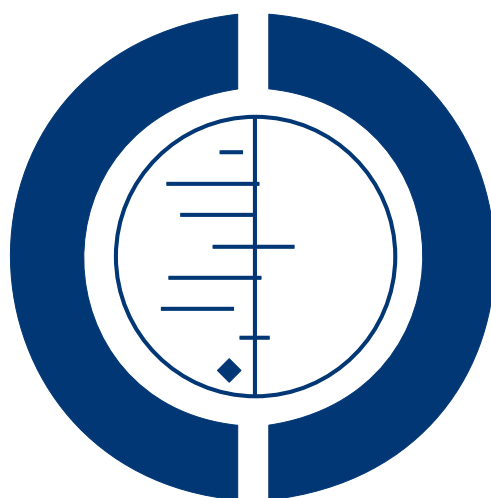


# Intrarectal quinine versus intravenous or intramuscular quinine for treating *Plasmodium falciparum* malaria (Review)

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[Intervention Review]

# Intrarectal quinine versus intravenous or intramuscular quinine for treating *Plasmodium falciparum* malaria

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## ABSTRACT

### Background

In children with falciparum malaria, a proprietary quinine preparation (adjusted to make it less acidic) administered rectally may be easier to use and less painful than intramuscular or intravenous administration. However, rectal quinine may be less effective.

### Objectives

To compare intrarectal quinine with intravenous or intramuscular quinine for treating malaria caused by *Plasmodium falciparum*.

### Search strategy

In May 2008, we searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (*The Cochrane Library* 2008, Issue 2), MEDLINE, EMBASE, LILACS, and CINAHL. We also searched conference proceedings, contacted individual researchers and a pharmaceutical company, and checked reference lists.

### Selection criteria

Randomized and quasi-randomized controlled trials comparing intrarectal quinine with intramuscular and intravenous quinine for treating people with uncomplicated and severe *Plasmodium falciparum* malaria.

### Data collection and analysis

We independently assessed each trial's risk of bias quality and extracted data, including adverse event data. We analysed dichotomous data using the odds ratio and continuous data using the mean difference.

### Main results

Ten randomized controlled trials, all involving children only (total of 1417 children), fulfilled the inclusion criteria. The same investigator was involved in nine of the trials. Seven trials compared proprietary intrarectal with intravenous quinine, and seven trials compared it with intramuscular treatment. We detected no statistically significant difference between intrarectal and intravenous or intramuscular routes for death, parasite clearance by 48 hours and seven days, parasite clearance time, fever clearance time, coma recovery time, duration of hospitalization, and time to drinking. The trials reporting on these outcomes were small, which resulted in large confidence intervals for all outcomes apart from duration of hospitalization. One large trial (898 children) reported that intrarectal was less painful than intramuscular administration.

## Authors' conclusions

We detected no difference in the effect on parasites and clinical illness for intrarectal quinine, but most trials were small. Pain may be less with intrarectal proprietary, buffered quinine preparations (made less acidic by adjustment of the pH to 4.5). Further larger trials in patients with severe malaria and in adults are required before the intrarectal route can be recommended.

## PLAIN LANGUAGE SUMMARY

### Intrarectal quinine versus intravenous or intramuscular quinine for treating *Plasmodium falciparum* malaria

Quinine given through the rectum may be as effective as intravenous and intramuscular quinine for treating uncomplicated *Plasmodium falciparum* malaria. The data reviewed also lead to the conclusion that a diluted proprietary quinine solution (made less acidic by adjustment to a pH of 4.5) given intrarectally using a syringe for two to three days has less harmful effects compared with intramuscular quinine given for the same time period. Administration of intrarectal quinine (made less acidic by adjustment to a pH of 4.5) is significantly less painful than intramuscular injection of quinine. More trials are needed for patients with severe malaria and in adults.

## BACKGROUND

*Plasmodium falciparum* malaria often causes serious illness, and occurs mainly in Africa, South-East Asia, and South America. It is estimated that 300 to 500 million episodes of clinical malaria and more than one million deaths occur in children aged less than five years in Africa every year (RBM 2005).

Uncomplicated malarial illness is usually treated with drugs given orally (WHO 2000). Vomiting is a prominent feature in 30 to 50 per cent of people with *P. falciparum* malaria (Piarroux 1993; Kortepeter 1998; Anothay 2000; Sowunmi 2000). People who present to hospital with severe malaria or persistent vomiting (regardless of severity of disease) require other routes of administration, sometimes by intravenous infusion (into a blood vessel), intramuscular injection (direct into the muscle) (White 1982), or via the nasogastric route (tube from the nose to the stomach). These different routes of administration require trained staff and equipment, which may be in short supply in low-income and middle-income countries.

Despite emerging resistance to commonly used drugs, such as chloroquine and mefloquine, the malaria parasites remain sensitive to quinine in Africa (Bjorkman 1991; Jelinek 1995). In some parts of South-East Asia, however, decreasing sensitivity to quinine has been detected (RBM 2001).

Although intramuscular injection is the most common route of quinine administration used in low-income and middle-income countries, adverse effects have been reported (Barnes 1999a). In some of these countries, it is the most common cause of lower limb

paralysis when given mistakenly into the sciatic nerve (Carayon 1960; Bourrel 1982; Barnes 1993). Other reported harmful effects of intramuscular quinine injections are bacterial and viral infections including tetanus (Yen 1994), poliomyelitis (Wyatt 1989; Wyatt 1992), and human immunodeficiency virus (HIV) (Wyatt 1984; Hoelscher 1994). Intramuscular injection involves causing pain repeatedly with each dose, and venepuncture for establishing intravenous access is painful and may have to be repeated. A less painful and safer alternative to intravenous and intramuscular administration is therefore worth evaluating.

The intrarectal route has been used to give quinine (Barnes 1996a). Health workers with minimal training can give intrarectal quinine to people who are either vomiting or comatose. This provides early treatment of the illness and is one of the strategies of the World Health Organization initiative 'Roll Back Malaria' (RBM 2002). However, disadvantages of using the intrarectal route are local irritation, diarrhoea, and expulsion of the medication (Barnes 1999b). The likelihood of intrarectal irritation has been reduced by the development of less acidic quinine gluconate (in Quinimax), which is adjusted to a pH of 4.5. People may also reject suppositories and other intrarectal formulations in preference for the intramuscular route because injections are perceived as a more effective treatment, particularly in people who are seriously ill (Wyatt 1984).

This review summarizes existing trials that compare the effectiveness and safety of intrarectal quinine with other routes of admin-

istration in people with malaria caused by *P. falciparum*.

## OBJECTIVES

To compare intrarectal quinine with intravenous or intramuscular quinine for treating malaria caused by *P. falciparum*.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomized and quasi-randomized controlled trials.

#### Types of participants

Adults and children with *P. falciparum* malaria confirmed by blood-slide examination.  
Both uncomplicated and severe falciparum malaria are included.

#### Types of interventions

##### Intervention

Intrarectal quinine.

##### Control

Intravenous or intramuscular quinine.  
*Quinine may be used as a single therapy or in combination.*

#### Types of outcome measures

##### Primary

Death.

##### Secondary

- Parasite clearance by 48 hours (number of participants free of parasites by 48 hours).
- Parasite clearance by day seven (number of participants free of parasites by day seven).
- Parasite clearance time.
- Fever clearance time.
- Duration of hospitalization.

- Coma recovery time.
- Time to drinking or eating.

#### Adverse events

- Serious events that result in death, are life-threatening, require hospitalization, or result in discontinuation of treatment (such as local pain, abscess formation, and paralysis).
- Mild and moderate (as classified or defined by trial investigators), including vertigo and tinnitus.

### Search methods for identification of studies

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

#### Databases

We searched the following databases using the search terms and strategy described in [Appendix 1](#): Cochrane Infectious Diseases Group Specialized Register (May 2008); Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (2008, Issue 2); MEDLINE (1966 to May 2008); EMBASE (1974 to May 2008); LILACS (1982 to May 2008); and CINAHL (1982 to May 2008). We also searched the *metaRegister of Controlled Trials (mRCT)* using the terms 'malaria', 'quinine or quinimax', and 'rectal or intrarectal'.

#### Conference proceedings

We searched the following conference proceedings for relevant abstracts: Third European Congress on Tropical Medicine and International Health, 8 to 11 September 2002, Lisbon, Portugal; Third MIM Pan-African Malaria Conference, 18 to 22 November 2002, Arusha, Tanzania; and the Fourth MIM Pan-African Malaria Conference, 11 to 14 November 2005, Yaoundé, Cameroon.

#### Researchers and pharmaceutical companies

For unpublished or ongoing trials, we contacted individual researchers working in the field and the pharmaceutical company Sanofi-Synthelabo, which manufactures Quinimax suppositories and intrarectal cream, in June 2004.

#### Reference lists

We also checked the reference lists of all studies identified by the above methods.

## Data collection and analysis

### Selection of studies

We scanned the results of the literature search for potentially relevant trials and retrieved the full reports for all published and unpublished trials identified. We independently assessed the eligibility of the trials for inclusion in the review using the stated inclusion criteria. We listed the excluded studies and the reason for excluding them in the '[Characteristics of excluded studies](#)'. We resolved any disagreements through discussion or by consulting an Editor of the Cochrane Infectious Diseases Group.

