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[Intervention Review]

# Malaria chemoprophylaxis in sickle cell disease

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## ABSTRACT

### Background

Malaria is the most common precipitating cause of crises in sickle cell disease in malaria-endemic countries. Health professionals often recommend life-long malaria chemoprophylaxis for people with sickle cell disease living in these areas. It is therefore important we have good evidence of benefit.

### Objectives

To assess the effects of routine malaria chemoprophylaxis in people with sickle cell disease.

### Search methods

We searched the Cochrane Infectious Diseases Group Specialized Register (January 2006), Cochrane Cystic Fibrosis and Genetic Disorders Group Specialized Register (July 2006), CENTRAL (*The Cochrane Library* 2006, Issue 1), MEDLINE (1966 to January 2006), EMBASE (1974 to January 2006), LILACS (1982 to January 2006), and reference lists. We also contacted organizations and pharmaceutical companies.

### Selection criteria

Randomized and quasi-randomized controlled trials comparing chemoprophylaxis with any antimalarial drug given for a minimum of three months compared with a placebo or no intervention.

### Data collection and analysis

Two authors independently applied the inclusion criteria, assessed the risk of bias in the trials, and extracted data. Dichotomous data were analysed using risk ratios (RR) and presented with 95% confidence intervals (CI).

### Main results

Two trials with a total of 223 children with homozygous sickle cell disease met the inclusion criteria. A randomized controlled trial in Nigeria compared two different antimalarial drugs with a placebo, and reported that chemoprophylaxis reduced sickle cell crises (RR 0.17, 95% CI 0.04 to 0.83; 97 children), hospital admissions (RR 0.27, 95% CI 0.12 to 0.63; 97 participants), and blood transfusions (RR 0.16, 95% CI 0.05 to 0.56; 97 participants). A quasi-randomized controlled trial of 126 children in Uganda compared an antimalarial drug plus antibiotics with no antimalarial plus placebo. Chemoprophylaxis reduced the number of episodes of malaria and dactylitis, and increased mean haemoglobin values in this trial.

### Authors' conclusions

It is beneficial to give routine malaria chemoprophylaxis in sickle cell disease in areas where malaria is endemic.

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**Malaria chemoprophylaxis in sickle cell disease (Review)**

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Update pending

New contributors needed

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## PLAIN LANGUAGE SUMMARY

### **In areas where malaria is common, malaria drug prophylaxis benefits people with sickle cell disease**

Sickle cell disease is a blood disorder, and means the part of the red blood cell that carries oxygen from the lungs to the body tissues (haemoglobin) is abnormal. It is a genetic disorder and occurs when people inherit abnormal genes from both parents. It is more common in people originating from tropical Africa, and the Caribbean, Mediterranean, Indian, and Middle Eastern regions. Some types of sickle cell disease cause more severe symptoms than others, but in general people with the disease may be tired and weak (due to anaemia), and have severe and recurrent pain in the bones (referred to as crises), have more infections, more problems with breathing, and more chance of having a stroke. Sickle cell disease contributes to the death of children in the first five years of life, and infants aged six to 12 months are particularly at risk. Malaria infection is known to trigger a sickle cell crisis. So preventing malaria in people with sickle cell disease may also help to reduce crises and all the problems that go along with it. Health professionals often recommend life-long drugs to prevent malaria infections (chemoprophylaxis) for people with sickle cell disease living in these high risk areas for malaria. However, it is important to assess how effective this may be and what the adverse effects there might be from taking these drugs over a long period of time. This review of trials identified two small trials involving 223 people with homozygous sickle cell disease (commonly called sickle cell anaemia). These showed benefit in terms of reducing the number of sickle cell crises, blood transfusions, hospital admissions, and increasing the mean haemoglobin levels, but they did not collect data on potential adverse effects. More research is needed, therefore, to be sure of the benefits and to assess possible problems of drug resistance, and other potential long-term adverse effects that may be associated with continuous treatment.

