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Sulfadoxine-pyrimethamine plus artesunate versus sulfadoxine-pyrimethamine plus amodiaquine for treating uncomplicated malaria (Review)

Bukirwa H, Critchley JA

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[Intervention Review]

Sulfadoxine-pyrimethamine plus artesunate versus sulfadoxine-pyrimethamine plus amodiaquine for treating uncomplicated malaria

Hasifa Bukirwa[1], Julia A Critchley[2]

[1]Makerere University Medical School, Kampala, Uganda. [2]Institute of Health and Society, Newcastle University, Newcastle, UK

Contact address: Hasifa Bukirwa, Makerere University Medical School, Mulago Hospital Complex, PO Box 24943, Kampala, Uganda. hbukirwa@muucsf.org, h_bukirwa@yahoo.ca.

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ABSTRACT

Background

Artemisinin-based combination treatments are strongly advocated, but supplies are limited. Sulfadoxine combined with amodiaquine is an alternative non-artemisinin combination.

Objectives

To compare sulfadoxine-pyrimethamine plus amodiaquine (SP plus AQ) with sulfadoxine-pyrimethamine plus artesunate (SP plus AS) for treating uncomplicated *Plasmodium falciparum* malaria.

Search methods

We searched the Cochrane Infectious Diseases Group Specialized Register (October 2005), CENTRAL (*The Cochrane Library* 2005, Issue 4), MEDLINE (1966 to October 2005), EMBASE (1988 to October 2005), LILACS (October 2005), and reference lists. We also contacted researchers and organizations working in this field.

Selection criteria

Randomized controlled trials comparing SP plus AS with SP plus AQ for treating uncomplicated *P. falciparum* malaria.

Data collection and analysis

Two authors independently applied the inclusion criteria, extracted data, and assessed methodological quality. The primary outcome measure was treatment failure (parasitological or clinical evidence of treatment failure between start of treatment and day 28). We calculated the risk ratio (RR) with 95% confidence intervals (CI) for dichotomous data.

Main results

Four trials (775 participants) met the inclusion criteria. All were from areas of high and seasonal malaria transmission in Africa. Fewer participants using SP plus AQ failed treatment by day 28 (RR 0.59, 95% CI 0.42 to 0.83; 652 participants, 3 trials). Even excluding new infections, SP plus AQ performed better (RR 0.62, 95% CI 0.40 to 0.96; 649 participants, 3 trials). There was no statistically significant difference between the two treatments for treatment failure at day 14 (RR 1.14, 95% CI 0.47 to 2.78; 775 participants, 4 trials). SP plus AS was more effective at reducing gametocyte carriage at day seven (RR 2.31, 95% CI 1.36 to 3.92; 220 participants, 1 trial). One trial reported that one person − in the SP plus AQ group − developed severe malaria. Adverse events were poorly reported, but did not seem to differ in type and number between the two treatment combinations.

Authors' conclusions

SP plus AQ performed better at controlling treatment failure at day 28, but was not as good as SP plus AS at reducing gametocyte carriage at day seven. Careful consideration of local resistance patterns is required because resistance to sulfadoxine-pyrimethamine and amodiaquine are high in many areas. In order to delay development of resistance to artesunate, the combination with sulfadoxine-pyrimethamine should only be considered where both drugs are known to be effective. Data on adverse events are still lacking.

8 May 2019

No update planned

Intervention not in general use or been superseded

Historical question. The WHO does not recommend non-artemisinin combinations. No update intended.

PLAIN LANGUAGE SUMMARY

Sulfadoxine-pyrimethamine plus artesunate versus sulfadoxine-pyrimethamine plus amodiaquine for treating uncomplicated malaria

Sulfadoxine-pyrimethamine plus amodiaquine (SP plus AQ) performed better than sulfadoxine-pyrimethamine plus artesunate (SP plus AS) when treating uncomplicated malaria

Malaria is a parasitic disease spread by mosquitoes that kills thousands of people worldwide. Artemisinin-based combination treatments are strongly advocated, but uncertainty about their availability (and cost) remains a major concern. The review includes four small randomized controlled trials, all from Africa, comparing SP plus AS with SP plus AQ for treating uncomplicated malaria. SP plus AQ performed better at destroying blood parasites at 28 days, although resistance to the drugs may have increased since the trials were performed. Adverse events were poorly reported.

