants did not collect a blood slide at randomization but these were included in the trial analysis. Only 8 (0.1%) participants recruited in Bangladesh did not have a blood slide at randomization.

Effects of interventions

See: **Summary of findings for the main comparison** Pre-referral rectal artesunate compared to placebo for severe malaria

Comparison: Artesunate given rectally before referral to a health facility versus placebo

All cause mortality

Overall, there was no evidence of a difference in mortality with rectal artesunate compared to placebo for all participants analyzed in the trial (all ages across African and Asian sites) (RR 0.86; 95% CI 0.69 to 1.06; 12,068 participants; Analysis 1.1). There was also

no evidence of a difference in the intention-to-treat analysis of all randomized participants which included those excluded from the trial's primary analysis due to negative blood smears or receiving an antimalarial injection before randomization (RR 0.89; 95% CI 0.75 to 1.05; 17,826 participants; Analysis 1.1).

In young children (aged 6 to 72 months; African and Asian sites) rectal artesunate was associated with a reduced risk of death compared to placebo (RR 0.74; 95% CI 0.59 to 0.93; 8050 participants; Analysis 1.2), although the magnitude of this effect varied between the African (RR 0.81; 95% CI 0.63 to 1.04; 6040 participants) and the Asian sites (RR 0.45; 95% CI 0.24 to 0.85; 2010 participants).

In older children and adults (Asian sites only) rectal artesunate was associated with a more than two-fold increase in the risk of death compared to placebo (RR 2.21; 95% CI 1.18 to 4.15; P = 0.01; 4018 participants; Analysis 1.3).

Neurodisability

Neurodisability as an outcome in the trial was rare with only 15 participants diagnosed with a disability (2/5918 in the artesunate group versus 13/5819 in the placebo group). This difference reached statistical significance (RR 0.15; 95% CI 0.03 to 0.67; 11,737 participants; Analysis 1.4), but when we re-analyzed including the 5543 randomized participants excluded from the trial's primary analysis the result was no longer statistically significant (RR 0.68; 95% CI 0.35 to 1.30; 17,280 participants; Analysis 1.4).

Severe malaria on admission

There was no difference in the proportion of participants with severe malaria (coma, repeated convulsions, or prostration) on arrival at a healthcare facility between those given rectal artesunate or placebo (RR 1.01; 95% CI 0.90 to 1.14; 12,068 participants; Analysis 1.5). This finding was consistent for all age categories and trial regions.

Parasitaemia on admission

There was no difference between the rectal artesunate or placebo groups in the proportion of participants with parasitaemia on admission (RR 1.00; 95% CI 0.98 to 1.02; 17,826 participants; Analysis 1.6).

Proportion reaching hospital within six hours

There was also no difference between the two groups in the proportion of participants who reached a healthcare facility within six hours (RR 0.99, 95% CI 0.98 to 1.01; 12,068 participants; Analysis 1.7). However, the proportion that had not reached a hospital within this period was very different between regions where almost half of all participants in Africa failed to reach a facility within six hours (2686/6040; 44.5%) compared to less than 10% in Asia (399/6028; 6.6%) (Table 1).

DISCUSSION

Summary of main results

Rectal artesunate as a pre-referral intervention showed diverging effects on all cause mortality in different age groups with severe or complicated malaria. In young children rectal artesunate probably reduces the risk of death by 26% (moderate quality evidence) while in older children and adults rectal artesunate may increase risk of death (low quality evidence).

The risk of neurodisability was low with both rectal artesunate and placebo, without a statistically significant difference between groups (low quality evidence).

Overall completeness and applicability of evidence

The single included trial was conducted to evaluate the use of rectal artesunate in a very specific scenario; rural communities without access to injectable antimalarials, and as such includes a placebo control group rather than the prior standard of care; parenteral artesunate or quinine. The findings of this review are therefore only directly applicable to similar settings. Indeed, despite extensive searching we found no trials comparing pre-referral rectal artesunate with either intramuscular quinine, artesunate or artemether.

The trial included a mix of African and Asian trial sites across a range of malaria transmission settings. However, there are several differences between the study sites which complicate interpretation of the results (Table 1). Older children and adults were only enrolled in Asia, making it impossible to determine if the harm detected in older children and adults is specific to Asia or consistent across regions, and trial participants in Bangladesh were able to access definitive care much quicker than those in Africa, which may explain the lower mortality seen at the Asian sites.