## BACKGROUND

Sickle cell disease is an inherited blood condition. It is more common in people with their origins in Equatorial Africa, and the Caribbean, Mediterranean, Indian, and Middle Eastern regions (Serjeant 1997; WHO 2000). It is caused by abnormalities in the production of haemoglobin, which is the part of the red blood cell that carries oxygen from the lungs to the body tissues. Sickle cell disease occurs when people inherit from both parents abnormal genes responsible for haemoglobin production.

There are two common genotypes:

- Homozygous sickle cell disease (also known as sickle cell anaemia), where the sickle cell gene responsible for the production of abnormal haemoglobin S is inherited from both parents.
- Sickle cell/haemoglobin C disease, where the person inherits one sickle cell gene from one parent, and another abnormal haemoglobin gene (haemoglobin C) from the other.

Two other genotypes are less common:

- Sickle cell/beta + thalassaemia, where the person inherits one sickle cell gene from one parent, and another abnormal haemoglobin gene (thalassaemia) from the other. This is a mild form of the disease in which haemoglobin A is present.
- Sickle cell/beta 0 thalassaemia, where the person inherits one sickle cell gene from one parent, and another abnormal haemoglobin gene (beta 0 thalassaemia) from the other. This is a severe form of the disease in which haemoglobin A is absent (Serjeant 1997; Ashley-Koch 2000).

The frequency of the different genotypes found in sickle cell disease varies with populations. The highest frequencies of homozygous sickle cell disease in the world occur in sub-Saharan Africa where 3% to 4% of the populations are affected (WHO 2000). In Jamaica, homozygous sickle cell disease is the most common (1 in 300), followed by sickle cell/haemoglobin C disease (1 in 500), with the thalassaemia variants being much less common (Serjeant 1997). The pattern in Nigeria is similar (Adekile 1999).

The sickle cell gene occurs commonly in areas of the world with intense malaria transmission. One of the reasons that the sickle cell gene has persisted is that it appears to be of benefit in 'carriers' of the gene. Carriers are people with one sickle cell gene and one normal haemoglobin gene. These people have some resistance to infection with *Plasmodium falciparum* malaria (Serjeant 1997; Adekile 1999; Ashley-Koch 2000).

The illness seen in different genotypes varies with some causing more severe disease. Different forms of sickle cell disease may manifest the same problems and complications, some of which are potentially life threatening. Homozygous sickle cell disease and sickle cell/beta 0 thalassaemia tend to be more severe, whereas sickle cell/haemoglobin C disease and sickle cell/beta + thalassaemia are milder (Serjeant 1997).

The clinical manifestations of the disease are anaemia, recurring episodes (crises) of severe excruciating pain in the bones, an increased susceptibility to infections, the acute chest syndrome (a life threatening pneumonia-like illness), and cerebrovascular accidents (strokes) (Serjeant 1997; Ashley-Koch 2000).

Sickle cell disease appears to contribute to mortality especially in the first five years of life (Molineaux 1979a; Fleming 1989; Leikin 1989; Athale 1994; Platt 1994). Infants aged six to 12 months are particularly at risk (Rogers 1978; Serjeant 1997). In the USA, homozygous sickle cell disease reduces life expectancy to an average of 42 years for men and 48 years for women, even with specialized care and services (Platt 1994).

Malaria is the most common precipitating cause of crises in sickle cell disease in countries where malaria is endemic (Konotey-Ahulu 1971a; Fleming 1989). Mortality and morbidity are increased in people with both sickle cell disease and malaria (Aluoch 1997; Ashley-Koch 2000). One study found malaria parasites were the commonest infecting organism in people with homozygous sickle cell disease requiring hospitalizations in Nigeria (Maharajan 1983). Another study reported malaria infection as the precipitating cause in 133 of 848 consecutive admissions for crises in homozygous sickle cell disease in a hospital in Ghana (Konotey-Ahulu 1971b).