BACKGROUND

Malaria is a mosquito-borne disease that is the leading cause of morbidity and mortality in sub-Saharan Africa, affecting 300 to 500 million people every year (WHO 2000a). Of the four malaria parasite species that infect humans, *Plasmodium falciparum* is most common and can cause severe malaria. Uncomplicated malaria is the more frequent presentation but can progress to severe malaria if not adequately treated. The level of immunity to malaria varies with transmission intensity of the setting and age. Residents of high malaria transmission areas usually develop a level of immunity to malaria that increases with age up to about five years. This immunity may protect an individual from developing severe malaria. In areas of low and seasonal malaria transmission, people do not develop immunity and are therefore more susceptible to development of severe malaria.

Effective malaria treatment is important to minimize the effects of malaria and is a major control strategy (WHO 2000a). Parasite resistance to many of the available antimalarial drugs continues to be a problem and makes effective treatment of malaria episodes difficult. Chloroquine had been first-line treatment until the 1990s when parasite resistance led to its replacement with other regimens (White 1998). Parasites have developed resistance to sulfadoxine-pyrimethamine rapidly because its long half life encourages the selection of the resistant parasites; some fear that it will become completely ineffective (WHO 1988; Warsame 2002). As a consequence, the search for effective antimalarial regimens continues; new antimalarial drugs are not being developed fast enough to meet the demand, and new ways of using already available drugs are being explored.

Combination therapy, when two or more antimalarial drugs with different modes of action are used together, is a widely recommended strategy for increasing the effectiveness of the component drugs and delaying the development of resistance to them (White 1999). In particular, artemisinin-based combination treatments are recommended because the artemisinin drug produces rapid clinical and parasitological response, may delay the development of resistance, and may reduce malaria transmission by killing gametocytes (Adjuik 2004).

Several countries in Africa have either changed or are considering changing their treatment policies to artesunate (an artemisinin drug) combined with amodiaquine, or other artemisinin-containing regimens. Although artemisinin-based combinations have been shown to be effective, implementing any policy involving their use could be faced with several problems, namely poor availability since artemisinin drugs are not yet widely available in Africa and may not be for some time because of low production, comparatively high cost, dosing complexity, and the lack of clinical experience with artemisinin-based combinations (Bloland 2003).

SP and amodiaquine are both widely available and inexpensive. There has been interest in combining these two drugs, and recent studies in Africa have explored this possibility. The studies have shown that SP combined with amodiaquine (SP plus amodiaquine) may be comparable to SP combined with artesunate (SP plus artesunate) for treating malaria (Bloland 2003). The World Health Organization's Roll Back Malaria programme recommends using SP plus amodiaquine in areas where efficacy of both drugs is high (RBM 2003a).

The use of these combinations may be associated with unwanted adverse effects, possibly not observed when either drug is used singly. In particular there have been concerns about the safety profile of amodiaquine (Olliaro 2004), though a recent systematic review found no evidence of increased risks of serious adverse events (MacLehose 2003). Sulfadoxine-pyrimethamine is rarely associated with severe adverse reactions in standard treatment (Sturchler 1993). Some artemisinin derivatives have been associated with fatal neurotoxicity in animals, and transient first-degree heart block has been reported in a few people taking artemisinin drugs, but artesunate itself seems to be well tolerated (Brewer 1994; Kain 1995; WHO 2000b). It is however still important to look out for any adverse events that may occur. We therefore compared SP plus amodiaquine with SP plus artesunate for treating uncomplicated *P. falciparum* malaria.

We have examined pragmatic outcomes, which include clinical endpoints. Treatment failure by day 28 is our primary outcome because this captures the majority of failures with these drugs, and recent evidence has shown that measures before this time underestimate the true failure rate (RBM 2003b; Stepniewska 2004). Parasitaemia after day 14 could be the result of a new infection and some studies detect these new infections using polymerase chain reaction (PCR) analysis, a method that can be used to differentiate between new and old infections; we also examined the outcome of treatment failure by day 28 with new infections excluded.

OBJECTIVES

To compare sulfadoxine-pyrimethamine plus artesunate (SP plus AS) with sulfadoxine-pyrimethamine plus amodiaquine (SP plus AQ) for treating uncomplicated *P. falciparum* malaria.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials.

Types of participants

Adults and children with microscopically confirmed *P. falciparum* malaria. We only included trials where participants had uncomplicated *P. falciparum* malaria as defined by the World Health Organization (WHO 2001).