The finding that rectal artesunate reduced the risk of death in young children but increased the risk of death in older children and adults is both unexpected and difficult to explain. There is some evidence that the profile of severe or complicated malaria differs between children and adults (WHO 1990), but a review of artemisinin-derivatives in severe malaria has shown consistent benefits in children and adults with only variation in the magnitude of the benefit (Sinclair 2012). We attempted to understand this finding but without other trials to confirm or refute the findings we can not provide a plausible explanation. The small number of deaths recorded in older children and adults in Asia raises

the possibility that this is a chance finding, but other explanatory factors may be the higher dose administered, differences in the care received, or a true differential effect of age in the host response to severe malaria. Undoubtedly, this finding has implications for policy recommendations regarding rectal artesunate in older children and adults.

The primary analysis in the trial excluded a large proportion of the randomized participants. This decision was made before unblinding, and we did not detect major differences in results when these participants were added back into the analysis. The rationale for the time and age cut-offs used in the analysis are less clear.

Despite the limitations, and questions arising from this single trial, it is unlikely that a trial of this size will ever be repeated due to the challenges of recruiting an adequate sample size, and the decline in malaria transmission globally. There is also the ethical question of the use of a placebo in a potentially life threatening situation with little option for rapid intervention if the condition deteriorates. Consequently, the observed harmful effect in children older than 72 months and adults may remain unexplained.

Quality of the evidence

We assessed the quality of the evidence using the GRADE approach, and our judgements are presented in Summary of findings for the main comparison.

We consider the data available from the trial sites in Asia to provide only *low quality evidence* of a benefit in young children and a harm in older children and adults. The main limitation was the low number of events (deaths) in both age categories at this site, which means the trial was not powered to confidently detect these effects. This limitation raises the possibility that these are both chance findings. We have therefore downgraded for serious imprecision, and for serious inconsistency due to the opposite effects in the two age groups; a finding which is both unexpected and unexplained. However, we considered the data in young children from Africa and Asia to provide *moderate quality evidence* of a reduction in death with rectal artesunate in this age group. This means that we have moderate confidence that rectal artesunate is beneficial in this age group. We downgraded the evidence from high due to the inconsistency in effect between the two regions (with a smaller effect seen in Africa). We also considered downgrading for imprecision because the result in Africa did not reach statistical significance without the addition of the Asian data. However, after discussion we did not consider this issue sufficient to further downgrade.

We also note that the absolute benefit of pre-referral rectal artesunate in young children is relatively small, saving just 10 more lives per 1000 people treated than referral alone (with placebo). This is of smaller magnitude than the additional benefits of parenteral artesunate versus parenteral quinine (26 additional lives saved per 1000 people treated, Sinclair 2012).

Potential biases in the review process

We did not identify any specific bias in our review process.

Agreements and disagreements with other studies or reviews

We found no other reviews of pre-referral rectal artesunate. We did however find three reviews of trials evaluating the effect of rectal artemisinins compared to conventional treatments for severe malaria (parenteral artemisinins and quinine) in hospital-based care settings (Gomes 2008; Karunajeewa 2007; Wilairatana 1997). The most recent of these reviews (Gomes 2008) used individual patient data from three published and three unpublished studies to compare rectal and parenteral artemisinin-derivatives. However, none of the studies in the review directly compared rectal with parenteral artesunate, or directly assessed pre-referral treatment. The review authors concluded that rectal artesunate was effective at reducing parasitaemia during the first 24 hours after treatment and could be an option in remote rural settings (Gomes 2008) and this formed the background for the included trial (Gomes 2009). The authors of the single included trial in our review concluded that "if patients with severe malaria cannot be treated orally and access to injections will take several hours, a single inexpensive artesunate suppository at the time of referral substantially reduces the risk of death or permanent disability". We would suggest an amendment to limit the conclusion to children aged between 6 and 72 months.

AUTHORS' CONCLUSIONS

Implications for practice

In rural settings without access to injectable antimalarials, rectal artesunate probably reduces mortality in young children (6 to 72 months old) being transported to hospital for further care. However, the unexpected finding of possible higher mortality in older children and adults should be taken into account when forming national and local policies about pre-referral treatment.