### Data extraction and management

We independently extracted data including methods, participants, interventions, and outcomes, and recorded the data on standard forms. For all outcomes, we extracted the number of participants randomized and the number analysed in each treatment group for each trial. For dichotomous outcomes, we extracted the number of participants experiencing the event and the number of participants in each treatment arm. For continuous outcomes, we extracted the mean and a measure of variance for each treatment arm. Where we required additional unpublished data, we attempted to contact the trial authors.

### Assessment of risk of bias in included studies

We independently assessed the risk of bias of each trial and resolved any disagreements through discussion or by consulting an Editor of the Cochrane Infectious Diseases Group. We considered generation of allocation sequence and allocation concealment to be adequate, inadequate, or unclear according to [Jüni 2001](#). We noted whether the participant, carer, or outcome assessor was blind to the intervention. The inclusion of all randomized participants in the final analysis was considered as adequate if greater than 90%. We assessed whether a sample size calculation for outcomes investigated was conducted, and we also assessed whether the authors analysed outcome data for all originally randomized participants regardless of whether they completed treatment or dropped out of the study subsequently.

### Assessment of heterogeneity

We assessed heterogeneity by visually examining the forest plots (for overlapping confidence intervals and outliers) and using the chi-squared test for heterogeneity with a 10% level of statistical significance. Because we detected statistically significant heterogeneity for diarrhoea (an adverse event), we used the DerSimonian and Laird random-effects model to pool data for this outcome.

### Assessment of reporting biases

We intended to investigate publication bias using funnel plots but considered this to be inappropriate in view of the small number of included trials.

### Data synthesis

We analysed data using [Review Manager 5](#). We compared outcome measures using the odds ratio (OR) for dichotomous data (death and parasite clearance by 48 hours and seven days) and the mean difference (MD) for continuous data (parasite clearance time, fever clearance time, and duration of hospitalization), and presented each result with a 95% confidence interval (CI). We used the fixed-effect model for those without statistically significant heterogeneity (see below). We pooled data on the same interventions (same route of administration and drug regimen) where appropriate and conducted separate analyses for the intravenous and intramuscular control regimens. We presented adverse event data in a table, a meta-analysis, and in a narrative summary of the findings.

### Subgroup analysis and investigation of heterogeneity

We intended to use subgroup analyses or meta-regression to explore participant age (less than five years versus five years or more), disease severity (uncomplicated versus severe), and different galenic quinine formulations (solution, intrarectal cream, or suppositories) as potential sources of heterogeneity, but we were unable to because the uniformity of the age of participants (children aged less than 15 years only), and the small number of trials of people with severe disease and different galenic formulations.

## RESULTS

### Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

### Trial selection

The search strategy identified 19 potentially relevant studies. We excluded seven studies because they were not randomized and controlled, and two studies because they contained a narrative review of previous studies without data on randomized controlled trials (see '[Characteristics of excluded studies](#)'). The 10 randomized controlled trials (1417 children), one of which was quasi-randomized, that fulfilled the inclusion criteria are summarized below and detailed in the '[Characteristics of included studies](#)'. The same investigator was involved in nine of the trials.

## Participants

The trials recruited children up to 15 years of age who were hospital inpatients in Burkina Faso (three trials), Niger (five trials), Togo (one trial), or Uganda (one trial). The trials' inclusion criteria included the degree of parasitaemia (six trials), vomiting (five trials), and disease severity (three trials). Different exclusion criteria were used: diarrhoea (all trials); treatment with antimalarial drugs before admission (nine trials); other documented causes of fever (six trials); and forms of severe malaria (six trials).

## Trial comparisons

We grouped the trials according to whether they compared intrarectal with intravenous or intramuscular quinine.

Seven trials (397 children) compared intrarectal with intravenous quinine. Five trials (239 children) compared intrarectal quinine given for two to three days with intravenous quinine given for the same duration (Barennes 1995; Barennes 1996a; Barennes 1998; Barennes 2003; Pussard 2004). One trial compared duration of intrarectal and intravenous quinine administration, which was determined by the ability to take medication orally (Achan 2007), and another trial compared single doses of intrarectal quinine and intravenous quinine that were followed by a three-day course of oral quinine (Barennes 1999). Participants that had a two-day quinine course completed a total of five days of treatment with oral chloroquine (Barennes 1998) or oral quinine (Barennes 2003; Pussard 2004), or a total of seven days with oral quinine (Achan 2007). Five trials gave intrarectal quinine as a diluted quinine solution in a syringe (Barennes 1995; Barennes 1998; Pussard 2004; Achan 2007), one trial used an intrarectal cream (Barennes 1996a), and another trial used a quinine suppository (Barennes 1999).

Seven trials (1182 children) compared intrarectal with intramuscular quinine. Four trials compared intrarectal and intramuscular quinine given for three days (Barennes 1995; Barennes 1996a; Assimadi 2002; Barennes 2006); one trial gave them for two days (Pussard 2004); one trial gave a single dose of intrarectal or intramuscular quinine followed by three days of oral quinine (Barennes 1999); and one trial did not mention the duration of treatment (Barennes 2001). Four trials gave rectal quinine in form of Quinimax, diluted in a syringe (Barennes 1995; Barennes 2001; Assimadi 2002; Barennes 2006), one trial used an intrarectal cream (Barennes 1996a), and another used suppositories (Barennes 1999).

## Outcomes

Each trial reported on at least one of the review's pre-specified outcomes. They also reported on other outcomes that are not analysed in this systematic review: time for parasitaemia to fall by 50% (three trials); percentage of initial parasitaemia after 24 hours (one trial) and 48 hours (three trials); number of parasites at 24

hours (one trial); time to sit (two trials); time to walk (one trial); body temperature at 24 and 48 hours (one trial); time for body temperature to fall below 37.5 °C (one trial); number with early treatment failure on day three (one trial), late clinical failure (one trial), and late parasitological failure (one trial); number with fever recurrence on day seven (one trial); and time until oral quinine tolerated (one trial).

## Source of funding

The only pharmaceutical company producing a intrarectal quinine preparation, Quinimax, sponsored six of the trials (Barennes 1995; Barennes 1998; Barennes 2001; Pussard 2004; Barennes 2006; Achan 2007).

## Risk of bias in included studies

### General of allocation sequence

Four trials did not describe the method used to generate the allocation sequence (Barennes 1996a; Assimadi 2002; Barennes 2003; Pussard 2004). Five trials used adequate methods: three used random-numbers tables (Barennes 1998; Barennes 1999; Barennes 2001); and two used computerized randomization (Barennes 2006; Achan 2007). One trial used an inadequate method - alternate allocation (quasi-randomization) (Barennes 1995).

### Allocation concealment

Only two of the trials used procedures to conceal allocation (Barennes 2006; Achan 2007), and these were adequate according to Jüni 2001.

### Blinding

Only one trial was double blinded by using rectal and intravenous placebo preparations in addition to the drug given through the other route (Achan 2007). There was no blinding of the outcome assessor.

### Inclusion of all randomized participants in the final analysis

One trial excluded one participant (1.3%) from the analysis (Barennes 1998). Another trial could only analyse the parasite clearance time for 20/66 (30%) of trial participants without providing a reason for the missing participants (Barennes 1995). A further trial reported on patient attrition due to death, deterioration, or lack of attendance (Barennes 2006). The other seven trials did not report on any exclusions or drop outs of randomized participants.

## Intention-to-treat analysis

Two trials analysed data on an intention-to-treat basis (Barennes 2006; Achan 2007).

## Power calculations

Two trials reviewed a power calculation to determine the number of participants required to achieve sufficient statistical power to detect a statistically significant difference for an outcome (Barennes 2006; Achan 2007).

## Effects of interventions

### Intrarectal versus intravenous quinine

#### Primary and secondary outcome measures

There was no statistically significant difference between intrarectal and intravenous quinine for: number of deaths (276 participants, 5 trials, Analysis 1.1); parasite clearance at 48 hours (44 participants, 2 trials, Analysis 1.2); parasite clearance time (186 participants, 2 trials, Analysis 1.3); fever clearance time (186 participants, 2 trials, Analysis 1.4); duration of hospitalization (76 participants, 1 trial, Analysis 1.5); and coma recovery time (186 participants, 2 trials, Analysis 1.6). All participants had cleared their parasites by day seven in the five trials that reported this (Barennes 1995; Barennes 1996a; Barennes 1999; Barennes 2003; Pussard 2004).

Barennes 1998 (76 participants) reported on time to drinking and found that these were similar for the intrarectal group (median 32 hours, range 8 to 40 hours) and intravenous group (median 24 hours, range 8 to 54 hours).

Achan 2007 (110 participants, 1 trial) was the only trial to report on time to begin oral intake and found no statistically significant difference between the intrarectal group (mean 27.5 hours, 95% CI 21.9 to 33.2) and intravenous group (mean 24.1 hours, 95% CI 18.7 to 29.6).

#### Adverse events

Three trials commented on adverse events and specifically reported the absence of rectal irritation and diarrhoea in two trials (Barennes 1998; Barennes 2003). Barennes 2003 also reported mucoid stools in four children in the intrarectal group.

