

# Chlorproguanil-dapsone for treating uncomplicated malaria (Review)

Bukirwa H, Garner P, Critchley JA



**THE COCHRANE  
COLLABORATION®**

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2010, Issue 1

<http://www.thecochranelibrary.com>



## TABLE OF CONTENTS

HEADER . . . . .	1
ABSTRACT . . . . .	1
PLAIN LANGUAGE SUMMARY . . . . .	2
BACKGROUND . . . . .	2
OBJECTIVES . . . . .	3
METHODS . . . . .	3
RESULTS . . . . .	6
DISCUSSION . . . . .	10
AUTHORS' CONCLUSIONS . . . . .	11
ACKNOWLEDGEMENTS . . . . .	11
REFERENCES . . . . .	11
CHARACTERISTICS OF STUDIES . . . . .	13
DATA AND ANALYSES . . . . .	22
Analysis 1.1. Comparison 1 One-dose regimen (with 1.2 mg chlorproguanil) versus chloroquine, Outcome 1 Parasitaemia.	24
Analysis 1.2. Comparison 1 One-dose regimen (with 1.2 mg chlorproguanil) versus chloroquine, Outcome 2 Treatment failure.	24
Analysis 2.1. Comparison 2 One-dose regimen (with 1.2 mg chlorproguanil) versus sulfadoxine-pyrimethamine, Outcome 1 Parasitaemia.	25
Analysis 2.2. Comparison 2 One-dose regimen (with 1.2 mg chlorproguanil) versus sulfadoxine-pyrimethamine, Outcome 2 Treatment failure.	26
Analysis 2.3. Comparison 2 One-dose regimen (with 1.2 mg chlorproguanil) versus sulfadoxine-pyrimethamine, Outcome 3 Adverse events.	26
Analysis 3.1. Comparison 3 Three-dose regimen (with 1.2 mg chlorproguanil) versus sulfadoxine-pyrimethamine, Outcome 1 Parasitaemia.	27
Analysis 3.2. Comparison 3 Three-dose regimen (with 1.2 mg chlorproguanil) versus sulfadoxine-pyrimethamine, Outcome 2 Treatment failure.	27
Analysis 3.3. Comparison 3 Three-dose regimen (with 1.2 mg chlorproguanil) versus sulfadoxine-pyrimethamine, Outcome 3 Haemoglobin.	28
Analysis 3.4. Comparison 3 Three-dose regimen (with 1.2 mg chlorproguanil) versus sulfadoxine-pyrimethamine, Outcome 4 Adverse events.	28
Analysis 4.1. Comparison 4 Three-dose regimen (with 2.0 mg chlorproguanil) versus sulfadoxine-pyrimethamine (previous SP failures), Outcome 1 Parasitaemia.	29
Analysis 4.2. Comparison 4 Three-dose regimen (with 2.0 mg chlorproguanil) versus sulfadoxine-pyrimethamine (previous SP failures), Outcome 2 Treatment failure.	29
Analysis 4.3. Comparison 4 Three-dose regimen (with 2.0 mg chlorproguanil) versus sulfadoxine-pyrimethamine (previous SP failures), Outcome 3 Adverse events.	30
Analysis 5.1. Comparison 5 Three-dose regimen (with 2.0 mg chlorproguanil) versus sulfadoxine-pyrimethamine (new attendees), Outcome 1 Parasitaemia.	30
Analysis 5.2. Comparison 5 Three-dose regimen (with 2.0 mg chlorproguanil) versus sulfadoxine-pyrimethamine (new attendees), Outcome 2 Presence of fever.	31
Analysis 5.3. Comparison 5 Three-dose regimen (with 2.0 mg chlorproguanil) versus sulfadoxine-pyrimethamine (new attendees), Outcome 3 Treatment failure by day 7.	31
Analysis 5.4. Comparison 5 Three-dose regimen (with 2.0 mg chlorproguanil) versus sulfadoxine-pyrimethamine (new attendees), Outcome 4 Treatment failure by day 14.	32
Analysis 5.5. Comparison 5 Three-dose regimen (with 2.0 mg chlorproguanil) versus sulfadoxine-pyrimethamine (new attendees), Outcome 5 Haemoglobin.	32
Analysis 5.6. Comparison 5 Three-dose regimen (with 2.0 mg chlorproguanil) versus sulfadoxine-pyrimethamine (new attendees), Outcome 6 Adverse events.	33
Analysis 5.7. Comparison 5 Three-dose regimen (with 2.0 mg chlorproguanil) versus sulfadoxine-pyrimethamine (new attendees), Outcome 7 Serious adverse events (Allouche 2004).	34
WHAT'S NEW . . . . .	34

HISTORY . . . . .	34
CONTRIBUTIONS OF AUTHORS . . . . .	34
DECLARATIONS OF INTEREST . . . . .	35
SOURCES OF SUPPORT . . . . .	35
DIFFERENCES BETWEEN PROTOCOL AND REVIEW . . . . .	35
INDEX TERMS . . . . .	35

[Intervention Review]

# Chlorproguanil-dapsone for treating uncomplicated malaria

Hasifa Bukirwa<sup>1</sup>, Paul Garner<sup>2</sup>, Julia A Critchley<sup>3</sup>

<sup>1</sup>Makerere University Medical School, Kampala, Uganda. <sup>2</sup>International Health Group, Liverpool School of Tropical Medicine, Liverpool, UK. <sup>3</sup>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](mailto:hbukirwa@muucsf.org). [h\\_bukirwa@yahoo.ca](mailto:h_bukirwa@yahoo.ca).

**Editorial group:** Cochrane Infectious Diseases Group.

**Publication status and date:** Stable (no update expected for reasons given in 'What's new'), published in Issue 1, 2010.

**Review content assessed as up-to-date:** 13 August 2004.

**Citation:** Bukirwa H, Garner P, Critchley JA. Chlorproguanil-dapsone for treating uncomplicated malaria. *Cochrane Database of Systematic Reviews* 2004, Issue 4. Art. No.: CD004387. DOI: 10.1002/14651858.CD004387.pub2.

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

## ABSTRACT

### Background

In Africa, malaria is often resistant to chloroquine and sulfadoxine-pyrimethamine. Chlorproguanil-dapsone is a potential alternative.

### Objectives

To compare chlorproguanil-dapsone with other antimalarial drugs for treating uncomplicated falciparum malaria.

### Search strategy

We searched the Cochrane Infectious Diseases Group Specialized Register (May 2004), CENTRAL (*The Cochrane Library* 2004, Issue 2), MEDLINE (1966 to May 2004), EMBASE (1988 to May 2004), LILACS (May 2004), Biosis Previews (1985 to May 2004), conference proceedings, and reference lists, and contacted researchers working in this field.

### Selection criteria

Randomized and quasi-randomized controlled trials comparing chlorproguanil-dapsone to other antimalarial drugs.

### Data collection and analysis

Two reviewers independently applied the inclusion criteria, extracted data, and assessed methodological quality. We calculated the risk ratio (RR) for dichotomous data and mean difference for continuous data, and presented them with 95% confidence intervals (CI).

### Main results

Six trials (n = 3352) met the inclusion criteria. Chlorproguanil-dapsone (with 1.2 mg chlorproguanil) as a single dose had fewer treatment failures than chloroquine (1 trial), but more treatment failures and people with parasitaemia at day 28 than sulfadoxine-pyrimethamine (3 trials).

Two trials compared the three-dose chlorproguanil-dapsone (with 2 mg chlorproguanil) regimen with sulfadoxine-pyrimethamine in new attendees. There were fewer treatment failures with chlorproguanil-dapsone by day 7 (RR 0.30, 95% CI 0.19 to 0.49; n = 827, 1 trial) and day 14 (RR 0.36, 95% CI 0.24 to 0.53; n = 1709, 1 trial). Neither trial reported total failures by day 28. A further trial was carried out in participants selected because they had previously failed sulfadoxine-pyrimethamine.

Adverse event reporting was inconsistent between trials, but chlorproguanil-dapsone was associated with more adverse events leading to discontinuation of treatment compared with sulfadoxine-pyrimethamine (RR 4.54, 95% CI 1.74 to 11.82; n = 829, 1 trial). It was also associated with more red blood cell disorders (RR 2.86, 95% CI 1.33 to 6.13; n = 1850, 1 trial).

---

**Chlorproguanil-dapsone for treating uncomplicated malaria (Review)**

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

1

## Authors' conclusions

There are insufficient data about the effects of the current standard chlorproguanil-dapsone regimen (three-dose, 2 mg chlorproguanil). Randomized controlled trials that follow up to day 28, record adverse events, and use an intention-to-treat analysis are required to inform any policy decisions.

2008: We do not plan to update this review because chlorproguanil-dapsone has been withdrawn (see the 'What's new' statement).

## PLAIN LANGUAGE SUMMARY

### Chlorproguanil-dapsone for treating malaria

Chlorproguanil-dapsone was withdrawn in 2008, and the review will not be updated.

## BACKGROUND

Prompt and effective malaria treatment can prevent uncomplicated malaria from developing into more severe illness. The World Health Organization (WHO) promotes this as a major component of national malaria control programmes (WHO 2000). However, identifying effective drugs or combinations of drugs is hampered by antimalarial drug resistance. This is a problem in many African countries where the disease is common and the burden is high (WHO 1999).

The *Plasmodium falciparum* parasite is responsible for most of the malaria burden in Africa (WHO 1999). For decades, chloroquine was the first-line treatment for falciparum malaria, but parasite resistance has led to this being replaced (White 1998). Several East, Central, and Southern African countries (such as Malawi, Kenya, Botswana, and South Africa) have changed their national policy for first-line treatment to sulfadoxine-pyrimethamine. Other countries, such as Uganda, are using combinations of sulfadoxine-pyrimethamine and chloroquine (Verhoeff 1997; D'Alessandro 2001).

One problem with sulfadoxine-pyrimethamine is that parasites can develop resistance to it relatively quickly. Sulfadoxine and pyrimethamine act on two different enzymes in the folate biosynthetic pathway, which are essential for the survival of the malaria parasites. Specific parts of the parasite's DNA code for these enzymes, and they can mutate in such a way that the enzyme still functions but is protected from the effect of sulfadoxine and pyrimethamine. Sulfadoxine-pyrimethamine has a long half-life, which encourages the selection of the mutant (resistant) parasites, and resistance can develop rapidly (Triglia 1999). Resistance to

sulfadoxine-pyrimethamine is already widespread in South-East Asia and South America, and is becoming more common in Africa (WHO 1988; Warsame 2002).

A more recent and potential alternative to sulfadoxine-pyrimethamine is the combination of chlorproguanil and dapsone. Like sulfadoxine-pyrimethamine, chlorproguanil-dapsone is an antifolate drug combination (White 1998). This combination acts on two sequential steps of the *Plasmodium* (malaria parasite) folate biosynthetic pathway. First, dapsone prevents the formation of folic acid, and then chlorproguanil interferes with the conversion of folic acid to folinic acid. This theoretically means the effects of the two drugs are synergistic (Thompson 1972).

Chlorproguanil and dapsone have both been used for malaria prophylaxis. Chlorproguanil, as Lapudrine, has been used singly whereas dapsone has been used in combination with pyrimethamine (Maloprim). In The Gambia, chlorproguanil has been used for over five years with no reported resistance developing, but there is concern over cross-resistance between chlorproguanil and pyrimethamine (Greenwood 1989; Allen 1990). The development of resistance to chlorproguanil-dapsone should be slow because both drugs are rapidly eliminated from the body (mean half life of dapsone is 20 to 30 hours, chlorproguanil 12 to 20 hours) and therefore exert low selection pressure for resistance (Curtis 2002). However similarities in the mechanism of development of resistance between sulfadoxine-pyrimethamine and chlorproguanil-dapsone may limit the effectiveness of chlorproguanil-dapsone (Le Bras 2003).

Dapsone has adverse effects (Thompson 1972), including

methaemoglobinaemia, haemolysis, and anaemia (red blood cell disorders). They are thought to occur after long-term continuous use and are more frequent with doses of 100 mg or more per day (Wolf 2002). More serious adverse effects include agranulocytosis and hypersensitivity. Other adverse effects with dapsone include dermatitis, hepatitis, anorexia, nausea, vomiting, headache, nervousness, blurred vision, haematuria, drug fever, and psychoses (Ozawa 2002).

Chlorproguanil-dapsone was developed mainly for use in Africa as a replacement for the rapidly failing sulfadoxine-pyrimethamine. Chlorproguanil-dapsone (LapDap) has been approved for general use in the United Kingdom by the UK Medicines and Healthcare products Regulatory Agency, and has been launched in Zambia, Kenya, Cameroon, Ghana, and Nigeria (GlaxoSmithKline 2003; ZANA 2003). The current standard is a fixed-ratio tablet of 2.0:2.5 mg/kg (80:100 mg adult formulation and 15:18.75 mg paediatric formulation) of chlorproguanil and dapsone respectively, taken once daily for three days. However, lower doses of chlorproguanil have previously been tested.

We have summarized the evidence for the role of the chlorproguanil-dapsone combination for treating uncomplicated falciparum malaria. We have used the WHO's definition in order to differentiate between the uncomplicated and severe (complicated) forms of malaria (WHO 2001). Our primary outcomes are positive blood slide for *P. falciparum* on day 14 and day 28. In areas of intense transmission, positive blood smears after day 14 may be the result of new infections or a recrudescence of the old infection. Polymerase chain reaction (PCR) can be used to differentiate between new and old infections.

## OBJECTIVES

To compare chlorproguanil-dapsone with other antimalarial drugs for treating uncomplicated falciparum malaria.