Implications for research

The concerns about increased mortality with pre-referral rectal artesunate in older children and adults will not be resolved without further trials. However, it is unlikely that these trials will be done, due to the large sample size required and the ethical issues related to the use of a placebo group.

ACKNOWLEDGEMENTS

The academic editor for this review was Professor Paul Garner.

We thank the Cochrane Infectious Diseases Group for their support of this project.The editorial base for the Cochrane Infectious Diseases Group is funded by the UK Department for International Development for the benefit of developing countries.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Gomes 2009

Methods	Community-based individually randomized placebo-controlled Length of follow-up: 7 to 30 days Mortality was assessed at the clinic and during home visits carried out 7 to 30 days after randomization (median 14 days)
Participants	17,826 participants recruited from 291 rural villages in Africa (Ghana, Tanzania; 142) and Asia (Bangladesh; 149) Intervention group (rectal artesunate)=8954, control group (placebo)= 8872 Number analyzed and reported in trial result: 12,068 (intervention= 6072, control= 5996) 46% of participants (n = 5504) were female and information on gender was missing for two participants; (one in each group) Age range: 6 to 72 months (African and Asian trial sites); participants > 72 months recruited only from sites in Bangladesh (Asia) Inclusion criteria: suspected malaria determined by trained resident recruiters, and participants unable to swallow Exclusion criteria at screening: not stated Reported baseline characteristics did not show any differences between the trial groups
Interventions	Artesunate (100 mg and 400 mg for the younger children and older children and adults respectively) versus placebo Participant received either artesunate or placebo suppository of identical appearance, sealed in a waterproof sachet. After insertion, the buttocks held together for about 10 min to prevent expulsion. Participants were considered included in trial on successful insertion even if the suppository was later expelled
Outcomes	Mortality at 7 to 30 days after randomization Permanent disability 7 to 30 days after randomization Eight participants (0·07%), all in the placebo group, were lost to follow- up
Notes	Different malaria transmission characteristics: high (Ghana, Tanzania); low and unstable (Bangladesh) The trial was conducted between August 2000 and July 2006. Treatment administered by resident village recruiters with little previous medical knowledge and no research experience; they got monitored by field supervisors Data for participants > 72 months old were from one site Access to and quality of available care at referral hospital was notably different between African and Asian sites Determination of alternative diagnosis was ruled out by expert opinion Trial Registration: http://www.controlled-trials.com/ISRCTN83979018; http://www.controlled-trials.com/ISRCTN46343627; http://www.controlled-trials.com/ISRCTN76987662
Risk of bias	

Gomes 2009 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	used computer generated block-balanced boxes of 4 or 8 random allocations
Allocation concealment (selection bias)	Low risk	Consecutively numbered treatment boxes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All trial staff were blinded until after the endpoints were finalized
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Although some participants initially randomized were excluded from analysis, this was done before unblinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	5758 (32%) of participants were excluded from the analysis after randomization. This was documented as a pre-unblinding decision in trial publication
Selective reporting (reporting bias)	Low risk	The protocol is available and the trial authors addressed all of the important and pre-specified outcomes
Other bias	Unclear risk	Difference in age distribution of recruited participants and in proportion of participants without blood slide at recruitment between the African and Asian regions,

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aceng 2005	Rectal artesunate given in hospital
Barnes 2004	Rectal artesunate given in hospital and patients with moderate malaria included
Gomes 2010	Rectal artesunate given in hospital
Karunajeewa 2006	Rectal artesunate given in hospital
Kitua 2010	Discussion of Gomes 2009
Krishna 2001	Excluded patients with severe malaria