An increased number of malaria attacks and deaths were observed in people with homozygous sickle cell disease who were not taking malaria chemoprophylaxis (Colbourne 1956; Adeyoye 1971; Molineaux 1979a). Fewer deaths and crises were reported with malaria chemoprophylaxis, while growth, quality of life, as well as resistance to other infections, were thought to be improved (Konotey-Ahulu 1971a; Fleming 1989). Therefore many authorities recommend life-long malaria prophylaxis in people with homozygous sickle cell disease. Antimalarial drugs used for chemoprophylaxis include proguanil, pyrimethamine, and mefloquine (Okuonghae 1992; Ogala 1999; Nwokolo 2001).

Several factors have to be considered when starting life-long malaria chemoprophylaxis. Poor adherence may occur as it is difficult to take drugs regularly. Adverse drug effects may develop, such as hair loss and mouth ulcers with proguanil, and neuropsychiatric reactions with mefloquine (WHO 2001). The development of natural immunity to malaria (particularly in children) could be impaired by chemoprophylaxis with the potential risk of severe malaria on stopping the treatment (Otoo 1988; Salako 2000). Drug resistance may develop increasing the cost of treating patients, since newer antimalarials are more expensive (WHO 1990). It is therefore important to assess the benefits and harms of this life-long intervention carefully.

## OBJECTIVES

To assess the effects of routine malaria chemoprophylaxis in people with sickle cell disease.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomized and quasi-randomized controlled trials.

#### Types of participants

Adults and children with sickle cell disease (proven by electrophoresis or DNA tests as appropriate) in a malaria-endemic zone. This includes people with homozygous sickle cell disease, sickle-cell/haemoglobin C disease, sickle cell/beta + thalassaemia, and sickle cell/beta 0 thalassaemia.

## Types of interventions

### Intervention

Chemoprophylaxis with any antimalarial drug given for a minimum of three months.

### Control

Placebo or no intervention.

## Types of outcome measures

### Primary

- Death.
- Sickle cell painful crises (episodes of severe pain in the bones or abdomen).
- Severe anaemia (haemoglobin concentration 5 g/dL or less) requiring blood transfusions.

### Secondary

- Malaria infection (diagnosed from blood film examinations).
- Hospital admissions.
- Haemoglobin concentrations in the absence of symptoms attributable to sickle cell disease or infection.
- Adverse events that are fatal, life threatening, require hospitalization, or result in the discontinuation of treatment.

## 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 (January 2006); Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (2006, Issue 1); MEDLINE (1966 to January 2006); EMBASE (1974 to January 2006); LILACS (1982 to January 2006). We also searched Current Controlled Trials ([www.controlled-trials.com](http://www.controlled-trials.com); January 2006) using malaria and sickle cell as search terms.

We also searched the haemoglobinopathies specialized register of controlled trials held at the editorial base of the Cochrane Cystic Fibrosis and Genetic Disorders Group (July 2006) using malaria and sickle cell as search terms.

### Organizations and pharmaceutical companies

In 2002, we contacted the Georgia Comprehensive Sickle Cell Center (Atlanta, USA), the Sickle Cell Association of Ghana, the Jamaican Sickle Cell Unit of the Medical Research Council of Jamaica, and the pharmaceutical companies AstraZeneca UK Ltd (manufacturers of proguanil) and GlaxoSmithKline UK (manufacturers of pyrimethamine), for information about unpublished and ongoing trials.

### Reference lists

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

## Data collection and analysis

### Selection of studies

We independently screened the results of the search strategy for potentially relevant trials and independently assessed them for inclusion in the review using a pre-designed eligibility form based on the inclusion criteria.

### Data extraction and management

We independently extracted data on the trial characteristics including the methods, participants, interventions, and outcomes. We resolved disagreements through discussion or by consulting an Editor of the Cochrane Infectious Diseases Group.

### Assessment of risk of bias in included studies

Using a pre-designed validity form, we independently assessed the risk of bias in the included trials using generation of the allocation sequence, allocation concealment, blinding, and the inclusion of all randomized participants. We assessed the methods used to generate the allocation sequence and conceal allocation to be adequate or inadequate according to [Jüni 2001](#). We described who was blinded in each trial, and assessed the number of randomized participants included in the final analysis to be adequate if 90% or over.