## METHODS

**Table 1. Classification of response to treatment<sup>d</sup>**

Expression	Definition
Early treatment failure	Development of danger signs or severe malaria on day 1, day 2, or day 3, in the presence of parasitaemia; or parasitaemia on day 2 higher than day 0 count irrespective of axillary temperature; or parasitaemia on day 3 with axillary temperature 37.5 °C or higher; or parasitaemia on day 3 of 25% of count on day 0

## Criteria for considering studies for this review

### Types of studies

Randomized and quasi-randomized controlled trials.

### Types of participants

Adults and children with microscopically confirmed uncomplicated falciparum malaria (WHO 2001).

### Types of interventions

#### Intervention

Chlorproguanil-dapsone.

#### Control

Current drug regimens for treating uncomplicated falciparum malaria.

### Types of outcome measures

#### Primary

- Presence of falciparum malaria parasites on day 14.
- Presence of falciparum malaria parasites on day 28, adjusted for new infection using PCR analysis.

#### Secondary

- Parasite clearance time.
- Time to fever clearance.
- Treatment failure (early treatment failure, late treatment failure (late clinical failure, and late parasitological failure) (WHO 2002; see Table 1 for definitions).

**Table 1. Classification of response to treatment<sup>a</sup>** (Continued)

Late clinical failure	Development of danger signs or severe malaria after day 3 in the presence of parasitaemia, without previously meeting any of the criteria of early treatment failure; or presence of parasitaemia and axillary temperature 37.5 °C or higher on any day from day 4 to day 14, without previously meeting any of the criteria of early treatment failure
Late parasitological failure	Presence of parasitaemia on day 14 and axillary temperature < 37.5 °C, without previously meeting any of the criteria of early treatment failure or late clinical failure
Adequate clinical and parasitological response	Absence of parasitaemia on day 14 irrespective of axillary temperature without previously meeting any of the criteria of early treatment failure or late clinical failure or late parasitological failure

<sup>a</sup>Source: WHO 2002.

- Use of antipyretic (paracetamol, other).
- Mean haemoglobin.

#### **Adverse events**

- Serious adverse events: adverse events that lead to death, require hospitalization or prolongation of existing hospitalization, are life threatening, or result in persistent or significant disability or incapacity.
  - Adverse events that require the discontinuation of treatment.
  - Number of people experiencing 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 Table 2: Cochrane Infectious Diseases Group Specialized Register (May 2004); Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (2004, Issue 2); MEDLINE (1966 to May 2004); EMBASE (1988 to May 2004); LILACS (May 2004); and Biosis Previews (1985 to May 2004).

**Table 2. Detailed search strategies**

Search set	CIDG SR <sup>a</sup>	CENTRAL	MEDLINE <sup>b</sup>	EMBASE <sup>b</sup>	LILACS <sup>b</sup>	Biosis Previews <sup>b</sup>
1	chlorproguanil	CCG-DDS	chlorproguanil	chlorproguanil	chlorproguanil	chlorproguanil
2	chlorguanide	chlorproguanil-dapsone	chlorguanide	chlorguanide	chlorguanide	chlorguanide
3	lapudrine	chlorproguanil/dapsone	lapudrine	lapudrine	lapudrine	lapudrine
4	dapsone	lapdap	dapsone	dapsone	dapsone	dapsone
5	CCG-DDS	malaria	CCG-DDS	CCG-DDS	CCG-DDS	CCG-DDS
6	chlorproguanil-dapsone	1-4/OR	chlorproguanil-dapsone	chlorproguanil-dapsone	chlorproguanil-dapsone	chlorproguanil-dapsone
7	chlorproguanil/dapsone	5 and 6	chlorproguanil/dapsone	chlorproguanil/dapsone	chlorproguanil/dapsone	chlorproguanil/dapsone
8	lapdap	-	lapdap	lapdap	lapdap	lapdap
9	1-8/OR	-	1-8/OR	1-8/OR	1-8/OR	1-8/OR
10	malaria	-	malaria	malaria	malaria	malaria
11	9 and 10	-	9 and 10	9 and 10	9 and 10	9 and 10

<sup>a</sup>Cochrane Infectious Diseases Group Specialized Register.

<sup>b</sup>Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration ([Alderson 2004](#)); upper case: MeSH or EMTREE heading; lower case: free text term.

### Conference proceedings

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

### Researchers and pharmaceutical companies

We contacted scientists working in the field of malaria, and GlaxoSmithKline, the pharmaceutical company that manufactures chlorproguanil-dapsone (LapDap), for any unpublished trials.

### 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 or by contacting the authors for clarification and additional information.

### 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 the 'Characteristics of included studies'. We had intended to primarily consider trials with intention-to-treat analysis, but only two trials had any outcomes analysed in this way (Allouche 2004; Sulo 2002).

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 assessed the methodological quality of the included trials using generation of allocation sequence, allocation concealment, blinding of the participants and clinicians, and loss to follow up. We have classed generation of allocation sequence and allocation concealment as adequate, inadequate, or unclear according to Juni 2001. We considered loss to follow up as adequate (acceptable) if it was 10% or lower. We classed blinding as open (all parties are aware of treatment), single blind (participant or care provider/assessor is aware of the treatment given), or double blind (trial uses a placebo or a double dummy technique such that neither the participant or care provider/assessor know which treatment is given).

### Data synthesis

We analysed data using Review Manager 5. We calculated the risk ratio (RR) for dichotomous data and mean difference (MD) for continuous data, and presented both with 95% confidence intervals (CI). We assessed heterogeneity among included trials by visually inspecting forest plots and carrying out a chi-squared test for heterogeneity (statistical significance at 10% level). We have stratified analyses according to dosing regimen of chlorproguanil-dapsone. We used the fixed-effect model to pool data because we did not detect heterogeneity.

Although we planned to carry out subgroup analyses based on the following subgroups, we did not perform this because few trials were identified. This may be possible in future updates of this review.

- Participant age ( $\leq 5$  years versus  $> 5$  years).
- Setting of the trial: (1) high versus low endemicity (high = hyperendemicity or holoendemicity and low = hypoendemicity or mesoendemicity); and (2) level of resistance to the comparator drug.

## RESULTS

### Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Six trials ( $n = 3352$ ) met our inclusion criteria ('Characteristics of included studies'). We excluded two trials ('Characteristics of excluded studies') and one trial is ongoing ('Characteristics of ongoing studies').

Three of the included trials were multicentred (Watkins 1988; Sulo 2002; Allouche 2004), and because the sites for Sulo 2002 and Allouche 2004 were in different countries, we have reported the results from each centre separately by labelling each site by country, for example Sulo-Kenya and Allouche-Gabon.

### Source of funding

The Wellcome Trust and African Medical & Research Foundation (AMREF) funded Watkins 1988. Keuter 1990 did not state the source of funding. The WHO and the Wellcome Trust funded Amukoye 1997. The LapDap Product Development Team (PDT), which includes GlaxoSmithKline Pharmaceuticals, funded Mutabingwa 2001. The WHO and GlaxoSmithKline Pharmaceuticals funded Sulo 2002, and along with the Department for International Development (UK) also funded Allouche 2004.

### Location and participants

All the trial sites were conducted in areas of high malaria transmission in Africa: five in Kenya (Watkins 1988 (Kilifi and Entasopia); Keuter 1990; Amukoye 1997; Sulo 2002; Allouche 2004); two in Malawi (Sulo 2002; Allouche 2004) and Tanzania (Mutabingwa 2001; Allouche 2004); one in Gabon (Allouche 2004); and one in Nigeria (Allouche 2004).

Four trials included children aged between 1 and 6 years, one included children aged 3 to 13 years, and one included schoolgirls and pregnant women (Keuter 1990).

One trial compared chlorproguanil-dapsone with sulfadoxine-pyrimethamine in participants who had already failed on sulfadoxine-pyrimethamine (Mutabingwa 2001).

### Intervention

All trials compared chlorproguanil-dapsone with sulfadoxine-pyrimethamine. One trial also included a chloroquine arm (Keuter 1990).

### Dose and regimen

Dose and regimen varied across trials. Two trials used 1.2 mg/kg chlorproguanil and 2.4 mg/kg dapsone: [Keuter 1990](#) administered it as a single dose; and [Amukoye 1997](#) administered it as a single dose in one group and as daily dose for three days in another group. [Watkins 1988](#) used a single dose of 1.2 mg/kg chlorproguanil and 8 mg/kg dapsone in Kilifi, and 1.2 mg/kg chlorproguanil and 2.4 mg dapsone in Entasopia. The 1.2 mg/kg chlorproguanil dose used in [Amukoye 1997](#), [Keuter 1990](#), and [Watkins 1988](#) is lower than the dose in the currently standard fixed-ratio tablet and as used in the other three trials. Three trials used 2 mg/kg chlorproguanil and 2.5 mg/kg dapsone for three days ([Mutabingwa 2001](#); [Sulo 2002](#); [Allouche 2004](#)).

### Length of follow up

Length of follow up ranged from seven days to one year ([Sulo 2002](#)), although [Sulo 2002](#) only reported on review outcomes (treatment failure and adverse events) at day 7. Three trials followed participants up to day 28 ([Watkins 1988](#); [Keuter 1990](#); [Amukoye 1997](#)), but none of these used the current standard dosing schedule. [Mutabingwa 2001](#) and [Sulo 2002](#) reported outcomes at day 7, and [Allouche 2004](#) up to day 14.

### Resistance

Resistance to the comparator drug is mentioned in four trials: resistance to sulfadoxine-pyrimethamine was low in Kenya (Kil-

ifi) ([Sulo-Kenya](#)); present to some extent in Malawi (Blantyre) ([Sulo-Malawi](#)); and high in the Tanzania trial ([Mutabingwa 2001](#)). Resistance to chloroquine was high in Kenya ([Keuter 1990](#)), but the level of resistance to sulfadoxine-pyrimethamine is not clear in this trial. [Watkins 1988](#) and [Amukoye 1997](#) do not describe the background resistance to sulfadoxine-pyrimethamine, but it may be inferred to be low because the trials were carried out at an earlier time period in the same area as [Sulo-Kenya](#).

### Outcomes

All but one trial reported the presence of parasites at various time points ([Sulo 2002](#)); [Allouche 2004](#) provided data on parasitaemia on request. No trials reported on parasite clearance time and time to fever clearance. We obtained data on fever at various time points from [Allouche 2004](#) on request. Treatment failure was reported by all the trials. We were unable to present data on the use of antipyretics because the only trials that mentioned them – [Amukoye 1997](#) and [Sulo 2002](#) – either gave them uniformly or did not give sufficient detail to allow further analyses. All trials mentioned adverse events, but only some described the procedure to identify them.

### Risk of bias in included studies

The methodological quality of the included trials is summarized in [Table 3](#).

**Table 3. Methodological quality of included studies**

Trial	Allocation sequence	Allocation concealed	Blinding	Loss to follow up
<a href="#">Allouche 2004</a>	Adequate	Adequate	Double blinded <sup>a</sup>	Adequate (< 10%)
<a href="#">Amukoye 1997</a>	Adequate	Adequate	Double blinded <sup>b</sup>	Inadequate (13.4%)
<a href="#">Keuter 1990</a>	Inadequate (3-block allocation)	Inadequate	Open	Inadequate (> 18% at 4 weeks)
<a href="#">Mutabingwa 2001</a>	Inadequate (alternate)	Inadequate	Open	Adequate (< 10%)
<a href="#">Sulo 2002</a>	Adequate	Adequate	Double blinded <sup>a</sup>	Adequate (< 10%)
<a href="#">Watkins 1988</a>	Inadequate (alternate)	Unclear	Not described	Adequate (< 10%)

<sup>a</sup>Participants, providers, and assessors blinded.

<sup>b</sup>Participants and assessors blinded; provider not blinded.

Generation of allocation sequence was adequate in three trials, and inadequate in the trials that allocated treatment to women in blocks of three according to the order that they came in (Keuter 1990) and the two that used alternate allocation (Watkins 1988; Mutabingwa 2001).

For allocation concealment, three trials used adequate methods (Amukoye 1997; Sulo 2002; Allouche 2004), and three used inadequate methods (Watkins 1988; Keuter 1990; Mutabingwa 2001).

For blinding, the three trials with adequate allocation concealment also concealed the allocation to the participants and to the assessors. Two trials had no blinding, and one did not describe methods for blinding (Watkins 1988).

For losses to follow up, no trial included all the enrolled participants in the final analysis. Losses to follow up were less than 10% in four trials (Watkins 1988; Mutabingwa 2001; Sulo 2002; Allouche 2004), 13.4% in Amukoye 1997, and over 18% in Keuter 1990.

## Effects of interventions

### One-dose chlorproguanil-dapsone regimen (with 1.2 mg chlorproguanil)

#### Versus chloroquine

One trial with a 28-day follow up assessed this regimen (Keuter 1990).

#### Parasitaemia

Parasitaemia tended to be lower with chlorproguanil-dapsone at days 7, 14, 21, and 28 (Analysis 1.1). However, this was not statistically significant for the two primary review outcomes of day 14 (RR 0.55, 95% CI 0.17 to 1.80; n = 153) and day 28 (RR 0.77, 95% CI 0.34 to 1.74; n = 110).

#### Treatment failure by day 28

Chlorproguanil-dapsone had fewer treatment failures than chloroquine (RR 0.41, 95% CI 0.26 to 0.63; n = 165, Analysis 1.2).

#### Adverse events

This trial did not describe any procedure to identify adverse events, and none were reported.