DATA AND ANALYSES

Comparison 1. Pre-referral artesunate vs Placebo

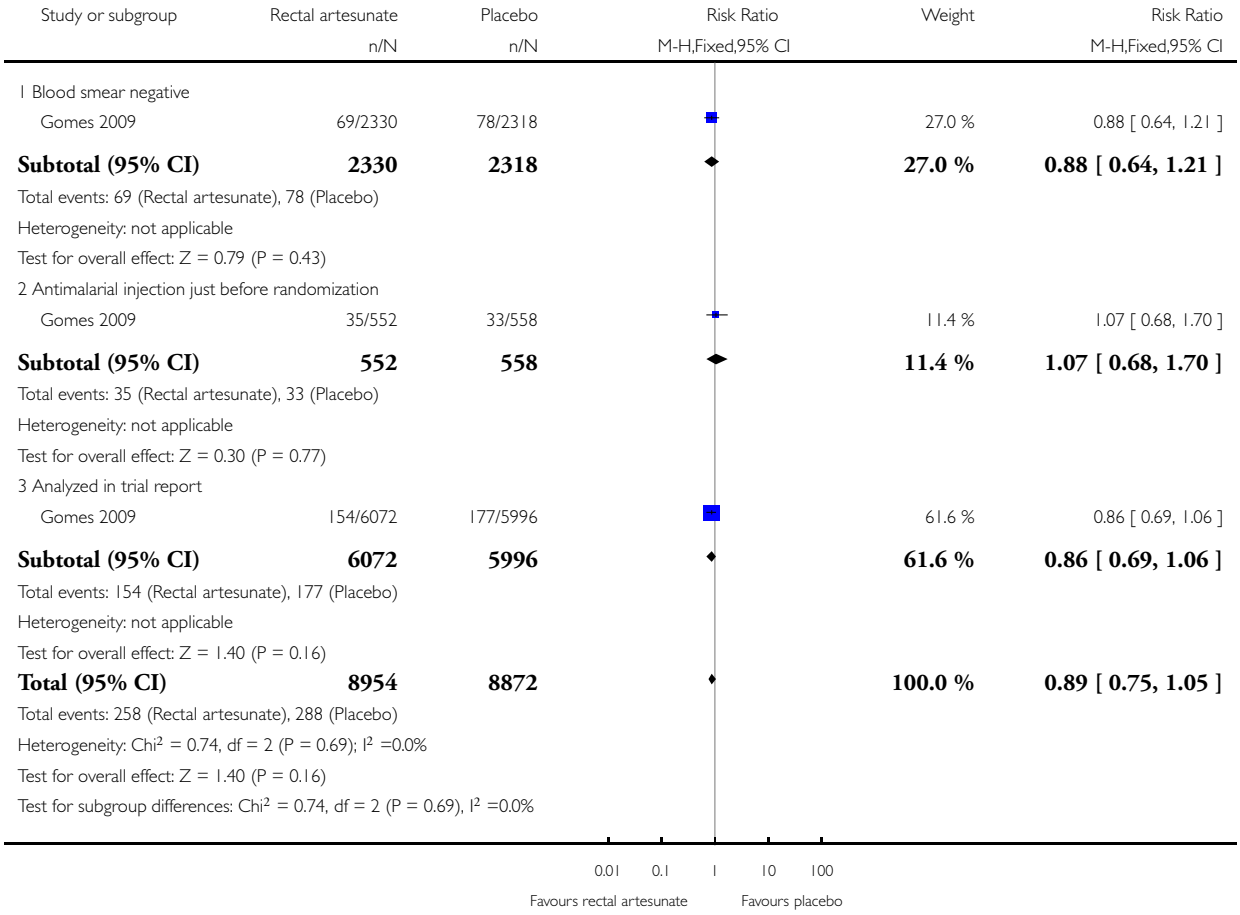
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All cause mortality (all enrolled)	1	17826	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.75, 1.05]
1.1 Blood smear negative	1	4648	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.64, 1.21]
1.2 Antimalarial injection just before randomization	1	1110	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.68, 1.70]
1.3 Analyzed in trial report	1	12068	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.69, 1.06]
2 All cause mortality (young children)	1	8050	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.59, 0.93]
2.1 Africa	1	6040	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.63, 1.04]
2.2 Asia	1	2010	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.24, 0.85]
3 All cause mortality (older children/adults)	1	4018	Risk Ratio (M-H, Fixed, 95% CI)	2.21 [1.18, 4.15]
4 Neurodisability (all participants)	1	17280	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.35, 1.30]
4.1 Excluded in trial analysis	1	5543	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [0.62, 3.36]
4.2 Analyzed in trial report	1	11737	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.03, 0.67]
5 Severe malaria on admission (coma, repeated convulsions or prostration)	1	12068	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.90, 1.14]
5.1 Asia (6 to 72 months)	1	2010	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.74, 1.30]
5.2 Asia (older child/adult)	1	4018	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.81, 1.33]
5.3 Africa (6 to 72 months)	1	6040	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.87, 1.19]
6 Proportion with parasitaemia on admission	1	17826	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.98, 1.02]
7 Proportion reaching a hospital within 6 hours	1	12068	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.98, 1.01]
7.1 Africa	1	6040	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.95, 1.04]
7.2 Asia	1	6028	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.98, 1.01]

Analysis 1.1. Comparison 1 Pre-referral artesunate vs Placebo, Outcome 1 All cause mortality (all enrolled).