Types of interventions

SP plus AS versus SP plus AQ.

Types of outcome measures

Primary

Treatment failure by day 28, defined as parasitological or clinical evidence of treatment failure between start of treatment and day 28; this includes new infections.

Secondary

- Treatment failure, defined as parasitological or clinical evidence of treatment failure between start of treatment and day 28; excludes new infections detected by PCR where reported.

- Time to parasite clearance, defined as the first negative blood slide.
- Time to fever clearance, defined as the time between the start of treatment and the temperature returning to normal and remaining so for at least 48 hours.
- Presence of gametocytes at day 28.

Adverse events

- Serious adverse events, defined as a sign, symptom, or intercurrent illness that is fatal, life-threatening, or requires hospital admission.
- Adverse events leading to discontinuation of treatment.
- Other adverse events.

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 (October 2005); Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2005, Issue 4); MEDLINE (1966 to October 2005); EMBASE (1980 to October 2005); and LILACS (1982 to October 2005).

Researchers and pharmaceutical companies

For unpublished and ongoing trials, we contacted individual researchers working in the field and the following pharmaceutical companies: Arenco (France), Mepha (Switzerland), Rhone-Poulenc Rorer (France); Propharma (Scotland), Novartis (Switzerland), Sanofi-Winthrop (France), Dafra (Belgium), Guilin Pharmaceutical Company (China), Kunning Pharmaceutical Corporation (Malaysia), Thua Thien Pharmaceutical Company (Viet Nam), and the National Pharmaceutical Plant Company (Viet Nam).

Reference lists

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

Data collection and analysis

Selection of studies

Hasifa Bukirwa (HB) scanned the results of the literature search, retrieved potentially relevant trials, and checked the eligibility with Julia Critchley (JC) using a standard form. We resolved ambiguity by discussion.

Data extraction and management

HB and JC independently extracted trial characteristics and data. Where the number randomized and the numbers analysed were inconsistent, we calculated the percentage loss to follow up and reported this in 'Characteristics of included studies. We had intended to primarily consider trials that used an intention-to-treat analysis, but only one trial approximated such an analysis, two used a per-protocol analysis, and the fourth did not specify the method although it was clearly not an intention-to-treat analysis.

For dichotomous outcomes, we recorded the number of participants experiencing the event in each group of the trial. For continuous outcomes, we extracted the arithmetic means and standard deviations for each group.

Assessment of risk of bias in included studies

HB and JC independently assessed the methodological quality of the included trials. We classed the generation of allocation sequence and allocation concealment as adequate, inadequate, or unclear according to Jüni 2001. We considered the inclusion of all randomized participants in the analysis to be adequate (acceptable) if it was 90% or more. We described who was blinded, such as the participants and care providers or assessors.

Data synthesis

We analysed data using Review Manager 4.2. We calculated the risk ratio (RR) with 95% confidence intervals (CI) for dichotomous data. We assessed heterogeneity among included trials by visually inspecting forest plots, carrying out a chi-squared test for heterogeneity (statistical significance at 10% level) and calculating I^2 statistic. We used the fixed-effect model to pool data because we did not detect heterogeneity.

We planned to carry out subgroup analyses based on the following subgroups but this was not possible. We could not subgroup by participant age (less than five years versus greater or equal to five years) because all the identified trials were done in one age group. There were too few trials allow any meaningful subgroup analyses for trial setting, namely high (hyperendemicity or holoendemicity) versus low endemicity (hypoendemicity or mesoendemicity) and level of resistance to the comparator drug. Subgroup analyses may be possible in future updates of this review.

RESULTS

Description of studies

Four trials (775 participants) met our inclusion criteria (*see* 'Characteristics of included studies'). They were carried out in areas of high and seasonal malaria transmission in Africa. All trials were single centre trials, except for Rwagacondo 2003, which was conducted at three sites within Rwanda. We have used the published analysis, which combined data from the three sites.

Source of funding

The four trials were supported by international and bilateral organizations such as the World Health Organization, and one, Mockenhaupt 2005, also had contributions in the form of the study drugs from pharmaceutical companies.

Location

All trials were conducted in Africa: Mockenhaupt 2005 in a hyperendemic area of Ghana; Abacassamo 2004 in an area of seasonal transmission in Mozambique; Rwagacondo 2003 described transmission as stable with seasonal peaks at the trial site in Rwanda; and Dorsey 2002 was conducted in a mesoendemic area of Uganda.