Achan 2007, which included only children with cerebral malaria, there was no significant difference between the groups in the number of children with vomiting, diarrhoea, or presence of soft or liquid stools (110 participants for each outcome, Analysis 1.7).

### Intrarectal versus intramuscular quinine

#### Primary and secondary outcome measures

More people cleared parasites at 48 hours in the intramuscular group than in the intrarectal quinine group (OR 0.15, 95% CI 0.02 to 0.89; 84 participants, 2 trials, Analysis 1.2), while parasite clearance time was longer in the participants treated with intrarectal quinine (MD 19.10 hours, 95% CI 5.20 to 33.00; 20 participants, 1 trial, Analysis 1.3).

For all other outcome measures there was no statistically significant difference between intrarectal and intramuscular quinine: number of deaths (1110 participants, 6 trials, Analysis 1.1); fever clearance time (1022 participants, 3 trials, Analysis 1.4); duration of hospitalization (58 participants, 1 trial, Analysis 1.5); and coma recovery time (58 participants, 1 trial, Analysis 1.6). Four trials reported that all participants had cleared their parasites by day seven (Barennes 1995; Barennes 1996a; Barennes 1999; Pussard 2004). Barennes 2006 reported on time to oral intake and found there was no statistically significant difference between the intrarectal group (mean 1.3 days, 95% CI 0.2 to 2.3) and intramuscular group (mean 1.3, 95% CI 0.5 to 2.0).

#### Adverse events

Data on adverse events were accessible to statistical analysis in four trials (Barennes 1995; Assimadi 2002; Barennes 2006; Achan 2007); see Analysis 1.8 (random-effects model). Assimadi 2002 reported no statistically significant difference between painful swelling at the site of application (64 participants) or pain at the injection site (64 participants). Barennes 2006 reported that pain during administration occurred in 9/450 participants given intrarectal quinine and 404/448 participants given intramuscular quinine (OR 0.00, 95% CI 0.00 to 0.00), with a test result for overall effect of  $Z = 16.41$  ( $P < 0.00001$ ). There was no statistically significant difference in the number of participants with mild diarrhoea between the groups (1022 participants, 3 trials).

The largest trial conducted so far, Barennes 2006, also documented adverse events affecting stool consistency and content, pain in the rectum, effects on the rectal mucosa, as well as effects specific to intramuscular administration (Appendix 2). Comparison of the adverse effects accessible to meta-analysis is shown in Analysis 1.8. A further trial reported that all children given intramuscular quinine complained of pain at the injection point and that intrarectal administration was associated with an increase frequency of mucoid stools (Pussard 2004).

Three trials that commented on adverse events did not separate the results for the intrarectal, intramuscular, and intravenous groups (Barennes 1995; Barennes 1996a; Barennes 1999). They specifically reported the absence of rectal irritation (all three trials) and diarrhoea (Barennes 1996a; Barennes 1999). Barennes 1996a also observed slight pain at the injection site in the intramuscular group.

## DISCUSSION

Eight out of the 10 trials that met the inclusion criteria included less than 80 participants. This small number of participants increased the probability of missing a clinically important difference between groups. Neither data from individual trials nor pooled data were able to prove equivalence of intrarectal quinine with other modes of administration. To demonstrate equivalence for the outcome mortality with a difference in mortality of 2% as a range of equivalence and 8% mortality with a power of 80% and a two-sided 95% CI for the difference in mortality, a sample size of at least 3893 would be required in each group. For an equivalence trial with coma recovery time of four hours as range of equivalence and 12 hours as standard deviation, at least 189 participants would be required in each group to demonstrate equivalence with 80% power and a 95% CI for the difference (Eisenhut 2008). A lack of a power calculation may have led to small trial sizes. Only for the outcomes of death, fever clearance time, and mild diarrhoea (an adverse event) were there two or more trials available for a meta-analysis. Only three of the trials documented the use of adequate randomization; adequate randomization was particularly important because blinding of participant and carer was not possible. This has increased the risk of a selection bias. All but one trial were conducted with participation of one author, H Barennes. The only pharmaceutical company producing an intrarectal quinine preparation, Quinimax, sponsored six of the trials (Barennes 1995; Barennes 1998; Barennes 2001; Pussard 2004; Barennes 2006; Achan 2007).

There was no statistically significant difference between intrarectal and parenteral quinine administration in terms of death, course of *P. falciparum* malaria, or diarrhoea. Intrarectal administration also had the benefit of being less painful.

Parasite clearance time was longer in participants given intrarectal quinine as compared with intramuscular treatment in one trial (Barennes 1995). More participants in the intramuscular quinine group had cleared their parasites compared with the intrarectal group (Pussard 2004). Parasite clearance was not different when intrarectal administration was compared with intravenous administration in another trial (Barennes 1998), and parasite clearance by 48 hours was not different between intrarectal and intravenous groups in one trial (Pussard 2004). These discrepancies may have arisen by chance because of the small trial sizes, and in one trial (Barennes 1995) parasite clearance time may have been shorter in the intramuscular group because parasitaemia was higher at baseline in the intrarectal group.

We observed statistically significant heterogeneity when analysing the mild diarrhoea adverse event outcome. This may have been due to different definitions of diarrhoea, which was only clearly defined in one trial (Barennes 2006), and the large weight attributed in the meta-analysis to one small trial in which two out of five participants in the control group were affected (Barennes

1995). Persistent pain at the injection site due to inflammation with the recurrence of fever seemed to be common with intramuscular injection and is an adverse effect not observed with the intrarectal route. It has to be taken into consideration in the design of future trials comparing the two modes of administration. The occurrence of rectal mucosal ulcerations with intrarectal administration and its significance should also be assessed in all future trials. Adverse effects unique to the methods of intramuscular administration (sciatic nerve injury, infections with other viral and bacterial pathogens through contaminated needles) or intravenous injection (infections) are absent in intrarectal administration and cannot be addressed in a trial setting where administration is performed by trained personnel with adequate supply of consumables.

Future systematic reviews need to address whether other antimalarial drugs like artemisinin derivatives are comparable in effectiveness administered rectally compared to intravenous or intramuscular applications in severe malaria in all age groups.

The trials fulfilling the inclusion criteria for this review included only children, and the results may therefore not be equally applicable to adults.

Only three small, randomized controlled trials (245 children) that included participants with severe malaria compared intrarectal with intravenous (Barennes 1998; Achan 2007) or intramuscular treatment (Barennes 2001). Limited data are therefore available on the effectiveness of intrarectal quinine in life-threatening forms of malaria.

## AUTHORS' CONCLUSIONS

### Implications for practice

No differences in effectiveness with intrarectal administration has been detected in this review, and the intrarectal route is associated with less pain than parenteral administration one trial. Thus intrarectal application may be preferred for uncomplicated falciparum malaria in children in cases in which administration of antimalarial drugs by mouth is not possible. There is insufficient evidence of the effectiveness of intrarectal quinine in severe *P. falciparum* malaria in children.

### Implications for research

To investigate this further would require large-scale randomized controlled trials, with adequate methods to conceal allocation to investigate intrarectal quinine in severe *P. falciparum* malaria in children and in all forms of *P. falciparum* malaria in adults. Such trials need to be adequately powered by use of a sample size calculation based on key outcomes including mortality. Ongoing studies evaluating artemisinin derivatives in severe malaria need to be considered as they may be potential comparators. Further trials

should focus on adverse effects including short-term and long-term effects on the rectal mucosa with intrarectal administration. Persistent pain at the injection site due to inflammation with the recurrence of fever seemed to be common with intramuscular injection and is an adverse effect not observed with the intrarectal route. It has to be taken into consideration in the design of future trials comparing the two modes of administration. Trials investigating the use of intrarectal quinine in the primary care setting, its role in preventing hospital admission, and early treatment in the community preventing complications associated with late presentation at healthcare facilities are also desirable, although the results of the forthcoming trial of artemisinin derivatives to prevent severe malaria developing will need to be considered in planning these studies.