Review: Pre-referral rectal artesunate for severe malaria

Comparison: 1 Pre-referral artesunate vs Placebo

Outcome: 1 All cause mortality (all enrolled)



Analysis 1.2. Comparison 1 Pre-referral artesunate vs Placebo, Outcome 2 All cause mortality (young children).

Review: Pre-referral rectal artesunate for severe malaria

Comparison: 1 Pre-referral artesunate vs Placebo

Outcome: 2 All cause mortality (young children)

Study or subgroup	Rectal Artesunate n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Africa					
Gomes 2009	109/3041	133/2999		81.4 %	0.81 [0.63, 1.04]
Subtotal (95% CI)	**3041**	**2999**		**81.4 %**	**0.81 [0.63, 1.04]**
Total events: 109 (Rectal Artesunate), 133 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.68 (P = 0.093)					
2 Asia					
Gomes 2009	14/1022	30/988		18.6 %	0.45 [0.24, 0.85]
Subtotal (95% CI)	**1022**	**988**		**18.6 %**	**0.45 [0.24, 0.85]**
Total events: 14 (Rectal Artesunate), 30 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.48 (P = 0.013)					
Total (95% CI)	**4063**	**3987**		**100.0 %**	**0.74 [0.59, 0.93]**
Total events: 123 (Rectal Artesunate), 163 (Placebo)					
Heterogeneity: Chi^2 = 2.86, df = 1 (P = 0.09); I^2 =65%					
Test for overall effect: Z = 2.55 (P = 0.011)					
Test for subgroup differences: Chi^2 = 2.86, df = 1 (P = 0.09), I^2 =65%					

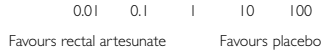
Analysis 1.3. Comparison 1 Pre-referral artesunate vs Placebo, Outcome 3 All cause mortality (older children/adults).

Review: Pre-referral rectal artesunate for severe malaria

Comparison: 1 Pre-referral artesunate vs Placebo

Outcome: 3 All cause mortality (older children/adults)

Study or subgroup	Rectal Artesunate n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gomes 2009	31/2009	14/2009		100.0 %	2.21 [1.18, 4.15]
Total (95% CI)	**2009**	**2009**		**100.0 %**	**2.21 [1.18, 4.15]**
Total events: 31 (Rectal Artesunate), 14 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.48 (P = 0.013)					
Test for subgroup differences: Not applicable					

