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Chloroquine or amodiaquine combined with sulfadoxine-pyrimethamine for treating uncomplicated malaria
(Review)

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[Intervention Review]

Chloroquine or amodiaquine combined with sulfadoxine-pyrimethamine for treating uncomplicated malaria

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ABSTRACT

Background

Chloroquine (CQ), amodiaquine (AQ), and sulfadoxine-pyrimethamine (SP) are inexpensive drugs, but treatment failure is a problem. Combination therapy may reduce treatment failure. CQ or AQ plus SP are affordable options of combination treatment, but there is debate about their effectiveness.

Objectives

To assess the combination of CQ or AQ plus SP compared with SP alone for first-line treatment of uncomplicated falciparum malaria.

Search methods

We searched the Cochrane Infectious Diseases Group Specialized Register (April 2005), CENTRAL (*The Cochrane Library* Issue 2, 2005), MEDLINE (1966 to April 2005), EMBASE (1974 to April 2005), LILACS (1982 to April 2005), Science Citation Index (1981 to April 2005), African Index Medicus (1993 to 1998), and reference lists. We also contacted researchers at relevant organizations and a pharmaceutical company.

Selection criteria

Randomized controlled trials in adults or children with uncomplicated *Plasmodium falciparum* malaria were eligible for inclusion. The main outcomes of interest were total and clinical failure at day 28 follow up and serious adverse events.

Data collection and analysis

Two people independently applied the inclusion criteria. One author extracted data and another checked them independently. We used risk ratio (RR) and 95% confidence intervals (CI).

Main results

Twelve trials (2107 participants) met the inclusion criteria. A meta-analysis of five AQ trials (461 participants) showed a statistically significant reduction in total failure at day 28 with the combination therapy (RR 0.64, 95% CI 0.46 to 0.91), and meta-analysis of three trials (384 participants) showed a significant reduction in clinical failure at day 28 (RR 0.23, 95% CI 0.11 to 0.49). The statistical significance in the total failure analysis was sensitive to losses to follow up. Data from two CQ trials showed no advantage for total failure with combination therapy at day 28. There was no evidence from the included trials of serious adverse events.

Authors' conclusions

The evidence base is not strong enough to support firm conclusions. The available evidence suggests that AQ plus SP can achieve less treatment failure than SP, but this might depend on existing levels of parasite resistance to the individual drugs.

Addendum, 2008: The World Health Organization (in 2006) recommended that monotherapy should not be used for treating malaria. Therefore the authors do not intend to update this review.

24 April 2019

No update planned

Intervention not in general use or been superseded

As monotherapy is no longer recommended by the World Health Organization for malaria treatment (since 2006), the authors do not intend to update this review.

PLAIN LANGUAGE SUMMARY

Chloroquine or amodiaquine combined with sulfadoxine-pyrimethamine for treating uncomplicated malaria

Using amodiaquine and sulfadoxine-pyrimethamine together to treat uncomplicated malaria instead of sulfadoxine-pyrimethamine alone may reduce treatment failure; adding chloroquine to sulfadoxine-pyrimethamine may not be beneficial

Chloroquine, amodiaquine, and sulfadoxine-pyrimethamine are relatively inexpensive drugs to treat malaria. Treatment failure is a problem when these drugs are used alone because malaria parasites have become resistant to them. Based on evidence from randomized controlled trials, a combination of amodiaquine plus sulfadoxine-pyrimethamine may reduce treatment failure in some locations. It appears less likely that chloroquine plus sulfadoxine-pyrimethamine will have a treatment benefit over sulfadoxine-pyrimethamine alone.

BACKGROUND

Chloroquine (CQ) is a cheap and well-tolerated 4-aminoquinoline drug. It is still widely used to treat uncomplicated malaria even in areas where *Plasmodium falciparum* malaria parasites show significant levels of resistance to it. Amodiaquine (AQ) is similar to CQ but is more potent. It is used less widely and resistance to it is less common, although there is some cross-resistance with CQ. The antifolate drug sulfadoxine-pyrimethamine (SP) is also inexpensive, effective against parasites resistant to CQ and AQ, and the single-dose standard treatment is rarely associated with severe adverse reactions (WHO 1990; Sturchler 1993). SP has customarily been used to replace failing CQ or AQ as first-line treatment of uncomplicated malaria because it is available and affordable. However, the selective pressure exerted when SP is used alone, and the relatively long time that SP remains in the body, is thought to have contributed to the emergence of malaria parasites resistant to SP (Watkins 1993).

Combination therapy has been advocated for some years for the treatment of uncomplicated malaria, to improve clinical effectiveness and slow down the emergence of drug resistance to individual drugs (White 1999). International health agencies recently declared that artemisinin combination therapy must urgently be made widely available, but many countries, particularly in Africa, cannot afford to purchase artemisinin drugs. Although malaria parasite resistance has reduced the effectiveness of the 4-aminoquinolines and SP, for some countries these drugs are currently the only affordable option for combination therapy.

Some countries faced with increasing treatment failure rates have already implemented a change in first-line treatment policy from CQ or AQ alone to CQ or AQ plus SP, whilst others have opted to replace CQ or AQ alone with SP (RBM 2001; Wongsrichanalai 2002; EANMAT 2003). The combination of CQ or AQ plus SP may still be able to slow down the progress of resistance in areas where resistance to either drug component has not yet reached a high level (Watkins 2005). Also, since CQ and AQ have antipyretic and anti-inflammatory properties that SP does not have, combination therapy may relieve clinical symptoms faster than SP alone. However, opinion on the effectiveness of this strategy varies.

OBJECTIVES

To assess the combination of CQ or AQ plus SP compared with SP alone for first-line treatment of uncomplicated falciparum malaria.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials.

Types of participants

Adults and children with uncomplicated *P. falciparum* malaria, symptomatic or asymptomatic, with *P. falciparum* parasitaemia.

Types of interventions

CQ or AQ plus SP compared with SP alone.

Types of outcome measures

Primary

- Total failure by day 28, defined as the presence of symptomatic or asymptomatic *P. falciparum* parasitaemia at any point during follow up to day 28 (RBM 2003).
- Clinical failure by day 28, defined as the presence of symptomatic *P. falciparum* parasitaemia at any point during follow up to day 28 (RBM 2003).

Secondary

- Total failure by day 14, defined as the presence of symptomatic or asymptomatic *P. falciparum* parasitaemia at any point during follow up to day 14 (RBM 2003).
- Clinical failure by day 14, defined as the presence of symptomatic *P. falciparum* parasitaemia at any point during follow up to day 14 (RBM 2003).
- Early treatment failure, as defined by the World Health Organization (WHO 1996; RBM 2001; WHO 2002; RBM 2003).
- Adverse events during treatment or follow up were classified as fatal, life threatening, requiring hospitalization, or resulting in discontinuation of treatment.

Search methods for identification of studies

Databases

We searched the following databases using the search terms and strategy described in Appendix 1: Cochrane Infectious Diseases Group Specialized Register (April 2005); Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (Issue 2, 2005); MEDLINE (1966 to April 2005); EMBASE (1974 to April 2005); LILACS (1982 to April 2005); and Science Citation Index (SCI) (1981 to April 2005).

We searched the African Index Medicus from 1993 to 1998 using the search terms malaria, chloroquine, amodiaquine, sulfadoxine, sulphadoxine, pyrimethamine, and Fansidar. This database is currently unavailable for new searches.

Researchers, organizations, and pharmaceutical companies

We contacted researchers at the following organizations for unpublished and ongoing trials: Steering Committee on Drugs for Malaria (CHEMAL), World Health Organization; the London School of Hygiene and Tropical Medicine; the Wellcome Trust Research Unit, Nairobi; the World Health Organization in Viet Nam. We also contacted a pharmaceutical company, Hoffmann-La Roche (Switzerland), which manufactures Fansidar (sulfadoxine-pyrimethamine).

Reference lists

We checked the references listed of all eligible trials identified by the above methods.

Data collection and analysis

Selection of studies

The first author (HM) screened all items identified by the search strategy and obtained the full reports of potentially relevant trials. The first author and a second person independently applied the inclusion criteria to the full reports. Any disagreement was resolved

by discussion. Trial authors were contacted where clarification was needed.

Data extraction and management

The first author extracted data using a standard form and the second author (KJ) checked the accuracy of the data extracted. Disagreements were resolved by discussion. Where possible, we extracted data on the number of participants enrolled, randomized to each treatment group, treated, evaluated, excluded, lost to follow up, and withdrawn. We extracted data on the outcome measures as the number of events for each measure of effect reported in each trial. Where necessary, we used the reported data to calculate a best estimate of total failure and clinical failure. Trial investigators were asked to provide missing information where possible.

Assessment of risk of bias in included studies

The first author assessed the risk of bias in the included trials, and a second person checked the assessment; discrepancies were resolved by discussion. The adequacy of the generation of the random allocation sequence and concealment of the allocation schedule was assessed according to [Jüni 2001](#). Descriptive data were collected on whether participants, providers, and outcome assessors were blind to the treatment given. We considered the inclusion of all randomized participants to be adequate if at least 80% of the randomized participants completed follow up.

Data synthesis

We combined total failure, clinical failure, and early treatment failure data separately using meta-analysis in [Review Manager 4.2](#). We stratified the trials by the aminoquinoline used (AQ or CQ).

We presented the results for each outcome in each individual trial in forest plots as a risk ratio (RR) value with a 95% confidence interval (CI). We used a chi-squared test to assess statistical heterogeneity ($P < 0.1$ was considered statistically significant) and I^2 was used to assess the proportion of total variation due to heterogeneity ([Higgins 2003](#)). We used a fixed-effect model to obtain pooled estimates of effect from trials that were sufficiently homogeneous. We examined the robustness of combined effects using the random-effects model in sensitivity analyses.