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\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

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

#### Achan 2007

Methods	<p><b>Design:</b> randomized controlled trial</p> <p><b>Generation of allocation sequence:</b> computer randomization</p> <p><b>Allocation concealment:</b> assignments sealed in opaque numbered envelopes; preparation of drugs and placebos in a separate room by separate treatment nurses</p> <p><b>Blinding:</b> double blind</p> <p><b>Inclusion of all randomized participants in the final analysis:</b> 100% (110/110)</p>
Participants	<p><b>Number:</b> 110 children aged 6 months to 5 years</p> <p><b>Inclusion criteria:</b> children aged 6 months to 5 years with cerebral malaria (as defined by the World Health Organization)</p> <p><b>Exclusion criteria:</b> Blantyre coma score <math>\geq 3</math>; diarrhoea; anal pathology; quinine given in the previous 48 hours</p>
Interventions	<ol style="list-style-type: none"> <li>1. Intravenous quinine base (8 mg/kg of quinine base) given as Quinimax 8 hourly until oral treatment possible</li> <li>2. Intrarectal quinine base 20 mg/kg as the buffered proprietary preparation Quinimax as initial dose followed by 15 mg/kg of quinine base 8 hourly until oral treatment possible</li> </ol>
Outcomes	<ol style="list-style-type: none"> <li>1. Parasite clearance time</li> <li>2. Coma recovery time</li> <li>3. Fever clearance time</li> <li>4. Time to begin oral intake</li> <li>5. Time to sit unsupported</li> <li>6. Adverse events</li> </ol>
Notes	<p><b>Location:</b> Uganda</p> <p><b>Date:</b> September 2003 to January 2004</p> <p><b>Source of funding:</b> Sanofi-Synthelabo, Gentilly, France</p>

#### Assimadi 2002

Methods	<p><b>Design:</b> randomized controlled trial</p> <p><b>Generation of allocation sequence:</b> not described</p> <p><b>Allocation concealment:</b> not used</p> <p><b>Blinding:</b> not used</p> <p><b>Inclusion of all randomized participants in the final analysis:</b> not reported</p>
Participants	<p><b>Number:</b> 64 children aged 0 to 15 years</p> <p><b>Inclusion criteria:</b> positive thick film; uncomplicated malaria with vomiting; single seizure with post-ictal loss of consciousness &lt; 30 minutes; clinical prostration without neurological signs</p> <p><b>Exclusion criteria:</b> diarrhoea; quinine in preceding week; any rectal-anal anomaly</p>
Interventions	<ol style="list-style-type: none"> <li>1. Intramuscular quinine base (12.5 mg/kg 12 hourly for 72 hours)</li> <li>2. Intrarectal quinine (15 mg/kg 12 hourly for 72 hours); Quinimax, the buffered proprietary preparation was diluted with water and injected with a syringe</li> </ol>

**Assimadi 2002** (Continued)

Outcomes	1. Death 2. Parasite clearance by 48 hours 3. Adverse events
Notes	<b>Location:</b> Togo <b>Date:</b> November 1998 to August 1999 <b>Source of funding:</b>

**Barenes 1995**

Methods	<b>Design:</b> quasi-randomized controlled trial <b>Generation of allocation sequence:</b> alternate allocation <b>Allocation concealment:</b> not used <b>Blinding:</b> not used <b>Inclusion of all randomized participants in the final analysis:</b> parasite clearance time only analysed for 30% (20/66) trial participants with no reason for the missing participants
Participants	<b>Number:</b> 66 children aged 2 to 15 years <b>Inclusion criteria:</b> > 1000 asexual <i>Plasmodium falciparum</i> parasites/ $\mu$ L; acute malaria with vomiting; slight coma and restlessness of convulsions warranting parenteral therapy; consent <b>Exclusion criteria:</b> deep coma; diarrhoea; other documented causes of fever; other antimalarial in preceding week
Interventions	1. Intrarectal quinine (11.8 mg/kg base 12 hourly for 3 days); given as the buffered proprietary preparation Quinimax diluted with 2 mL of water and administered with a 5 mL syringe 2. Intravenous quinine (7.4 mg/kg base 12 hourly for 3 days) 3. Intramuscular quinine (7.4 mg/kg base 12 hourly for 3 days)
Outcomes	1. Parasite clearance by day 7 2. Parasite clearance time 3. Fever clearance time 4. Death 5. Adverse events
Notes	<b>Location:</b> Niger <b>Date:</b> 1992 to 1994 <b>Source of funding:</b> Sanofi-Synthelabo, Gentilly, France

**Barenes 1996a**

Methods	<b>Design:</b> randomized controlled trial <b>Generation of allocation sequence:</b> not described <b>Allocation concealment:</b> not used <b>Blinding:</b> not used <b>Inclusion of all randomized participants in the final analysis:</b> not reported
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**Barenes 1996a** (Continued)

Participants	<p><b>Number:</b> 21 children aged 2 to 14 years</p> <p><b>Inclusion criteria:</b> &gt; 1000 asexual <i>Plasmodium falciparum</i>/μL; acute malaria with vomiting; slight coma; no neurological symptoms of cerebral malaria</p> <p><b>Exclusion criteria:</b> coma score &lt; 12 on Glasgow coma scale; other documented causes of fever; diarrhoea; other antimalarial in preceding week</p>
Interventions	<ol style="list-style-type: none"> <li>1. Intrarectal quinine (8 mg/kg base 8 hourly for 3 days); administered as quinine gluconate as quinine cream, a buffered proprietary preparation</li> <li>2. Intramuscular quinine (4.7 mg/kg base 8 hourly for 3 days)</li> <li>3. Intravenous quinine (4.7 mg/kg base 8 hourly for 3 days)</li> </ol>
Outcomes	<ol style="list-style-type: none"> <li>1. Death</li> <li>2. Parasite clearance by day 7</li> <li>3. Adverse events</li> </ol>
Notes	<p><b>Location:</b> Niger</p> <p><b>Date:</b> July to December 1993</p> <p><b>Source of funding:</b></p>

**Barenes 1998**

Methods	<p><b>Design:</b> randomized controlled trial</p> <p><b>Generation of allocation sequence:</b> random-numbers tables</p> <p><b>Allocation concealment:</b> not used</p> <p><b>Blinding:</b> not used</p> <p><b>Inclusion of all randomized participants in the final analysis:</b> 98.7% (76/77); 1 participant excluded</p>
Participants	<p><b>Number:</b> 77 children aged 2 to 15 years</p> <p><b>Inclusion criteria:</b> &gt; 1000 asexual <i>Plasmodium falciparum</i>/μL; unrousable coma</p> <p><b>Exclusion criteria:</b> other cases of coma; severe anaemia; diarrhoea; antimalarials within preceding 48 hours</p>
Interventions	<ol style="list-style-type: none"> <li>1. Intrarectal quinine (11.8 mg/kg quinine base once, then 8.8 mg/kg 8 hourly for 2 days); quinine base was given as Quinimax solution as buffered proprietary solution diluted in water via a 5 mL syringe</li> <li>2. Intravenous quinine (4.7 mg/kg base 8 hourly for 2 days)</li> </ol> <p>Both groups received oral chloroquine for 3 days after this</p>
Outcomes	<ol style="list-style-type: none"> <li>1. Death</li> <li>2. Parasite clearance time</li> <li>3. Fever clearance time</li> <li>4. Days in hospital</li> <li>5. Coma recovery time</li> <li>6. Time to drinking</li> <li>8. Adverse events</li> </ol>
Notes	<p><b>Location:</b> Niger</p> <p><b>Date:</b> July to December 1995</p> <p><b>Source of funding:</b> Sanofi-Synthelabo, Gentilly, France</p>

**Barenes 1999**

Methods	<b>Design:</b> randomized controlled trial <b>Generation of allocation sequence:</b> random-numbers tables <b>Allocation concealment:</b> not used <b>Blinding:</b> not used <b>Inclusion of all randomized participants in the final analysis:</b> not reported
Participants	<b>Number:</b> 15 children aged 2 to 14 years <b>Inclusion criteria:</b> > 1000 asexual <i>Plasmodium falciparum</i> /μL <b>Exclusion criteria:</b> severe malaria; diarrhoea; other causes of fever; other antimalarial within preceding 48 hours
Interventions	1. Intravenous quinine (4.74 mg/kg quinine base immediately) 2. Intramuscular quinine (4.74 mg/kg quinine base immediately) 3. Intrarectal quinine as buffered proprietary solution (11.85 mg/kg base immediately) All groups given oral Quinimax (8 mg/kg 8 hourly for 3 days)
Outcomes	1. Death 2. Parasite clearance by day 7 3. Adverse events
Notes	<b>Location:</b> Niger <b>Date:</b> 1996 <b>Source of funding:</b>

**Barenes 2001**

Methods	<b>Design:</b> randomized controlled trial <b>Generation of allocation sequence:</b> random-numbers tables <b>Allocation concealment:</b> not used <b>Blinding:</b> not used <b>Inclusion of all randomized participants in the final analysis:</b> not reported
Participants	<b>Number:</b> 58 children aged 2 to 15 years <b>Inclusion criteria:</b> clinically severe malaria as defined by the World Health Organization <b>Exclusion criteria:</b> any rectal-anal pathology; diarrhoea; pre-existing major illness apart from malaria; immediate life-threatening condition (eg decompensating anaemia or shock)
Interventions	1. Intrarectal quinine base (17.9 mg/kg immediately, then 11.75 mg/kg 12 hourly); given as Quinimax as buffered, proprietary solution diluted with 2 to 4 mL of water through a syringe 2. Intramuscular quinine base (7.5 mg/kg 12 hourly)
Outcomes	1. Death 2. Fever clearance time 3. Duration of hospitalization 4. Coma recovery time
Notes	<b>Location:</b> Niger; paper reports two sites Dosso and Niamey (published as <a href="#">Barenes 1998</a> ) <b>Date:</b> 1995 to 1996 <b>Source of funding:</b> Sanofi-Synthelabo, Gentilly, France

