

Chemoprophylaxis and intermittent treatment for preventing malaria in children (Review)

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ABSTRACT

Background

Malaria causes repeated illness in children living in endemic areas. Policies of giving antimalarial drugs at regular intervals (prophylaxis or intermittent treatment) are being considered for preschool children.

Objectives

To evaluate prophylaxis and intermittent treatment with antimalarial drugs to prevent malaria in young children living in malaria-endemic areas.

Search strategy

We searched the Cochrane Infectious Diseases Group Specialized Register (August 2007), CENTRAL (*The Cochrane Library* 2007, Issue 3), MEDLINE (1966 to August 2007), EMBASE (1974 to August 2007), LILACS (1982 to August 2007), *mRCT* (February 2007), and reference lists of identified trials. We also contacted researchers.

Selection criteria

Individually randomized and cluster-randomized controlled trials comparing antimalarial drugs given at regular intervals (prophylaxis or intermittent treatment) with placebo or no drug in children aged one month to six years or less living in a malaria-endemic area.

Data collection and analysis

Two authors independently extracted data and assessed methodological quality. We used relative risk (RR) or weighted mean difference with 95% confidence intervals (CI) for meta-analyses. Where we detected heterogeneity and considered it appropriate to combine the trials, we used the random-effects model (REM).

Main results

Twenty-one trials (19,394 participants), including six cluster-randomized trials, met the inclusion criteria. Prophylaxis or intermittent treatment with antimalarial drugs resulted in fewer clinical malaria episodes (RR 0.53, 95% CI 0.38 to 0.74, REM; 7037 participants, 10 trials), less severe anaemia (RR 0.70, 95% CI 0.52 to 0.94, REM; 5445 participants, 9 trials), and fewer hospital admissions for any cause (RR 0.64, 95% CI 0.49 to 0.82; 3722 participants, 5 trials). We did not detect a difference in the number of deaths from any cause (RR 0.90, 95% CI 0.65 to 1.23; 7369 participants, 10 trials), but the CI do not exclude a potentially important difference. One trial reported three serious adverse events with no statistically significant difference between study groups (1070 participants). Eight trials measured morbidity and mortality six months to two years after stopping regular antimalarial drugs; overall, there was no statistically significant difference, but participant numbers were small.

Authors' conclusions

Prophylaxis and intermittent treatment with antimalarial drugs reduce clinical malaria and severe anaemia in preschool children.

PLAIN LANGUAGE SUMMARY

Preschool children taking antimalarial drugs regularly are less likely to get malaria or severe anaemia, but more trials are needed to show whether survival is improved

Most children in areas where malaria is endemic are semi-immune against serious malaria by the age of seven, but for children under five the disease can be serious, and a million worldwide die each year from malaria. The review of 21 trials found that children taking regular antimalarial prophylaxis or intermittent treatment were less likely to get malaria, severe anaemia, or be admitted to hospital, but there was no change in the overall death rate. The benefits are similar in intermittent treatment of infants and prolonged prophylaxis, but long-term deleterious effects, including the possibility that it may interfere with the development of children's immunity to malaria, are unknown for either regimen. Further trials with long-term follow up are needed.

BACKGROUND

Malaria

Malaria, common in the tropics and subtropics, is caused by *Plasmodium* parasites transmitted to humans by the bite of infected female anopheline mosquitoes. People who live in or visit areas where malaria commonly occurs (endemic areas) are at risk of becoming infected. Infected people may show no sign of illness (asymptomatic) or may develop fever, chills, malaise, and headache (symptomatic malaria). The severity of infection varies from mild (uncomplicated) to life threatening (severe). Among the four human species of malaria parasites, *Plasmodium falciparum* is the main species that causes severe malaria and is most frequently encountered in sub-Saharan Africa. People with severe malaria become very ill, may develop severe anaemia, convulsions, or become unconscious, and, in some cases, die. Severe malaria is more likely to occur in people who lack or have low immunity to malaria (Gilles 2000). Children living in areas where malaria is endemic will have acquired natural immunity to malaria by the time they are seven to 10 years old (Branch 1998; Warrell 2001). Preschool children living in malarious areas have inadequate immunity to malaria; this explains why most of the one million malaria deaths that occur each year in endemic areas of sub-Saharan Africa occur in this age group (Snow 1999).

Malaria control strategy

Malaria control aims to reduce illness and death from malaria. The World Health Organization's (WHO's) global malaria control strategy recommends a multi-pronged control approach that combines multiple preventive interventions with prompt diagnosis and treatment of symptomatic persons with efficacious antimalarial drugs (WHO 2000; RBM 2005). Artemisinin-based combination treatment (ACT) regimens have replaced chloroquine in most malaria-endemic countries as the first-line treatment for uncomplicated *P. falciparum* malaria due to widespread parasite resistance to latter. The effectiveness of ACT has been proven by several randomized controlled trials, but access to prompt treatment with ACTs has remained low in most parts of sub-Saharan Africa due to limited resources for health care (RBM 2005). Recent reports show

that less than a third of sick under-five African children sick with malaria receive prompt treatment with ACTs (UNICEF 2007).