We conducted the main analyses using data reported for participants who were evaluable at follow up; see the 'Characteristics of included studies' for the proportion of missing data for each trial. We explored the potential impact of attrition on the meta-analysis by considering the amount of missing data and potential best-case and worst-case scenarios. The latter were based on the intention-to-treat principle using the number of randomized eligible patients as the denominator. If the only data available were per-protocol, we did not use them in the meta-analysis.

The small number of trials included in the meta-analyses precluded meaningful use of funnel plots or sensitivity analyses based on trial characteristics.

We used narrative methods to synthesize adverse event outcomes.

RESULTS

Description of studies

Twelve published trials met the inclusion criteria 'Characteristics of included studies' and we excluded 12 studies ('Characteristics of excluded studies'). Overall, 2107 adults and children were included of whom 1739 completed follow up. One trial had an AQ plus SP and a CQ plus SP treatment group ([Gasasira 2003](#)), so the subtotals quoted in the monotherapy groups of the two comparisons below both include the SP control group (140 participants). None of the trials included pregnant women.

AQ plus SP versus SP alone

Of the eight trials that made this comparison, one was conducted in China in 1985 ([Huang 1988](#)), two in Mozambique in 1986 ([Schapira 1988](#); [Dinis 1990](#)), four in Uganda between 1999 and 2002 ([Staedke 2001](#); [Dorsey 2002](#); [Schellenberg 2002](#); [Gasasira 2003](#)), and one in Cameroon in 2001 ([Basco 2002](#)). A total of 1312 participants were enrolled of whom 1109 completed follow up. We obtained data concerning treatment of first episodes of uncomplicated malaria from the [Dorsey 2002](#) trial authors because they were not reported in the published paper.

The recent use of antimalarials was an exclusion criterion in the three older trials, which excluded their use in the previous eight days ([Dinis 1990](#)), 14 days ([Schapira 1988](#)), and 28 days ([Huang 1988](#)). One of the more recent trials also excluded participants who had taken antimalarials within the previous 14 days ([Dorsey 2002](#)). Baseline data for two trials suggest that self medication ([Basco 2002](#)) or antimalarial use in the previous two weeks ([Gasasira 2003](#)) was similar between groups. The baseline data for [Staedke 2001](#) suggest that antimalarial use in the previous two weeks was slightly higher in the AQ plus SP group. The remaining included trial, [Schellenberg 2002](#), did not mention previous use of antimalarials.

CQ plus SP versus SP alone

Five trials made this comparison, one conducted in Papua New Guinea in 1980 ([Darlow 1982](#)), one in The Gambia in 1995 ([Bojang 1998](#)), one in Laos in 2001 ([Schwöbel 2003](#)), and two in Uganda between 2001 and 2002 ([Gasasira 2003](#); [Ndyomugenyi 2004](#)). A total of 942 participants were enrolled of which 770 completed follow up.

One of the older trials listed the use of antimalarials in the previous seven days as an exclusion criterion ([Darlow 1982](#)). Baseline data reported in two of the recent trials suggested that antimalarial and any drug use in the previous week ([Schwöbel 2003](#)) or antimalarial use in the previous two weeks ([Gasasira 2003](#)) was similar between groups. One trial specified self-medication during the trial in the exclusion criteria, but the baseline data showed that CQ use within the two weeks prior to the trial was twice as common in the CQ plus SP group as the SP group ([Ndyomugenyi 2004](#)). The remaining included trial did not mention previous the use of antimalarials ([Bojang 1998](#)).

Risk of bias in included studies

See [Appendix 2](#) for a summary of the assessment of the risk of bias in the trials. Further details are located in the 'Characteristics of included studies'. With few exceptions, the available information does not provide much reassurance of the quality of most of the published data.

All 12 trials were described as randomized, but only five used adequate methods to generate the sequence. Two trials described adequate allocation concealment (Huang 1988; Dorsey 2002). Two trials reported double blinding (Bojang 1998; Huang 1988). Only one trial described adequate sequence generation and concealment, together with blinding of the outcome assessors; however treatment outcome for the first episode of uncomplicated malaria was not the primary objective of the study (Dorsey 2002).

In seven trials at least 80% of randomized participants were evaluated for the primary outcome, although in one of these there was a moderate imbalance in attrition between the CQ plus SP and the SP alone groups (Gasasira 2003), and in another the number of participants originally assigned to each treatment group was unclear (Darlow 1982). One trial provided no information to assess attrition (Dinis 1990). Attrition over all the trials was about 18%; the proportion cannot be determined precisely because of incomplete and inconsistent reporting.

Effects of interventions

Details on how we derived estimates of total failure and clinical failure from the data in each trial report are in Appendix 3 and Appendix 4, respectively. We did not include one trial, Darlow 1982, in the meta-analysis because the number of participants originally assigned to each treatment was unclear; this was the only trial that reported treatment switching of some participants, from CQ plus SP to SP alone, after randomization.

The main meta-analyses use a fixed-effect model and data reported for participants who were evaluable at follow up. Too few trials reported adequate allocation concealment or blinding to explore possible associations between those measures of the risk of bias in the trials and the estimate of treatment effect. Some trials had substantial losses to follow up, the impact of which we explored using sensitivity analyses of best-case and worst-case scenarios. In best-case scenarios, we assumed that all participants lost to follow up had a successful outcome. This did not substantially change any of the meta-analysis results. Reinstating participants lost to follow up as failures (worst-case scenario) caused a shift in all point estimates away from favouring combination therapy. This moved the pooled point estimates closer to the line of no effect. This changed the meta-analysis findings for total and clinical failure at day 28 in the AQ trials analysis, and at day 14 in the CQ trials analysis. All the meta-analysis results are described below.

AQ plus SP versus SP

Total failure by day 28 (5 trials, 461 participants)

The largest trial (Schellenberg 2002), which contributed most data to the pooled effect size, showed no difference between combination therapy and SP alone. The pooled effect was statistically significantly in favour of combination therapy (RR 0.64, 95% CI 0.46 to 0.91). The test for statistical heterogeneity had borderline statistical significance, but with so few trials this test is not very meaningful. I^2 , which does not intrinsically depend on the number of trials, suggests that around half of the variability in the point estimates is due to chance rather than heterogeneity. A meta-analysis using the random-effects model rendered the pooled effect size not statistically significant. When we included the participants who were lost to follow up as failures (worst-case scenario) in the pooled analysis using the fixed-effect model, there

was no longer a statistically significant difference between the combination therapy and SP alone. See Analysis 1.1.

Clinical failure by day 28 (3 trials, 384 participants)

The pooled effect size was statistically significantly in favour of combination therapy (RR 0.23, 95% CI 0.11 to 0.49). The individual trial results look consistent in the forest plot, heterogeneity accounting for less than 30% of the variability, and the pooled result was robust to analysis using a random-effects model (RR 0.26, 95% CI 0.10 to 0.73). When we included participants lost to follow up as failures in the analysis using the fixed-effect model, the difference remained statistically significant but with a smaller margin (RR 0.73, 95% CI 0.55 to 0.97). See Analysis 1.2.

Total failure by day 14 (5 trials, 971 participants)

There were no events in either treatment arm in one of the trials (Basco 2002). In the other four trials the direction of effect was consistently in favour of combination therapy, but heterogeneity is evident in the size of effect between trials. Three of the trials were conducted at the same location in Uganda between 1999 and 2002 (Staedke 2001; Dorsey 2002; Gasasira 2003). The SP failure rate is similar in all four trials, but it is not obvious from the trial descriptions why the AQ plus SP failure rate at the Uganda location was much higher between July 2000 and August 2001 (Dorsey 2002) and March 2001 and January 2002 (Gasasira 2003). This meta-analysis and the analysis of total failure at day 28 have only one trial in common (Schellenberg 2002). See Analysis 1.3.

Clinical failure by day 14 (5 trials, 961 participants)

The same trials in the analysis of total failure at day 14 provided data to estimate clinical failure at day 14. The pattern of effect is similar to total failure, in favour of combination therapy with statistically significant inconsistency in effect size between trials. See Analysis 1.4.

Early treatment failure (5 trials, 1003 participants)

The meta-analysis showed a statistically significant benefit in favour of combination therapy (RR 0.23, 95% CI 0.09 to 0.57). There was no apparent heterogeneity between the trial results. See Analysis 1.5.

Adverse events

This review focussed on adverse events that were fatal, life threatening, required hospitalization, or resulted in discontinuation of treatment. See Appendix 5 for a summary of pertinent information from the trials.

Three of the eight trials gave some information about how and when adverse events were monitored, but only two described systematic methods of data collection and classification (Schellenberg 2002; Gasasira 2003). All but one trial provided baseline data (Appendix 5); there was no obvious imbalance between comparator groups in relation to the adverse events reported. In general attrition was similar for the assessment of adverse events and other outcome measures.

Two of the four trials that included adults specified pregnancy in the exclusion criteria (Huang 1988; Dinis 1990). Exclusion criteria for other trials included allergy to sulfa drugs (Staedke 2001; Gasasira 2003), allergy to sulphonamides (Basco 2002), allergy to treatment

drugs (Dinis 1990), sensitivity to trial drugs (Schellenberg 2002), and history of adverse reaction to trial drugs (Dorsey 2002).