**Barenes 2003**

Methods	<b>Design:</b> randomized controlled trial <b>Generation of allocation sequence:</b> not described <b>Allocation concealment:</b> not used <b>Blinding:</b> not used <b>Inclusion of all randomized participants in the final analysis:</b> not reported
Participants	<b>Number:</b> 48 children aged 2 to 15 years <b>Inclusion criteria:</b> > 1000 asexual <i>Plasmodium falciparum</i> /μL; vomiting impeding any oral treatment <b>Exclusion criteria:</b> unconscious (Blantyre coma scale < 4); other forms of severe malaria; diarrhoea; other documented causes of fever; antimalarial treatment within preceding week
Interventions	1. Intravenous quinine bichlorhydrate 2. Intrarectal quinine bichlorhydrate (no data on buffering of solution) 3. Intravenous cinchona alkaloid 4. Intrarectal cinchona alkaloid (no data on buffering of solution); given diluted in a syringe <b>Dose:</b> 8 mg/kg quinine base 8 hourly <b>Duration:</b> 2 days All received oral quinine to complete 5 days of treatment
Outcomes	1. Parasite clearance by 48 hours 2. Parasite clearance by day 7
Notes	<b>Location:</b> Burkina Faso <b>Date:</b> not stated <b>Source of funding:</b>

**Barenes 2006**

Methods	<b>Design:</b> randomized controlled trial <b>Generation of allocation sequence:</b> computer randomization <b>Allocation concealment:</b> sealed envelope <b>Blinding:</b> not used <b>Inclusion of all randomized participants in the final analysis:</b> detailed analysis of drop outs given
Participants	<b>Number:</b> 898 children aged 1 to 15 years <b>Inclusion criteria:</b> < 15 years; non severe <i>Plasmodium falciparum</i> malaria with >1000 asexual parasites/μL in which antimalarials could not be administered by mouth <b>Exclusion criteria:</b> diarrhoea; anal lesion; traditional enema in the previous week
Interventions	1. Intrarectal quinine base (20 mg/kg 12 hourly for 3 days); Quinimax was given as buffered, proprietary gluconate solution diluted with water in a syringe 2. Intramuscular quinine base (12.5 mg/kg 12 hourly for 3 days)
Outcomes	1. Death 2. Fever clearance time 3. Time to oral intake 4. Adverse events

**Barenes 2006** (Continued)

Notes	<b>Location:</b> Burkina Faso <b>Date:</b> 2000 and 2001 <b>Source of funding:</b> Sanofi-Synthelabo, Gentilly, France
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**Pussard 2004**

Methods	<b>Design:</b> randomized controlled trial <b>Generation of allocation sequence:</b> unknown <b>Allocation concealment:</b> not used <b>Blinding:</b> not used <b>Inclusion of all randomized participants in the final analysis:</b> 100% (60/60)
Participants	<b>Number:</b> 60 children; aged 4 to 162 months <b>Inclusion criteria:</b> children with moderate malaria and > 1000 asexual <i>Plasmodium falciparum</i> parasites/ $\mu$ L and requiring parenteral treatment <b>Exclusion criteria:</b> severe malaria (cerebral malaria, severe hypoglycaemia, or anaemia); diarrhoea; anatomical abnormalities of the rectum and antimalarial treatment within the preceding week
Interventions	1. Intrarectal quinine base either 8 mg/kg or 16 mg/kg 8 hourly or 12 mg/kg or 20 mg/kg 12 hourly for 48 hours; preparation used was Quinimax (buffered proprietary solution of quinine as gluconate) 2. Intramuscular quinine 12 mg/kg 12 hourly for 48 hours 3. Intravenous quinine 8 mg/kg 8 hourly for 48 hours
Outcomes	1. Parasite clearance at 24, 48, and 72 hours 2. Parasite count (number of parasites/ $\mu$ L) at 24 hours 3. Body temperature at 24 and 48 hours
Notes	<b>Location:</b> Burkina Faso <b>Date:</b> unknown <b>Source of funding:</b> Sanofi-Synthelabo, Gentilly, France

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

Barenes 1989	Not a randomized controlled trial
Barenes 1993	Not a randomized controlled trial
Barenes 1994	Letter not containing data on randomized controlled trials
Barenes 1996b	Comparison of different doses of intrarectal quinine only; no control group
Barenes 1999b	Summary of observations and narrative review of previous trial without data on a randomized controlled trial

(Continued)

Landais 2007	Not a randomized controlled trial
Ndiaye 2007	Not a randomized controlled trial
Pussard 1996	Not a randomized controlled trial; review of intrarectal administration of antimalarial drugs
Thera 2007	Not a randomized controlled trial

## DATA AND ANALYSES

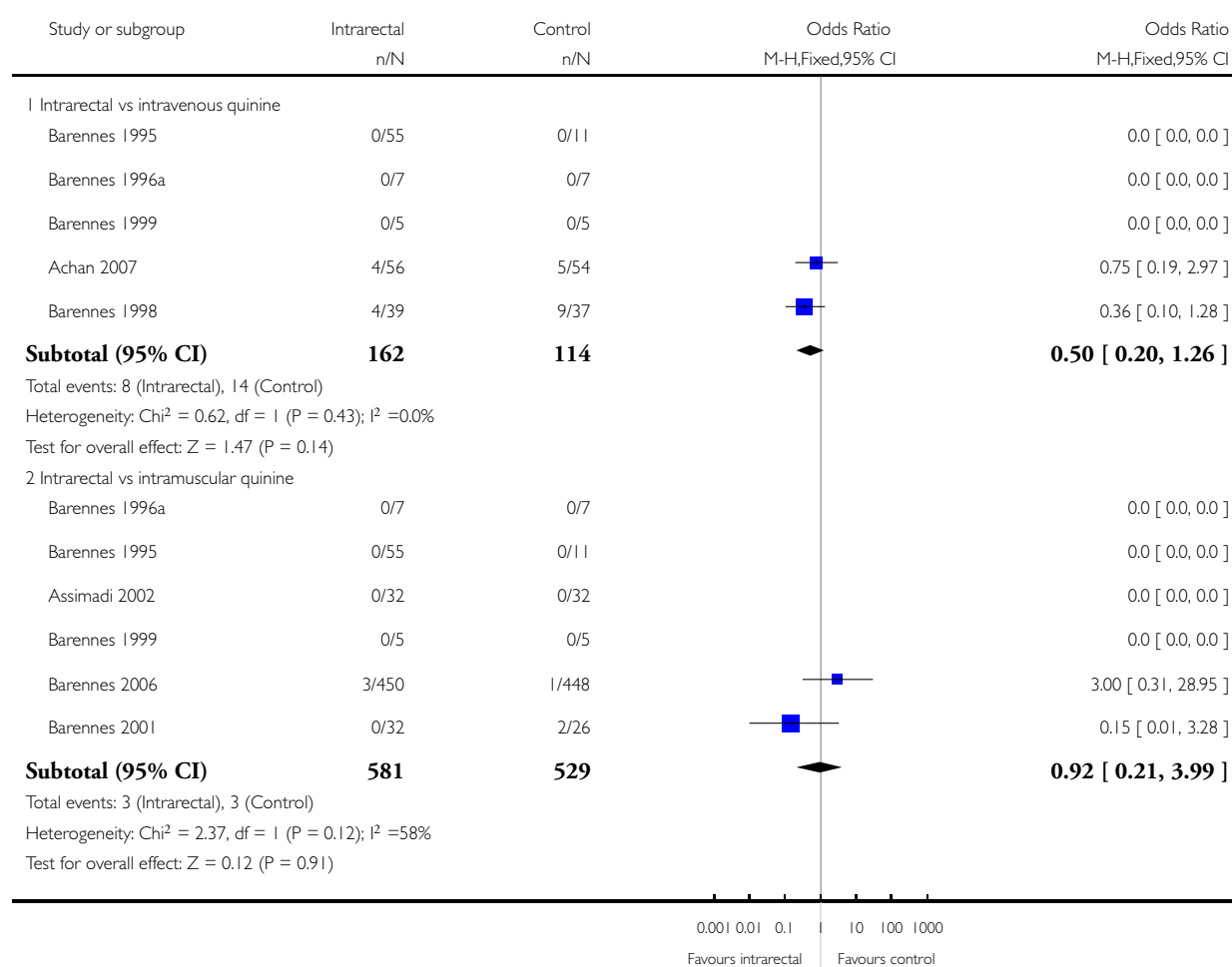
### Comparison 1. Intrarectal quinine vs intravenous and intramuscular quinine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	8		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Intrarectal vs intravenous quinine	5	276	Odds Ratio (M-H, Fixed, 95% CI)	0.50 [0.20, 1.26]
1.2 Intrarectal vs intramuscular quinine	6	1110	Odds Ratio (M-H, Fixed, 95% CI)	0.92 [0.21, 3.99]
2 Parasite clearance by 48 hours	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Intrarectal vs intravenous quinine	2	44	Odds Ratio (M-H, Fixed, 95% CI)	2.24 [0.37, 13.70]
2.2 Intrarectal vs intramuscular quinine	2	84	Odds Ratio (M-H, Fixed, 95% CI)	0.15 [0.02, 0.89]
3 Parasite clearance time (hours)	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Intrarectal vs intravenous quinine	2	186	Mean Difference (IV, Fixed, 95% CI)	-0.67 [-5.79, 4.44]
3.2 Intrarectal vs intramuscular quinine	1	20	Mean Difference (IV, Fixed, 95% CI)	19.1 [5.20, 33.00]
4 Fever clearance time (hours)	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Intrarectal vs intravenous quinine	2	186	Mean Difference (IV, Fixed, 95% CI)	-0.31 [-4.53, 3.91]
4.2 Intrarectal vs intramuscular quinine	3	1022	Mean Difference (IV, Fixed, 95% CI)	2.55 [-1.40, 6.50]
5 Duration of hospitalization (days)	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1 Intrarectal vs intravenous quinine	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
5.2 Intrarectal vs intramuscular quinine	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
6 Coma recovery time (hours)	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Intrarectal vs intravenous quinine	2	186	Mean Difference (IV, Fixed, 95% CI)	2.04 [-2.31, 6.38]
6.2 Intrarectal vs intramuscular quinine	1	58	Mean Difference (IV, Fixed, 95% CI)	-0.80 [-6.94, 5.34]
7 Adverse events: intrarectal vs intravenous quinine	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
7.1 Vomiting	1		Odds Ratio (M-H, Random, 95% CI)	Not estimable
7.2 Diarrhoea	1		Odds Ratio (M-H, Random, 95% CI)	Not estimable
7.3 Soft stools	1		Odds Ratio (M-H, Random, 95% CI)	Not estimable
7.4 Liquid stools	1		Odds Ratio (M-H, Random, 95% CI)	Not estimable
8 Adverse events: intrarectal vs intramuscular quinine	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Painful swelling	1	64	Odds Ratio (M-H, Random, 95% CI)	0.13 [0.01, 2.62]
8.2 Pain at injection site	1	64	Odds Ratio (M-H, Random, 95% CI)	0.10 [0.01, 1.89]
8.3 Mild diarrhoea	3	1022	Odds Ratio (M-H, Random, 95% CI)	1.51 [0.10, 23.26]