Cochrane Reviews have confirmed the effectiveness of insecticide-treated nets in reducing malaria morbidity and mortality in preschool children (Lengeler 2004) and pregnant women (Gamble 2006), but coverage of this intervention in most sub-Saharan African countries lags far behind global targets. By 2005 less than a third of the endemic countries in this region had attained 30% coverage for children under five years, far below the Roll Back Malaria targets of 60% and 80% for 2005 and 2010 respectively (RBM 2005). Indoor residual spraying is another vector control measure recommended by the WHO for community protection, but it is expensive and requires high coverage to be effective (WHO 2006). Such high levels of coverage would be difficult to attain in many endemic areas, especially those with high perennial transmission.

Prevention using drugs

Prophylaxis and intermittent treatment are widely used drug-based methods for preventing malaria. Prophylaxis refers to "the administration of a drug in such a way that its blood concentration is maintained above the level that inhibits parasite growth, at the pre-erythrocytic or erythrocytic stage of the parasite's life-cycle, for the duration of the period at risk" (Greenwood 2006). Drugs used for malaria prophylaxis are usually given in daily or weekly doses. Intermittent treatment, also known as 'intermittent preventive treatment' or 'intermittent presumptive treatment' (IPT) "involves administration of a full therapeutic course of an anti-malarial drug to the whole of a population at risk, whether or not they are known to be infected, at specific times with the aim of preventing mortality or morbidity" (Greenwood 2006).

The WHO recommends prophylaxis for people without immunity who visit malarial areas and intermittent treatment for pregnant women resident in endemic areas (WHO 2000; RBM 2005). These recommendations are supported by systematic reviews of randomized controlled trials (Croft 2000; Garner 2006). Preschool children in malaria-endemic countries are vulnerable to severe malaria and could potentially benefit from prophylaxis, but the WHO does not recommend drug prophylaxis for this age

group due to unresolved controversies on possible adverse consequence of prolonged prophylaxis and difficulties that could attend large-scale delivery of the intervention (RBM 2005; Greenwood 2006).

Following early reports of the benefits of intermittent preventive treatment of infants (IPTi) with sulfadoxine-pyrimethamine, there has been a growing global interest in the potential role of IPTi as an important addition to existing measures to reduce malaria morbidity and mortality in children living in endemic communities (Schellenberg 2001; Egan 2005). The theory is that intermittent treatment is likely to have fewer adverse events than prophylaxis because it is taken less often and is easier to deliver through clinics, reducing poor adherence with self administration. While some experts believe that intermittent treatment is of benefit through some mechanism that is qualitatively different to prophylaxis, others suggest it is basically the same mechanism (White 2005). We have included both types of intervention in this review with a view to explore whether the different types of administration explain differences in effects between trials. Even so, any such effect will be difficult to attribute to whether the administration is prophylaxis or intermittent treatment as these two interventions are confounded by the drug used, the year of the trial, and thus the prevailing drug-resistance pattern.

Some scientists are concerned that prophylaxis and intermittent treatment in children may impair the acquisition of natural immunity to malaria and therefore make them more vulnerable to severe malaria when they grow older (WHO 1993). Research has shown that young African children who received malaria prophylaxis for a long time had lower levels of malaria antibodies than their counterparts, but there is no evidence that this increased the risk of dying from malaria later in life (Otoo 1988b; Greenwood 2004). Also, there are concerns that the widespread use of antimalarial drugs for prophylaxis in young children could increase the resistance of the malaria parasites to these drugs (WHO 1990; WHO 1993; Alexander 2007); however, the design of a randomized controlled trial will not detect this. Drug resistance to sulfadoxine-pyrimethamine is already widespread, and it is unclear how policies of providing this drug for prophylaxis or intermittent treatment will impact on this trend or how the spread of resistance will affect its use for this purpose.

Although the questions over safety, sustainability, and public health impact of this intervention remain, the potential gains are large in terms of a possible effect on malaria episodes, anaemia, and mortality (Menon 1990; Schellenberg 2001). The uncertainties about the potential benefits and harms of giving prophylaxis or intermittent treatment routinely to all young children living in malaria-endemic areas make it necessary to review available evidence on this intervention strategy.

OBJECTIVES

To evaluate prophylaxis and intermittent treatment with antimalarial drugs to prevent malaria in young children living in malaria-endemic areas.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomized controlled trials. The randomization unit may be the individual participant or a cluster (eg household).

Types of participants

Children aged one month to six years or less living in an area where malaria is endemic.

Types of intervention

Intervention

Antimalarial drugs given at regular intervals irrespective of dose. This includes a suppressive low dose (prophylaxis) and a full treatment course (intermittent treatment).