There was one reported death, which occurred in the SP group, attributed to the progression of malaria (Schellenberg 2002). Abnormal liver enzymes were reported in one child treated with SP alone, but this was not accompanied by symptoms and resolved without medical intervention within two weeks (Gasasira 2003). No consequences were elucidated with regard to reported breathing problems in Schellenberg 2002 (AQ plus SP 10/104; SP 17/99) or sinus bradycardia in Huang 1988 (AQ plus SP 8/48; SP 0/21).

CQ plus SP versus SP

Total failure by day 28 (2 trials, 376 participants)

Bojang 1998 found no statistically significant difference between combination therapy and SP alone (RR 0.50, 95% CI 0.21 to 1.18; 291 participants). A sensitivity analysis on the number of participants lost to follow up did not change the finding.

The second trial, Darlow 1982, concluded that CQ plus SP had no advantage over SP alone in terms of treatment failure based on parasitaemia. The trials were not pooled because Darlow 1982 reported only per-protocol data.

Clinical failure by day 28

No data available.

Total failure by day 14 (3 trials, 400 participants)

The pooled risk ratio was 0.59 (95% CI 0.40 to 0.88) in favour of combination therapy, with the individual trial results appearing consistent. The pooled estimate was robust to an analysis using the random-effects model (RR 0.60, 95% CI 0.40 to 0.89), but the statistically significant difference was lost when we included the participants that were lost to follow up as failures. See Analysis 1.3.

Clinical failure by day 14 (3 trials, 400 participants)

The pooled estimate largely reflects the results of the largest trial (Gasasira 2003), a borderline statistically significant difference in favour of combination therapy (RR 0.51, 95% CI 0.26 to 0.99). This difference was no longer statistically significant when we included participants that were lost to follow up as failures. See Analysis 1.4.

Early treatment failure (3 trials, 400 participants)

The pooled analysis showed no statistically significant difference between combination therapy and SP alone. One trial, Gasasira 2003, contributed most of the data. A sensitivity analysis on the number of participants lost to follow up did not change the finding. See Analysis 1.5.

Adverse events

This review focussed on adverse events that were fatal, life threatening, required hospitalization, or resulted in discontinuation of treatment. See Appendix 5 for a summary of pertinent information from the trials.

Two of the four trials gave some information about how and when adverse events were monitored (Darlow 1982; Ndyomugenyi 2004), but none described systematic methods of data collection and classification. All trials provided baseline data; there was no obvious imbalance between comparator groups in relation to the

adverse events reported. In general, attrition was similar for the assessment of adverse events and beneficial effects.

One of two trials that included adults specified pregnancy in the exclusion criteria (Schwöbel 2003).

Two participants in Darlow 1982 were found to have glucose-6-phosphate dehydrogenase deficiency, an inherited condition in which affected individuals develop haemolysis with specific recognized drugs such as sulfadoxine, but there was no evidence of haemolysis in either participant. Technically, vomiting led to the withdrawal of CQ plus SP therapy when seven out of eight children who vomited in Darlow 1982 were switched to the SP group after that drug alone was re-administered, but the reason for this was not explained. None of the other trials reported withdrawal of treatment because of adverse events, but exclusion of participants for non-compliance with treatment or post-enrolment or post-treatment withdrawal of consent was not fully reported.

DISCUSSION

This review includes outcome data for 1739 participants from 12 randomized controlled trials conducted in disparate malaria endemic areas. The trials span the last two decades, although each was conducted at a time when there was known to be some degree of malaria parasite resistance to CQ or AQ, or both, and in some cases to SP. The most recent data are largely from trials conducted in Africa, particularly Uganda. The findings suggest a beneficial effect of AQ plus SP combination therapy at day 28 compared with SP alone, possibly due to a better clinical cure rate. The evidence available from randomized controlled trials suggests that CQ plus SP combination therapy may not have a treatment benefit over SP alone.

Synthesizing the data from these trials is problematic for several reasons in addition to the dissimilarities of location and time. A major obstacle to synthesizing data from different trials is the change over time in the standard protocol for the assessment of antimalarial drug efficacy and consequently the outcomes measured in clinical trials. Our approach was to use the data that were reported to calculate a common measure of treatment effect that could be pooled across trials, and users could readily comprehend. This was not straightforward and in some cases we had to settle for best estimates, which might have caused some of the inconsistency between trial results in our analyses.

Most of the trials are small and few trials could be pooled for the primary outcomes because almost half of them stopped follow up at day 14, which limits the possibility of increasing statistical power through meta-analysis. Stopping follow up at day 14 in the assessment of drug efficacy against *P. falciparum* malaria is likely to underestimate the treatment failure rate (Stepniewska 2004).

Variation in the risk of bias in the trials poses an important threat to the reliability of the findings from meta-analyses because of bias. The methodological quality of most randomized controlled trials in this area is open to question because insufficient information is reported to assess it. Despite longstanding empirical evidence of an association between inadequate allocation concealment and overestimation of treatment effects (Schulz 1995; Kunz 2002), this aspect of the design of randomized controlled trials is hardly ever clearly reported. Several potentially eligible trials reported as randomized turned out not to be when further information was

obtained, so this could also be true of trials included in this review for which further information is not available.

In some of our analyses, notably total failure at day 28 in the comparison of AQ plus SP with SP alone, the number of participants lost to follow up has the potential to change observed differences in treatment effect from statistically significant to non-significant. This introduces uncertainty in the findings from individual trials and consequently from meta-analyses that include those trials.

The trials included in this review do not show evidence of serious adverse events with AQ plus SP or CQ plus SP drug combinations as used in the treatment of uncomplicated malaria (bearing in mind that half of the trials reported excluding participants at higher risk of sensitivity reactions to trial drugs). In this area, as is true of reports of randomized controlled trials generally, adverse event reporting is inadequate ([Ioannidis 2001](#); [Loke 2001](#)). The trials in this review did not include pregnant women and so do not provide evidence about the safety of these drugs in pregnancy.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence base does not support firm conclusions about AQ plus SP or CQ plus SP combination therapy compared with SP alone. The main reasons are the small number of randomized controlled trials that followed participants for 28 days and uncertainty in relation to the risk of bias in the trials.

The available evidence suggests that AQ plus SP can achieve less treatment failure than SP, a benefit that might depend on the local existing level of parasite resistance to the individual drugs. The available randomized comparisons show no evidence of a significant reduction in treatment failure with CQ plus SP compared with SP alone.

Implications for research

Artemisinin combination therapy is currently recommended by the World Health Organization, but supply is not assured. Chloroquine resistance has reached such high levels in most settings that it is

currently not a treatment option. If AQ plus SP is considered to be an option by policy makers, trials will help inform their decisions, although there is likely to be debate as to whether such trials should compare AQ plus SP with artemisinin combination therapies rather than with SP alone.

Furthermore, there needs to be more consistency and clarity in the reporting of outcome measures of effectiveness in trials of treatment for uncomplicated malaria. This is important to enable synthesis of the many disparate trials that malaria research generates. The effectiveness outcomes reported must be meaningful to users who need to make decisions about changing clinical practice or policy. Clinical trial design should always include systematic monitoring of adverse effects.

To help decision makers assess the evidence, trial reports should adhere to the CONSORT statement ([Altman 2001](#); [Ioannidis 2004](#)).

Addendum, 2008: As monotherapy is no longer recommended by the World Health Organization for malaria treatment ([WHO 2006](#)), the authors do not intend to update this review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Basco 2002

Methods	<p>Generation of allocation sequence: computer generated; random assignment in blocks</p> <p>Allocation concealment: not reported</p> <p>Blinding: not reported</p> <p>Inclusion of all randomized participants in the analysis: 96% at day 14 (number excluded or lost to follow up before day 14 for amodiaquine (AQ) plus sulfadoxine-pyrimethamine (SP) = 3/65 and for SP = 2/64); 91% at day 28 (number lost to follow up at day 28 for AQ plus SP = 3/62 and for SP = 3/62)</p> <p>Length of follow up: 28 d</p>
Participants	<p>Number enrolled: 129 children aged 3 months to 10 years</p> <p>Inclusion criteria: < 10 years; febrile; <i>Plasmodium falciparum</i> > 2000 asexual/μL (thick film); erythrocyte sedimentation rate (ESR) > 15%</p> <p>Exclusion criteria: signs of severe/complicated malaria; severe malnutrition; concomitant infectious disease; sulphonamides allergy</p> <p>Participants who used other antimalarials during follow up were excluded from analysis</p>
Interventions	<p>1. AQ plus SP AQ: 30 mg/kg over 3 d SP: S 25 mg/kg; P 1.25 mg/kg; single dose on day 0</p> <p>2. SP alone (dose as above)</p> <p>Treatment supervised; paracetamol if temperature > 38.5 °C; amoxicillin if bacterial infection during follow up</p>
Outcomes	<p>Outcomes used in this review:</p> <ol style="list-style-type: none"> 1. Treatment failure by day 28 2. Clinical failure by day 28 3. Total failure by day 14

Basco 2002 (Continued)

4. Clinical failure by day 14
5. Early treatment failure
6. Adverse events

See [Appendix 3](#) for details on method used to derive total failure values from reported data and [Appendix 4](#) for details on method used to derive clinical failure values from reported data

Other reported outcome measures not used in review: (a) Clinical (using [WHO 1996](#) definition): early treatment failure, late treatment failure, adequate clinical response with positive/negative smear, fever clearance time (h), reported side effects; (b) Parasitological: negative smear at days 2, 3, 7, 14, and 28

Notes	<p>Location: Cameroon</p> <p>Date: January to March 2001</p> <p>Malaria endemicity: holoendemic (participants included migrants from low transmission areas as well as locals)</p> <p>Drug resistance: possible AQ and SP resistance</p> <p>Method of determining parasite density: parasitaemia estimated/1000 white blood cells</p> <p>Drugs source: not reported</p> <p>Other notes: trial also included an AQ treatment group</p>
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Bojang 1998