### Data synthesis

Where appropriate, we analysed data in [Review Manager 5](#), using risk ratios (RR) and with 95% confidence intervals (CI) for dichotomous data. The included trials did not report continuous data and there were too few trials to assess heterogeneity; methods for these situations will be used should such data become available.

## RESULTS

### Description of studies

We identified five potentially relevant trials. Two met the inclusion criteria ([Warley 1965](#); [Eke 2003](#); see '[Characteristics of included studies](#)') and three were excluded (see '[Characteristics of excluded studies](#)').

[Warley 1965](#) was conducted in Uganda in 1962 on 126 children with homozygous sickle cell disease who attended a clinic over a two-year period. The trial was conducted in an area of stable malaria where transmission occurred all year round. The intervention group was given chloroquine tablets as malaria chemoprophylaxis every week. Children aged below three years received 100 mg and those above three years received 200 mg of chloroquine. The intervention group also received long-acting benzathine penicillin injections of 1,200,000 units (all age groups) as antibiotic prophylaxis. The control group were given sterile water injections. The main outcome measures were episodes of malaria, dactylitis (swelling or tenderness of bones of the hands or feet), and haemoglobin levels.

[Eke 2003](#) was conducted in Nigeria on 97 children with homozygous sickle cell disease who were attending clinic. The trial was held over a nine-month period in an area of stable malaria endemicity. This included the rainy season, which is the period of maximum malaria transmission. Participants were aged one to 16 years and were treated with curative doses of antimalarial drugs on enrolment into the trial. They were then divided into three groups each to receive pyrimethamine (0.5 mg/kg/week) or proguanil

(1.5 mg/kg/day) as malaria chemoprophylaxis, or placebo (vitamin C 1 mg/kg/day). The main outcome measures were episodes of malaria, bone pain crises (recurrent bilateral pattern of bone pains and including dactylitis), haemolytic crisis (presence of jaundice, anaemia, or splenomegaly in the absence of other precipitating cause), aplastic crisis (bone marrow aplasia from malarial infection), number of hospitalizations, number of blood transfusions, mean haemoglobin levels, and mean parasite density.

### Risk of bias in included studies

See 'Characteristics of included studies' for details.

The allocation sequence was generated by alternate allocation in Warley 1965 and by block randomization (one in six) in Eke 2003. Allocation was therefore inadequately concealed in Warley 1965, while it was adequate in Eke 2003 as participants selected their intervention groups from sealed, opaque envelopes. Both trials were open: Warley 1965 was open because of the different routes of administration of the interventions, and the regimens were different in Eke 2003. Less than 30% of the participants were followed up for 12 months in Warley 1965 (inadequate), whereas Eke 2003 followed more than 90% of participants for nine months (adequate).

### Effects of interventions

#### Chloroquine plus benzathine penicillin versus placebo (Warley 1965)

Chemoprophylaxis significantly reduced the number of episodes of dactylitis (swelling and tenderness of the bones of the hands or feet) 12 months after treatment ( $P < 0.1$ , trial authors' calculation); data were derived from the published average cumulative incidence of dactylitis (Table 1). Chemoprophylaxis also significantly reduced the number of episodes of malaria after 12 months of prophylaxis (RR 0.16, 95% CI 0.07 to 0.39; 157 children, Analysis 1.1) and increased the mean haemoglobin ( $P < 0.02$ , trial authors' calculation). Death, severe anaemia (requiring blood transfusions), hospital admissions, and adverse events were not reported.

#### Proguanil or pyrimethamine versus placebo (Eke 2003)

Data for the antimalarial drugs were pooled in the analyses. Chemoprophylaxis did not reduce the number of deaths (97 children, Analysis 2.1), and the one death that was reported occurred in the placebo group and was attributed to viral hepatitis and presumed overwhelming septicaemia. Chemoprophylaxis did however have a positive impact on reducing the number of painful sickle cell crises (RR 0.17, 95% CI 0.04 to 0.83; 97 children, Analysis 2.2) and blood transfusions required from episodes of severe anaemia (RR 0.16, 95% CI 0.05 to 0.56; 97 children, Analysis 2.3).