#### Versus sulfadoxine-pyrimethamine

Three trials compared a one-dose regimen with sulfadoxine-pyrimethamine (Watkins 1988; Keuter 1990; Amukoye 1997).

#### Parasitaemia

More participants treated with chlorproguanil-dapsone than sulfadoxine-pyrimethamine had parasitaemia by day 14 and day 28

(Analysis 2.1); the difference was statistically significant at day 28 (RR 3.11, 95% CI 2.28 to 4.24; n = 527).

#### Treatment failure by day 28

The risk of treatment failure was much higher for the chlorproguanil-dapsone group compared with the sulfadoxine-pyrimethamine group (RR 2.77, 95% CI 1.86 to 4.10; n = 547, Analysis 2.2).

#### Adverse events

Only Amukoye 1997 reported this, with no events with chlorproguanil-dapsone compared with three serious adverse events ("parasitaemic and admitted to hospital") in the sulfadoxine-pyrimethamine group. This was not statistically significant (Analysis 2.3).

### Three-dose chlorproguanil-dapsone regimen (with 1.2 mg chlorproguanil)

#### Versus sulfadoxine pyrimethamine

One trial assessed this regimen (Amukoye 1997).

#### Parasitaemia

At day 28, statistically significantly more participants treated with chlorproguanil-dapsone had parasitaemia compared with those treated with sulfadoxine-pyrimethamine (RR 2.07, 95% CI 1.41 to 3.03; n = 294, Analysis 3.1). No results were reported for parasitaemia at day 14, and no statistically significant difference was detected at day 7 (Analysis 3.1).

#### Treatment failure by day 28

Chlorproguanil-dapsone was associated with statistically significantly more treatment failures than sulfadoxine-pyrimethamine (RR 2.27, 95% CI 1.27 to 4.05; n = 294, Analysis 3.2).

#### Mean haemoglobin

No statistically significant difference in mean haemoglobin was demonstrated between participants when assessed on days 0, 7, 14, 21, and 28 (Analysis 3.3).

#### Adverse events

One adverse event was recorded with chlorproguanil-dapsone, and three serious adverse events ("parasitaemic and admitted to hospital") with sulfadoxine-pyrimethamine; the difference was not statistically significant (Analysis 3.4).

### Three-dose chlorproguanil-dapsone regimen (with 2.0 mg chlorproguanil)

#### Versus sulfadoxine-pyrimethamine (previous sulfadoxine-pyrimethamine failures)

One trial examined people who had failed on sulfadoxine-pyrimethamine and needed re-treatment (Mutabingwa 2001).

### Parasitaemia

No results were available for day 14 or day 28, but by day 7 chlorproguanil-dapsone was statistically significantly better at clearing parasites than sulfadoxine-pyrimethamine (RR 0.11, 95% CI 0.04 to 0.34; n = 90, [Analysis 4.1](#)).

#### Treatment failure by day 7

There were statistically significantly fewer treatment failures with chlorproguanil-dapsone by day 7 (RR 0.11, 95% CI 0.04 to 0.33; n = 92, [Analysis 4.2](#)).

#### Treatment failure by day 28

This was not reported.

### Adverse events

Only one adverse event, which occurred in the sulfadoxine-pyrimethamine group, was reported; and the difference in the number of adverse events was not statistically significantly different ([Analysis 4.3](#)).

### Versus sulfadoxine-pyrimethamine (new attendees)

Two trials assessed this regimen ([Sulo 2002](#); [Allouche 2004](#)).

### Parasitaemia

[Allouche 2004](#) reported that parasitaemia was statistically significantly lower with chlorproguanil-dapsone at day 7 (RR 0.31, 95% CI 0.15 to 0.63; n = 1850) and day 14 (RR 0.56, 95% CI 0.37 to 0.85; n = 1850); see [Analysis 5.1](#).

### Presence of fever

[Allouche 2004](#) reported no statistically significant difference in the presence of fever (defined as temperature  $\geq 37.5$  °C) at day 7 (RR 0.77, 95% CI 0.42 to 1.42; n = 1850) or day 14 (RR 1.58, 95% CI 0.79 to 3.17; n = 1850); see [Analysis 5.2](#).

#### Treatment failure by day 7

[Sulo 2002](#) reported that chlorproguanil-dapsone was associated with statistically significantly fewer treatment failures than sulfadoxine-pyrimethamine (RR 0.30, 0.19 to 0.49; n = 827, [Analysis 5.3](#)).

#### Treatment failure by day 14

[Allouche 2004](#) reported that chlorproguanil-dapsone was associated with statistically significantly fewer treatment failures than sulfadoxine-pyrimethamine (RR 0.36, 95% CI 0.24 to 0.53; n = 1709, [Analysis 5.4](#)). [Sulo 2002](#) did not report this outcome.

#### Treatment failure by day 28

Neither trial reported this outcome.

### Mean haemoglobin

[Allouche 2004](#) assessed mean haemoglobin on days 0, 3, 7, and 14 ([Analysis 5.5](#)). Day 14 haemoglobin was only measured for a small number of participants whose day 7 results caused concern. Mean haemoglobin tended to be lower for participants on chlorproguanil-dapsone than sulfadoxine-pyrimethamine at each time point, but this was statistically significant only at day 7 (MD -0.40 g/dL, 95% CI -0.62 to -0.18; n = 1701).

### Adverse events

Adverse events recorded included vomiting, diarrhoea, anorexia, abdominal pain, pneumonia, severe malaria, skin rash, red blood cell disorders, gastrointestinal disorders, and death; see [Analysis 5.6](#) and [Analysis 5.7](#). There were no statistically significant differences in the number of participants on chlorproguanil-dapsone reporting any adverse event compared with sulfadoxine-pyrimethamine (RR 0.97, 95% CI 0.87 to 1.09; n = 2679).

Both trials reported serious adverse events. [Sulo 2002](#) reported severe malaria leading to hospitalization (n = 60) and death (n = 1), with no statistically significant difference between the groups (RR 0.99, 95% CI 0.61 to 1.61, n = 829). [Allouche 2004](#) defined serious adverse events as serious "Treatment Emergent Signs and Symptoms (TESS)" (see [Analysis 5.7](#)), and also reported no statistically significant difference between the two groups (RR 1.00, 95% CI 0.34 to 2.97; n = 1850), although serious red blood cells disorders appeared more common in people treated with chlorproguanil-dapsone.

[Sulo 2002](#) reported on adverse events leading to discontinuation of treatment, and that they were more common with chlorproguanil-dapsone than sulfadoxine-pyrimethamine (RR 4.54, 95% CI 1.74 to 11.82; n = 829).

The primary outcome for [Allouche 2004](#) was safety and accordingly provided more adverse event data than the other trials (see [Table 4](#)). There were more TESS probably related to the intervention in the chlorproguanil-dapsone group (RR 1.62, 95% CI 1.09 to 2.40; n = 1850). The most commonly reported adverse events were red blood cells disorders. These were also more common on chlorproguanil-dapsone compared with sulfadoxine-pyrimethamine (80/1480 on chlorproguanil-dapsone, 7/370 on sulfadoxine-pyrimethamine; RR 2.86, 95% CI 1.33 to 6.13, n = 1850). Clinically significant methaemoglobinaemia (defined as values exceeding 10%) was also seen far more frequently on chlorproguanil-dapsone compared with sulfadoxine-pyrimethamine, but this was only measured in one site (Kenya) and was not statistically significant (RR 15.78, 95% CI 0.97 to 257.15). There was a statistically significant difference in mean methaemoglobin (reported as a percentage of total haemoglobin) on day three in favour of sulfadoxine-pyrimethamine (MD 3.8 g/dL, 95% CI 3.4 to 4.2). There was a tendency for anaemia, haemolysis, and haemolytic anaemia to be more common in participants treated with chlorproguanil-dapsone, but these were not statistically significant.

**Table 4. Additional adverse event data from Allouche 2004**

Adverse event (TESS <sup>a</sup> )	Chlorproguanil-dapsone (n/N)	Sulfadoxine-pyrimethamine (n/N)	RR or MD <sup>b</sup>
TESS <sup>a</sup> probably related to study medication	168/1480	26/370	RR 1.62, 95% CI 1.09 to 2.40
Red blood cell disorders	80/1480	7/370	RR 2.86, 95% CI 1.33 to 6.13
Anaemia	51/1480	7/370	RR 1.82, 95% CI 0.83 to 3.98
Methaemoglobinaemia <sup>c</sup>	22/230	0/80	RR 15.78, 95% CI 0.97 to 257.15
Day 3 mean methaemoglobin <sup>d</sup> (95% confidence interval)	4.2 (3.8 to 4.6), n = 301	0.4 (0.4 to 0.5), n = 77	MD 3.8, 95% CI 3.4 to 4.2
Haemolysis	6/1480	0/370	RR 3.26, 95% CI 0.18 to 57.68
Haemolytic anaemia	4/1480	0/370	RR 2.25, 95% CI 0.12 to 41.78

<sup>a</sup>TESS: Treatment Emergent Signs and Symptoms.

<sup>b</sup>Risk ratio (RR) or mean difference (MD) presented with 95% confidence intervals (CI).

<sup>c</sup>Defined as value > 10%, carried out only in Kenya site.

<sup>d</sup>Percentage of total haemoglobin.

## DISCUSSION

The trials were of variable methodological quality. Three trials had adequate generation of allocation sequence, allocation concealment, and double blinding (Amukoye 1997; Sulo 2002; Allouche 2004), but only two of these had losses to follow up of less than 10% (Sulo 2002; Allouche 2004). Only two trials carried out any intention-to-treat analyses (Sulo 2002; Allouche 2004). Mutabingwa 2001 was carried out with participants who had already failed on sulfadoxine-pyrimethamine, and it cannot be regarded as a first-line comparison between chlorproguanil-dapsone and sulfadoxine-pyrimethamine.

Three trials using the lower dose of chlorproguanil (1.2 mg) examined day 28 parasitaemia and treatment failure (Watkins 1988; Keuter 1990; Amukoye 1997). The results show that both the one-dose regimen (3 trials) and three-dose regimen (1 trial) were

generally less effective than one-dose sulfadoxine-pyrimethamine regimen.

One trial using the current standard dosing regimen (with 2 mg chlorproguanil) compared this with sulfadoxine-pyrimethamine in participants who were selected on the basis of previous failure to sulfadoxine-pyrimethamine (Mutabingwa 2001). It is therefore difficult to draw any conclusions about comparative effectiveness of these two drugs given that the participants selected are more likely to have infections resistant to sulfadoxine-pyrimethamine.

No information is available at 28 days using the current standard dosing regimen (with 2 mg chlorproguanil) for parasitaemia or treatment failure by day 28. One trial measured this according to the stated methods (Sulo 2002), but did not report results for it; and the most recent trial, Allouche 2004, stopped follow up at day 14. Some recent evidence suggests day 14 treatment failure may have no predictive value in identifying true failures (Stepniowska 2004). There is thus currently insufficient evidence to be clear whether chlorproguanil-dapsone is superior or inferior to sulfadoxine-pyrimethamine.

All the trials mentioned adverse events, but only two described the procedure to assess them (Sulo 2002; Allouche 2004), which creates uncertainty over the completeness of these data. Also, the day of treatment when adverse events occurred were not always reported, and thus it was not possible to report this information in this review. Serious adverse events tended to be commoner with chlorproguanil-dapsone, but overall this was not statistically significant. Red blood cells disorders were more common in participants treated with chlorproguanil-dapsone, and Looareesuwan 2004 comments on aspects of safety in a *Lancet* editorial.

Although Keuter 1990 included pregnant women, it is still not possible to conclusively determine the effectiveness and safety of chlorproguanil-dapsone in this group because participants were a mixed group, numbers for important outcomes were sometimes too few, and adverse event outcomes were not reported.

## AUTHORS' CONCLUSIONS

### Implications for practice

No data are available after day 14 for the current standard chlor-

proguanil-dapsone regimen (three doses, 2 mg chlorproguanil), and therefore there is insufficient evidence to know whether this drug is inferior or superior to current regimens of chloroquine or sulfadoxine-pyrimethamine.

2008: Chlorproguanil-dapsone was withdrawn in 2008 (see the 'What's new' statement), and the review will not be updated.

### Implications for research

2008: Chlorproguanil-dapsone was withdrawn in 2008 (see the 'What's new' statement).

## ACKNOWLEDGEMENTS

Hasifa Bukirwa developed this review during a 12-month training Fellowship organized by the Effective Health Care Alliance Programme (EHCAP) at the Liverpool School of Tropical Medicine, funded by the Department for International Development (UK).

## REFERENCES

### References to studies included in this review

#### Allouche 2004 {published and unpublished data}

Allouche A, Bailey W, Barton S, Bwika J, Chimpeni P, Falade CO, et al. Comparison of chlorproguanil-dapsone with sulfadoxine-pyrimethamine for the treatment of uncomplicated falciparum malaria in young African children: double-blind randomised controlled trial. *Lancet* 2004;**363**(9424):1843–8.

#### Allouche-Gabon {published and unpublished data}

Gabon site of Allouche 2004 multicentre trial.

#### Allouche-Kenya {published and unpublished data}

Kenya site of Allouche 2004 multicentre trial.

#### Allouche-Malawi {published and unpublished data}

Malawi site of Allouche 2004 multicentre trial.

#### Allouche-Nigeria {published and unpublished data}

Nigeria site of Allouche 2004 multicentre trial.

#### Allouche-Tanzania {published and unpublished data}

Tanzania site of Allouche 2004 multicentre trial.