Participants

All the four trials were in children aged between six months and five years.

Interventions

All trials compared SP plus AQ with SP plus AS. All trials also had additional arms that were not pertinent to this review: Mockenhaupt 2005 and Dorsey 2002 included a sulfadoxine-pyrimethamine alone arm; Abacassamo 2004 had an amodiaquine plus artesunate arm; and Rwagacondo 2003 had an amodiaquine alone arm.

Dose and regimen

The trials used similar dose and regimens for SP plus AS and SP plus AQ.

Length of follow up

Follow up was 28 days for Mockenhaupt 2005 and Rwagacondo 2003. Abacassamo 2004 followed participants for 21 days and Uganda had total follow up per participant of one year, although individual episodes were followed up to 28 days.

Drug resistance

Resistance to sulfadoxine-pyrimethamine was reported in two trials. Rwagacondo 2003 reported resistance to sulfadoxine-pyrimethamine between 11% and 45% and Dorsey 2002 reported it as common: a study done around the same period as the Ugandan trial reported parasitological failure levels of about 61% with sulfadoxine-pyrimethamine (Talisuna 2004).

Outcomes

Treatment failure was reported by all the trials either at day 14 or 28 or both. One trial, Dorsey 2002, reported on progression to severe malaria. Mockenhaupt 2005 reported on gametocyte carriage at day seven and Abacassamo 2004 at day 14. Three trials mentioned adverse events, but none of them in sufficient detail.

Risk of bias in included studies

Generation of allocation sequence was adequate in three trials; it was unclear in one trial that did not mention the method of generation (Rwagacondo 2003). For allocation concealment, one trial used adequate methods (Abacassamo 2004) and the other three did not provide this information). Two trial reports mentioned blinding: Dorsey 2002 used a placebo in the sulfadoxine-only arm to blind the participants and study investigators; and Mockenhaupt 2005 used a double dummy placebo technique to blind participants from the intervention, but it was not clear who else was blinded. Three trials did not include all the enrolled participants in the final analysis: Mockenhaupt 2005 and Abacassamo 2004 included adequate numbers of the enrolled participants in the final analysis (90% and 91% respectively). Dorsey 2002 had a one-year follow up and included 89%, which we classed as inadequate. The fourth trial, Rwagacondo 2003, did not provide this information.

Effects of interventions

Treatment failure by day 28

Three trials reported results for this outcome (Dorsey 2002; Rwagacondo 2003; Mockenhaupt 2005). Fewer participants failed treatment with SP plus AQ (RR 0.59, 95% CI 0.42 to 0.83; 652 participants, 3 trials; comparison 01-01), with a consistent effect across all trials and no evidence of heterogeneity (I^2 = 0%). When new infections were excluded, SP plus AQ still performed better (RR 0.62, 95% CI 0.40 to 0.96; 649 participants, 3 trials; comparison 01-02).

Treatment failure by day 14

Fewer people failed treatment with SP plus AS in three of the four trials, but the overall effect was not statistically significant (RR 1.14, 95% CI 0.47 to 2.78; 775 participants, 4 trials; comparison 01-03).

Treatment failure: progression to severe malaria

Dorsey 2002 reported one participant with severe malaria − in the SP plus AQ group (comparison 01-04).

Gametocyte carriage

Mockenhaupt 2005 reported that fewer participants in the SP plus AS group had gametocytes at day seven (RR 2.31, 95% CI 1.36 to 3.92; 220 participants; comparison 01-05). Abacassamo 2004 reported a similar trend at day 14, but the difference was not statistically significant (113 participants, comparison 01-06).

Adverse events

Most trials did not clearly describe the methods for reporting adverse events or the precise numbers of events. Abacassamo 2004 reported "no severe adverse reactions attributable to treatment", Rwagacondo 2003 reported "no major drug related adverse effects", and Dorsey 2002 reported "no severe adverse reactions to trial drugs" and that "mild adverse reactions did not differ between the three treatment groups". Mockenhaupt 2005 did not mention adverse events.

DISCUSSION

Four trials are included in this review. The data come from mainly high malaria transmission areas in Africa, but the level of background resistance to the component drugs of the combinations is not clear. All trials enrolled children aged six to 59 months.

The methodological quality of the included trials could not be conclusively determined as a consequence of poor reporting but is believed to be generally good. Three trials had adequate generation of allocation sequence, but only one had adequate allocation concealment and only two used blinding. None of the trials included all the enrolled participants in the final analysis, although losses to follow up were within acceptable limits and the reasons for exclusion and loss to follow up were always given.