Control

Placebo or no drug.

Types of outcome measures

Primary

- Clinical malaria.
- Severe anaemia (as defined by the trial authors).

Secondary

- Death from any cause.
- Hospital admission for any cause.
- Blood transfusion.
- Parasitaemia.
- Enlarged spleen.
- Need for second-line antimalarial drug.
- Haemoglobin (or haematocrit).
- Impact on routine immunization.

Adverse events

- Any adverse event.
- Serious adverse events (defined as life threatening, or requiring the drug be discontinued).

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Infectious Diseases Group methods used in reviews.

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 01: Cochrane Infectious Diseases Group Specialized Register (August 2007); Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (2007, Issue 3); MEDLINE (1966 to August 2007); EMBASE (1974 to August 2007); and LILACS (1982 to August 2007). We also searched the *meta*Register of Controlled Trials (*m*RCT) using 'malaria', 'child*', 'intermittent', 'prevent*' and 'IPT' as search terms (February 2007).

Researchers

We contacted researchers working in the field for unpublished and ongoing trials.

Reference lists

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

METHODS OF THE REVIEW

Trial selection

We independently screened the results of the literature search for potentially relevant trials and then obtained the full reprints. We independently assessed their eligibility using a form based on the inclusion criteria. Each trial report was scrutinized to ensure that multiple publications from the same trial were included only once. The trial's investigators were contacted for clarification if any eligibility criteria were unclear. We resolved disagreements through discussion, and when necessary, by consulting a member of the Cochrane Infectious Diseases Group editorial team. We listed the excluded studies and the reasons for their exclusion.

Assessment of the methodological quality

We independently assessed the methodological quality of each trial. We assessed generation of allocation sequence and allocation concealment as adequate, unclear, or inadequate according to Juni 2001. We reported whether or not the participants, care provider, or assessor were blinded in each trial. We classified inclusion of all randomized participants as adequate if at least 90% of participants were followed up to the trial's completion; otherwise we classified inclusion as inadequate. We attempted to contact the authors if this information was not specified or if it was unclear. We resolved any disagreements by discussion between review authors.

Data extraction

We independently extracted data from the included trials using a data extraction form. We resolved disagreements through discussion and, when necessary, by consulting a member of the Cochrane Infectious Diseases Group editorial team. We contacted the corresponding publication author in the case of unclear or missing data.

We aimed to extract data according to the intention-to-treat principle (all randomized participants should be analysed in the groups to which they were originally assigned). Where there was discrepancy in the number randomized and the numbers analysed in each treatment group, we calculated the percentage loss to follow up in each group and reported this information.

For dichotomous outcomes from individually randomized trials, we recorded the number of participants experiencing the event and the number analysed in each treatment group. For continuous outcomes, we extracted arithmetic means and standard deviations for each treatment group together with the numbers analysed in each group. Where data were reported using geometric means, we recorded this information and extract a standard deviation on the log scale. For count data, we extracted the total number of events in each group and the total amount of person-time at risk in each group. We also recorded the total number of participants in each group.

For trials randomized using clusters, we recorded the number of clusters in the trial, the average size of clusters, and the randomization unit (eg household or institution). The statistical methods used to analyse the trial were documented along with details describing whether these methods adjusted for clustering or other covariates. When reported, estimates of the intra-cluster correlation (ICC) coefficient for each outcome were recorded. Trial investigators were contacted to request missing information. Where results have been adjusted for clustering, we extracted the point estimate and the 95% confidence interval (CI). Where the results were not adjusted for clustering, we extracted the same data as for the individually randomized trials.

Data analysis

We used Review Manager 4.2 for data analysis. All results were presented with 95% CI. We grouped trials into those of prophylaxis and intermittent treatment. We also stratified analyses according to the trials' randomization units and correct analysis method (individually randomized trials and cluster-randomized trials with cluster-adjusted analyses).

Individually randomized trials

We computed relative risks (RR) for dichotomous data and calculated weighted mean differences (WMD) for normally distributed continuous data, and presented both with 95% CI. Where count data were summarized using rate ratios, we combined them on the log scale using the generic inverse variance method and reported them on the natural scale. We aimed to perform an

intention-to-treat analysis where the trial authors accounted for all randomized participants; however, if there was loss to follow up we performed a complete-case analysis.

Cluster-randomized trials

When the results of cluster-randomized trials had been adjusted for clustering, we combined the adjusted measures of effect in the analysis using the generic inverse variance method. When the results were not adjusted for clustering we planned to obtain additional information to enable us adjust for the design effect and then combine them in meta-analysis. However, we could not adjust the results of five cluster-randomized trials because the required information such as the average cluster size (m) and the intra-cluster correlation coefficient (ICC) were not reported and could not be estimated. It was therefore not possible to include these trials in meta-analysis or sensitivity analysis. Cluster-randomized trials without cluster-adjusted analyses were entered into tables.