#### Amukoye 1997 {published data only}

Amukoye E, Winstanley PA, Watkins WM, Snow RW, Hatcher J, Mosobo M, et al. Chlorproguanil-dapsone: effective treatment for uncomplicated falciparum malaria. *Antimicrobial Agents and Chemotherapy* 1997;**41**(10):2261–4.

#### Keuter 1990 {published data only}

Keuter M, van Eijk A, Hoogstrate M, Raasveld M, van de Ree M, Ngwawe WA, et al. Comparison of chloroquine, pyrimethamine and sulfadoxine, and chlorproguanil and dapsone as treatment for falciparum malaria in pregnant and non-pregnant women, Kakamega District, Kenya. *BMJ* 1990;**301**(6750):466–70.

#### Mutabingwa 2001 {published data only}

Mutabingwa T, Nzila A, Mberu E, Nduati E, Winstanley P, Hills E, et al. Chlorproguanil-dapsone for treatment of drug-resistant falciparum malaria in Tanzania. *Lancet* 2001;**358**(9289):1218–23.

#### Sulo 2002 {published data only}

Sulo J, Chimpeni P, Hatcher J, Kublin JG, Plowe CV, Molyneux ME, et al. Chlorproguanil-dapsone versus sulfadoxine-pyrimethamine for sequential episodes of uncomplicated falciparum malaria in Kenya and Malawi: a randomised clinical trial. *Lancet* 2002;**360**(9340):1136–43.

#### Sulo-Kenya {published data only}

Kenya site of Sulo 2002 multicentre trial.

#### Sulo-Malawi {published data only}

Malawi site of Sulo 2002 multicentre trial.

#### Watkins 1988 {published data only}

Watkins WM, Brandling-Bennett AD, Nevill CG, Carter JY, Boriga DA, Howells RE, et al. Chlorproguanil/dapsone for the treatment of non-severe Plasmodium falciparum malaria in Kenya: a pilot study. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1988;**82**(3):398–403.

### References to studies excluded from this review

#### Trigg 1997 {published data only}

Trigg JK, Mbwana H, Chambo O, Hills E, Watkins W, Curtis CF. Resistance to pyrimethamine/sulfadoxine in Plasmodium falciparum in 12 villages in northeast Tanzania and a test of chlorproguanil/dapsone. *Acta Tropica* 1997;**63**(2-3):185–9.

**Wilairatana 1997** *{published data only}*

Wilairatana P, Kyle DE, Looareesuwan S, Chinwongprom K, Amradee S, White NJ, et al. Poor efficacy of antimalarial biguanide-dapsone combinations in the treatment of acute, uncomplicated, falciparum malaria in Thailand. *Annals of Tropical Medicine and Parasitology* 1997;**91**(2):125–32.

**References to ongoing studies****Laloo 2004** *{unpublished data only}*

Laloo D, Winstanley, P, Molyneux M, Wootton D, Phiri N. A pragmatic trial examining the effect of compliance upon clinical effectiveness and cost effectiveness of LapDap<sup>TM</sup> (CPG-DDS) when compared to sulfadoxine-pyrimethamine (SP) and Co-artem (AM-LU) for the treatment of uncomplicated falciparum malaria in Malawi. Unpublished 2004.

**Additional references****Alderson 2004**

Alderson P, Green S, Higgins J, editors. Highly sensitive search strategies for identifying reports of randomized controlled trials in MEDLINE. Cochrane Reviewer's Handbook 4.2.2 [updated March 2004]; Appendix 5b. In: The Cochrane Library. The Cochrane Collaboration. Chichester, UK: John Wiley & Sons, Ltd.; 2004, Issue 2.

**Allen 1990**

Allen SJ, Otoo LN, Cooke GA, O'Donnell A, Greenwood BM. Sensitivity of Plasmodium falciparum to chlorproguanil in Gambian children after five years of continuous chemoprophylaxis. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1990;**84**(2):218.

**Curtis 2002**

Curtis J, Maxwell CA, Msuya FHM, Mkongewa S, Allouche A, Warhurst DC. Mutations in dhfr in Plasmodium falciparum infections selected by chlorproguanil-dapsone treatment. *Journal of Infectious Diseases* 2002;**186**(12):1861–4.

**D'Alessandro 2001**

D'Alessandro U, Buttiens H. History and importance of antimalarial drug resistance. *Tropical Medicine and International Health* 2001;**6**(11):845–8.

**GlaxoSmithKline 2003**

GlaxoSmithKline. MHRA approves anti-malarial LapDap. [www.gsk.com/press/archive/press2003/press\\_08062003.htm](http://www.gsk.com/press/archive/press2003/press_08062003.htm) (accessed 16 October 2003).

**Greenwood 1989**

Greenwood BM, Greenwood AM, Smith AW, Menon A, Bradley AK, Snow RW, et al. A comparative study of Lapudrine (chlorproguanil) and Maloprim (pyrimethamine and dapsone) as chemoprophylactics against malaria in Gambian children. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1989;**83**(2):182–8.

**Jüni 2001**

Jüni P, Altman DG, Egger M. Systematic reviews in healthcare: Assessing the quality of controlled clinical trials. *BMJ* 2001;**323**(7303):42–6.

**Le Bras 2003**

Le Bras J, Durand R. The mechanisms of resistance to antimalarial drugs in Plasmodium falciparum. *Fundamental & Clinical Pharmacology* 2003;**17**(2):147–53.

**Looareesuwan 2004**

Looareesuwan S, Imwong M, Wilairatana P. Chlorproguanil-dapsone for malaria in Africa. *Lancet* 2004;**363**(9424):1838–9.

**Ozawa 2002**

Ozawa H, Maruyama Y. A 50-year history of new drugs in Japan: the developments of antileprosy drugs and their epidemiological aspects [Oyo Yakuri Kenkyurai]. *Yakushigaku Zasshi* 2002;**37**(1):76–83.

**Review Manager 5**

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.0. Copenhagen, England: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008.

**Stepniewska 2004**

Stepniewska K, Taylor WRJ, Mayxay M, Smithius F, Guthmann JP, Barnes K, et al. The in vivo assessment of antimalarial drug efficacy in falciparum malaria. Unpublished 2004.

**Thompson 1972**

Thompson PE, Werbel LM. *Antimalarial agents: chemistry and pharmacology*. Vol. 12, New York and London: Academic Press, 1972.

**Triglia 1999**

Triglia T, Cowman AF. Mechanism of resistance to sulfa drugs. *Drug Resistance Updates* 1999;**2**:15–9.

**Verhoeff 1997**

Verhoeff FH, Brabin BJ, Masache P, Kachale B, Kazembe P, Van der Kaay HJ. Parasitological and haematological responses to treatment of Plasmodium falciparum malaria with sulfadoxine-pyrimethamine in southern Malawi. *Annals of Tropical Medicine and Parasitology* 1997;**91**(2):133–40.

**Warsame 2002**

Warsame M, Abdillahi A, Nur Duale A, Nur Ismail A, Hassan AM, Mohamed A, et al. Therapeutic efficacy of chloroquine and sulfadoxine/pyrimethamine against Plasmodium falciparum infection in Somalia. *Bulletin of the World Health Organization* 2002;**80**(9):704–8.

**White 1998**

White NJ. Drug resistance in malaria. *British Medical Bulletin* 1998;**54**(3):703–15.

**WHO 1988**

World Health Organization. Development of recommendations for the protection of short-stay travellers to malaria endemic areas: Memorandum from two WHO Meetings. *Bulletin of the World Health Organization* 1988;**66**(2):177–96.

**WHO 1999**

World Health Organization. Rolling back malaria. *The world health report : 1999 : Making a difference*. Geneva: World Health Organization, 1999:49–63.

**WHO 2000**

World Health Organization. WHO Expert Committee on Malaria. WHO Technical Report Series 892. [mosquito.who.int/docs/ecr20.pdf](http://mosquito.who.int/docs/ecr20.pdf) (accessed 10 March 2003).

**WHO 2001**

World Health Organization. Severe malaria in the African region: results of a multicentre study. *Malaria Liason Bulletin of the Malaria Programme WHO/AFRO* 2001; Vol. 4, issue 2.

**WHO 2002**

World Health Organization. Cluster on Communicable Diseases. *Monitoring antimalarial drug resistance : report of a WHO consultation, Geneva, Switzerland, 3-5 December 2001*. Geneva: World Health Organization, 2002.

**WHO 2008**

World Health Organization. Antimalarial chlorproguanil-dapsone (LapDap™) withdrawn following demonstration of post-treatment haemolytic anaemia in G6PD deficient patients in a Phase III trial of chlorproguanil-dapsone-artesunate (Dacart™) versus artemether-lumefantrine (Coartem®) and confirmation of findings in a comparative trial of LapDap™ versus Dacart™. Information Exchange System Alert No. 117 ([www.who.int/medicines/publications/drugalerts/Alert`117`LapDap.pdf](http://www.who.int/medicines/publications/drugalerts/Alert%20117%20LapDap.pdf)) 4 March 2008.

**Wolf 2002**

Wolf R, Matz H, Orion E, Tuzun B, Tuzun Y. Dapsone. *Dermatology Online Journal* (accessed 23 January 2003); Vol. 8, issue 1.

**ZANA 2003**

Zambia News Agency. New anti-malaria drug launched. [www.zana.gov.zm/news/viewnews.cgi?category=7&cid=1064068189](http://www.zana.gov.zm/news/viewnews.cgi?category=7&cid=1064068189) (accessed 16 October 2003).

\* *Indicates the major publication for the study*

## CHARACTERISTICS OF STUDIES

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

#### Allouche 2004

Methods	Randomized controlled trial (randomized parallel design). Double placebo was used Multicentre trial with sites in Gabon ( <a href="#">Allouche-Gabon</a> ), Kenya ( <a href="#">Allouche-Kenya</a> ), Malawi ( <a href="#">Allouche-Malawi</a> ), Nigeria ( <a href="#">Allouche-Nigeria</a> ), and Tanzania ( <a href="#">Allouche-Tanzania</a> ) Length of follow up: 14 days Intention-to-treat analysis: used for some of the safety outcomes
Participants	Enrolled 1850 children aged 12 to 120 months Inclusion criteria: pure asexual <i>P. falciparum</i> parasitaemia 2000 to 100,000 parasites/ $\mu$ L blood Exclusion criteria: severe malaria; parasitaemia > 100,000/ $\mu$ L, haemoglobin < 6.5 g/dL; convulsions; concomitant infection or disease; allergy to sulfonamides; antimalarial treatment within past 7 days; and use of any of interventions within past 30 days
Interventions	1. Chlorproguanil (2 mg/kg) + dapsone (2.5 mg/kg), once daily for 3 days (3-dose regimen) 2. Sulfadoxine (25 mg/kg) + pyrimethamine (1.25 mg/kg), 1 dose
Outcomes	1. Parasite carriage on days 3, 7, and 14 2. Haematological and biochemical tests done on days 0 and 7 3. Treatment failure 4. Treatment Emergent Signs and Symptoms (TESS)
Notes	Trial location: 5 African countries (Gabon, Kenya, Malawi, Nigeria, and Tanzania) Trial dates: 13 March to 14 December 2000 Treatment failure outcome: data missing for 8% of participants in chlorproguanil-dapsone group and 7% in sulfadoxine-pyrimethamine group

#### Allouche-Gabon

Methods	Gabon site in <a href="#">Allouche 2004</a>
Participants	-
Interventions	-
Outcomes	-
Notes	-

#### Allouche-Kenya

Methods	Kenya site in <a href="#">Allouche 2004</a>
Participants	-

**Allouche-Kenya** (Continued)

Interventions	-
Outcomes	-
Notes	-

**Allouche-Malawi**

Methods	Malawi site in <a href="#">Allouche 2004</a>
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Allouche-Nigeria**

Methods	Nigeria site in <a href="#">Allouche 2004</a>
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Allouche-Tanzania**

Methods	Tanzania site in <a href="#">Allouche 2004</a>
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Amukoye 1997**

Methods	Randomized controlled trial (randomized parallel design) Length of follow up: 28 days Intention-to-treat analysis: not used
Participants	Enrolled 511 febrile children (6 to 71 months) Inclusion criteria: children attending hospital included if well enough for outpatient management; resident within study area; capillary haemoglobin level of 5 g/dL or greater; uncomplicated pure falciparum malaria parasites between 2000 and 250,000/ $\mu$ L blood Exclusion criteria: concurrent infection; allergy to sulfonamides; treatment with sulfadoxine-pyrimethamine or pyrimethamine-sulfalene within 2 months, or treatment with chloramphenicol, or co-trimoxazole, erythromycin, or tetracycline within last week
Interventions	1. Chlorproguanil (1.2 mg/kg) + dapsone (2.4 mg/kg), 1 dose 2. Chlorproguanil (1.2 mg/kg) + dapsone (2.4 mg/kg), 3 doses over 3 days 3. Sulfadoxine (25 mg/kg) + pyrimethamine (1.25 mg/kg), 1 dose Antipyretic used in all participants
Outcomes	1. Fever on day 2 2. Parasite carriage on days 0, 2, 7, and trial end point 3. Mean haemoglobin (g/dL) on days 0, 2, 7, 14, 21, and 28 4. Treatment failure 5. Adverse events 6. Self-reported compliance
Notes	Trial location: Kenya Trial dates: July 1993 to April 1995 Loss to follow up were withdrawals due to vomiting study medication