For the secondary outcome measures, the number of hospital admissions was significantly reduced by chemoprophylaxis (RR 0.27, 95% CI 0.12 to 0.63; 97 participants, Analysis 2.5). There was no statistically significant difference in the number of malaria infections (97 children, Analysis 2.4), defined as body temperatures  $> 37.5$  °C and malaria parasitaemia, or mean haemoglobin concentrations in the steady state (97 children, Analysis 2.6). No adverse events due to the drugs were reported.

## DISCUSSION

We identified two trials that compared malaria chemoprophylaxis with no intervention or placebo in children with homozygous sickle cell disease. Eke 2003 had antimalarial chemoprophylaxis as the sole intervention, while Warley 1965 had antimalarial chemoprophylaxis intervention combined with antibiotics. Both trials showed improved clinical outcomes.

Warley 1965 reported improved outcomes of fewer episodes of malaria, dactylitis, and higher mean haemoglobin levels with chemoprophylaxis. It could be argued that this was the result of the combined effect of the antimalarial and antibiotic prophylaxis. Either bacterial infections or malaria can precipitate a crisis in sickle cell disease, although the reduction in malaria infections was most probably due to the antimalarial intervention. Eke 2003 showed reduced episodes of bone pain crises, hospital admissions, and blood transfusions that were solely due to the effects of the antimalarial prophylaxis. It had been previously reported that malaria chemoprophylaxis in sickle cell disease reduces morbidity from malaria infections and is thought to improve resistance to other infections as well (Konotey-Ahulu 1971a; Fleming 1989). Eke 2003 supports this finding as malaria chemoprophylaxis not only improved clinical outcomes and decreased hospitalization rates from malaria infections, but from other causes as well.

The trials did not address the important issues of drug resistance to antimalarial chemotherapy, which may explain the varying results obtained from the chemoprophylaxis group or the potential for impairment of development of natural immunity to malaria.

In areas where malaria is endemic, chemoprophylaxis is often prescribed to people with homozygous sickle cell disease. We have found evidence to support this practice. We found no evidence to confirm or refute the benefits of malaria chemoprophylaxis in other types of sickle cell disease, that is, sickle-cell/haemoglobin C disease, sickle cell/beta + thalassaemia, and sickle cell/beta 0 thalassaemia.

## AUTHORS' CONCLUSIONS

### Implications for practice

Malaria chemoprophylaxis is widely used in homozygous sickle cell disease (commonly called sickle cell anaemia) because of the associated morbidity and mortality. Existing policies recommending prophylaxis have been based on case reports, observational studies, and consensus. The trials included in this review support these policies in people with homozygous sickle cell disease. There is inadequate evidence to support or refute giving routine antimalarial chemoprophylaxis in other forms of sickle cell disease in areas where malaria is endemic.

### Implications for research

Randomized controlled trials are required to evaluate the use of malaria chemoprophylaxis in sickle cell disease. In homozygous sickle cell disease there is such a strong clinical relationship between sickle cell crises, anaemia, and malaria that it would be difficult to justify another placebo-controlled trial. As those with homozygous sickle cell disease are often placed on chemoprophylaxis in endemic areas, a comparison of the different antimalarial regimens, such as proguanil versus pyrimethamine or proguanil versus mefloquine, could be made. In the other forms of

the disease, antimalarial drugs, such as proguanil, pyrimethamine, and mefloquine, should be given as prophylaxis with placebo or other proven methods of preventing malaria (such as insecticide-treated bed nets) as the control intervention. Trials evaluating specific methods to ensure adherence to long-term drug therapy, development of drug resistance, and adverse events with the drugs should also be carried out.