All trials compared SP plus AQ with SP plus AS, and all used the same dose and regimens and in a similar population. This has made comparison of reported outcomes possible.

Reported outcomes were treatment failure, progression to severe malaria, and gametocyte carriage. Three trials mentioned adverse events, but none of them in sufficient detail and none described the procedure to assess them, which create uncertainty over the completeness of these data. Some of the trials reported on symptom resolution (parasite clearance and fever clearance), but this was not reported in a format that could be used in this review and therefore it has not been possible to report them here.

The combination of SP plus AQ resulted in better cure of malaria when assessed at day 28. At day 14 the result was not conclusive and it is not possible to determine which, if any, treatment is better

than the other at this point. These observed effects may be because the longer acting amodiaquine still offers protection beyond day 14 compared to artesunate, which is quickly eliminated from the body and whose effect in the combination lasts a short time. If artesunate has disappeared from the patient's system and there is resistance to sulfadoxine-pyrimethamine then day 28 cure rates are likely to be very low unless the patient has some level of immunity to malaria.

SP plus AS was better at controlling gametocytes than SP plus AQ. This result, as may be expected, is because the artesunate component (like the other artemisinin drugs) is effective in destroying gametocytes.

There are presently insufficient data to determine the effects of the two treatments on outcomes such as symptom resolution and adverse events.

Although there was little statistical heterogeneity in results across trials, some caution is still required to generalize from four small trials carried out at different times, in separate parts of Africa, and with different malaria transmission intensities. All these trials took place at a time of rapid spread of sulfadoxine-pyrimethamine resistance and the emergence of amodiaquine resistance. Resistance patterns may have worsened since the trials were carried out, particularly for the SP plus AQ combination. Resistance to sulfadoxine-pyrimethamine has spread rapidly across Africa and manifests initially as recrudescence of the same parasite genotype between 14 and 28 days or longer. Combination therapy with sulfadoxine-pyrimethamine is therefore likely to be a 'stop-gap' measure until artemisinin-based combination therapies are widely available, or limited to areas with documented low sulfadoxine-pyrimethamine resistance. It is possible that sulfadoxine-pyrimethamine may not be recommended at all for first-line treatment of any malaria in Africa in the future. The SP plus AQ combination should therefore only be considered where both sulfadoxine-pyrimethamine and amodiaquine resistance (measured at 28 days) are known to be low. It is particularly important that effective drugs (such as artesunate, with no documented resistance) are protected and not exposed to the possibility of developing resistance by partnering them with ineffective drugs. This also implies that SP plus AS combination therapy should only be considered where both drugs are known to be effective.

AUTHORS' CONCLUSIONS

Implications for practice

In these trials, SP plus AQ was better than SP plus AS at controlling treatment failure at day 28, but there are insufficient data to determine performance at day 14. Careful consideration of local resistance patterns is however required, as resistance to both sulfadoxine-pyrimethamine and amodiaquine are high in many areas and may be worsening. In order to delay development of resistance to artesunate, the SP plus AS combination should only be considered in areas where both drugs are known to be effective. Data on adverse events are still lacking.

Implications for research

Randomized controlled trials that include outcomes on symptom resolution and adverse effects are needed. These are not only important to help further assess effectiveness and safety but are also of particular interest to people with malaria. Trial methodology needs to be reported more clearly. Research in other locations (such as Central Asia) where sulfadoxine-pyrimethamine is more effective might be useful.

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CHARACTERISTICS OF STUDIES

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

Abacassamo 2004

Methods	Randomized open trial Generation of allocation sequence: random permuted block Allocation concealment: not mentioned Blinding: not mentioned Inclusion of all randomized participants: no (113/124) Length of follow up: 21 days
Participants	Number: 124 enrolled, 113 analysed Inclusion criteria: children 6 to 59 months living within the study area; axillary temperature 37.5 °C to 40 °C; acute non-complicated *Plasmodium falciparum*; parasitaemia 2000 to 100,000 asexual parasites/µL of blood; parent or guardian written informed consent Exclusion criteria: danger signs (not able to drink, eat or breastfeed; severe vomiting – > 2 times in 24 hours; unconscious and unable to sit or stand; signs of severe malaria – cerebral malaria defined as inability to localize pain; severe anaemia – haemoglobin < 5 g/dL or a packed cell volume less < 15% or with spontaneous bleeding and repeated generalized convulsions
Interventions	1. Sulfadoxine-pyrimethamine (SP) plus amodiaquine (AQ) 2. SP plus artesunate (AS) AQ: 10 mg/kg/day for 3 days AS: 4 mg/kg/day for 3 days SP: 25 mg/kg sulfadoxine and 1.25 mg/kg pyrimethamine Third arm not relevant to review: AQ plus AS
Outcomes	1. Therapeutic response, according World Health Organization (WHO) 1996 definitions (reference in Abacassamo 2004) 2. Presence of fever 3. Gametocyte carriage