**Keuter 1990**

Methods	Quasi-randomized controlled trial (parallel design, block allocation) Length of follow up: 6 weeks Intention-to treat-analysis: not used
Participants	Enrolled 158 adult pregnant women attending primary care hospital, and 105 non-pregnant secondary school girls of reproductive age Inclusion criteria for pregnant women: 20 to 36 weeks of pregnancy; asexual parasitaemia 500 to 100,000 asexual forms/ $\mu$ L blood; negative urine sample for sulfonamides Inclusion criteria for school girls not given Exclusion criteria: none stated
Interventions	1. Chloroquine base (25 mg/kg) over 3 days 2. Sulfadoxine (1500 mg) + pyrimethamine (75 mg), 1 dose 3. Chlorproguanil (1.2 mg/kg) + dapsone (2.4 mg/kg), 1 dose
Outcomes	1. Parasite carriage on days 7, 14, 21, 28 up to 42 2. Mean haemoglobin and change from the start value on day 28 3. Treatment failure 4. Adverse events

**Keuter 1990** (Continued)

Notes	<p>Trial location: Kenya</p> <p>Trial dates: March to July 1988</p> <p>Mean parasitaemia given at entry only and by gravity (not intervention)</p>
-------	--

**Mutabingwa 2001**

Methods	<p>Quasi-randomized controlled trial</p> <p>Trial had two stages:</p> <ol style="list-style-type: none"> <li>1. sulfadoxine-pyrimethamine used alone;</li> <li>2. then either sulfadoxine-pyrimethamine or chlorproguanil-dapsone used in parallel in failures on sulfadoxine-pyrimethamine</li> </ol> <p>Length of follow up: 7 days</p> <p>Intention-to-treat analysis: not used</p>
Participants	<p>Enrolled 92 febrile children &lt; 5 years old</p> <p>Inclusion criteria: &lt; 5 years; pure infection of <i>Plasmodium falciparum</i> of at least 2000 parasites/<math>\mu</math>L; not suffering from severe and complicated malaria; able to take study drugs by oral route; parent/guardian available to give consent. (These were the inclusion criteria for the primary study. It is not clear whether they followed for the secondary study where chlorproguanil-dapsone was used. It was specified that children who failed on initial treatment with sulfadoxine-pyrimethamine and had a positive blood slide plus axillary temperature <math>\geq 37.5</math> °C.)</p> <p>Exclusion criteria: none stated</p>
Interventions	<ol style="list-style-type: none"> <li>1. Chlorproguanil (2 mg/kg) + dapsone (2.5 mg/kg), 3 doses</li> <li>2. Sulfadoxine (25 mg/kg) + pyrimethamine (1.25 mg/kg), 1 dose</li> </ol>
Outcomes	<ol style="list-style-type: none"> <li>1. Fever clearance time</li> <li>2. Parasite carriage at day 7</li> <li>3. Treatment failure at day 7</li> <li>4. Adverse events</li> </ol>
Notes	<p>Trial location: north-east Tanzania</p> <p>Trial dates: April 1998 to May 1999</p> <p>North-east Tanzania has hyperendemic to holoendemic malaria transmission</p> <p>The trial had primary and secondary study groups: primary study group was treated with sulfadoxine-pyrimethamine; participants who had a positive blood smear on day 7 and were febrile (<math>\leq 37.50</math> °C) constituted the secondary study group; secondary study group treated alternatively with either sulfadoxine-pyrimethamine or chlorproguanil-dapsone</p> <p>16 participants potentially eligible for secondary study were excluded after the primary stage, but no reasons given</p>

## Sulo 2002

Methods	Randomized controlled trial (parallel treatment groups) Multicentre trial with one arm in Kilifi, Kenya ( <a href="#">Sulo-Kenya</a> ) and other arm in Blantyre, Malawi ( <a href="#">Sulo-Malawi</a> ) Length of follow up: aimed at 1 year when incidence of malaria episodes was recorded and same drug given for each episode Intention-to-treat analysis: used only for treatment failure outcome
Participants	Enrolled febrile children aged 3 to 71 months: 410 in Kilifi and 500 in Blantyre Inclusion criteria: uncomplicated malaria; well enough for outpatient care; capillary haemoglobin at least 70 g/L; falciparum parasitaemia below 250,000/ $\mu$ L blood Exclusion criteria: children with concurrent infection; allergy to sulfonamides; or treatment within last week with sulfadoxine-pyrimethamine, pyrimethamine-sulfalene, mefloquine, amodiaquine, halofantrine, or quinine; chloroquine treatment at an earlier date was not an exclusion criterion
Interventions	1. Chlorproguanil (2 mg/kg) + dapsone (2.5 mg/kg), once daily for 3 days (3-dose regimen) 2. Sulfadoxine (25 mg/kg) + pyrimethamine (1.25 mg/kg), 1 dose followed with placebo for 2 days All participants were given paracetamol
Outcomes	1. Malaria incidence (not used in this review) 2. Development of severe malaria 3. Treatment failure 4. Completion of 1 year of follow up 5. Death 6. Severe anaemia 7. Vomiting of study medication 8. Serious adverse drug reactions
Notes	Trial location: Kilifi, Kenya and Blantyre, Malawi Trial dates: July 1996 to August 1998 for the Kenya site; and January 1997 to January 1999 for the Malawi site Kilifi is on the Kenyan coast with year round malaria transmission and low resistance to sulfadoxine-pyrimethamine (11.3% reported in same multicentre trial) Blantyre, Malawi has year round transmission of malaria and relatively high resistance to sulfadoxine-pyrimethamine (20.2% reported in the same multicentre trial)

## Sulo-Kenya

Methods	Kenya site in <a href="#">Sulo 2002</a>
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Sulo-Malawi**

Methods	Malawi site in <a href="#">Sulo 2002</a>
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Watkins 1988**

Methods	Quasi-randomized controlled trial (parallel trial) Multicentre trial: Kilifi and Entasopia, Kenya Length of follow up: 28 day
Participants	Enrolled 112 children between 6 to 13 years at Kilifi and 3 to 13 years at Entasopia Inclusion criteria: falciparum on thick blood film; patient not acutely ill; negative Dill-Glazko test for 4-aminoquinolines and Bratton-Marshall test for sulfonamides in urine Exclusion criteria: none stated
Interventions	1. Chlorproguanil (1.2 mg/kg) + dapsone (8 mg/kg), 1 dose, Kilifi 2. Chlorproguanil (1.2 mg/kg) + dapsone (2.4 mg/kg), 1 dose, Entasopia 3. Chlorproguanil (1.2 mg/kg), 1 dose, Kilifi 4. Sulfadoxine (24 mg/kg) + pyrimethamine (1.2 mg/kg), 1 dose
Outcomes	1. Parasite carriage at days 7, 14, 21, and 28 2. Parasite clearance time 3. Treatment failure 4. Adverse events
Notes	Trial location: Kilifi and Entasopia, Kenya Trial dates: March 1988 (Kilifi) and December 1988 (Entasopia) Kilifi is on the east coast of Kenya with hyperendemic to holoendemic transmission Entasopia is on the south-western wall of the Rift Valley with seasonal malaria transmission (unclear if hyperendemic) Background resistance to sulfadoxine-pyrimethamine is unclear

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

Trigg 1997	Community study from north-east Tanzania excluded because not all participants had falciparum malaria and severity was not clear
Wilairatana 1997	Chlorproguanil-dapsone was compared to proguanil-dapsone, itself not currently used for treating malaria

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

### Lalloo 2004

Trial name or title	A pragmatic trial examining the effect of compliance upon clinical effectiveness and cost effectiveness of LapDap (chlorproguanil-dapsone) when compared to sulfadoxine-pyrimethamine and Co-artem (artemether-lumefantrine) for the treatment of uncomplicated falciparum malaria in Malawi
Methods	
Participants	Adults and children > 6 months (and who weigh > 10 kg) who present to the outpatient department of Ndirande Health Centre with uncomplicated falciparum malaria
Interventions	<ol style="list-style-type: none"><li>1. Chlorproguanil-dapsone will be dosed using the “graduated pole” system (the appropriate number of pre-packed tablets will be given on a height basis)</li><li>2. Sulfadoxine-pyrimethamine (standard Malawi guidelines)</li><li>3. Artemether-lumefantrine (recommended World Health Organization schedule)</li></ol>
Outcomes	<ol style="list-style-type: none"><li>1. Adequate clinical and parasitological response on day 14 using modified World Health Organization criteria</li><li>2. Presence or absence of parasitaemia on day 28</li><li>3. Compliance with the randomized regimens</li></ol>
Starting date	2004
Contact information	David Lalloo (dlaloo@liverpool.ac.uk)
Notes	-

## DATA AND ANALYSES

### Comparison 1. One-dose regimen (with 1.2 mg chlorproguanil) versus chloroquine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitaemia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Day 7	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.2 Day 14	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.3 Day 21	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.4 Day 28	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Treatment failure	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

### Comparison 2. One-dose regimen (with 1.2 mg chlorproguanil) versus sulfadoxine-pyrimethamine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitaemia	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Day 7	3	548	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [0.58, 4.36]
1.2 Day 14	2	250	Risk Ratio (M-H, Fixed, 95% CI)	1.68 [0.42, 6.76]
1.3 Day 21	2	241	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [0.68, 3.02]
1.4 Day 28	3	527	Risk Ratio (M-H, Fixed, 95% CI)	3.11 [2.28, 4.24]
2 Treatment failure	3	547	Risk Ratio (M-H, Fixed, 95% CI)	2.77 [1.86, 4.10]
3 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Serious	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.2 Any	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

### Comparison 3. Three-dose regimen (with 1.2 mg chlorproguanil) versus sulfadoxine-pyrimethamine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitaemia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Day 7	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.2 Day 28	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Treatment failure	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Haemoglobin	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Day 0	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
3.2 Day 7	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
3.3 Day 14	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
3.4 Day 21	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
3.5 Day 28	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
4 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

4.1 Serious	1	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.2 Requiring discontinuation of treatment	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.3 Any	1	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

#### Comparison 4. Three-dose regimen (with 2.0 mg chlorproguanil) versus sulfadoxine-pyrimethamine (previous SP failures)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitaemia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Day 7	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Treatment failure	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Any	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

#### Comparison 5. Three-dose regimen (with 2.0 mg chlorproguanil) versus sulfadoxine-pyrimethamine (new attendees)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitaemia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Day 7	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.2 Day 14	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Presence of fever	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Day 7	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.2 Day 14	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3 Treatment failure by day 7	2	827	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.19, 0.49]
4 Treatment failure by day 14	5	1709	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.24, 0.53]
5 Haemoglobin	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1 Day 0	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
5.2 Day 7	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
5.3 Day 14	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
6 Adverse events	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Serious	2	829	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.61, 1.61]
6.2 Requiring discontinuation of treatment	2	829	Risk Ratio (M-H, Fixed, 95% CI)	4.54 [1.74, 11.82]
6.3 Any	3	2679	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.87, 1.09]
7 Serious adverse events (Allouche 2004)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.1 Red blood cell disorders	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7.2 Convulsions	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7.3 Other	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

7.4 Total serious "Treatment Emergent Signs and Symptoms (TESS)" (as described by author)

1

Risk Ratio (M-H, Fixed, 95% CI)

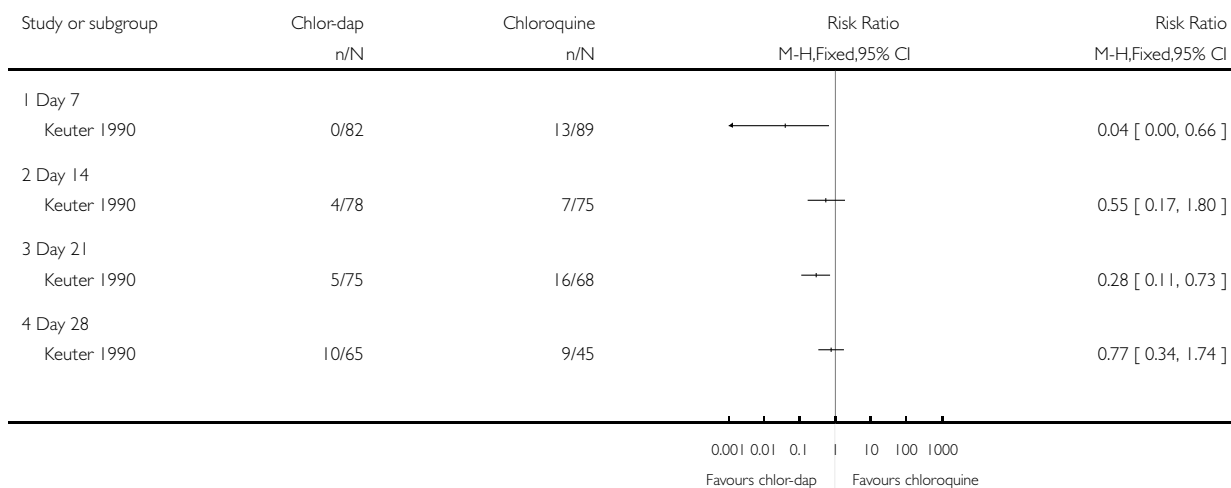
Not estimable

**Analysis 1.1. Comparison 1 One-dose regimen (with 1.2 mg chlorproganil) versus chloroquine, Outcome 1 Parasitaemia.**

Review: Chlorproguanil-dapsone for treating uncomplicated malaria

Comparison: 1 One-dose regimen (with 1.2 mg chlorproganil) versus chloroquine

Outcome: 1 Parasitaemia

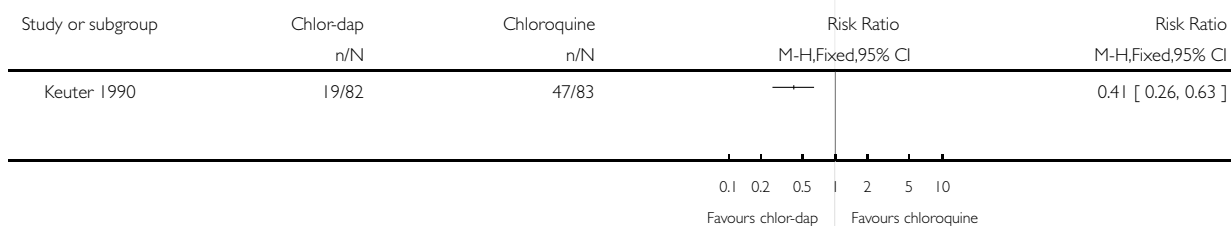


**Analysis 1.2. Comparison 1 One-dose regimen (with 1.2 mg chlorproganil) versus chloroquine, Outcome 2 Treatment failure.**