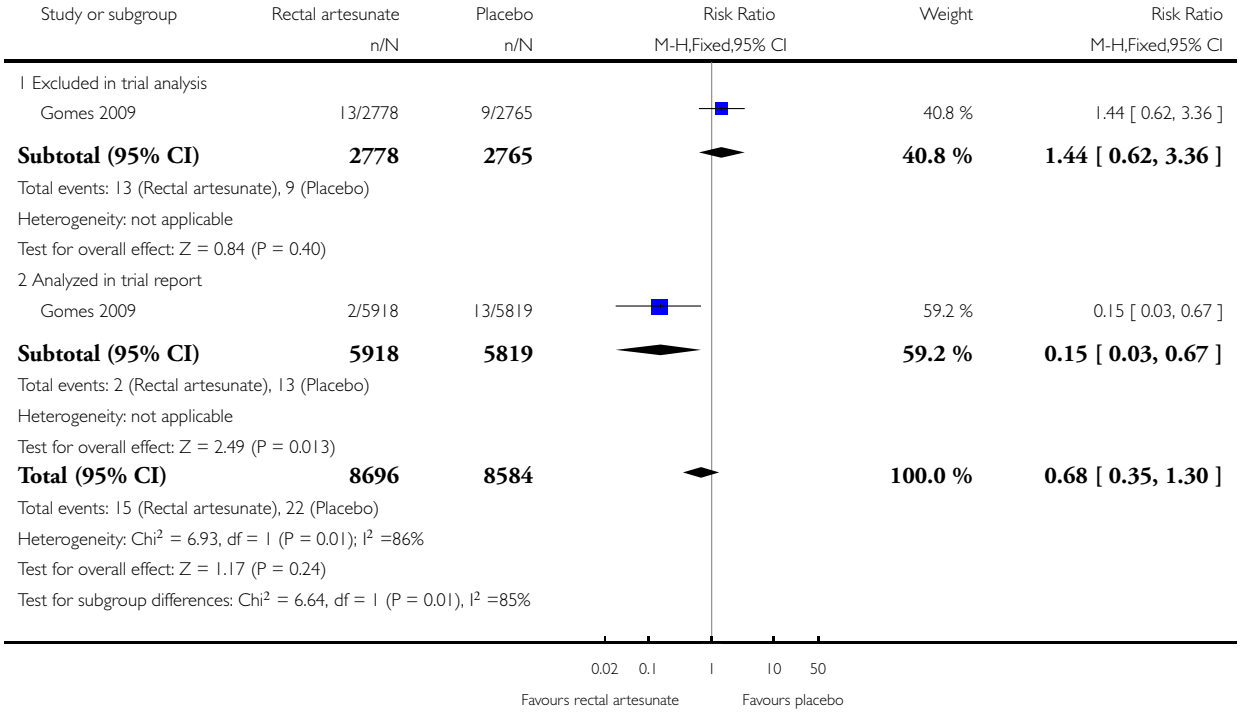


Analysis 1.4. Comparison 1 Pre-referral artesunate vs Placebo, Outcome 4 Neurodisability (all participants).

Review: Pre-referral rectal artesunate for severe malaria

Comparison: 1 Pre-referral artesunate vs Placebo

Outcome: 4 Neurodisability (all participants)



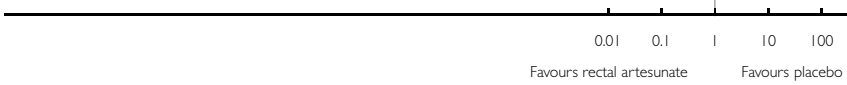
Analysis 1.5. Comparison 1 Pre-referral artesunate vs Placebo, Outcome 5 Severe malaria on admission (coma, repeated convulsions or prostration).

Review: Pre-referral rectal artesunate for severe malaria

Comparison: 1 Pre-referral artesunate vs Placebo

Outcome: 5 Severe malaria on admission (coma, repeated convulsions or prostration)

Study or subgroup	Rectal artesunate n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Asia (6 to 72 months)					
Gomes 2009	88/1022	87/988		18.2 %	0.98 [0.74, 1.30]
Subtotal (95% CI)	**1022**	**988**		**18.2 %**	**0.98 [0.74, 1.30]**
Total events: 88 (Rectal artesunate), 87 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.16 (P = 0.88)					
2 Asia (older child/adult)					
Gomes 2009	120/2009	116/2009		23.8 %	1.03 [0.81, 1.33]
Subtotal (95% CI)	**2009**	**2009**		**23.8 %**	**1.03 [0.81, 1.33]**
Total events: 120 (Rectal artesunate), 116 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.27 (P = 0.79)					
3 Africa (6 to 72 months)					
Gomes 2009	289/3041	280/2999		58.0 %	1.02 [0.87, 1.19]
Subtotal (95% CI)	**3041**	**2999**		**58.0 %**	**1.02 [0.87, 1.19]**
Total events: 289 (Rectal artesunate), 280 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.22 (P = 0.82)					
Total (95% CI)	**6072**	**5996**		**100.0 %**	**1.01 [0.90, 1.14]**
Total events: 497 (Rectal artesunate), 483 (Placebo)					
Heterogeneity: Chi^2 = 0.09, df = 2 (P = 0.96); I^2 =0.0%					
Test for overall effect: Z = 0.24 (P = 0.81)					
Test for subgroup differences: Chi^2 = 0.09, df = 2 (P = 0.96), I^2 =0.0%					