Abacassamo 2004 *(Continued)*

Notes	Location: Mozambique Date: February to June 2002 Funding: DBL/INS joint research programme and the WHO/Special Programme for Research and Training in Tropical Diseases (TDR)

Dorsey 2002

Methods	Randomized placebo controlled trial Generation of allocation sequence: computer-generated randomization list Allocation concealment: not mentioned Blinding: participants and study investigators blinded Inclusion of all randomized participants: no (93/122) Length of follow up: 14 days
Participants	Number: 211 children enrolled Inclusion criteria: children 6 months to 5 years old; no history of treatment for malaria in previous 2 weeks or fever in last 48 h; no history of adverse reactions to any of the study drugs; no history of sickle cell disease; haemoglobin 50 g/L or more; willingness to remain in the city of Kampala and follow the study protocol for the next 12 months; parent or guardian written informed consent
Interventions	1. Sulfadoxine-pyrimethamine (SP) plus amodiaquine (AQ) 2. SP plus artesunate (AS) AQ: 10 mg/kg/day for 2 days and 5 mg/kg for 1 day AS: 4 mg/kg/day for 3 days SP: 25 mg/kg sulfadoxine and 1.25 mg/kg pyrimethamine; single dose Third arm not relevant to review: SP plus vitamin C placebo
Outcomes	1. Treatment failure at day 14 and 28; at day 28 both adjusted and unadjusted for new infections 2. Mentions adverse events but did not report any 3. Parasite carriage reported for episodes not patients 3. Presence of fever 4. Mentioned adverse events but did not give details by treatment arm
Notes	Location: Mulago Hospital, Kampala, Uganda Date: July 2000 to August 2001 Follow up was 14 days for each episode of malaria over 1-year period Funding: Fogarty International Center/National Institutes of Health and the UNDP/World Bank/World Health Organization (WHO) Special Programme for Research and Training in Tropical Diseases (TDR)

Mockenhaupt 2005

Methods	Randomized placebo controlled trial

Mockenhaupt 2005 *(Continued)*

	Generation of allocation sequence: computer-generated block randomization Allocation concealment: not mentioned Blinding: participants, not clear whom else Inclusion of all randomized participants: no (264/293) Length of follow up: 28 days
Participants	Number: 293 enrolled, 273 analysed at day 14, and 264 analysed at day 28 Inclusion criteria: children 6 to 59 months attending Bulpeila Health Centre; mono-infection with *Plasmodium falciparum*; parasitaemia 2000 to 100,000 asexual parasites/µL of blood; axillary temperature at least 37.5 °C; body weight > 5 kg; absence of severe malnutrition; no other causes of febrile illness; no danger signs and no severe and complicated malaria; haemoglobin at least 5 g/dL; and parent or guardian written informed consent Exclusion criteria: known hypersensitivity to study drugs; detection during follow up of mixed malarial infections; and development of concomitant disease which would interfere with classification of treatment outcome
Interventions	1. Sulfadoxine-pyrimethamine (SP) plus amodiaquine (AQ) 2. SP plus artesunate (AS) AQ: 10 mg/kg/day for 3 days plus AS placebo AS: 4 mg/kg/day for 3 days plus AQ placebo SP: 25 mg/kg sulfadoxine and 1.25 mg/kg pyrimethamine; single dose Third arm not relevant to review: SP alone (plus AQ and AS placebos once a day for 3 days)
Outcomes	1. Treatment failure according to the World Health Organization (WHO) classification; at day 28 both adjusted and unadjusted for new infections 2. Presence of malaria parasites at various time points up to day 28 3. Presence of fever at various time points up to day 28 4. Gametocyte prevalence at day 7
Notes	Location: Tamale, Northern Region, Ghana Date: August to December 2002 Funding: World Health Organization; Dafra Pharma (Belgium) and Park-Davis (Senegal) provided study medication