Methods	<p>Generation of allocation sequence: computer generated</p> <p>Allocation concealment: sequentially numbered envelopes</p> <p>Blinding: participants and investigators</p> <p>Inclusion of all randomized participants in the analysis: 65% of those recruited, and 72% of those treated were evaluated at day 28 (number excluded = 44/44; number lost to follow up at day 28 for chloroquine (CQ) plus sulfadoxine-pyrimethamine (SP) = 61/202 and for SP = 53/203)</p> <p>Length of follow up: 28 d</p>
Participants	<p>Number available for analysis: 405 children with a mean age of 4 years</p> <p>Inclusion criteria: 1 to 10 years; febrile; <i>Plasmodium falciparum</i> > 5000 asexual/μL (thick film)</p> <p>Exclusion criteria: severe malaria; coexisting illness</p>
Interventions	<ol style="list-style-type: none"> 1. CQ plus SP CQ: 30 mg/kg over 3 d SP: S 25 mg/kg; P 1.25 mg/kg; single dose on day 1 2. Placebo over 3 d + SP single dose (dose as above) on day 1 <p>Treatment supervised; paracetamol if axial temperature > 38.5 °C</p>
Outcomes	<p>Outcome used in this review:</p> <ol style="list-style-type: none"> 1. Total failure by day 28 <p>See Appendix 3 for details on method used to derive total failure values from reported data</p> <p>Other reported outcome measures not used in review: (a) Clinical: return to clinic with symptoms within 1 week (clinical outcome); (b) Parasitological: parasitaemia at day 7 and day 28</p>

Bojang 1998 (Continued)

Notes	Location: The Gambia
	Date: July to December 1995
	Malaria endemicity: not reported
	Drug resistance: CQ resistance
	Method of determining parasite density: parasitaemia estimated as 1 parasite/high power field = 500/ μ L in 100 high power fields
	Drugs source: Fansidar, Roche

Darlow 1982

Methods	Generation of allocation sequence: method not specified
	Allocation concealment: not reported
	Blinding: not reported
	Inclusion of all randomized participants in the analysis: 87% of those admitted were evaluated at day 28 (no exclusions reported; number lost to follow up at day 28 was 7/85 (8%); 7 participants switched from chloroquine (CQ) plus sulfadoxine-pyrimethamine (SP) to SP after vomiting treatment)
	Length of follow up: 28 d
Participants	Number enrolled: 85 children aged 2 months to 12 years
	Inclusion criteria: paediatric; febrile; <i>Plasmodium falciparum</i> < 50 to 850,000/ μ L (thick film)
	Exclusion criteria: cerebral symptoms; severe malaria or second diagnosis; antimalarials in previous week (no urine test)
Interventions	1. CQ plus SP CQ: 10 mg/kg single dose SP: S 25 to 42 mg/kg; P 1 to 2.1 mg/kg; single dose
	2. SP (dose as above)
	Treatment supervised Aspirin or paracetamol if necessary
Outcomes	Outcomes used in this review: 1. Adverse events
	Unable to derive total or clinical failure from available data
	Other reported outcome measures not used in review: (a) Clinical: fever clearance time (h), adverse events; (b) Parasitological: parasitaemia at days 0 to 7, 14, 21, and 28, sens, RI, RII, RIII
Notes	Location: Papua New Guinea
	Date: June to Oct 1980
	Malaria endemicity: "highly malarious" with stable transmission
	Drug resistance: not reported
	Method of determining parasite density: parasitaemia estimated/200 white blood cells or as percentage infected red blood cells

Darlow 1982 (Continued)

Drugs source: Fansidar, Roche

Dinis 1990

Methods	<p>Generation of allocation sequence: method not specified</p> <p>Allocation concealment: sealed envelopes</p> <p>Blinding: microscopists</p> <p>Inclusion of all randomized participants in the final analysis: only numbers evaluated (at day 28) were reported (no exclusions or loss to follow up reported)</p> <p>Length of follow up: 28 d</p>
Participants	<p>Number available for analysis: 59 adults + children with mean age of 28 years</p> <p>Inclusion criteria: > 10 years; febrile; <i>Plasmodium falciparum</i> > 400 asexual/μL (thick film)</p> <p>Exclusion criteria: complicated malaria; pregnancy; allergy to treatment drugs; antimalarials in previous 8 days (no urine test)</p>
Interventions	<p>1. Amodiaquine (AQ) plus sulfadoxine-pyrimethamine (SP) AQ: 25 mg/kg over 3 d SP: S 25mg/kg; P 1.25 mg/kg; single dose on day 3</p> <p>2. SP (dose as above) + placebo on days 2 and 3</p> <p>Supervision not specified</p>
Outcomes	<p>Outcomes used in this review:</p> <ol style="list-style-type: none"> 1. Total failure by day 28 2. Adverse events <p>See Appendix 3 for details on method used to derive total failure values from reported data</p> <p>Other reported outcome measures not used in review: (a) Clinical: fever clearance by day 7, adverse events; (b) Parasitological: parasitaemia at days 0 to 9, 14, 21, and 28, cure by day 7, sens, RI, RII, RIII</p>
Notes	<p>Location: Mozambique</p> <p>Date: May 1986 to June 1987</p> <p>Malaria endemicity: endemic area with perennial transmission</p> <p>Drug resistance: chloroquine resistance</p> <p>Method of determining parasite density: not reported</p> <p>Drugs source: AQ Pharmachemic, Belgium; Fansidar, Roche</p>

Dorsey 2002

Methods	<p>Generation of allocation sequence: community-based convenience sampling to recruit healthy children; all children in households enrolled and randomized to treatment for future episodes of uncomplicated malaria; block randomization; computer-generated list, stratified by age</p> <p>Allocation concealment: treatment allocation investigator not involved in enrolment</p>
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Dorsey 2002 (Continued)

	<p>Blinding: participants</p> <p>Inclusion of all randomized participants in the final analysis: 99% of those treated for first episodes of uncomplicated malaria were evaluated at day 14 (number excluded or lost to follow up at day 14 for amodiaquine (AQ) plus sulfadoxine-pyrimethamine (SP) = 0/59 and for SP = 1/57); 94% at day 28 (number excluded or lost to follow up at day 28 for AQ plus SP = 4/59 and for SP = 3/57); participants randomized while healthy</p> <p>Length of follow up: 14 and 28 d</p>
Participants	<p>Number available for analysis: 116 children aged 6 to 59 months treated for first episodes of uncomplicated malaria</p> <p>Inclusion criteria: <i>Plasmodium falciparum</i> $\geq$ 500/μL; febrile; healthy; no malaria treatment in past 2 weeks or fever in past 48 h; haemoglobin $\geq$ 5 g/dL</p> <p>Exclusion criteria: history of adverse reaction to study drugs; sickle cell disease; complicated malaria</p>
Interventions	<p>1. AQ plus SP AQ: 25 mg/kg over 3 d SP: S 25 mg/kg; P 1.25 mg/kg; single dose on day 0</p> <p>2. Placebo over 3 d + SP (dose as above)</p> <p>Treatment supervised; all participants supplied with paracetamol for 3 d to treat febrile symptoms</p>
Outcomes	<p>Outcomes used in this review:</p> <ol style="list-style-type: none"> 1. Total failure by day 14 2. Clinical failure by day 14 3. Clinical failure by day 28 (data from investigator) 4. Adverse events <p>See Appendix 3 for details on method used to derive total failure values from reported data and Appendix 4 for details on method used to derive clinical failure values from reported data</p> <p>Other outcome measures not used in review: (a) Clinical (using modified WHO 1996 definitions): early treatment failure, late treatment failure (modified to include parasitaemia and history of fever in past 48 h on days 4 to 14), adequate clinical response, adverse events were recorded; Unpublished data also obtained from investigator for day 28 outcomes; (b) Parasitological: sens, RI, RII, RIII</p>
Notes	<p>Location: Uganda (same location as Staedke 2001 and Gasasira 2003)</p> <p>Date: July 2000 to August 2001</p> <p>Malaria endemicity: mesoendemic</p> <p>Drug resistance: very high chloroquine resistance</p> <p>Method of determining parasite density: parasitaemia estimated/200 white blood cells</p> <p>Drugs source: Fansidar, Roche</p> <p>Other notes: trial also included an artesunate plus SP treatment group</p> <p>316 healthy children enrolled; 211 randomized to AQ/SP or SP</p> <p>Treatment outcome for the first episode of uncomplicated <i>P. falciparum</i> was not trial's primary objective; these data supplied by trial author on request</p>