Heterogeneity

We looked for heterogeneity by visually examining the forest plots, by using the chi-squared test for heterogeneity with a 10% level of statistical significance, and implementing the I^2 test statistic with a value of 50% used to denote moderate levels of heterogeneity. Where we detected heterogeneity and considered it appropriate to combine the trials, we used a random-effects model (REM) instead of the fixed-effect model. We explored heterogeneity by type of antimalarial drug and malaria transmission pattern (perennial or seasonal). For severe anaemia, we subgrouped trials by whether the children enrolled were from the general population or were selected because they were anaemic. We intended to explore the effects of participant age when the participants started taking the antimalarial drugs, but the trial data did not allow this.

We conducted a sensitivity analysis to investigate the robustness of the results to the quality components by including only those trials with adequate allocation concealment.

We had planned to examine funnel plots for asymmetry, which may be caused by factors such as publication bias, heterogeneity, and poor methodological quality, but there were too few trials in any one comparison to allow meaningful interpretation.

DESCRIPTION OF STUDIES

We assessed the search results and included 21 trials (see 'Characteristics of included studies'), excluded 58 studies (see 'Characteristics of excluded studies'), and identified seven ongoing studies (see 'Characteristics of ongoing studies').

Location

All 21 trials (19,394 participants) were conducted in Africa: one in each of Ethiopia, Senegal, Sierra Leone, Liberia, and Mozambique; two in Ghana and Kenya; and six in Tanzania and The Gambia.

The trials from The Gambia were conducted in the same population at different time points: Greenwood 1988 reported results from children in 15 villages between nine and 21 months of the trial; Greenwood 1989 was a subsidiary investigation comparing an additional antimalarial; Menon 1990 was conducted three to four years after the start of the prophylaxis and reported on the same villages; and Greenwood 1995 was conducted one year after the end of prophylaxis. Otoo 1988a was conducted six months after stopping prophylaxis and involved a cohort of five-year olds who had at least 50% compliance with prophylaxis. Schellenberg 2005 used the same study population as Schellenberg 2001; Schellenberg 2005 was an extended follow-up study that assessed the population 18 months after stopping treatment.

Malaria endemicity

The pattern of malaria transmission was perennial in trials from Ghana, Liberia, Mozambique, Sierra Leone, Tanzania, and one Kenyan trial (Desai 2003), and seasonal in The Gambia, Ethiopia, Senegal, and other trials from Ghana (Chandramohan 2005) and Kenya (Verhoef 2002). Seven trials also reported that the areas were holoendemic for malaria. Four more recent intermittent treatment trials reported entomological inoculation rates (infective bites per person per year) of 418 bites (Chandramohan 2005), 400 bites (Kobe 2007), 38 bites (Macete 2006), and 10 bites (Cissé 2006).

Trial design

Fifteen of the trials randomized individuals, while six randomized clusters (household units of families living within a compound). Five of the cluster-randomized trials did not adjust for design effect and did not report the average cluster size or intra-cluster correlation coefficient (ICC). Only Chandramohan 2005 adjusted for design effect using a REM to allow for intra-cluster correlation and other covariates (sex and urban-rural residence). We obtained figures that did not adjust for covariates and used them in the analysis. The intra-cluster correlation coefficients for outcomes are as follows: clinical malaria (ICC 0.075); all-cause hospital admissions (ICC 0.000); haematocrit less than 24% (ie severe anaemia; ICC 0.006); and all-cause death (ICC 0.000). The length of follow up varied from 10 weeks to six years, with one year most common.

Interventions

Summarized in Table 02.

Prophylaxis (11 trials)

The 11 prophylaxis trials were conducted between 1988 and 1997, and used chloroquine or pyrimethamine-dapsone. Two trials compared weekly doses of chloroquine – 5 mg/kg base or 100 mg (age less than one year) and 200 mg (age one to two years) – with placebo for 10 weeks (Wolde 1994) and one year (Hogh 1993). Eight trials compared pyrimethamine-dapsone (Maloprim or Deltaprim) with placebo; one trial also included a chlorproguanil arm (Greenwood 1989). Doses ranged between 25 and 50 mg for dapsone and between 3.125 and 12.5 mg for pyrimethamine. The pyrimethamine-dapsone was given either weekly (Alonso 1993; Lemnge 1997; Menendez 1997) or

fortnightly (Greenwood 1988; Otoo 1988a; Greenwood 1989; Menon 1990; David 1997) for five months (Alonso 1993), 10 months (Menendez 1997), one year (Greenwood 1988; David 1997; Lemnge 1997), two years (Otoo 1988a; Greenwood 1989), or until the children were aged five years (Menon 1990). Two of the eight trials evaluated outcomes after stopping the intervention at six months (Otoo 1988a) and one year (Greenwood 1995).