Rwagacondo 2003

Methods	Randomized open trial Generation of allocation sequence: not mentioned Allocation concealment: not mentioned Blinding: not mentioned Inclusion of all randomized participants: no (275/276) Length of follow up: 28 days
Participants	Number: 276 children enrolled

Rwagacondo 2003 *(Continued)*

	Inclusion criteria: children 6 to 59 months old; fever, temperature at least 37.5 °C; weight at least 5 kg; parasitaemia 1000 to 100,000 asexual parasites/µL of blood; *Plasmodium falciparum* pure infection; parent or guardian written informed consent Exclusion criteria: danger signs (not able to drink or breastfeed; vomiting > 2 times in 24 hours; recent history of convulsions; unconscious state or unable to sit or stand; signs of severe malaria; a packed cell volume < 15%; a clear history of adequate malaria treatment in the preceding 72 h; or evidence of chronic disease
Interventions	1. Sulfadoxine-pyrimethamine (SP) plus amodiaquine (AQ) 2. SP plus artesunate (AS) AQ: 10 mg/kg/day for 3 days AS: 4 mg/kg/day for 3 days SP: 25 mg/kg sulfadoxine and 1.25 mg/kg pyrimethamine Third arm not relevant to review: AQ alone
Outcomes	1. Treatment failure at day 28 both adjusted and unadjusted for new infections 2. Mentions adverse events but did not report any
Notes	Location: Rwanda in 3 sites of Kicukiro, Rukara and Mashesha health centres Date: May to August 2001 Funding: Belgian Development Co-operation (DGIS) in collaboration with the Prince Leopold Institute of Tropical Medicine (Antwerp, Belgium)

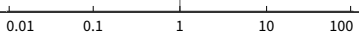
DATA AND ANALYSES

Comparison 1. Sulfadoxine-pyrimethamine (SP) plus artesunate (AS) versus SP plus amodiaquine (AQ)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure by day 28	3	652	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.42, 0.83]
2 Treatment failure by day 28 (excludes new infections)	3	649	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.40, 0.96]
3 Treatment failure by day 14	4	775	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.47, 2.78]
4 Treatment failure: progress to severe malaria	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Gametocyte carriage at day 7	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Gametocyte carriage at day 14	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Sulfadoxine-pyrimethamine (SP) plus artesunate (AS) versus SP plus amodiaquine (AQ), Outcome 1 Treatment failure by day 28.

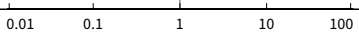
Study or subgroup	SP plus AQ n/N	SP plus AS n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dorsey 2002	9/59	13/54		18.52%	0.63[0.29,1.36]
Mockenhaupt 2005	12/137	19/127		26.9%	0.59[0.3,1.16]
Rwagacondo 2003	22/131	42/144		54.58%	0.58[0.36,0.91]
Total (95% CI)	**327**	**325**		**100%**	**0.59[0.42,0.83]**
Total events: 43 (SP plus AQ), 74 (SP plus AS)					
Heterogeneity: Tau^2=0; Chi^2=0.04, df=2(P=0.98); I^2=0%					
Test for overall effect: Z=3.04(P=0)					



Favours SP plus AQ — Favours SP plus AS

Analysis 1.2. Comparison 1 Sulfadoxine-pyrimethamine (SP) plus artesunate (AS) versus SP plus amodiaquine (AQ), Outcome 2 Treatment failure by day 28 (excludes new infections).

Study or subgroup	SP plus AQ n/N	SP plus AS n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dorsey 2002	3/56	11/54		24.3%	0.26[0.08,0.89]
Mockenhaupt 2005	8/137	7/127		15.76%	1.06[0.4,2.84]
Rwagacondo 2003	17/131	29/144		59.94%	0.64[0.37,1.12]
Total (95% CI)	**324**	**325**		**100%**	**0.62[0.4,0.96]**
Total events: 28 (SP plus AQ), 47 (SP plus AS)					
Heterogeneity: Tau^2=0; Chi^2=3.06, df=2(P=0.22); I^2=34.54%					
Test for overall effect: Z=2.16(P=0.03)					



Favours SP plus AQ — Favours SP plus AS

Analysis 1.3. Comparison 1 Sulfadoxine-pyrimethamine (SP) plus artesunate (AS) versus SP plus amodiaquine (AQ), Outcome 3 Treatment failure by day 14.