Gasasira 2003

Methods	<p>Generation of allocation sequence: computer-generated list</p> <p>Allocation concealment: not reported</p> <p>Blinding: outcome assessors</p> <p>Inclusion of all randomized participants in the analysis: 83% of those randomized, and 96% of those treated were evaluated at day 14 (number excluded after enrolment, but before randomization, for amodiaquine (AQ) plus sulfadoxine-pyrimethamine (SP) = 29/172, for chloroquine (CQ) plus SP = 12/170, and for SP = 24/171; number lost or excluded during follow up for AQ plus SP = 7/143, for CQ plus SP = 6/158, and for SP = 7/147); post-randomization (pre-treatment) losses to follow up higher in SP group (18%) than CQ plus SP group (10%)</p> <p>Length of follow up: 14 d</p>
Participants	<p>Number randomized: 513; Number enrolled: 448 children and adults aged 6 months to 50 years</p> <p>Inclusion criteria: > 6 months; febrile or fever in past 48 h; <i>Plasmodium falciparum</i> $\geq$ 2000 asexual/μL (thick film)</p> <p>Exclusion criteria: danger signs or symptoms severe malaria; concomitant febrile illness; sulpha drugs allergy</p> <p>Participants who used other antimalarials outside the trial excluded from analysis</p>
Interventions	<p>1. AQ plus SP AQ: 25 mg/kg over 3 d SP: S 25 mg/kg; P 1.25 mg/kg; single dose (day not reported)</p> <p>2. CQ plus SP CQ: 25 mg/kg over 3 d SP: dose as above</p> <p>3. Placebo over 3 days + SP (dose as above)</p> <p>Treatment supervised; all participants given paracetamol for 3 d</p>
Outcomes	<p>Outcomes used in this review:</p> <ol style="list-style-type: none"> Day 14 total failure Day 14 clinical failure Adverse events <p>See Appendix 3 for details on method used to derive total failure values from reported data and Appendix 4 for details on method used to derive clinical failure values from reported data</p> <p>Other outcome measures not used in review:</p> <p>(a) Clinical (using modified WHO 1996 definitions): early treatment failure, late treatment failure (modified to include rising parasitaemia and history of fever in past 48 h on days 4 to 14), adequate clinical response, fever on days 0 to 3 (graph), adverse events with causal relationship determined by clinician – mild, moderate, severe; (b) Parasitological: sens at day 14, RI at day 14, RII at day 14, RIII at day 14, positive/negative smear day 3</p>
Notes	<p>Location: Uganda (same location as Staedke 2001 and Dorsey 2002)</p> <p>Date: March 2001 to January 2002</p> <p>Malaria endemicity: mesoendemic</p> <p>Drug resistance: CQ resistance</p> <p>Method of determining parasite density: parasitaemia estimated/200 white blood cells</p> <p>Drugs source: Fansidar, Roche</p>

Gasasira 2003 (Continued)

Other notes: placebo not identical to study drugs

Huang 1988

Methods	<p>Generation of allocation sequence: centralized</p> <p>Allocation concealment: drugs serially coded by the World Health Organization</p> <p>Blinding: double</p> <p>Inclusion of all randomized participants in the final analysis: 96% of those admitted were evaluated at day 28 (no exclusions reported; number lost to follow up at day 28 for amodiaquine (AQ) plus sulfadoxine-pyrimethamine (SP) = 2/48 and for SP = 1/21)</p> <p>Length of follow up: 28 d</p>
Participants	<p>Number available for analysis: 69 adults and children</p> <p>Inclusion criteria: > 12 years; febrile; <i>Plasmodium falciparum</i> > 500 asexual/μL (thick film)</p> <p>Exclusion criteria: severe symptoms; renal insufficiency; mixed infections; pregnancy; antimalarials in previous 28 d (urine tested for aminoquinolines and sulphonamides)</p>
Interventions	<p>1. AQ plus SP AQ: 1800 mg over 3 d SP: S 1500 mg; P 75 mg; single dose on day 1</p> <p>2. SP (dose as above) plus placebo over 3 d</p> <p>Treatment supervised</p>
Outcomes	<p>Outcomes used in this review:</p> <ol style="list-style-type: none"> 1. Total failure by day 28 2. Adverse events <p>See Appendix 3 for details on method used to derive total failure values from reported data</p> <p>Other outcome measures not used in review: (a) Clinical: fever clearance time (h); (b) Parasitological: parasitaemia days 0 to 7, 14, 21, 28, parasite clearance time (h), cure day 7, adverse events</p>
Notes	<p>Location: China</p> <p>Date: 1985 to 1986</p> <p>Malaria endemicity: endemic area</p> <p>Drug resistance: chloroquine resistance</p> <p>Method of determining parasite density: parasitaemia estimated on thick film</p> <p>Drugs source: Fansidar, Roche</p> <p>Other notes: trial also included an AQ and AQ plus S treatment groups</p>

Ndyomugenyi 2004

Methods	<p>Generation of allocation sequence: random numbers list</p> <p>Allocation concealment: not reported</p>
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Ndyomugenyi 2004 (Continued)

Blinding: not reported

Inclusion of all randomized participants in the final analysis: 65% of those randomized were evaluated at day 14 (number that withdrew consent for chloroquine (CQ) plus sulfadoxine-pyrimethamine (SP) = 11/47 and for SP = 10/41; number lost to follow up for chloroquine (CQ) plus SP = 7/36 and for SP = 3/30)

Length of follow up: 14 d

Participants	<p>Number enrolled: 88 children and adults aged 1 to 46 years</p> <p>Inclusion criteria: > 6 months; febrile or fever in past 24 h; <i>Plasmodium falciparum</i> on thick film</p> <p>Exclusion criteria: signs of complicated malaria; other febrile illness; haemoglobin < 8 g/dL; self-medication</p> <p>Patients who self-medicated during follow up were excluded from the analysis</p>
Interventions	<p>1. CQ plus SP CQ: 25 mg/kg over 3 d SP: S 500 mg; P 25 mg; single dose (day not reported)</p> <p>2. SP (dose as above)</p> <p>First dose observed</p>
Outcomes	<p>Outcomes used in this review:</p> <ol style="list-style-type: none"> Day 14 total failure Day 14 clinical failure Adverse events <p>See Appendix 3 for details on method used to derive total failure values from reported data and Appendix 4 for details on method used to derive clinical failure values from reported data</p> <p>Other outcome measures not used in review: (a) Clinical (using WHO 1996 definitions): early treatment failure, late treatment failure, adequate clinical response, adverse events; (b) Parasitological: sens, RI, RII, RIII</p>
Notes	<p>Location: Uganda</p> <p>Date: October 2001</p> <p>Malaria endemicity: transmission low and unstable</p> <p>Drug resistance: not reported</p> <p>Method of determining parasite density: parasitaemia estimated/200 white blood cells</p> <p>Drugs source: not reported</p> <p>Other notes: trial also included a CQ treatment group</p>

Schapira 1988

Methods	<p>Generation of allocation sequence: method not specified</p> <p>Allocation concealment: sequentially numbered sealed envelopes</p> <p>Blinding: microscopists</p>
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Schapira 1988 (Continued)

Inclusion of all randomized participants in the final analysis: 47% evaluated at day 28 (number excluded after randomization for amodiaquine (AQ) plus sulfadoxine-pyrimethamine (SP) = 22/50 and for SP = 15/50; number lost to follow up at day 28 for AQ plus SP = 6/28 and for SP = 10/35)

Length of follow up: 28 d

Participants	<p>Number enrolled: 100 school children with mean age of 10 years, asymptomatic or mild symptomatic;</p> <p>Inclusion criteria: <i>Plasmodium falciparum</i> > 800 asexual/μL (thick film)</p> <p>Exclusion criteria: severe symptoms; antimalarials in previous 14 d (no urine test)</p> <p>Non-compliance with treatment was a reason for exclusion from the analysis</p>
Interventions	<p>1. AQ plus SP AQ: 25 mg/kg over 3 d SP: S 25 to 30 mg/kg; P 1.25 to 1.5 mg/kg; single dose on day 3</p> <p>2. SP (dose as above)</p> <p>Treatment supervised</p>
Outcomes	<p>Outcomes used in this review:</p> <p>1. Day 28 total failure</p> <p>See Appendix 3 for details on method used to derive total failure values from reported data</p> <p>Other outcome measures not used in review:</p> <p>(a) Parasitological: parasitaemia days 0 to 9, 14, 21, and 28, parasite clearance time (d), cure day 7, recrudescence, sens, RI, RII, RIII</p>
Notes	<p>Location: Mozambique</p> <p>Date: May to September 1986</p> <p>Malaria endemicity: endemic area, perennial transmission</p> <p>Drug resistance: chloroquine (CQ) and AQ resistance</p> <p>Method of determining parasite density: parasitaemia estimated/500 or /2000 white blood cells</p> <p>Drugs source: CQ Avloclor, ICI; AQ Pharmachemic; Fansidar, Roche</p> <p>Other notes: trial also included an AQ treatment group and a CQ treatment group</p>

Schellenberg 2002

Methods	<p>Generation of allocation sequence: computer-generated list</p> <p>Allocation concealment: sequential envelopes</p> <p>Blinding: open label</p> <p>Inclusion of all randomized participants in the analysis: 70% at day 14, 62% at day 28 (number excluded before treatment for amodiaquine (AQ) plus sulfadoxine-pyrimethamine (SP) = 2/121 and for SP = 3/120; number lost to follow up at day 28 for AQ plus SP = 41/119 and for SP = 38/117)</p> <p>Length of follow up: 28 d</p>
Participants	<p>Number enrolled: 241 children aged 2 to 2.4 years</p>

Schellenberg 2002 (Continued)

Inclusion criteria: 6 months to 5 years; febrile or fever in past 24 h; *Plasmodium falciparum* asexual > 2000/μL (thick film)

Exclusion criteria: signs severe/complicated malaria; chronic underlying disease; sensitivity to AQ or SP

Interventions	<p>1. AQ plus SP AQ: 25 mg/kg over 3 d SP: S 25 mg/kg; P 1.25 mg/kg; single dose (day not reported)</p> <p>2. SP (dose as above)</p> <p>Treatment supervised; 250 mg paracetamol 30 min prior to trial drug</p>
Outcomes	<p>Outcomes used in this review:</p> <ol style="list-style-type: none"> Day 28 total failure Day 28 clinical failure Day 14 total failure Day 14 clinical failure Adverse events <p>See Appendix 3 for details on method used to derive total failure values from reported data and Appendix 4 for details on method used to derive clinical failure values from reported data.</p> <p>Other outcome measures not used in review: (a) Clinical (using WHO 1996 definitions): early treatment failure, late treatment failure, adequate treatment response, fever clearance time, safety - number and timing of deaths, admissions, and outpatient attendances, adverse drug effects - symptoms, abnormal haematology or biochemistry during follow up; (b) Parasitological: sens, RI, RII</p>
Notes	<p>Location: Tanzania</p> <p>Date: May to August 1999</p> <p>Malaria endemicity: holoendemic</p> <p>Drug resistance: high chloroquine resistance (65%)</p> <p>Method of determining parasite density: parasitaemia estimated/200 white blood cells</p> <p>Drugs source: Shelys Pharmaceutical, Tanzania</p> <p>Other notes: trial also included an AQ treatment group</p>