Intermittent treatment (10 trials)

Six trials comprehensively used intermittent treatment for the primary prevention of anaemia and malaria in healthy young infants (Chandramohan 2005; Cissé 2006; Macete 2006; Kobbe 2007; Massaga 2003; Schellenberg 2001). Three trials selectively gave intermittent treatment to children who were already anaemic (Tomashek 2001; Verhoef 2002; Desai 2003). Schellenberg 2005 was an extended follow-up study of Schellenberg 2001 and assessed outcomes up to 18 months after stopping treatment.

Seven trials used standard treatment doses of sulfadoxine-pyrimethamine: Chandramohan 2005; Schellenberg 2001 administered medication to infants attending immunization services at the ages of two, three, and nine months; Macete 2006 at the ages of three, four, and nine months; Kobbe 2007 at the ages of three, nine, and 15 months; and Desai 2003, Tomashek 2001, and Verhoef 2002 administered medication every four weeks for a total of three doses. Cissé 2006 administered a combination of the standard dose of sulfadoxine-pyrimethamine plus artesunate (4 mg/kg body weight) once monthly for three consecutive months to children aged two to 59 months. Massaga 2003 administered a treatment course of amodiaquine (25 mg/kg over three days) within intervals of 60 days over six months.

Co-interventions

Seven trials gave iron supplements all participants (Menendez 1997; Schellenberg 2001; Tomashek 2001; Verhoef 2002; Desai 2003; Massaga 2003; Chandramohan 2005), three trials gave folic acid (Greenwood 1989; Tomashek 2001; Chandramohan 2005), and two trials also used insecticide-treated nets (Alonso 1993; Desai 2003). David 1997 used insecticide-treated nets, but we did not include the affected groups in the review.

Outcomes

Seventeen trials reported on the number of children developing malaria; 11 reported on total episodes. Eleven trials reported on severe anaemia, which had several definitions of packed-cell volume (PCV) less than 25% (three trials), less than 20% (one trial), or haemoglobin less than 7 g/dL (one trial). One trial classified haemoglobin concentration of 5.0 to 8.0 g/dL (equivalent to PCV 15% to 24%) as moderate anaemia, but, for the meta-analysis, we classified this as severe anaemia to be consistent with the range for other trials. Two trials did not specify the definition of severe anaemia. Other relevant outcomes reported were death (14 trials; 11 included in meta-analysis), hospital admission (six trials), parasitaemia (six trials), enlarged spleen (four trials), and adverse events (six trials). David 1997 reported only adverse events.

METHODOLOGICAL QUALITY

See Table 03 for a summary of the quality assessment by trial.

Generation of allocation sequence

Eleven trials used adequate methods to generate the allocation sequence — three used block randomization, and eight used a computer. Two trials that used an inadequate method (alternate allocation) and were included in the first version of the review have been excluded from the current version because quasi-randomization is no longer an inclusion criterion. The remaining 10 trials did not describe the method used; five of these randomized clusters of family unit.

Allocation concealment

Allocation concealment was adequate in the 11 trials that used identical and centrally coded drugs and placebo, or sealed, opaque envelopes; allocation concealment was unclear in the other trials.

Blinding

Eighteen trials blinded participants and care providers/assessors. One trial blinded only participants and assessors but not care providers (Tomashek 2001). Blinding was unclear in two trials (Wolde 1994; David 1997).

Inclusion of all randomized participants in the analysis

Eight trials included more than 90% of randomized participants in the analysis (defined in the review methods as adequate); four had greater than 10% attrition or accounted for less than 90% of randomized participants in data analysis (inadequate); the rest were unclear. Six trials reported an intention-to-treat analysis: Verhoef 2002, Cissé 2006, and Macete 2006 used intention-to-treat analysis for the primary outcome; and Massaga 2003, Chandramohan 2005, and Kobbe 2007 used the intention-to-treat approach for all outcomes.

RESULTS

Part one examines the effects on children during antimalarial prophylaxis or intermittent treatment. Part two explores the effects after the antimalarial drugs were stopped, seeking longer term effects on immunity.

Part 1. Effects on children during prophylaxis or intermittent treatment

Clinical malaria

Although the effect size varied markedly, the direction of effect consistently favoured the antimalarials over placebo (RR 0.53, 95% CI 0.38 to 0.74, REM; 7037 participants, 10 trials, Analysis 01.01). Intermittent treatment significantly reduced the risk of clinical malaria as shown in seven individually randomized trials (RR 0.50, 95% CI 0.31 to 0.80, REM; 4893 participants, Analysis 01.01) and reduced the incidence rate as shown in one cluster-randomized intermittent treatment trial (incidence rate ratio 0.76,

95% CI 0.68 to 0.85; 2485 participants, Analysis 02.01), while the reduction shown with prophylaxis did not reach statistical significance (2144 participants, 3 trials; Analysis 01.01).