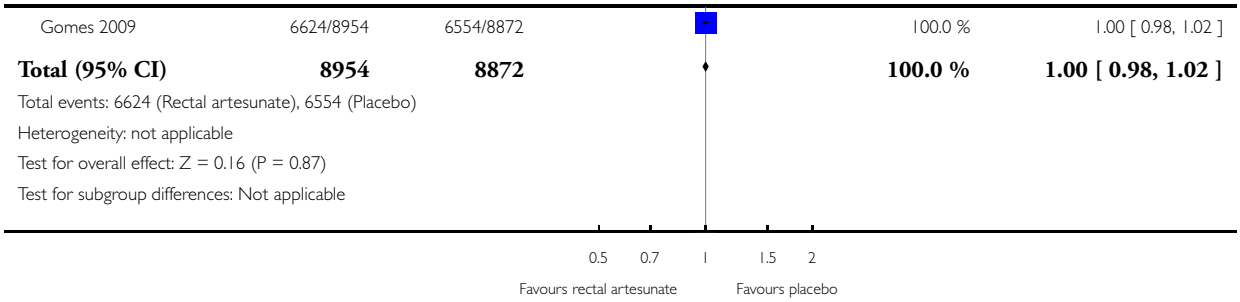
Analysis 1.6. Comparison 1 Pre-referral artesunate vs Placebo, Outcome 6 Proportion with parasitaemia on admission.

Review: Pre-referral rectal artesunate for severe malaria

Comparison: 1 Pre-referral artesunate vs Placebo

Outcome: 6 Proportion with parasitaemia on admission

Study or subgroup	Rectal artesunate n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gomes 2009	6624/8954	6554/8872		100.0 %	1.00 [0.98, 1.02]
Total (95% CI)	**8954**	**8872**		**100.0 %**	**1.00 [0.98, 1.02]**
Total events: 6624 (Rectal artesunate), 6554 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.16 (P = 0.87)					
Test for subgroup differences: Not applicable					