Schwöbel 2003

Methods	<p>Generation of allocation sequence: randomly sorted sealed envelopes distributed to 5 study sites</p> <p>Allocation concealment: participants who met the inclusion criteria were assigned an envelope which was then opened</p> <p>Blinding: not reported</p> <p>Inclusion of all randomized participants in the analysis: 88% of those enrolled were evaluated at day 14 (number excluded for chloroquine (CQ) plus sulfadoxine-pyrimethamine (SP) = 2/29 and for SP = 0/30; number lost to follow up for CQ plus SP = 3/27 and for SP = 2/30)</p> <p>Length of follow up: 14 d</p>
Participants	<p>Number enrolled: 59 adults and children with mean age of 16 years</p> <p>Inclusion criteria: 1 year or older; fever or history of fever; <i>Plasmodium falciparum</i> 1000 to 100,000 asexual/μL (thick film)</p>

Schwöbel 2003 (Continued)

	<p>Exclusion criteria: signs of severe malaria or danger signs; other febrile illness; pregnancy</p> <p>Participants treated by a third party during trial were excluded from the analysis</p>
Interventions	<p>1. CQ plus SP CQ: 25 mg/kg over 3 d SP: S not reported; P 1.25 mg/kg; single dose (day not reported)</p> <p>2. SP (dose as above)</p> <p>Supervision not reported; all febrile participants given paracetamol</p>
Outcomes	<p>Appendix 4 for details on method used to derive clinical failure values from reported data.</p> <p>Other outcome measures not used in review: (a) Clinical (using RBM 2001 draft of 2003 definitions): early treatment failure, late treatment failure, adequate clinical and parasitological response; (b) Parasitological: late parasitological failure</p> <p>Notes</p>
Notes	<p>Location: Laos</p> <p>Date: August to October 2001</p> <p>Malaria endemicity: perennial transmission</p> <p>Drug resistance: not reported</p> <p>Method of determining parasite density: parasitaemia estimated/200 white blood cells</p> <p>Drugs source: SP from Pharmamed</p> <p>Other notes: trial also included a CQ and a mefloquine treatment group</p>

Staedke 2001

Methods	<p>Generation of allocation sequence: computer-generated sequence</p> <p>Allocation concealment: not reported</p> <p>Blinding: microscopists</p> <p>Inclusion of all randomized participants in the analysis: 60% of those randomized overall, but 90% of those then enrolled in relevant treatment groups evaluated at day 14 - randomization preceded enrolment (number excluded for amodiaquine (AQ) plus sulfadoxine-pyrimethamine (SP) = 7/149 and for SP = 8/149; number lost to follow up for AQ plus SP = 4/142 and for SP = 10/141)</p> <p>Length of follow up: 14 d</p>
Participants	<p>Number enrolled: 298 adults and children, median age 4 years (range 6 months to 50 years)</p> <p>Inclusion criteria: symptomatic; <i>Plasmodium falciparum</i> 2000 to > 1,000,000 asexual/μL (thick film)</p> <p>Exclusion criteria: severe symptoms; < 5 kg; other febrile illness; sulfa drugs allergy; other antimalarials during follow up</p> <p>Participants who used additional antimalarials during follow up were excluded from the analysis</p>
Interventions	<p>1. AQ plus SP AQ: 25 mg/kg over 3 d SP: S 25 mg/kg; P 1.25 mg/kg; single dose (day not reported)</p>

Staedke 2001 (Continued)

2. SP plus placebo

Treatment supervised

Outcomes	<p>Outcomes used in this review:</p> <ol style="list-style-type: none"> 1. Day 14 total failure 2. Day 14 clinical failure 3. Adverse events <p>See Appendix 3 for details on method used to derive total failure values from reported data and Appendix 4 for details on method used to derive clinical failure values from reported data.</p> <p>Other outcome measures not used in review: (a) Clinical (using WHO 1996 definitions): early treatment failure, late treatment failure (modified to include rising parasitaemia and history of fever in past 48 h on days 4 to 14), adequate clinical response, fever days 0 to 3 (graph), patients monitored for potential adverse drug events; (b) Parasitological: sens, RI, RII, RIII, parasitaemia days 0, 3, 7, and 14</p>
Notes	<p>Location: Uganda (same location as Dorsey 2002 and Gasasira 2003)</p> <p>Date: September 1999 to July 2000</p> <p>Malaria endemicity: mesoendemic, seasonal transmission</p> <p>Drug resistance: high chloroquine resistance, SP resistance increasing</p> <p>Method of determining parasite density: parasitaemia estimated/200 white blood cells</p> <p>Drugs source: Fansidar Roche, AQ Camoquine Parke-Davis</p> <p>Other notes: trial also included an AQ treatment group</p>

RI: parasite clearance within 7 d followed by recrudescence ([WHO 1973](#)); RII: temporary marked reduction in parasitaemia ([WHO 1973](#)); RIII: no marked reduction in parasitaemia ([WHO 1973](#)); Sens: parasite clearance within 7 d of starting treatment and sustained to end of follow up ([WHO 1973](#)).

Notes: high power field (microscope x 100 objective); holoendemic: constant high transmission; hyperendemic: intense but seasonal transmission; mesoendemic: varying intensity of transmission depending on local circumstances.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Bakyaita 2005	Randomized controlled trial comparing CQ plus SP with AQ plus SP; no SP-only group
Blair 2003	Trial evaluated 4 monotherapies (CQ, AQ, mefloquine, and SP) and 4 combination therapies (AQ plus SP, CQ plus SP, mefloquine plus SP, and artesunate-SP); outcome data only for day 21 (not day 28 or 14); ballot with names of treatment decided the order of evaluation of treatment as CQ plus SP, AQ plus SP, and MQ plus SP suggests sequential rather than random allocation of treatments; published paper only reports evaluation of CQ, SP, and CQ plus SP
Checchi 2004	Non-random allocation: SP, AQ, and CQ plus SP tested sequentially
Hugosson 2003	allocation: participants given serial numbers before screening, enrolled participants consecutively assigned to treatment groups in the order CQ, SP, CQ plus SP, and SP plus paracetamol; participants overlap with excluded study Tarimo 2002
	Menard 20

Study	Reason for exclusion
Menard 2005	Non-random allocation: participants assigned alternately; also no direct comparison between CQ or AQ plus SP and SP alone; 2 separate studies conducted: CQ versus AQ versus SP between February and April 2002, and CQ plus SP versus AQ plus SP between December 2003 and March 2004
Ogwang 2003	Non-random allocation: first child allocated to CQ group, second child allocated to SP group, and third child allocated to CQ plus SP group; sequence then repeated
Pitmang 2005	Non-random allocation: participants assigned alternately to SP or chloroquine plus SP
Salah 2005	Non-random allocation: participants assigned alternately to SP or chloroquine plus SP
Sowunmi 2002	The 2003 paper reported several randomized comparisons conducted between 1996 and 2001, but these were not all part of a single trial. It duplicates the data in the 2002 paper, which is a report of the trial that included AQ plus SP and CQ plus SP. There was no SP-only comparator group in that trial
Talisuna 2004	Non-random allocation: treatments given in the order CQ plus SP, AQ plus SP, SP to the first 250 participants, then 2 participants given CQ plus SP, 1 AQ plus SP or SP
Tarimo 2002	Non-random allocation: first treatment allocated by spin of a coin, then participants allocated sequentially to treatment in the order CQ, SP, CQ plus SP, and SP plus paracetamol
Tjitra 1999	Non-random allocation: allocation to treatment determined by day of the week on which patients attended the health centre

AQ: amodiaquine; CQ: chloroquine; SP: sulfadoxine-pyrimethamine

DATA AND ANALYSES

Comparison 1. Chloroquine (CQ) or amodiaquine (AQ) combined with sulfadoxine-pyrimethamine (SP) versus SP alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total failure by day 28	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 AQ plus SP	5	461	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.46, 0.91]
2 Clinical failure by day 28	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 AQ plus SP	3	384	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.11, 0.49]
3 Total failure by day 14	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 AQ plus SP	5	971	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.25, 0.47]
3.2 CQ plus SP	3	400	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.40, 0.88]
4 Clinical failure by day 14	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 AQ plus SP	5	961	Risk Ratio (M-H, Fixed, 95% CI)	0.16 [0.08, 0.33]
4.2 CQ plus SP	3	400	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.26, 0.99]
5 Early treatment failure	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 AQ plus SP	5	1003	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.09, 0.57]
5.2 CQ plus SP	3	400	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.15, 1.55]

Analysis 1.1. Comparison 1 Chloroquine (CQ) or amodiaquine (AQ) combined with sulfadoxine-pyrimethamine (SP) versus SP alone, Outcome 1 Total failure by day 28.

Analysis 1.2. Comparison 1 Chloroquine (CQ) or amodiaquine (AQ) combined with sulfadoxine-pyrimethamine (SP) versus SP alone, Outcome 2 Clinical failure by day 28.