Review: Chlorproguanil-dapsone for treating uncomplicated malaria

Comparison: 1 One-dose regimen (with 1.2 mg chlorproganil) versus chloroquine

Outcome: 2 Treatment failure

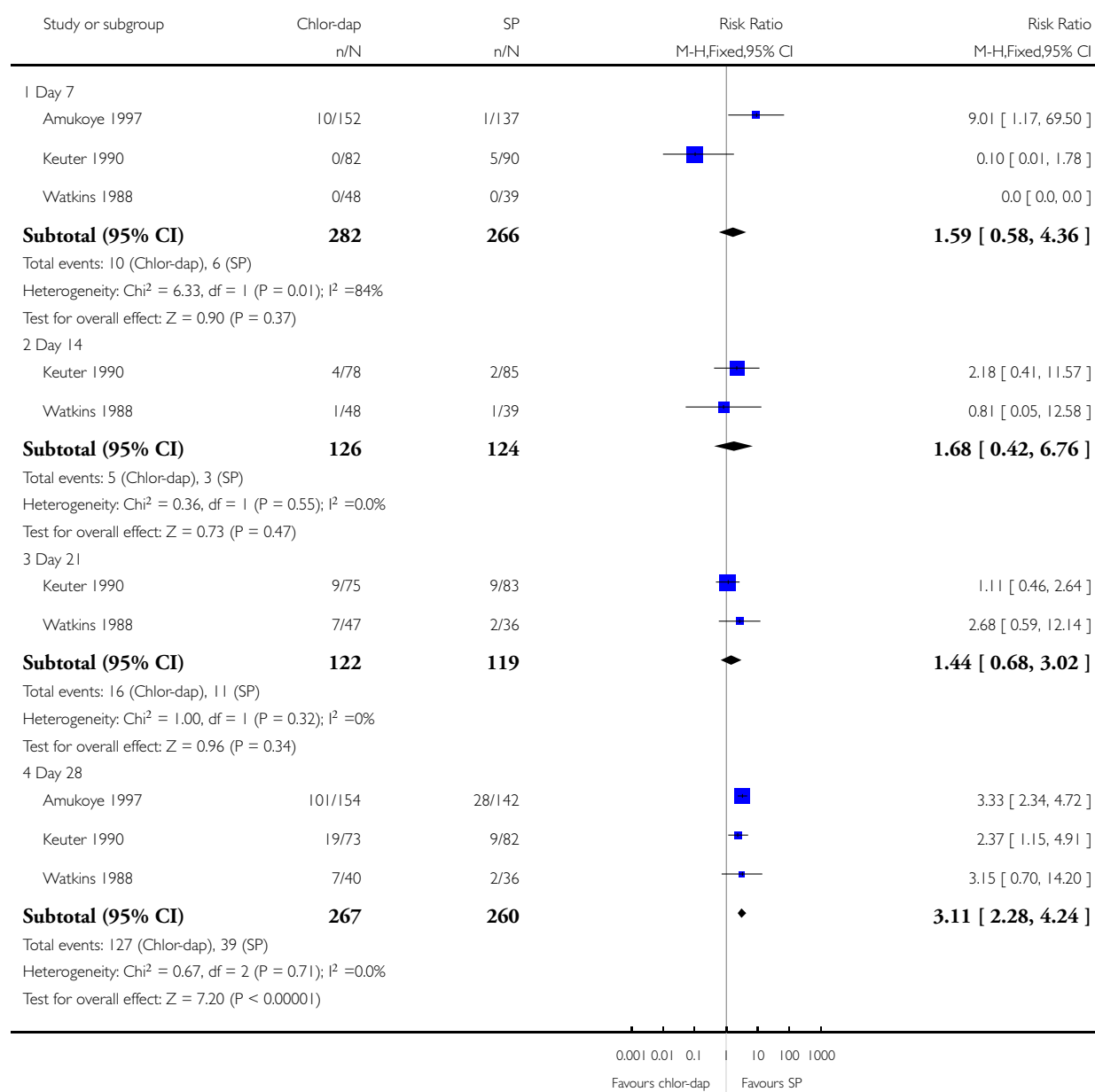


## Analysis 2.1. Comparison 2 One-dose regimen (with 1.2 mg chlorproguanil) versus sulfadoxine-pyrimethamine, Outcome 1 Parasitaemia.

Review: Chlorproguanil-dapsone for treating uncomplicated malaria

Comparison: 2 One-dose regimen (with 1.2 mg chlorproguanil) versus sulfadoxine-pyrimethamine

Outcome: 1 Parasitaemia

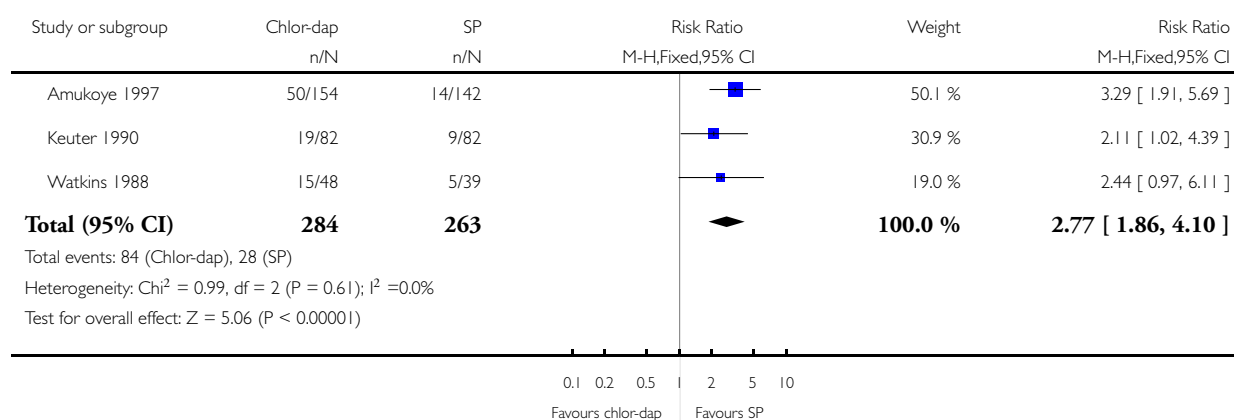


### Analysis 2.2. Comparison 2 One-dose regimen (with 1.2 mg chlorproguanil) versus sulfadoxine-pyrimethamine, Outcome 2 Treatment failure.

Review: Chlorproguanil-dapsone for treating uncomplicated malaria

Comparison: 2 One-dose regimen (with 1.2 mg chlorproguanil) versus sulfadoxine-pyrimethamine

Outcome: 2 Treatment failure

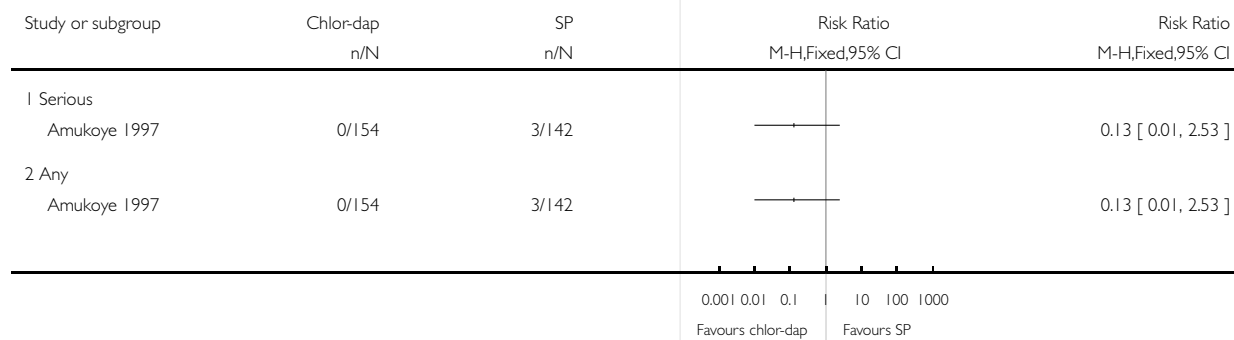


### Analysis 2.3. Comparison 2 One-dose regimen (with 1.2 mg chlorproguanil) versus sulfadoxine-pyrimethamine, Outcome 3 Adverse events.

Review: Chlorproguanil-dapsone for treating uncomplicated malaria

Comparison: 2 One-dose regimen (with 1.2 mg chlorproguanil) versus sulfadoxine-pyrimethamine

Outcome: 3 Adverse events

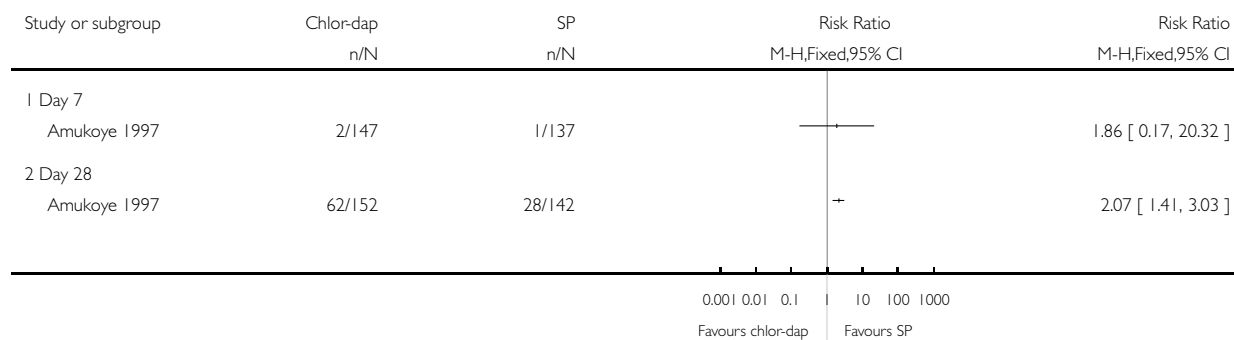


**Analysis 3.1. Comparison 3 Three-dose regimen (with 1.2 mg chlorproguanil) versus sulfadoxine-pyrimethamine, Outcome 1 Parasitaemia.**

Review: Chlorproguanil-dapsone for treating uncomplicated malaria

Comparison: 3 Three-dose regimen (with 1.2 mg chlorproguanil) versus sulfadoxine-pyrimethamine

Outcome: 1 Parasitaemia

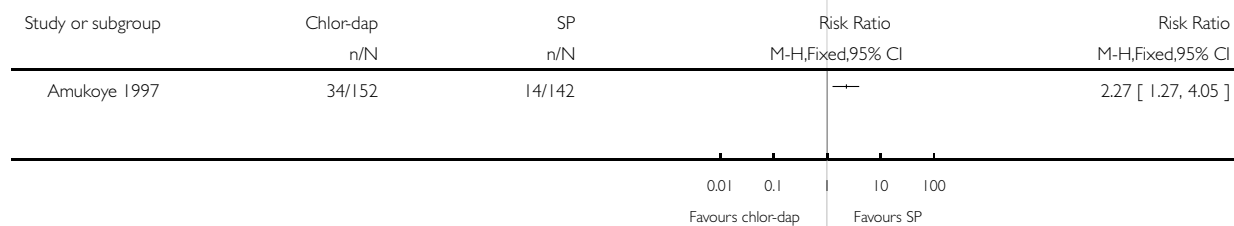


**Analysis 3.2. Comparison 3 Three-dose regimen (with 1.2 mg chlorproguanil) versus sulfadoxine-pyrimethamine, Outcome 2 Treatment failure.**

Review: Chlorproguanil-dapsone for treating uncomplicated malaria

Comparison: 3 Three-dose regimen (with 1.2 mg chlorproguanil) versus sulfadoxine-pyrimethamine

Outcome: 2 Treatment failure

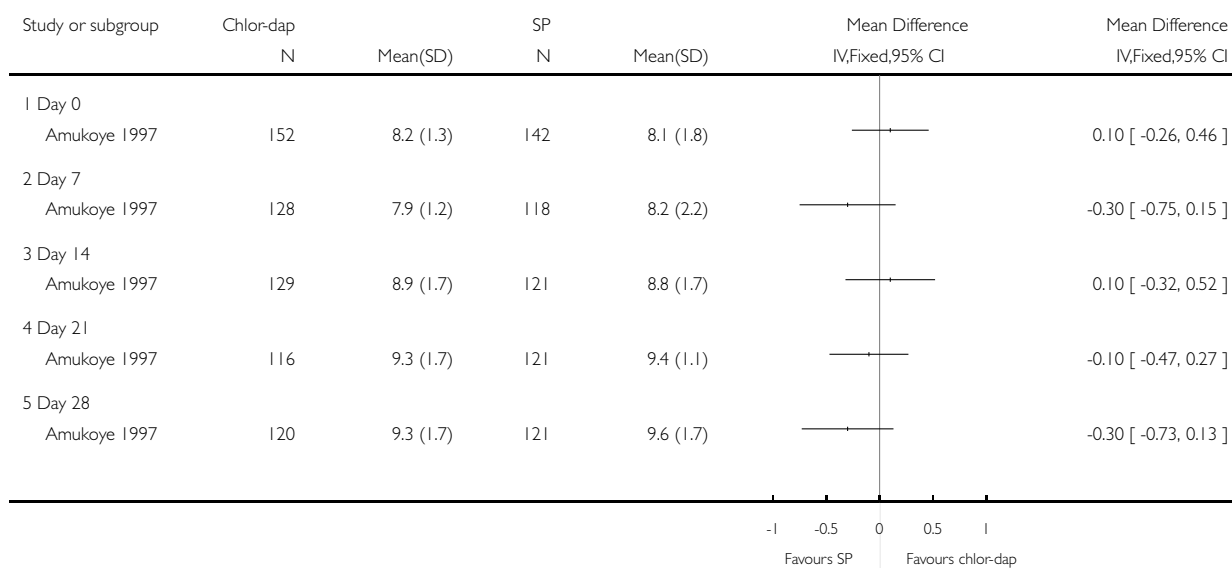


### Analysis 3.3. Comparison 3 Three-dose regimen (with 1.2 mg chlorproguanil) versus sulfadoxine-pyrimethamine, Outcome 3 Haemoglobin.