Statistically significant heterogeneity persisted when we analysed the trials according to type of antimalarial drug (Analysis 03.01) and seasonality (Analysis 04.01). We examined funnel plots for asymmetry – to explore possible effect of factors such as publication bias, heterogeneity, and poor methodological quality – but observed no definite pattern (symmetry or asymmetry) because there were too few included trials for each comparison.

We did not include five trials in the meta-analysis because they reported only event counts of malaria episodes and not the number of children developing one or more clinical malaria episodes. Greenwood 1988 reported 32 episodes of clinical malaria in 1515 observations among children treated with pyrimethamine-dapsone and 36 episodes in 1704 observations in the placebo group. Greenwood 1989 conducted a monthly morbidity report and physical examination on all children enrolled, and reported a lower prevalence in observations of fever and parasitaemia in children with pyrimethamine-dapsone (3/1204 examinations) compared with chlorproguanil (12/1425 examinations) or placebo (17/1299). Menon 1990 reported 34 and 38 clinical episodes of malaria in the treated group (2139 observations) and control group (1883 observations) respectively, and Lemnge 1997 reported a lower rate of clinical malaria episodes in participants in the pyrimethamine-dapsone group (87/2914) than in the control group (144/2938). Hogg 1993 did not provide the number of participants with the outcome but did report that chloroquine prophylaxis was protective for episodes of “possible clinical malaria” (odds ratio 0.49, 95% CI 0.35 to 0.69; trialists’ calculation).

Severe anaemia

The effect favoured the antimalarial drugs within the nine individually randomized trials (RR 0.70, 95% CI 0.52 to 0.94; REM; 5445 participants, Analysis 01.02) and the one cluster-randomized trial (incidence rate ratio 0.65, 95% CI 0.53 to 0.80; 2485 participants, Analysis 02.02). The point estimate in the only prophylaxis trial was clearly statistically significant (RR 0.48, 95% CI 0.34 to 0.67; 415 participants), while the difference in effects within the eight intermittent treatment trials was marginal (RR 0.76, 95% CI 0.57 to 1.02; 5030 participants).

Visual examination of the forest plot, chi-squared test, and I^2 test showed statistically significant heterogeneity. We explored the possible influence of explanatory variables on heterogeneity and the effect size by subgroup analysis. The analysis grouped by drug type was quite mixed with no apparent pattern (Analysis 03.02). Grouping by seasonality showed persistence of heterogeneity and statistically significant difference in effect in favour of the intervention group within trials conducted in perennial transmission areas. The analysis was less informative for seasonal transmission areas because only one trial contributed to the meta-analysis (Analysis 04.02).

We also stratified trials by whether the children enrolled were from the general population or were selected because they were anaemic (Analysis 05.01). In the five trials that enrolled healthy infants, severe anaemia was less frequent in the intervention group (RR 0.70, 95% CI 0.51 to 0.97; 4494 participants), but this was not so in the three trials that enrolled only anaemic children (RR 1.31, 95% CI 0.63 to 2.72; 536 participants).

We did not include one cluster-randomized trial (Greenwood 1988) in the meta-analysis because the authors did not adjust for the effect of clustering nor report relevant cluster characteristics to enable us calculate the intra-cluster correlation coefficient (ICC); we presented the data in Table 05. The calculated relative risk was not statistically significantly different between the antimalarial and placebo groups (241 participants; see Table 05).

Death from any cause

We detected no statistically significant difference between antimalarial drugs and placebo in all 10 individually randomized trials (7369 participants, Analysis 01.03) and one adjusted cluster-randomized trial (2485 participants, Analysis 02.03). There was no change when we stratified by prophylaxis trials (2313 participants, 2 trials) or the intermittent trials (5056 participants, 8 trials). One intermittent treatment trial, Tomashek 2001, reported six deaths among the trial participants but did not specify their intervention group; we obtained clarification from the trial authors and included these data in the meta-analysis.

We did not include three non-adjusted cluster-randomized prophylaxis trials in a meta-analysis; data presented in Table 05. Recalculation of the relative risk in two of these trials showed no statistically significant difference in this outcome (1727 participants, Greenwood 1988, Greenwood 1989, Table 05), while one trial showed statistically significant reduction in risk of death in favour of the intervention group (RR 0.51, 95% CI 0.26 to 0.98; 1792 participants, Menon 1990).

Hospital admission for any cause

Overall, the number of hospital admissions was lower in the antimalarial groups (RR 0.64, 95% CI 0.49 to 0.82; 3722 participants, 6 trials, Analysis 01.04), even when stratified by intervention: prophylaxis (RR 0.49, 95% CI 0.40 to 0.60; 303 participants, 1 trial); and intermittent treatment (RR 0.72, 95% CI 0.60 to 0.88; 3419 participants, 4 trials). The one cluster-randomized trial of intermittent treatment did not reach statistical significance (2485 participants, Analysis 02.04).