**Analysis 1.1. Comparison 1 Intrarectal quinine vs intravenous and intramuscular quinine, Outcome 1 Death.**Review: Intrarectal quinine versus intravenous or intramuscular quinine for treating *Plasmodium falciparum* malaria

Comparison: 1 Intrarectal quinine vs intravenous and intramuscular quinine

Outcome: 1 Death

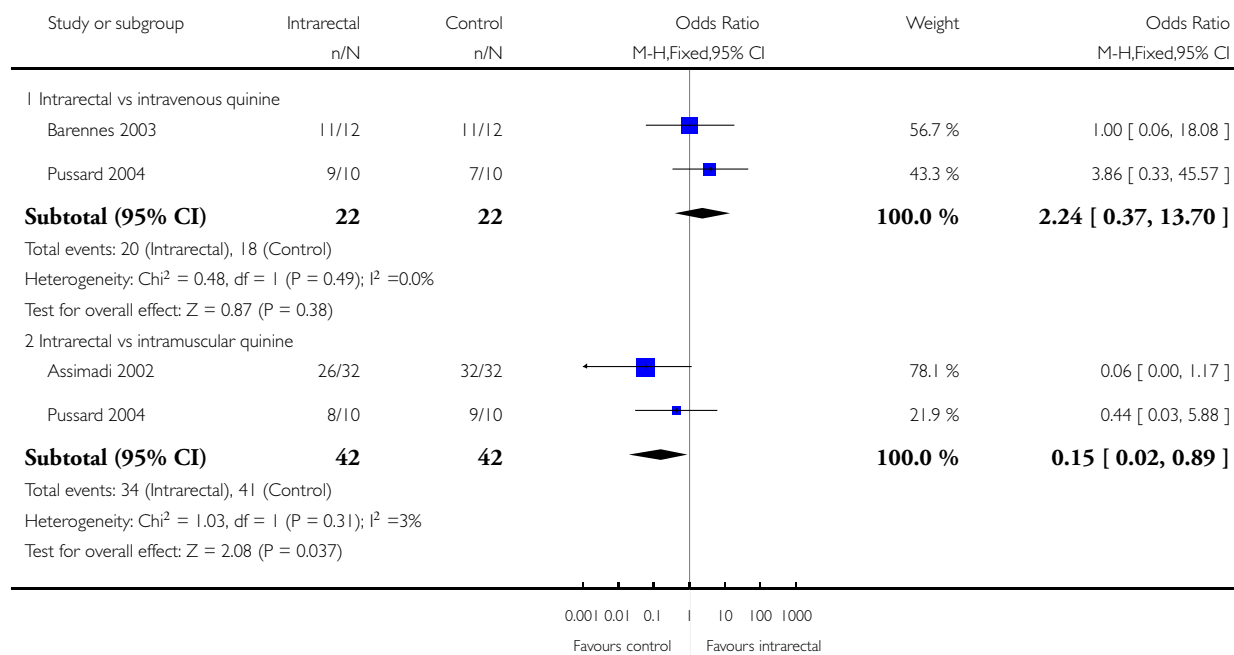


## Analysis 1.2. Comparison 1 Intrarectal quinine vs intravenous and intramuscular quinine, Outcome 2 Parasite clearance by 48 hours.

Review: Intrarectal quinine versus intravenous or intramuscular quinine for treating *Plasmodium falciparum* malaria

Comparison: 1 Intrarectal quinine vs intravenous and intramuscular quinine

Outcome: 2 Parasite clearance by 48 hours

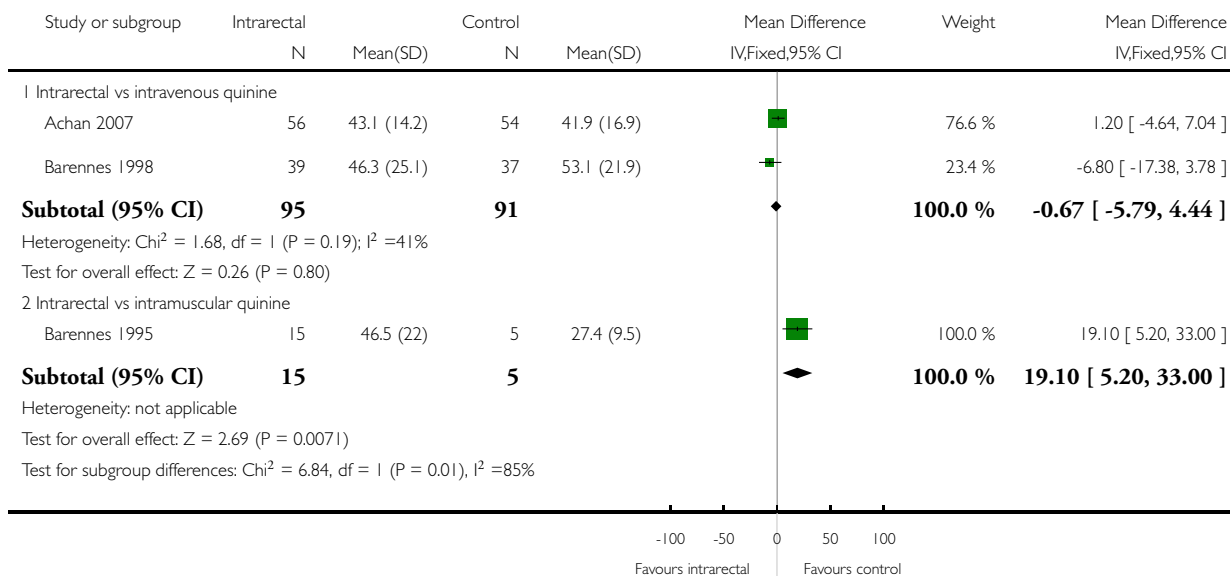


### Analysis 1.3. Comparison 1 Intrarectal quinine vs intravenous and intramuscular quinine, Outcome 3 Parasite clearance time (hours).

Review: Intrarectal quinine versus intravenous or intramuscular quinine for treating *Plasmodium falciparum* malaria

Comparison: 1 Intrarectal quinine vs intravenous and intramuscular quinine

Outcome: 3 Parasite clearance time (hours)