## ACKNOWLEDGEMENTS

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\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

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

**Eke 2003**

Methods	Randomized controlled trial  Generation of allocation sequence: block randomization (1 in 6); equal allocation  Allocation concealment: participants selected their intervention groups from sealed opaque envelopes  Blinding: none  Inclusion of all randomized participants in analysis: > 90% participants followed up for 9 months (32/35 proguanil group, 29/30 placebo group, and 100% pyrimethamine group)
Participants	97 children with homozygous sickle cell disease (sickle cell anaemia genotype SS)
Interventions	1. Pyrimethamine (0.5 mg/kg/week) 2. Proguanil (1.5 mg/kg/day) 3. Placebo (vitamin C; 1 mg/kg/day for 9 months)
Outcomes	1. Deaths 2. Malaria infections 3. Bone pain crises 4. Haemolytic crises 5. Aplastic crisis 6. Number of hospitalizations

**Malaria chemoprophylaxis in sickle cell disease (Review)**

**Eke 2003** *(Continued)*

7. Number of blood transfusions
8. Mean haemoglobin levels
9. Mean parasite density
10. Splenomegaly

Notes	Location: University of Port Harcourt Teaching Hospital, Nigeria
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**Warley 1965**

Methods	Quasi-randomized controlled trial  Generation of allocation sequence: alternate allocation  Allocation concealment: none  Blinding: none  Inclusion of all randomized participants in analysis: < 30% of participants followed up for 12 months (13/60 intervention group and 19/66 control group)
Participants	126 children with homozygous sickle cell disease (sickle cell anaemia genotype SS)
Interventions	<ol style="list-style-type: none"> <li>1. Chloroquine tablet (100 mg &lt; 3 years; 200 mg &gt; 3 years) plus benzathine penicillin injection (1,200,000 units)</li> <li>2. No tablets plus sterile water injection</li> </ol>
Outcomes	<ol style="list-style-type: none"> <li>1. Parasitaemia</li> <li>2. Dactylitis</li> <li>3. Mean haemoglobin</li> <li>4. Fall in haemoglobin</li> </ol>
Notes	Location: Mulago Hospital, Uganda  Date: August 1962 to May 1964

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

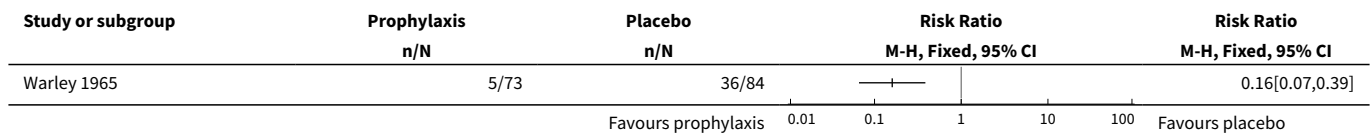
Study	Reason for exclusion
<a href="#">Hendrickse 1966</a>	Compared different antimalarial regimens in people with sickle cell anaemia; did not compare the interventions to placebo or to no intervention
<a href="#">Molineaux 1979b</a>	Longitudinal research project on epidemiology of malaria conducted in 1970 in Garki, Northern Nigeria
<a href="#">Terlouw 2004</a>	Study participants had the sickle cell trait (haemoglobin genotype AS) and not sickle cell disease

**DATA AND ANALYSES**
**Malaria chemoprophylaxis in sickle cell disease (Review)**

**Comparison 1. Chloroquine plus benzathine penicillin versus placebo**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Malaria episodes after 12 months of treatment	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

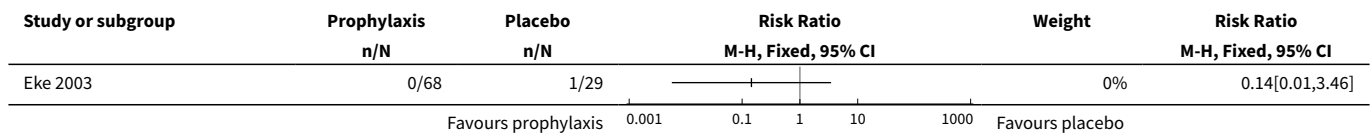
**Analysis 1.1. Comparison 1 Chloroquine plus benzathine penicillin versus placebo, Outcome 1 Malaria episodes after 12 months of treatment.**