Review: Chlorproguanil-dapsone for treating uncomplicated malaria

Comparison: 3 Three-dose regimen (with 1.2 mg chlorproguanil) versus sulfadoxine-pyrimethamine

Outcome: 3 Haemoglobin

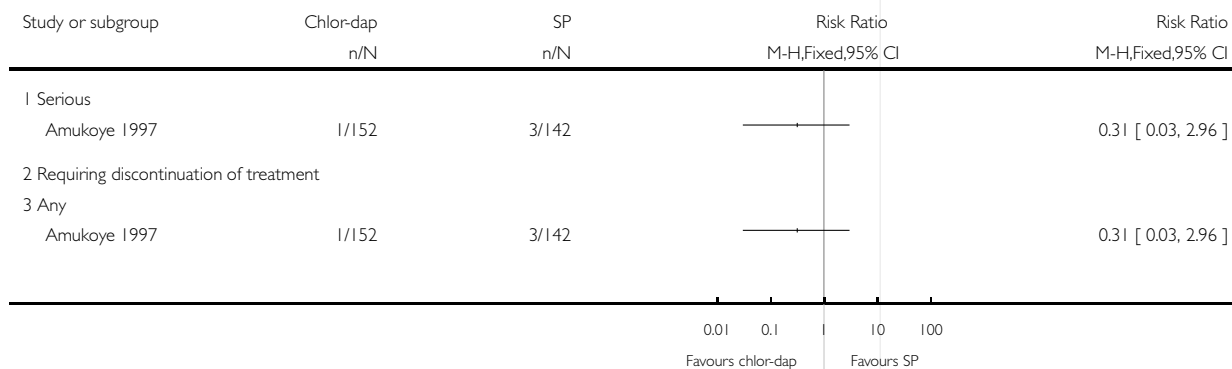


### Analysis 3.4. Comparison 3 Three-dose regimen (with 1.2 mg chlorproguanil) versus sulfadoxine-pyrimethamine, Outcome 4 Adverse events.

Review: Chlorproguanil-dapsone for treating uncomplicated malaria

Comparison: 3 Three-dose regimen (with 1.2 mg chlorproguanil) versus sulfadoxine-pyrimethamine

Outcome: 4 Adverse events

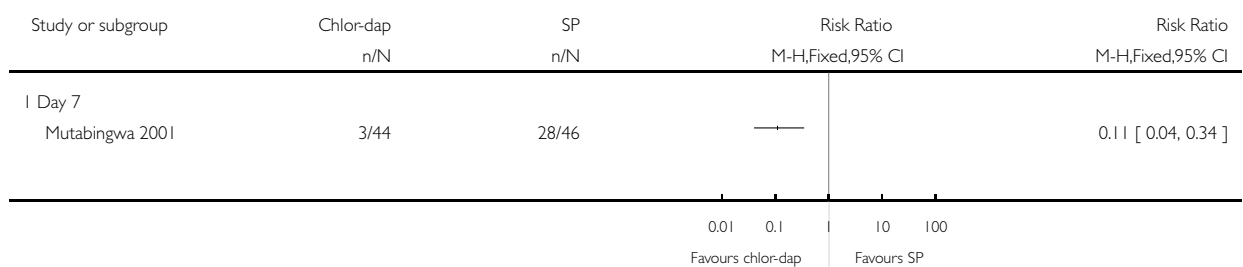


**Analysis 4.1. Comparison 4 Three-dose regimen (with 2.0 mg chlorproguanil) versus sulfadoxine-pyrimethamine (previous SP failures), Outcome 1 Parasitaemia.**

Review: Chlorproguanil-dapsone for treating uncomplicated malaria

Comparison: 4 Three-dose regimen (with 2.0 mg chlorproguanil) versus sulfadoxine-pyrimethamine (previous SP failures)

Outcome: 1 Parasitaemia

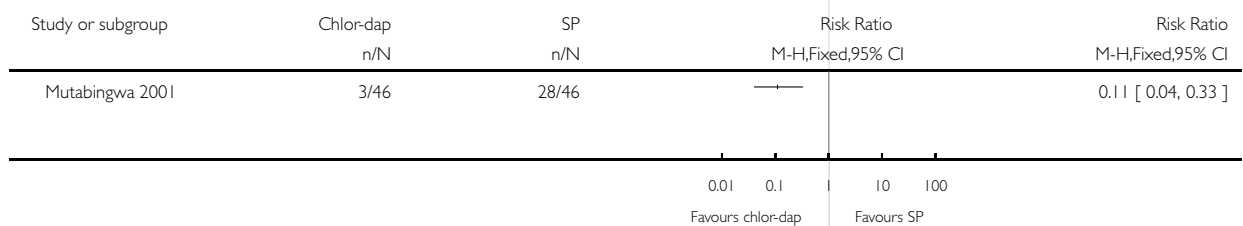


**Analysis 4.2. Comparison 4 Three-dose regimen (with 2.0 mg chlorproguanil) versus sulfadoxine-pyrimethamine (previous SP failures), Outcome 2 Treatment failure.**

Review: Chlorproguanil-dapsone for treating uncomplicated malaria

Comparison: 4 Three-dose regimen (with 2.0 mg chlorproguanil) versus sulfadoxine-pyrimethamine (previous SP failures)

Outcome: 2 Treatment failure

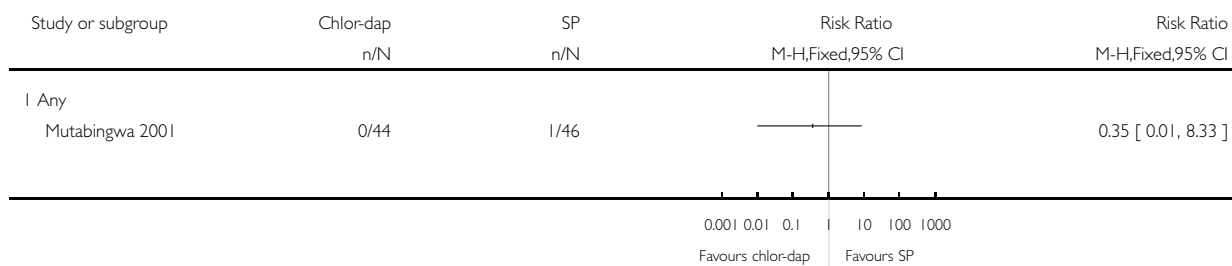


**Analysis 4.3. Comparison 4 Three-dose regimen (with 2.0 mg chlorproguanil) versus sulfadoxine-pyrimethamine (previous SP failures), Outcome 3 Adverse events.**

Review: Chlorproguanil-dapsone for treating uncomplicated malaria

Comparison: 4 Three-dose regimen (with 2.0 mg chlorproguanil) versus sulfadoxine-pyrimethamine (previous SP failures)

Outcome: 3 Adverse events

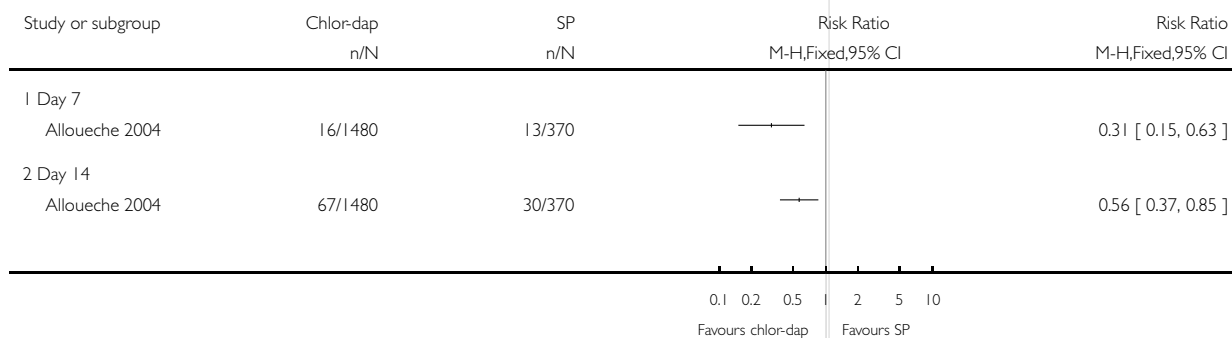


**Analysis 5.1. Comparison 5 Three-dose regimen (with 2.0 mg chlorproguanil) versus sulfadoxine-pyrimethamine (new attendees), Outcome 1 Parasitaemia.**

Review: Chlorproguanil-dapsone for treating uncomplicated malaria

Comparison: 5 Three-dose regimen (with 2.0 mg chlorproguanil) versus sulfadoxine-pyrimethamine (new attendees)

Outcome: 1 Parasitaemia

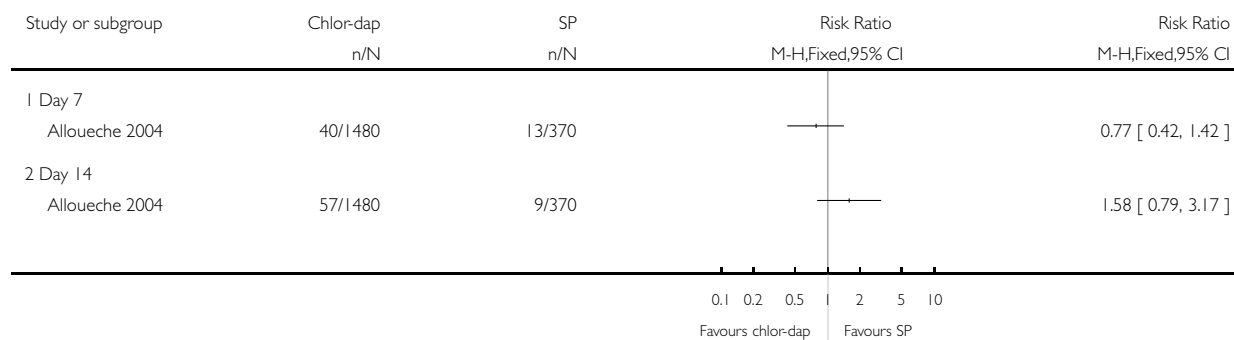


**Analysis 5.2. Comparison 5 Three-dose regimen (with 2.0 mg chlorproguanil) versus sulfadoxine-pyrimethamine (new attendees), Outcome 2 Presence of fever.**

Review: Chlorproguanil-dapsone for treating uncomplicated malaria

Comparison: 5 Three-dose regimen (with 2.0 mg chlorproguanil) versus sulfadoxine-pyrimethamine (new attendees)

Outcome: 2 Presence of fever

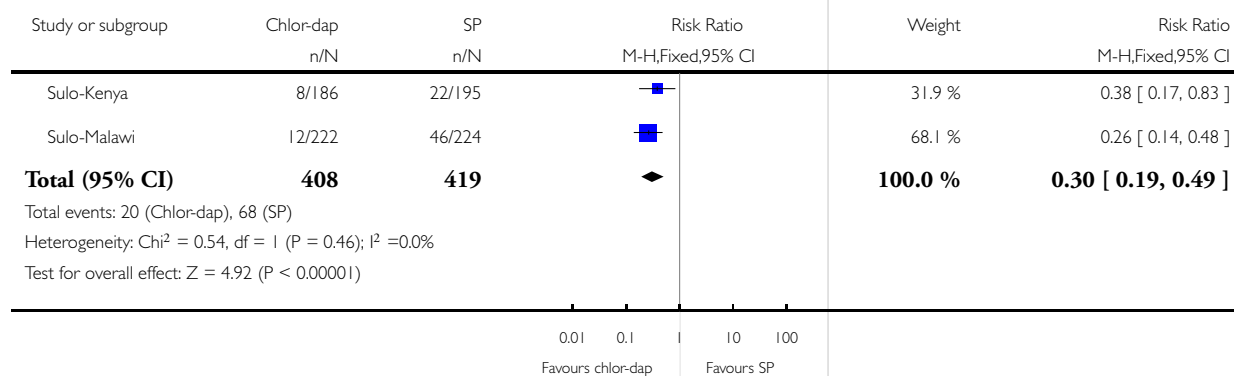


**Analysis 5.3. Comparison 5 Three-dose regimen (with 2.0 mg chlorproguanil) versus sulfadoxine-pyrimethamine (new attendees), Outcome 3 Treatment failure by day 7.**