Analysis 1.3. Comparison 1 Chloroquine (CQ) or amodiaquine (AQ) combined with sulfadoxine-pyrimethamine (SP) versus SP alone, Outcome 3 Total failure by day 14.

Analysis 1.4. Comparison 1 Chloroquine (CQ) or amodiaquine (AQ) combined with sulfadoxine-pyrimethamine (SP) versus SP alone, Outcome 4 Clinical failure by day 14.

Analysis 1.5. Comparison 1 Chloroquine (CQ) or amodiaquine (AQ) combined with sulfadoxine-pyrimethamine (SP) versus SP alone, Outcome 5 Early treatment failure.

APPENDICES

Appendix 1. Search methods: detailed search strategies

Search set	CIDG SR ^a	CENTRAL	MEDLINE ^b	EMBASE ^b	LILACS ^b	SCI
1	chloro-quine	malaria	malaria	malaria	malaria	malaria
2	amodi-aquine	chloroquine	chloroquine	chloroquine	chloroquine	chloroquine
3	sulfadox-ine	amodiaquine	amodiaquine	amodiaquine	amodiaquine	amodiaquine
4	sulpha-doxine	sulfadoxine	sulfadoxine	sulfadoxine	sulfadoxine	sulfadoxine
5	fansidar	sulphadoxine	sulphadoxine	pyrimethamine	sulphadoxine	sulphadoxine
6	—	pyrimethamine	pyrimethamine	4 and 5	pyrimethamine	pyrimethamine
7	—	4 or 5	4 or 5	fansidar	4 or 5	4 or 5

(Continued)

8	—	6 and 7	6 and 7	6 or 7	6 and 7	6 and 7
9	—	fansidar	fansidar	2 or 3	fansidar	fansidar
10	—	8 or 9	8 or 9	8 and 9	8 or 9	8 and 9
11	—	2 or 3	2 or 3	1 and 10	2 or 3	2 or 3
12	—	10 and 11	10 and 11	—	10 and 11	10 and 11
13	—	1 and 12	1 and 12	—	1 and 12	1 and 12

^aCochrane Infectious Diseases Group Specialized Register.

^bSearch terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration ([Higgins 2005](#)); upper case: MeSH or Emtree heading; lower case: free text term.

Appendix 2. Assessment of the risk of bias in the trials^a

Trial	Generation of allocation sequence	Allocation concealment	Blinding	Inclusion of randomized participants in final analysis ^b
Basco 2002	Unclear	Unclear	Not reported	Adequate
Bojang 1998	Adequate	Unclear	Double (participants and investigators)	Inadequate
Darlow 1982	Unclear	Unclear	Not reported	Appears adequate
Dinis 1990	Unclear	Unclear	Single (microscopist)	Unclear
Dorsey 2002	Adequate	Adequate	Single (participants)	Adequate
Gasasira 2003	Adequate	Unclear	Single (outcome assessors)	Inadequate (differential loss to follow up)
Huang 1988	Unclear	Adequate	Double	Adequate
Ndyomugenyi 2004	Adequate	Unclear	Not reported	Inadequate
Schapira 1988	Unclear	Unclear	Single (microscopist)	Inadequate
Schellenberg 2002	Unclear	Unclear	None	Inadequate
Schwöbel 2003	Unclear	Unclear	Not reported	Adequate
Staedke 2001	Adequate	Unclear	Single (microscopist)	Adequate

^aSee '[Assessment of risk of bias in included studies](#)' for the assessment methods and the '[Characteristics of included studies](#)' for the methods used in each trial.

^bFor primary outcomes.

Appendix 3. Total failure: method used to derive total failure values from reported data

Trial	Comparison	No. randomized/enrolled	Day	Total failure	Data to derive total failure
Basco 2002	AQ plus SP	65 randomized	28	0/59	59/59 had ACR with negative smear
	SP	64 randomized		9/59	50/59 had ACR with negative smear
	AQ plus SP	65 randomized	14	0/62	62/62 had ACR with negative smear
	SP	64 randomized		0/62	62/62 had ACR with negative smear
Bojang 1998	CQ plus SP	202 randomized and enrolled	28	7/141	5% of participants followed up at day 28 were parasitaemic
	SP	203 randomized and enrolled		15/150	10% of participants followed up at day 28 were parasitaemic
Dinis 1990	AQ plus SP	At least 50% of participants were not included in the analysis because of dropout before day 21	28	3/30	27/30 had parasitological success
	SP	At least 50% of participants were not included in the analysis because of dropout before day 21		4/29	25/29 had parasitological success
Dorsey 2002	AQ plus SP	59 treated	14	2/59	Data from investigator
	SP	57 treated		16/56	Data from investigator
Gasasira 2003	AQ plus SP	172 randomized; 143 enrolled/treated	14	1/136	135/136 had parasitological success
	CQ plus SP	170 randomized; 158 enrolled/treated		26/152	126/152 had parasitological success
	SP	171 randomized; 147 enrolled/treated		41/140	99/140 had parasitological success
Huang 1988	AQ plus SP	48 randomized	28	0/46	46/46 had parasitological success
	SP	21 randomized		1/20	19/20 had parasitological success
Ndyomugyenye 2004	CQ plus SP	47 randomized	14	2/29	27/29 had parasitological success
	SP	41 randomized		5/27	22/27 had parasitological success
Schapira 1988	AQ plus SP	50 randomized; 28 treated	28	0/22	22/22 had parasitological success

(Continued)

	SP	50 randomized; 35 treated		4/25	21/25 had parasitological success
Schellenberg 2002	AQ plus SP	121 randomized; 119 treated	28	32/84	Trial author reports that none of the participants with ETF fulfilled criteria for R1-3 resistance and were excluded from the analysis of parasitological efficacy; we therefore added the 3 ETFs to the numerator and denominator for parasitological failures to obtain total failure 52/81 had parasitological success = 29/81 failure + 3 ETF
	SP	120 randomized; 117 treated		38/87	49/82 had parasitological success = 33/82 failure + 5 ETF
	AQ plus SP	121 randomized; 119 treated	14	24/92	68/89 had parasitological success = 21/89 failure + 3 ETF
	SP	120 randomized; 117 treated		33/95	62/90 had parasitological success = 28/90 failure + 5 ETF
Schwöbel 2003	CQ plus SP	29 randomized	14	4/24	20/24 had ACPR
	SP	30 randomized		5/28	23/28 had ACPR
Staedke 2001	AQ plus SP	220 randomized; 149 enrolled/treated	14	15/138	LPF was not available from the paper, but we were able to derive it from available data as: LPF = ACR-S So TF = (ACR-S) + ETF + LTF = (134-123) + 1 + 3 = 15
	SP	232 randomized; 149 enrolled/treated		34/131	ACR-S + ETF + LTF = 118-97 (21) + 4 + 9 = 34

ACPR: adequate clinical and parasitological response; ACR: adequate clinical response; ACR-S: adequate clinical response minus parasitological success; AQ: amodiaquine; CQ: chloroquine; ETF: early treatment failure; LPF: late parasitological failure; LTF: late treatment failure; SP: sulfadoxine-pyrimethamine.

Appendix 4. Clinical failure: method used to derive clinical failure values from reported data

Trial	Comparison	No. randomized/enrolled	Day	Clinical failure	Data to derive clinical failure
Basco 2002	AQ plus SP	65 randomized	28	0/59	No participants with ETF or ACR with positive smear
	SP	64 randomized		8/59	No participants with ETF, 9 participants with ACR with positive smear, including 1 with LPF

(Continued)

	AQ plus SP	65 randomized	14	0/62	No participants with ETF or ACR with positive smear
	SP	64 randomized		0/62	No participants with ETF or ACR with positive smear
Dorsey 2002	AQ plus SP	59 treated	28	4/55	Data from investigator
	SP	57 treated		19/54	Data from investigator
	AQ plus SP	59 treated	14	1/59	Data from investigator
	SP	57 treated		13/56	Data from investigator
Gasasira 2003	AQ plus SP	172 randomized; 143 enrolled/treated	14	0/136	All 136 participants had ACR
	CQ plus SP	170 randomized; 158 enrolled/treated		11/152	141/152 participants had ACR
	SP	171 randomized; 147 enrolled/treated		21/140	119/140 participants had ACR
Ndyomugenyi 2004	CQ plus SP	47 randomized	14	0/29	All 29 participants had ACR
	SP	41 randomized		0/27	All 27 participants had ACR
Schellenberg 2002	AQ plus SP, SP	121 randomized; 119 treated	28, 14	—	Reported cumulative clinical failure rate
	SP	120 randomized; 117 treated		—	Reported cumulative clinical failure rate
Schwöbel 2003	CQ plus SP	29 randomized	14	1/24	Trial author reports that all LTFs were LPFs, therefore clinical failure = ETF
	SP	30 randomized		1/28	Trial author reports that all LTFs were LPFs, therefore clinical failure = ETF
Staedke 2001	AQ plus SP	220 randomized; 149 enrolled/treated	14	4/138	Clinical failure = ETF + LTF
	SP	232 randomized; 149 enrolled/treated		13/131	Clinical failure = ETF + LTF

ACR: adequate clinical response; AQ: amodiaquine; CQ: chloroquine; ETF: early treatment failure; LCF: late clinical failure; LPF: late parasitological failure; LTF: late treatment failure; S: parasitological success; SP: sulfadoxine-pyrimethamine.