Parasitaemia

Six trials contributed to the meta-analysis, which showed statistically significantly fewer children with parasitaemia in the antimalarial group compared with the placebo group (RR 0.44, 95% CI 0.23 to 0.86, REM; 2080 participants, Analysis 01.05). Within the respective trial groups the effects tended to favour the intervention, but the pooled results did not reach statistical significance

for the two prophylaxis trials (835 participants) nor the three intermittent treatment trials (1245 participants).

Data from two non-adjusted cluster-randomized trials (Greenwood 1988; Menon 1990) could not be included in meta-analysis, but they are presented in Table 05. They showed that fewer children in the intervention groups had parasitaemia the control groups (591 participants).

Enlarged spleen

Four trials (1589 participants), all using prophylaxis, reported on this outcome; two were included in meta-analysis, while two non-adjusted cluster-randomized trials were presented in Table 05. The meta-analysis showed that fewer children had enlarged spleens in the prophylaxis group compared with the placebo group (RR 0.39, 95% CI 0.15 to 0.99; REM; 995 participants, Analysis 01.06). Greenwood 1988 and Menon 1990 also reported statistically significantly fewer cases of enlarged spleen in the intervention than the control groups (594 participants, 2 trials; see Table 05).

Mean haematocrit

Two cluster-randomized trials of prophylaxis reported on mean haematocrit, but they could not be combined in a meta-analysis because there was insufficient information on adjustment for cluster effects. The data presented in Table 05 showed mean haematocrit to be statistically significantly higher in the prophylaxis group than the placebo group for Greenwood 1988 (WMD 2.70, 95% CI 1.39 to 4.01; 241 participants) and for Menon 1990 (WMD 1.60, 95% CI 0.70 to 2.50; 335 participants). One trial of intermittent treatment, Tomashek 2001, found no difference between the mean haemoglobin concentration of the antimalarial group (10.2 g/dL, 95% CI 9.9 to 10.5 g/dL) and the placebo group (10.2 g/dL, 95% CI 10.0 to 10.4 g/dL); (trialists' calculation). Hogg 1993 presented haematocrit data in graphs (unsuitable for meta-analysis). Lemnge 1997 reported significantly higher mean haematocrit levels for the antimalarial group than the placebo group but provided insufficient data for meta-analysis.

Impact on routine immunization

Schellenberg 2001 and Macete 2006 evaluated the effect of intermittent treatment on protective efficacy of childhood immunization when both interventions were given concurrently. Analysis 01.07 showed no statistically significant difference between intervention and control groups in the proportion of children that acquired adequate protective antibody titres to measles vaccine (695 participants), diphtheria vaccine (795 participants), and tetanus vaccine (645 participants). Macete 2006 also found no statistically significant difference in the proportion of participants in treatment and control groups with protective antibody titres following immunization for hepatitis B (495 participants) and polio (499 participants) (Analysis 01.07).

Adverse events

Nine trials reported adverse events; we included data from four trials in meta-analyses (Analyses 06.01 and 06.02). Kobbe 2007

reported two cases of Stevens-Johnson syndrome (a life-threatening severe skin reaction) in the sulfadoxine-pyrimethamine group and one in the control group with no statistically significant difference (1070 participants, Analysis 06.02). Macete 2006, which also used sulfadoxine-pyrimethamine, reported no severe cutaneous reactions. David 1997 reported hyperpigmented macules only in the pyrimethamine-dapsone group (886 participants, Analysis 06.01); Menendez 1997 reported that adverse events were mild with no statistically significant difference in the incidence of vomiting between the pyrimethamine-dapsone group and the placebo group (415 participants, Analysis 06.01). Cissé 2006 reported statistically significantly higher incidence in the sulfadoxine-pyrimethamine group of pruritus (RR 3.74, 95% CI 1.06 to 13.18; 941 participants), vomiting (RR 8.27, 95% CI 3.59 to 19.05; 941 participants), and nervousness (RR 1.39, 95% CI 1.13 to 1.70; 941 participants), but there was no statistically significant difference in the incidence of minor skin rash, diarrhoea, and dizziness (941 participants, Analysis 06.02). Table 04 shows details of reported adverse events that could not be included in meta-analyses. Massaga 2003, which used amodiaquine for intermittent treatment, reported no serious adverse events such as agranulocytosis.

Sensitivity analyses

No important differences in the results for clinical malaria, severe malaria, or death were observed when only the adequately concealed trials were included in the analyses (Analysis 07.01).