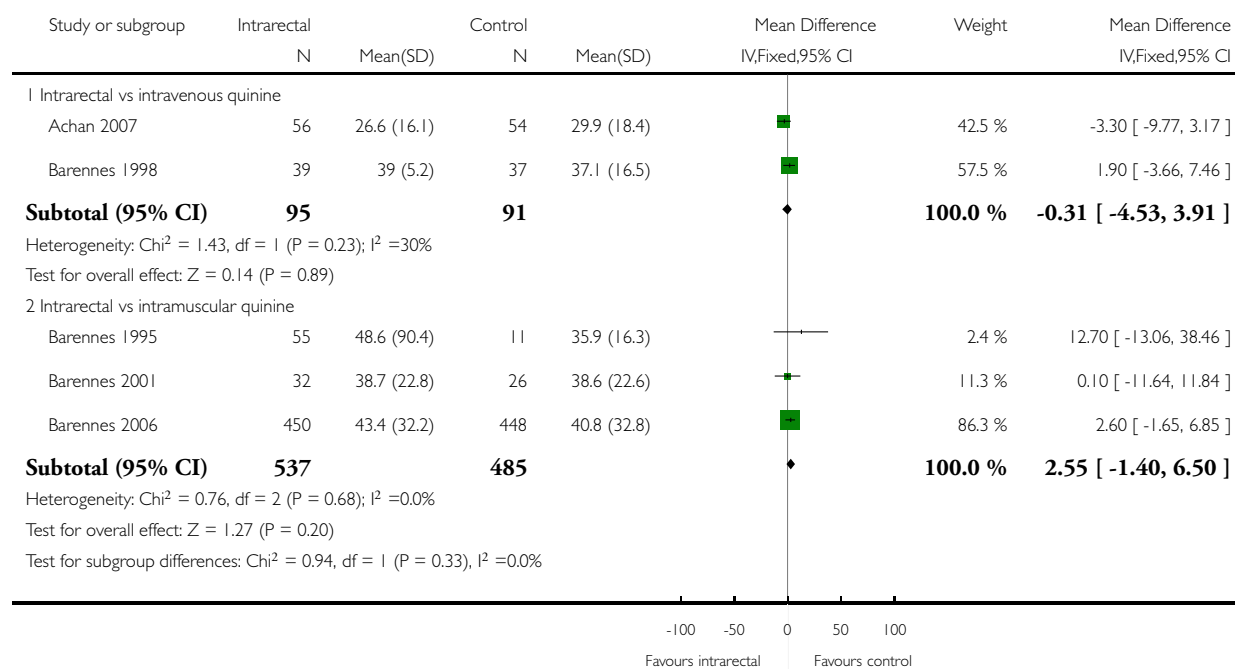


### Analysis 1.4. Comparison 1 Intrarectal quinine vs intravenous and intramuscular quinine, Outcome 4 Fever clearance time (hours).

Review: Intrarectal quinine versus intravenous or intramuscular quinine for treating *Plasmodium falciparum* malaria

Comparison: 1 Intrarectal quinine vs intravenous and intramuscular quinine

Outcome: 4 Fever clearance time (hours)

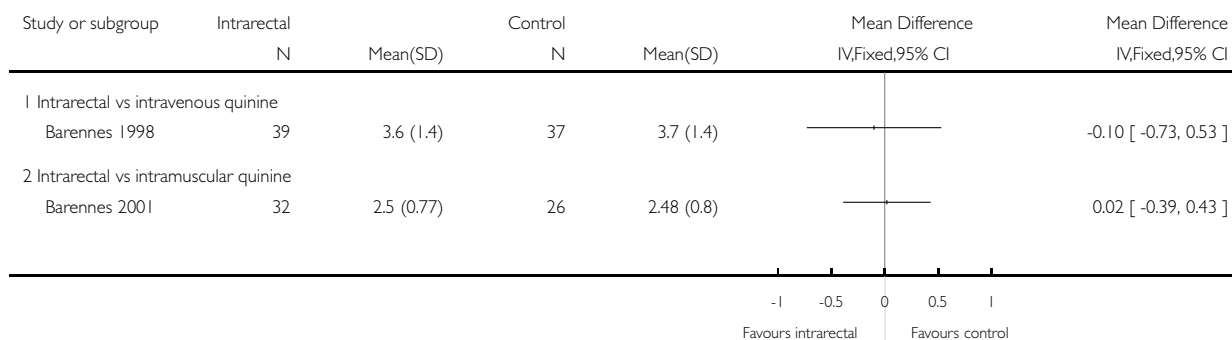


### Analysis 1.5. Comparison 1 Intrarectal quinine vs intravenous and intramuscular quinine, Outcome 5 Duration of hospitalization (days).

Review: Intrarectal quinine versus intravenous or intramuscular quinine for treating *Plasmodium falciparum* malaria

Comparison: 1 Intrarectal quinine vs intravenous and intramuscular quinine

Outcome: 5 Duration of hospitalization (days)

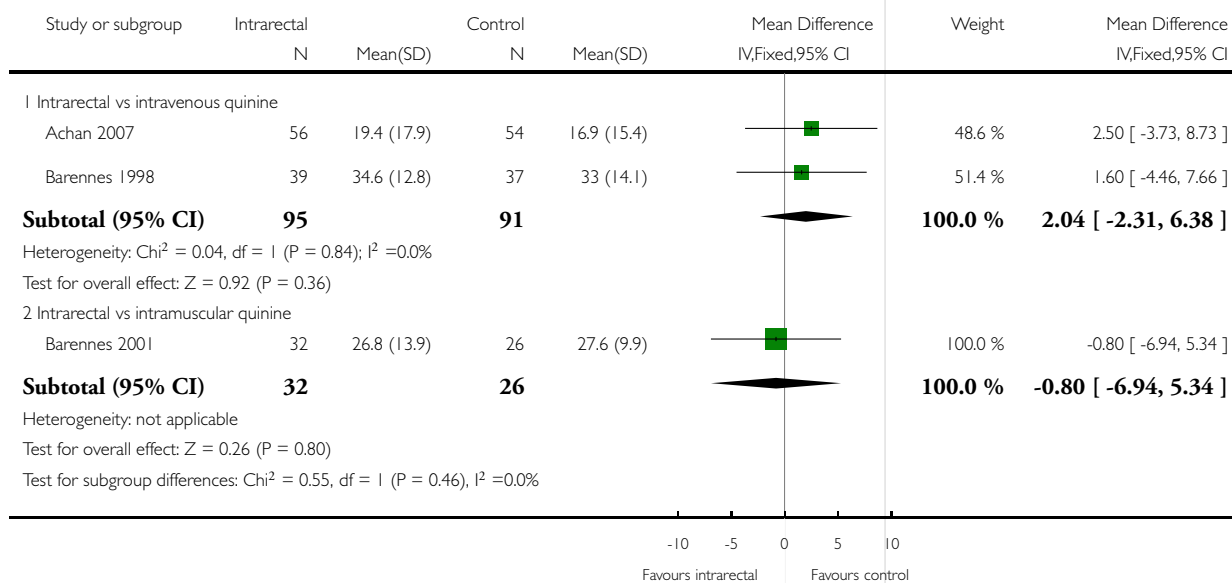


### Analysis 1.6. Comparison 1 Intrarectal quinine vs intravenous and intramuscular quinine, Outcome 6 Coma recovery time (hours).

Review: Intrarectal quinine versus intravenous or intramuscular quinine for treating *Plasmodium falciparum* malaria

Comparison: 1 Intrarectal quinine vs intravenous and intramuscular quinine

Outcome: 6 Coma recovery time (hours)

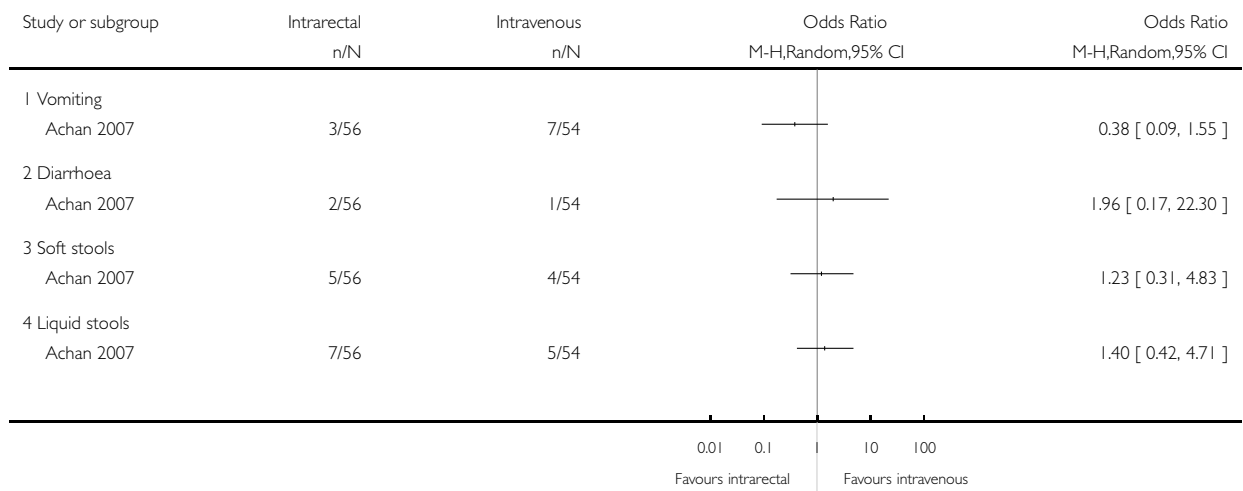


**Analysis 1.7. Comparison 1 Intrarectal quinine vs intravenous and intramuscular quinine, Outcome 7  
Adverse events: intrarectal vs intravenous quinine.**

Review: Intrarectal quinine versus intravenous or intramuscular quinine for treating *Plasmodium falciparum* malaria