Study or subgroup	SP plus AQ n/N	SP plus AS n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Abacassamo 2004	5/60	3/53		36.22%	1.47[0.37,5.87]
Dorsey 2002	1/59	0/54		5.93%	2.75[0.11,66.1]
Mockenhaupt 2005	3/141	4/132		46.97%	0.7[0.16,3.08]
Rwagacondo 2003	1/132	1/144		10.87%	1.09[0.07,17.27]
Total (95% CI)	**392**	**383**		**100%**	**1.14[0.47,2.78]**
Total events: 10 (SP plus AQ), 8 (SP plus AS)					
Heterogeneity: Tau^2=0; Chi^2=0.84, df=3(P=0.84); I^2=0%					
Test for overall effect: Z=0.3(P=0.77)					

Favours SP plus AQ — Favours SP plus AS

Analysis 1.4. Comparison 1 Sulfadoxine-pyrimethamine (SP) plus artesunate (AS) versus SP plus amodiaquine (AQ), Outcome 4 Treatment failure: progress to severe malaria.

Study or subgroup	SP plus AQ n/N	SP plus AS n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Dorsey 2002	1/59	0/54		2.75[0.11,66.1]

Favours SP plus AQ 0.001 0.1 1 10 1000 Favours SP plus AS

Analysis 1.5. Comparison 1 Sulfadoxine-pyrimethamine (SP) plus artesunate (AS) versus SP plus amodiaquine (AQ), Outcome 5 Gametocyte carriage at day 7.

Study or subgroup	SP plus AQ n/N	SP plus AS n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Mockenhaupt 2005	40/118	15/102		2.31[1.36,3.92]

Favours SP plus AQ 0.001 0.1 1 10 1000 Favours SP plus AS

Analysis 1.6. Comparison 1 Sulfadoxine-pyrimethamine (SP) plus artesunate (AS) versus SP plus amodiaquine (AQ), Outcome 6 Gametocyte carriage at day 14.

Study or subgroup	SP plus AQ n/N	SP plus AS n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Abacassamo 2004	3/60	0/53		6.2[0.33,117.27]

Favours SP plus AQ 0.001 0.1 1 10 1000 Favours SP plus AS

APPENDICES

Appendix 1. Search methods: detailed search strategies

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	EMBASE[b]	LILACS[b]
1	sulfadox-ine-pyrimetham**ine**-pyrimethamine	sulfadox-ine-pyrimethamine	sulfadoxine-pyrimethamine	sulfadoxine ADJ pyrimethamine	sulfadox-ine-pyrimethamine
2	fansidar	fansidar	fansidar	fansidar	fansidar
3	amodi-aquine	amodiaquine	amodiaquine	amodiaquine	amodiaquine
4	artesunate	artesunate	AMODIAQUINE	AMODIAQUINE	artesunate
5	—	1 or 2	ARTESUNATE	ARTESUNATE	1 or 2
6	—	3 and 5	artesunate	artesunate	3 and 5
7	—	4 and 5	1 or 2	1 or 2	4 and 5

(Continued)

8	—	—	3 or 4	3 or 4	6 and 7
9	—	—	5 or 6	5 or 6	—
10	—	—	7 and 8	7 and 8	—
11	—	—	7 and 9	7 and 9	—
12	—	—	10 and 11	10 and 11	—
13	—	—	MALARIA	malaria	—
14	—	—	malaria	MALARIA	—
15	—	—	13 or 14	PLASMODIUM-FALCIPARUM	—
16	—	—	12 and 15	13 or 14 or 15	—
17	—	—	—	12 and 16	—

[a]Cochrane Infectious Diseases Group Specialized Register.
[b]Search 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.

WHAT'S NEW

Date	Event	Description
4 November 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Hasifa Bukirwa extracted and analysed data, and drafted the review. Julia Critchley extracted data and edited the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Makerere University Malaria Project, Uganda.

External sources

- Department for International Development, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Amodiaquine [*therapeutic use]; Artemisinins [*therapeutic use]; Artesunate; Drug Combinations; Drug Therapy, Combination; Malaria, Falciparum [*drug therapy]; Pyrimethamine [*therapeutic use]; Randomized Controlled Trials as Topic; Sesquiterpenes [*therapeutic use]; Sulfadoxine [*therapeutic use]

MeSH check words

Humans