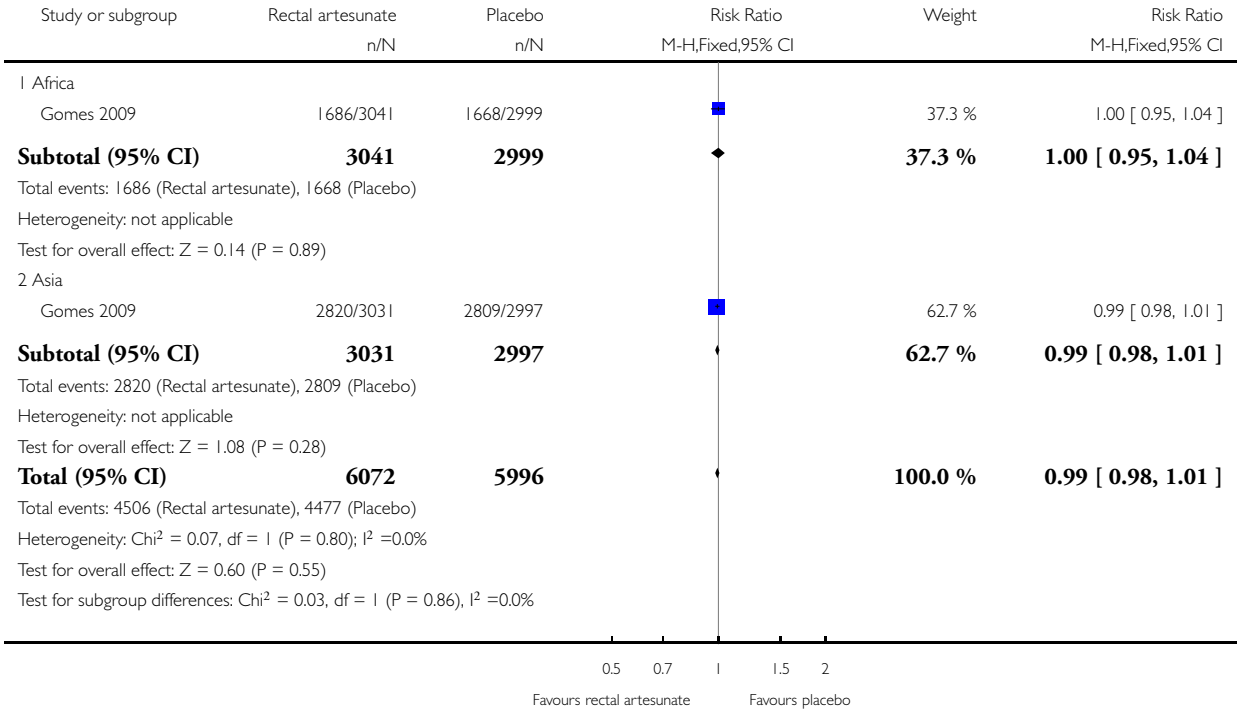


Analysis 1.7. Comparison 1 Pre-referral artesunate vs Placebo, Outcome 7 Proportion reaching a hospital within 6 hours.

Review: Pre-referral rectal artesunate for severe malaria

Comparison: 1 Pre-referral artesunate vs Placebo

Outcome: 7 Proportion reaching a hospital within 6 hours



ADDITIONAL TABLES

Table 1. Differences Between African and Asian sites

Feature	Africa	Asia
Number analyzed in trial report	6040	6028
Participants aged 6 to 72 months	6040	2010
Participants above 72 months	0	4018
Number without a blood slide	1020	8
Death within 6 hours after enrolment	81	27

Table 1. Differences Between African and Asian sites (*Continued*)

Not reached a hospital within 6 hours after randomization	2686	399

APPENDICES

Appendix 1. Search methods: detailed search strategies

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	EMBASE[b]	LILACS[b]
1	Arte*	Arte* ti, ab	Arte*	Arte*	Arte*
2	Dihydroarte*	Dihydroarte* ti, ab	Dihydroarte*	Dihydroarte*	Dihydroarte*
3	Beta-arte*	Beta-arte* ti, ab	Beta-arte*	Beta-arte*	Beta-arte*
4	1 or 2 or 3	1 or 2 or 3	1 or 2 or 3	1 or 2 or 3	1 or 2 or 3
5	intrarectal	suppositor* ti, ab	Suppositories [Mesh]	Suppository [Emtree]	intrarectal
6	rectal	Administration, rectal [Mesh]	suppositor* ti, ab	Suppositor* ti, ab	rectal
7	5 or 6	Intrarectal ti, ab	Administration, rectal [Mesh]	Rectal drug administration [Emtree]	5 or 6
8	4 and 7	Rectal ti, ab	Intrarectal ti, ab	Intrarectal ti, ab	4 and 7
9		5 or 6 or 7 or 8	Rectal ti, ab	Rectal ti, ab	
10		4 and 9	5 or 6 or 7 or 8 or 9	5 or 6 or 7 or 8 or 9	
11		Malaria ti, ab, MeSH	4 and 10	4 and 10	
12		10 and 11	Malaria [ti, ab, Mesh]	Malaria ti,ab,Emtree	
13			11 and 12	11 and 12	

a = Cochrane Infectious Diseases Group Specialized Register
b = Search terms for retrieving trials, developed by The Cochrane Collaboration (Lefebvre 2011), was also used in combination of the search terms reported in the above table to search these databases.

WHAT'S NEW

Date	Event	Description
20 August 2014	Amended	Corrected typographical error in the abstract

CONTRIBUTIONS OF AUTHORS

JO wrote the background to the protocol and the objectives. ME wrote the methods section and search terms. ME reviewed the draft manuscript. Both authors reviewed the final draft before submission.

For the review, JO analyzed the data and wrote the draft of the review and ME reviewed the draft of the review.

DECLARATIONS OF INTEREST

We have no conflicts of interest to declare.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed the primary outcome from "deaths from severe malaria" to "all cause mortality". The Cochrane Infectious Disease Group policy is that in severe malaria the main outcome should be all cause mortality because "deaths caused by malaria" is more subject to bias. The error was not detected previously by the co-ordinating editor and was also not detected by referees.

INDEX TERMS

Medical Subject Headings (MeSH)

*Rural Health; Administration, Rectal; Age Factors; Antimalarials [*administration & dosage]; Artemisinins [*administration & dosage]; Artesunate; Bangladesh; Emergency Medical Services [methods]; Ghana; Malaria [*drug therapy; mortality]; Tanzania

MeSH check words

Adult; Child; Child, Preschool; Humans; Infant