Appendix 5. Adverse events^a

Trial	Comparison	Exclusion criteria	Baseline	Data collection	Attrition	Findings
Basco 2002	AQ plus SP versus SP	Signs of severe/complicated malaria, severe malnutrition, concomitant infectious disease, sulphonamides allergy	Baseline data for those followed up to day 14 (range): age; sex; fever duration; self-medication; temperature; P. falciparum density; packed cell volume; P > 0.05; and look similar	Not reported	Side effects data for those followed up to day 14	None of the events reported were identified as fatal, life threatening, required hospitalization, or resulted in treatment discontinuation
Bojang 1998	CQ plus SP versus SP	Severe malaria, coexisting illness.	Baseline data for those treated (range, sd): age; sex; temperature; respiratory rate; P. falciparum density; packed cell volume; look similar	Not reported	Number assessed for adverse events not explicit	Not reported
Darlow 1982	CQ plus SP versus SP	Cerebral symptoms, severe malaria or second diagnosis, antimalarials in previous week	No baseline data shown. Reported no difference in age or initial parasite count between groups	Side effects were noted together with clinical course while patients were hospitalized at start of trial	Number assessed for adverse events not explicit	2 participants in the SP group were found to have glucose-6-phosphate dehydrogenase deficiency but neither developed haemolysis 7 patients who vomited following CQ plus SP were given only SP the second time (no explanation given)
Dinis 1990	AQ plus SP versus SP	Complicated malaria, pregnancy, allergy to study drugs, antimalarials in previous 8 days	Baseline data probably for those evaluated (sem): age; P. falciparum density; sulfadoxine mg/kg; histograms of % with symptoms on day 0; look similar	Not reported	Adverse effects data probably for those evaluated	There were no major adverse events (A. Schapira, personal communication)
Dorsey 2002	AQ plus SP versus SP	Complicated malaria, sickle cell disease, history of adverse reaction to study drugs.	Baseline data averaged over every episode treated during the 1-year study and with full follow up (range, CI, sd): temperature; P. falciparum density; haemoglobin; look similar. No data for only first episode uncomplicated P. falciparum	Not reported	No data for only first episode uncomplicated P. falciparum as included in this review	Reported that there were no severe adverse reactions

(Continued)

Gasasira 2003	AQ plus SP ver- sus SP; CQ plus SP versus SP	Danger signs or symptoms of severe malar- ia, concomitant febrile illness, sulpha drugs al- lergy.	Baseline data for those with complete follow up (CI): age; sex; temperature; haemoglobin; P. fal- ciparum density; an- timalarials in pre- vious 2 weeks; CQ urine test; look simi- lar	History taking on follow up days and any day pa- tients felt unwell, including assess- ment of adverse events; if an ad- verse event was suspected a sep- arate adverse event form was completed Clin- icians assessed causal relation- ship; if 'unlikely', excluded from analysis Adverse events graded mild, moder- ate, severe us- ing WHO Toxici- ty Grading Scale & National In- stitute Allergy Infectious Dis- eases, Division Microbial Infec- tious Diseases paediatric toxic- ity tables	Adverse events data for those with complete fol- low up. < 1% were exclud- ed for post-en- rolment with- drawal of con- sent	1 severe event in SP group: d14 elevated serum alanine amino- transferase (ALT) 500 IU/L (normal 0 to 32) and other liver en- zymes, in 3-year old child; asymptomatic, resolved within 2 weeks without treat- ment
Huang 1988	AQ plus SP versus SP	Severe symp- toms, renal in- sufficiency, preg- nancy, anti- malarials in pre- vious 28 days	No baseline data shown	Not reported	Adverse reac- tions data for those treated	Incomplete report- ing of adverse event severity by treatment received Report says most ad- verse reactions were mild and didn't re- quire special treat- ment Sinus bradycardia AQ plus SP 8/48, SP 0/21
Ndyomu- gyenyi 2004	CQ plus SP versus SP	Signs of compli- cated malaria, other febrile ill- ness, haemoglo- bin < 8 g/dL	Baseline data for those who did and did not complete fol- low up (range, sd): age; symptoms dura- tion; haemoglobin; P. falciparum den- sity; antimalarials and CQ in previous 2 weeks; look similar except CQ in previ- ous 2 weeks twice as common in CQ plus SP group as SP group (P = 0.007)	Symptoms that could be as- sumed to be treatment side effects were asked for on fol- low up days	Number as- sessed for ad- verse events not explicit. 21/88 were excluded for post-treat- ment with- drawal of con- sent	Reported that there were no major adverse events in either group

(Continued)

Schapira 1988	AQ plus SP versus SP	Severe symptoms, antimalarials in previous 14 d	Baseline data for those evaluated (sd): age; <i>P. falciparum</i> density; treatment dose/weight; look similar	Not reported	Not applicable	Not reported
Schellenberg 2002	AQ plus SP versus SP	Signs of severe/complicated malaria, chronic underlying disease, sensitivity to study drugs	Baseline data for those treated (range, CI): age; sex; temperature; weight; packed cell volume; <i>P. falciparum</i> density; symptoms; look similar	Standard form to facilitate detection of adverse events at all contact points; symptom report form based on NIH common toxicity criteria completed on follow up days	Safety data for those who were evaluable; 13/361 were withdrawn after randomization for unspecified reasons	Reported that there were no drug-related severe adverse reactions 1 death in SP group was clinically assessed as progression of malaria. Breathing problems: AQ plus SP 10/104, SP17/99
Schwöbel 2003	CQ plus SP versus SP	Signs of severe malaria/danger signs, other febrile illness, pregnancy	Baseline data for those evaluated (% only): age; sex; <i>P. falciparum</i> density; antimalarials and any drug use in previous week; look similar	Not reported	Not applicable; 5/119 were excluded for post-enrolment withdrawal of consent	Not reported
Staedke 2001	AQ plus SP versus SP	Severe symptoms, < 5 kg, other febrile illness, sulfa drugs allergy	Baseline data for those evaluated (% only): age; sex; temperature; symptoms duration; packed cell volume; <i>P. falciparum</i> density; antimalarials/CQ in past 2 weeks; SP in past 4 weeks; CQ urine test; palpable spleen; recent antimalarials looks a bit higher in AQ plus SP group; otherwise look similar	Patients monitored for potential adverse drug events (no further details)	Number assessed for adverse events not explicit; 1/298 were excluded for post-enrolment non-compliance	Reported that no severe adverse events were recorded during the study

AQ: amodiaquine; CI: confidence interval; CQ: chloroquine; *P. falciparum*: *Plasmodium falciparum*; sd: standard deviation; sem: standard error of the mean; SP: sulfadoxine-pyrimethamine.

^aThe terms adverse reactions, side effects, and safety appear in the table as used by the trial authors. These terms were not always used consistently within the same report and are unlikely to fit any one system of defining harms

WHAT'S NEW

Date	Event	Description
14 August 2008	Amended	Converted to new review format with minor editing. Reference to another review on this topic (Myint 2005), which was in press

Date	Event	Description
		when last version of this review published, has been removed as we were unable to trace this publication.
14 August 2008	Review declared as stable	As monotherapy is no longer recommended by the World Health Organization for malaria treatment (WHO 2006), the authors do not intend to update this review.

HISTORY

Protocol first published: Issue 2, 1997

Review first published: Issue 4, 1997

Date	Event	Description
31 August 2005	New citation required and conclusions have changed	<p>The original version summarized the evidence from five trials conducted between 1980 and 1995 that compared chloroquine (CQ) or amodiaquine (AQ) in combination with sulfadoxine-pyrimethamine (SP) to CQ, AQ, or SP alone (McIntosh 1997). The author added two more trials (McIntosh 2001) in a subsequent review update. Several more trials have since been published giving the author reason to update the review again. However, it was necessary this time to change some aspects of the review to ensure its relevance to current malaria control efforts in the light of increasing drug resistance.</p> <p>CQ or AQ alone are no longer comparators in the review; the focus of the review question now is whether CQ or AQ plus SP combination therapy is better than SP alone.</p> <p>The World Health Organization standardized protocol for monitoring drug efficacy has been modified over time (WHO 1965; WHO 1967; WHO 1973; WHO 1996; WHO 2002; RBM 2003) and this is reflected in the outcome measures reported in clinical trials. To summarize the findings from trials conducted at different times we chose the primary outcome measures of total failure and clinical failure (RBM 2003), which could be estimated from trials that used different classification systems for treatment response. Follow up to day 28 is preferred because of the longer elimination half life of SP and the risk of underestimating treatment failure at shorter assessment times (Stepniewska 2004). Time to fever clearance and time to parasite clearance are no longer included as outcome measures. Reliable synthesis of these data is problematic without individual patient data with which to perform intention-to-treat time to event analysis.</p> <p>Quasi-randomized controlled trials are no longer eligible for inclusion in line with current Cochrane Infectious Diseases Group guidance.</p>
27 August 2001	New search has been performed	Two new trials added and title changed from 'Treating uncomplicated malaria with chloroquine or amodiaquine combined with sulfadoxine-pyrimethamine'.

CONTRIBUTIONS OF AUTHORS

Heather McIntosh is the guarantor for this review. Katharine Jones became a co-author on the 2005 update, contributing independent decisions on study selection and data extraction.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK.

External sources

- Department for International Development, UK.

NOTES

Original version ([McIntosh 1997](#)): Heather McIntosh (HM) developed the protocol with support from Paul Garner (PG, Co-ordinating Editor) and advisors with topic expertise. HM conducted the original review as lead author with support from PG.

INDEX TERMS

Medical Subject Headings (MeSH)

Amodiaquine [*therapeutic use]; Chloroquine [*therapeutic use]; Drug Combinations; Drug Therapy, Combination; Malaria [*drug therapy]; Malaria, Falciparum [drug therapy]; Pyrimethamine [*therapeutic use]; Sulfadoxine [*therapeutic use]

MeSH check words

Adult; Humans