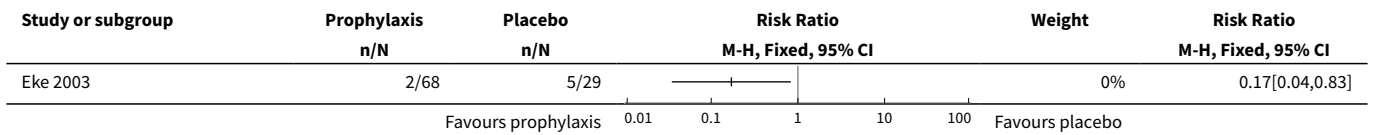
**Comparison 2. Proguanil or pyrimethamine (data combined) versus placebo**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2 Sickle cell crisis	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3 Blood transfusion	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4 Malaria infection	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5 Hospital admission	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6 Haemoglobin concentration	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

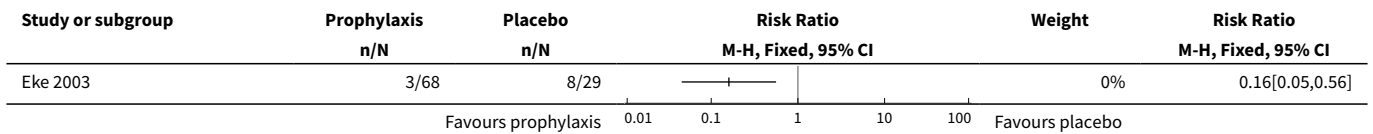
**Analysis 2.1. Comparison 2 Proguanil or pyrimethamine (data combined) versus placebo, Outcome 1 Death.**



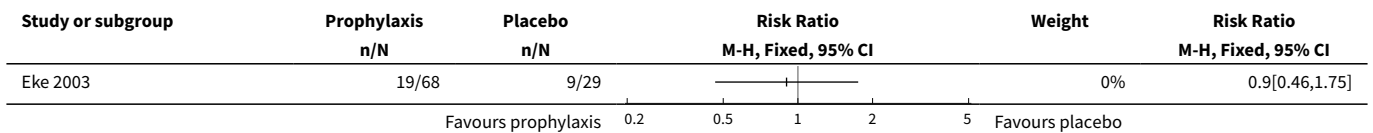
**Analysis 2.2. Comparison 2 Proguanil or pyrimethamine (data combined) versus placebo, Outcome 2 Sickle cell crisis.**



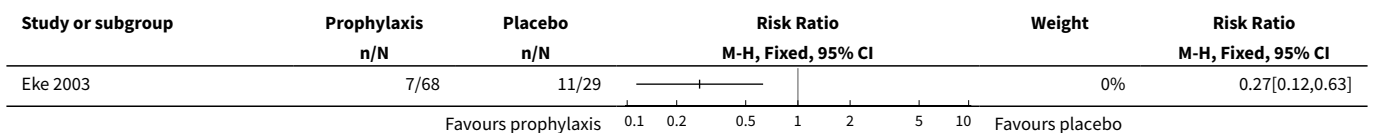
**Analysis 2.3. Comparison 2 Proguanil or pyrimethamine (data combined) versus placebo, Outcome 3 Blood transfusion.**



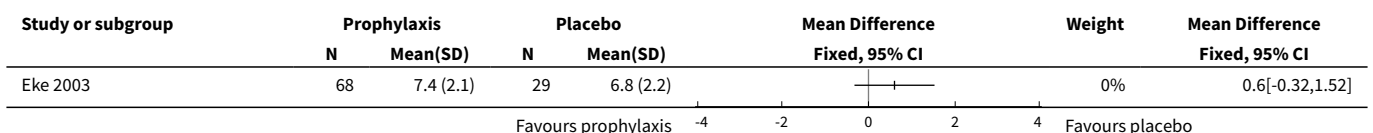
**Analysis 2.4. Comparison 2 Proguanil or pyrimethamine (data combined) versus placebo, Outcome 4 Malaria infection.**



**Analysis 2.5. Comparison 2 Proguanil or pyrimethamine (data combined) versus placebo, Outcome 5 Hospital admission.**



**Analysis 2.6. Comparison 2 Proguanil or pyrimethamine (data combined) versus placebo, Outcome 6 Haemoglobin concentration.**