Review: Chlorproguanil-dapsone for treating uncomplicated malaria

Comparison: 5 Three-dose regimen (with 2.0 mg chlorproguanil) versus sulfadoxine-pyrimethamine (new attendees)

Outcome: 3 Treatment failure by day 7

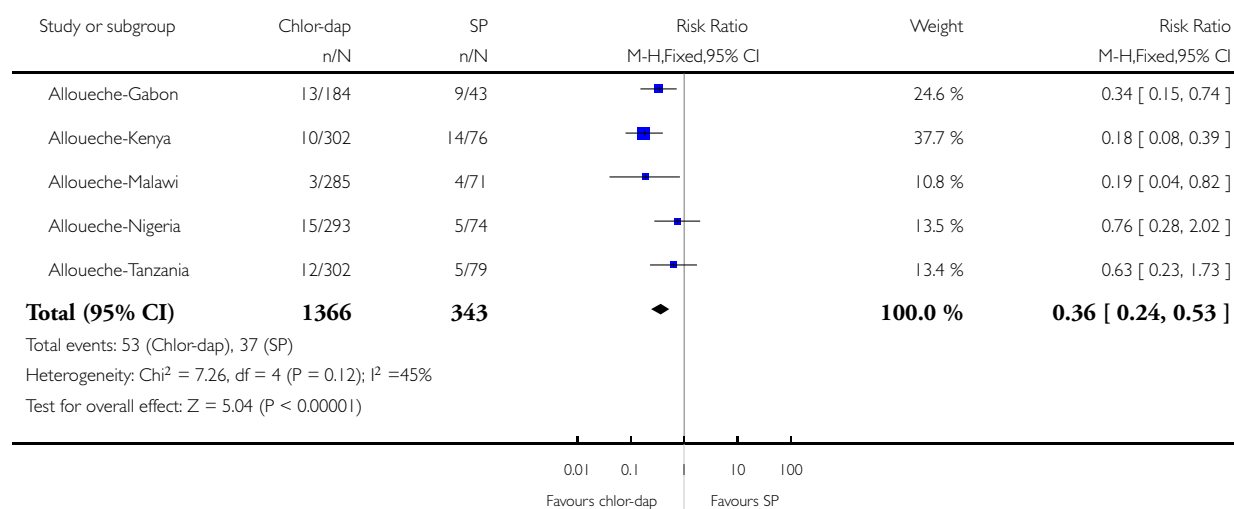


### Analysis 5.4. Comparison 5 Three-dose regimen (with 2.0 mg chlorproguanil) versus sulfadoxine-pyrimethamine (new attendees), Outcome 4 Treatment failure by day 14.

Review: Chlorproguanil-dapsone for treating uncomplicated malaria

Comparison: 5 Three-dose regimen (with 2.0 mg chlorproguanil) versus sulfadoxine-pyrimethamine (new attendees)

Outcome: 4 Treatment failure by day 14

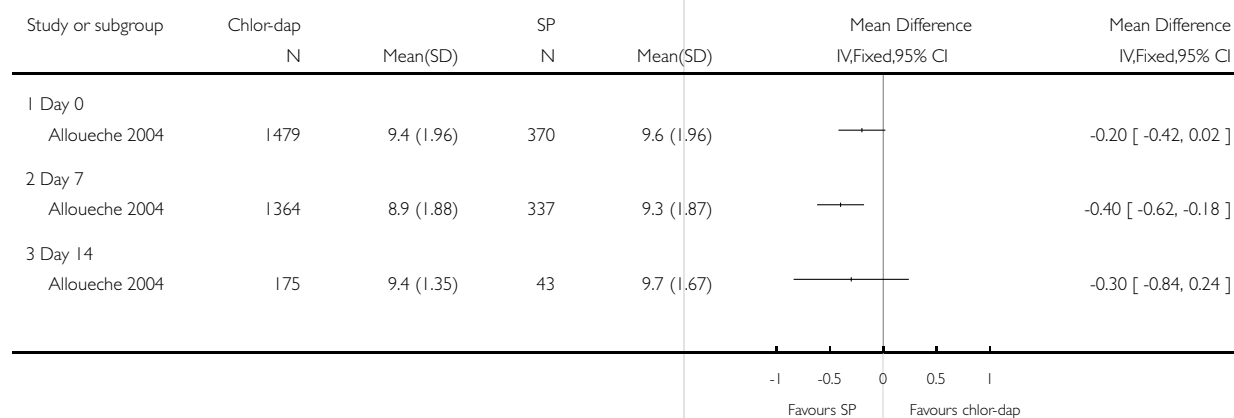


### Analysis 5.5. Comparison 5 Three-dose regimen (with 2.0 mg chlorproguanil) versus sulfadoxine-pyrimethamine (new attendees), Outcome 5 Haemoglobin.

Review: Chlorproguanil-dapsone for treating uncomplicated malaria

Comparison: 5 Three-dose regimen (with 2.0 mg chlorproguanil) versus sulfadoxine-pyrimethamine (new attendees)

Outcome: 5 Haemoglobin

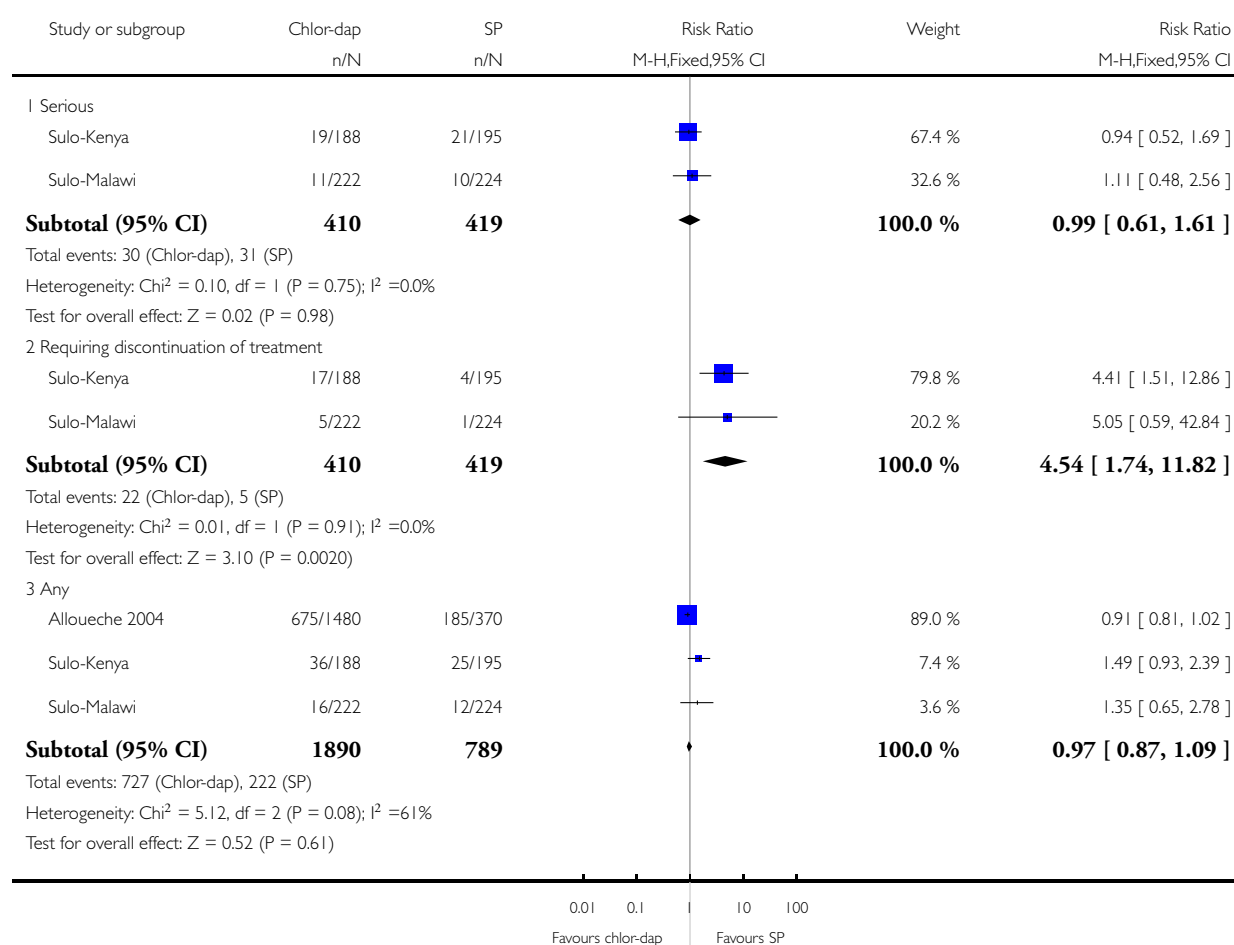


### Analysis 5.6. Comparison 5 Three-dose regimen (with 2.0 mg chlorproguanil) versus sulfadoxine-pyrimethamine (new attendees), Outcome 6 Adverse events.

Review: Chlorproguanil-dapsone for treating uncomplicated malaria

Comparison: 5 Three-dose regimen (with 2.0 mg chlorproguanil) versus sulfadoxine-pyrimethamine (new attendees)

Outcome: 6 Adverse events

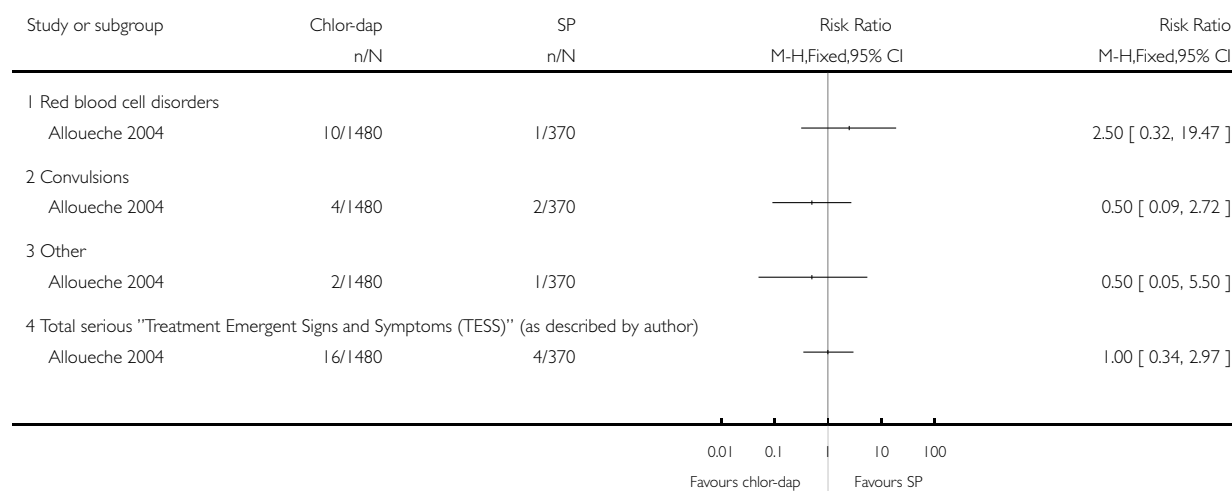


### Analysis 5.7. Comparison 5 Three-dose regimen (with 2.0 mg chlorproguanil) versus sulfadoxine-pyrimethamine (new attendees), Outcome 7 Serious adverse events (Allouche 2004).

Review: Chlorproguanil-dapsone for treating uncomplicated malaria

Comparison: 5 Three-dose regimen (with 2.0 mg chlorproguanil) versus sulfadoxine-pyrimethamine (new attendees)

Outcome: 7 Serious adverse events (Allouche 2004)



## WHAT'S NEW

Last assessed as up-to-date: 13 August 2004.

16 July 2008	Review declared as stable	This review, converted to a new review format with minor editing, will no longer be updated because chlorproguanil-dapsone (LapDap) has been "withdrawn following demonstration of post-treatment haemolytic anaemia in G6PD deficient patients in a Phase III trial of chlorproguanil-dapsone-artesunate (Dacart <sup>TM</sup> ) versus artemether-lumefantrine (Coartem®) and confirmation of findings in a comparative trial of LapDap <sup>TM</sup> versus Dacart <sup>TM</sup> " (WHO 2008)
--------------	---------------------------	--

## HISTORY

Protocol first published: Issue 1, 2004

Review first published: Issue 4, 2004

## CONTRIBUTIONS OF AUTHORS

Hasifa Bukirwa extracted and analysed data, and drafted the review. Julia Critchley extracted data, and along with Paul Garner, wrote the review.

## DECLARATIONS OF INTEREST

Paul Garner is employed by the University of Liverpool, who also employ academics involved with the development of the co-formulated commercial preparation of this combination. Julia Critchley is employed by the Liverpool School of Tropical Medicine, who also employ academics involved with the development of this combination.

## SOURCES OF SUPPORT

### Internal sources

- Liverpool School of Tropical Medicine, UK.

### External sources

- Department for International Development, UK.

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Types of outcomes: We have added “mean haemoglobin” because of its clinical importance, and used the mean difference to present these data.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Antimalarials [\*therapeutic use]; Chloroguanide [\*analogs & derivatives; \*therapeutic use]; Dapsone [\*therapeutic use]; Drug Combinations; Malaria [\*drug therapy]; Randomized Controlled Trials as Topic

### MeSH check words

Adult; Child; Humans