Comparison: 1 Intrarectal quinine vs intravenous and intramuscular quinine

Outcome: 7 Adverse events: intrarectal vs intravenous quinine

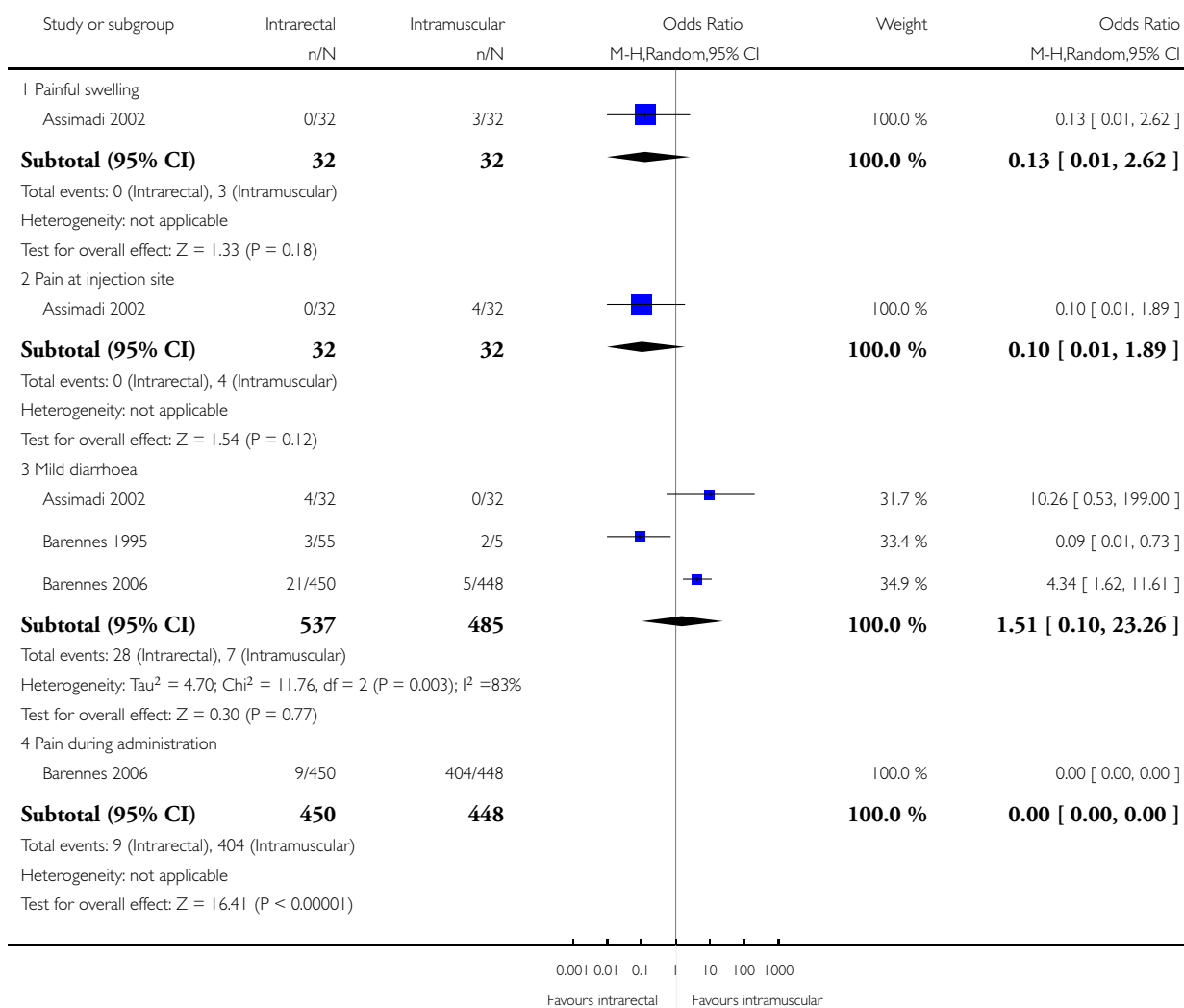


**Analysis 1.8. Comparison 1 Intrarectal quinine vs intravenous and intramuscular quinine, Outcome 8 Adverse events: intrarectal vs intramuscular quinine.**

Review: Intrarectal quinine versus intravenous or intramuscular quinine for treating *Plasmodium falciparum* malaria

Comparison: 1 Intrarectal quinine vs intravenous and intramuscular quinine

Outcome: 8 Adverse events: intrarectal vs intramuscular quinine



## APPENDICES

### Appendix I. Search methods: detailed search strategies

Search set	CIDG SR <sup>a</sup>	CENTRAL	MEDLINE <sup>b</sup>	EMBASE <sup>b</sup>	LILACS <sup>b</sup>	CINAHL <sup>b</sup>
1	quinine	QUININE	QUININE	QUININE	quinine	quinine
2	quinimax	quinine	quinine	quinine	Cinchona alkaloids	ADMINISTRATION, RECTAL
3	1 or 2	quinimax	quinimax	quinimax	1 or 2	rectal
4	rectal	CINCHONA ALKALOIDS	CINCHONA ALKALOIDS	CINCHONA ALKALOIDS	rectal	rectum
5	3 and 4	Cinchona alkaloid\$	Cinchona alkaloid*	Cinchona alkaloid\$	3 and 4	2 or 3 or 4
6	-	1 or 2 or 3 or 4 or 5	1 or 2 or 3 or 4 or 5	1 or 2 or 3 or 4 or 5	-	1 and 5
7	-	suppositor*	SUPPOSITORIES	SUPPOSITORY	-	-
8	-	ADMINISTRATION RECTAL	suppositor*	suppositor\$	-	-
9	-	intrarectal	ADMINISTRATION, RECTAL	RECTAL DRUG ADMINISTRATION	-	-
10	-	rectal	intrarectal	intrarectal	-	-
11	-	7 or 8 or 9 or 10	rectal	rectal	-	-
12	-	6 and 11	rectum	rectum	-	-
13	-	MALARIA	7 or 8 or 9 or 10 or 11 or 12	7 or 8 or 9 or 10 or 11 or 12	-	-
14	-	malaria	6 and 13	6 and 13	-	-
15	-	13 or 14	MALARIA	MALARIA	-	-
16	-	12 and 15	malaria	malaria	-	-
17	-	-	15 or 16	15 or 16	-	-
18	-	-	14 and 17	14 and 17	-	-

(Continued)

19	-	-	Limit 18 to human	Limit 18 to human	-	-
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<sup>a</sup>Cochrane Infectious Diseases Group Specialized Register.

<sup>b</sup>Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration ([Lefebvre 2008](#)); upper case: MeSH or EMTREE heading; lower case: free text term.

## Appendix 2. Descriptive adverse event data from Barennes 2006

Adverse event	Route of quinine administration	
	Intrarectal	Intramuscular
Mucoid stools	296/450 (65.7%)	22/448 (5.1%)
Blood in stool	21/450 (4.4%)	3/448 (0.7%)
Painful contraction of anal sphincter	65/450 (14.4%)	3 (0.66%)
Inflammation at the injection site	0	355/448 (80%)
Tenesmus	56/450 (12.4%)	3 (0.66%)
Number investigated by anoscopy with a single microulceration (small defect in the mucosa) healing within 24 hours	4/259	No data
Multiple microulcerations recovering by day 7	1/259	No data
Multiple microulcerations recovering by day 14	1/259	No data
Ulceration with cutaneous necrosis (skin decay)	1/259	No data
Difficulty in walking	No data	67/448 (15%)
Sciatic paresthesia (abnormal sensation in the sensory distribution of the sciatic nerve)	0	1/448 (0.2%)
Fever recurrence due to inflammation or infection of the injection site	No data	30/448 (6.6%)

## WHAT'S NEW

Last assessed as up-to-date: 27 August 2008.

2 June 2008	New citation required but conclusions have not changed	Update with inclusion of two new trials ( <a href="#">Pussard 2004</a> ; <a href="#">Achan 2007</a> ) and additional data from one previously included trial ( <a href="#">Barennes 2006</a> ). Title changed from "Intra-rectal quinine for treating <i>Plasmodium falciparum</i> malaria" to "Intra-rectal quinine versus intravenous or intramuscular quinine for treating <i>Plasmodium falciparum</i> malaria" to clarify the comparisons investigated and facilitate access for persons conducting a literature search.
13 May 2008	New search has been performed	New literature search.

## HISTORY

Protocol first published: Issue 1, 2003

Review first published: Issue 1, 2005

23 May 2005	Amended	Issue 3, 2005: Added reference to 'Other published versions of this review'.
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## CONTRIBUTIONS OF AUTHORS

Both authors participated in the development of the protocol, literature search, and data extraction for the original review and the update. Both authors entered data into Review Manager, and Michael Eisenhut wrote the review.

## DECLARATIONS OF INTEREST

None known.

## SOURCES OF SUPPORT

### Internal sources

- No sources of support supplied

### External sources

- Department for International Development, UK.

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

2005, Issue 1 (first review version): We used the term 'parasitaemia' in the 'Types of outcomes' in the protocol to encompass commonly used outcomes describing the presence of parasites in trial participants. We changed this to the more specific term 'parasite clearance' in the review because this is the most commonly used outcome in trials and hence the most useful outcome category for the review.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Administration, Rectal; Antimalarials [\*administration & dosage; chemistry]; Hydrogen-Ion Concentration; Injections, Intramuscular; Injections, Intravenous; Malaria, Falciparum [\*drug therapy]; Quinine [\*administration & dosage; chemistry]; Randomized Controlled Trials as Topic

### MeSH check words

Child; Humans