**ADDITIONAL TABLES**

**Table 1. Dactylitis crises 12 months after intervention, Warley 1965**

Dactylitis crises	Chemoprophylaxis	Placebo
Monthly cumulated incidence (estimated from published graph)	1.0	2.75
Participants	19	13
Episodes: cumulated incidence x no. participants	19	36

## APPENDICES

### Appendix 1. Search methods: search strategies for database

Search set	CIDG SR <sup>a</sup>	CENTRAL	MEDLINE <sup>b</sup>	EMBASE <sup>b</sup>	LILACS <sup>b</sup>
1	malaria	malaria	malaria	malaria	malaria
2	sickle cell disease	sickle cell disease	sickle cell disease	sickle cell disease	sickle cell disease
3	sickle cell anaemia	ANEMIA, SICKLE CELL	ANEMIA, SICKLE CELL	SICKLE-CELL-ANEMIA	sickle cell anaemia
4	2 or 3	haemoglobin SC	haemoglobin SC	HEMOGLOBINOPATHY	2 or 3
5	1 and 4	haemoglobin SS	haemoglobin SS	haemoglobin SC	1 and 4
6	—	haemoglobin SD	haemoglobin SD	haemoglobin SS	—
7	—	thalassaemia	thalassaemia	haemoglobin SD	—
8	—	drepanocyt*	drepanocyt*	thalassaemia	—
9	—	meniscocytosis	meniscocytosis	drepanocyt\$	—
10	—	2-9/or	2-9/or	2-9/or	—
11	—	1 and 10	1 and 10	1 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 ([Higgins 2005](#)); upper case: MeSH or Emtree heading; lower case: free text term.

## WHAT'S NEW

Date	Event	Description
21 July 2008	Amended	Converted to new review format with minor editing.

## HISTORY

Protocol first published: Issue 1, 2002

Review first published: Issue 3, 2003

Date	Event	Description
17 August 2006	New citation required and conclusions have changed	2006, Issue 4 (substantive update): The conclusions of the review have changed due to inclusion of information obtained from the new trials that have been carried out since it was first published. We have subjected the results of the included trials to meta-analysis. The search for trials has been updated.
11 August 2006	New search has been performed	2006, Issue 4 (substantive update): The conclusions of the review have changed due to inclusion of information obtained from the new trials that have been carried out since it was first published. We have subjected the results of the included trials to meta-analysis. The search for trials has been updated.
8 May 2003	Amended	2003, Issue 3 (first review version): The order of the outcome measures has changed from those in the protocol. This is because our primary interest is how the clinical manifestations of the disease are affected by malaria chemoprophylaxis. Sick cell painful crises and severe anaemia have been moved from secondary to primary outcome measures; and episodes of malaria has been moved to secondary outcome measures where it has been renamed malaria infection. We have also clarified in the secondary outcome measures that the steady state in which haemoglobin concentrations are measured is that in which symptoms attributable to sickle cell disease or infection are absent.

## CONTRIBUTIONS OF AUTHORS

Oluseyi Oniyangi wrote the protocol, extracted and analysed data, and drafted the review. Aika Omari helped write the protocol, extracted and analysed data, and helped draft the review. Both authors have been involved in updating the review.

## DECLARATIONS OF INTEREST

None known.

## SOURCES OF SUPPORT

### Internal sources

- Liverpool School of Tropical Medicine, UK.

### External sources

- Department for International Development, UK.

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## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

2003, Issue 3 (first review version): The order of the outcome measures has changed from those in the protocol. This is because our primary interest is how the clinical manifestations of the disease are affected by malaria chemoprophylaxis. Sickle cell painful crises and severe anaemia have been moved from secondary to primary outcome measures; and episodes of malaria has been moved to secondary outcome measures where it has been renamed malaria infection. We have also clarified in the secondary outcome measures that the steady state in which haemoglobin concentrations are measured is that in which symptoms attributable to sickle cell disease or infection are absent.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Antimalarials [\*therapeutic use]; Malaria [\*prevention & control]; Randomized Controlled Trials as Topic; Sickle Cell Trait [\*complications]

### MeSH check words

Child; Humans