Part 2. Effects on children after stopping intervention

Seven trials evaluated the impact after intervention was stopped: three prophylaxis trials (Otoo 1988a; Greenwood 1995; Menendez 1997); and four intermittent treatment trials (Chandramohan 2005; Schellenberg 2005; Cissé 2006; Kobbe 2007). These trialists reported outcomes assessed after intervention had been stopped for variable lengths of time: six months (Otoo 1988a); nine months (Kobbe 2007); four to 12 months corresponding to age 16 to 24 months (Chandramohan 2005); 12 months (Greenwood 1995; Menendez 1997; Cissé 2006); and 18 months (Schellenberg 2005). All four intermittent treatment trials contributed to the meta-analysis on clinical malaria, three on severe anaemia, and two on death rates, while one reported on the impact of intermittent treatment on measles immunization. Only one prophylaxis trial, Menendez 1997, contributed data for a meta-analysis (death). Other data on outcomes reported by the prophylaxis trials are presented in Table 05.

Clinical malaria

Four intermittent treatment trials assessed the incidence of clinical malaria after intervention was stopped at 16 to 24 months (Chandramohan 2005), 18 months (Schellenberg 2005), nine months (Kobbe 2007), and during next malaria transmission season (Cissé 2006). Meta-analyses showed no statistically significant difference in episodes of clinical malaria between intervention and control groups (4689 participants, Analyses 08.01 and 08.02).

One prophylaxis trial (Menendez 1997) reported that children that received pyrimethamine-dapsone prophylaxis had more episodes of clinical malaria than the placebo group the year following intervention (RR 1.8, 95% CI 1.3 to 2.6; trialists' calculation, Table 05). Two cluster-randomized trials reported the incidence of clinical malaria after pyrimethamine-dapsone prophylaxis had been stopped for one year (Greenwood 1995) and for six months (Otoo 1988a). Otoo 1988a reported no statistically significant difference in the number of clinical malaria episodes in the prophylaxis group compared with the placebo group (Table 05).

Severe anaemia

A meta-analysis of three intermittent treatment trials showed no statistically significant difference in the incidence of severe anaemia between the intervention and placebo groups (3816 participants, Analyses 08.03 and 08.04; Chandramohan 2005; Schellenberg 2005; Kobbe 2007). One prophylaxis trial (Menendez 1997) reporting on pyrimethamine-dapsone prophylaxis showed statistically significantly higher incidence of severe anaemia among the intervention group than control (RR 2.2, 95% CI 1.3 to 2.7; trialists' calculation, Table 05).

Death from any cause

Two intermittent treatment trials showed no statistically significant difference in the number of deaths: Kobbe 2007 (1070 participants, Analysis 08.05) and Chandramohan 2005 (2191 participants, Analysis 08.06).

Greenwood 1995 reported that the risk of dying within two years after stopping prophylaxis was similar in both groups (4/203 versus 5/200; Table 05), while Otoo 1988a reported no deaths in either group.

Parasitaemia

Otoo 1988a reported that parasitaemia was marginally statistically significantly lower in the prophylaxis group six months after stopping prophylaxis compared with the placebo group (RR 0.73, 95% CI 0.55 to 0.97; 77 participants, Table 05). Greenwood 1995 reported no statistically significant difference in the number of children with parasitaemia between the prophylaxis and the placebo groups (Table 05).

Enlarged spleen

Otoo 1988a and Greenwood 1995 reported this outcome; there was no statistically significant difference between the prophylaxis group and placebo group (Table 05).

Mean haematocrit

There was no statistically significant difference between the prophylaxis and control groups in Greenwood 1995 (WMD 0.30%, 95% CI -0.59% to 1.19%; 407 participants, Table 05).

Impact on routine immunization

Schellenberg 2005 reported that the prevalence of protective antibody titres against measles was not significantly different between the treated and placebo groups up to 18 months after the con-

current administration of immunization and intermittent treatment with sulfadoxine-pyrimethamine in infants (317 participants, Analysis 08.07).

DISCUSSION

All 21 trials included in the review were conducted in areas in Africa where *P. falciparum* is the predominant cause of malaria. Transmission patterns were variable: seasonal in 10 trials and perennial in 11. The 10 intermittent treatment trials were more recent and contributed more data to meta-analyses than the prophylaxis trials. Several of the prophylaxis trials reported outcomes in different publications, but we have been careful to ensure the same participants are not included twice in each meta-analysis.

All 10 intermittent treatment trials and two of the 11 prophylaxis trials described adequate methods of generating the allocation sequence. Nine intermittent treatment trials and one prophylaxis trial used adequate allocation concealment, while the rest did not report on this procedure. As adequate allocation concealment and randomization significantly improve the internal validity of randomized controlled trials (Schulz 1995), the failure of trial authors to describe these important processes could mean that these methods may not have been adequately applied. Trials lacking these methodological qualities are prone to bias and may give misleading results.

There was marked quantitative heterogeneity between many trials, which could be anticipated given the various types of antimalarial regimens, malaria endemicity, transmission patterns, drug-resistance patterns, adherence to the regimens, and trial quality. There is, however, an overall consistency towards benefit. Exploration of the heterogeneity with subgroup analysis by drug types and seasonality showed no consistent pattern.

Overall, both prophylaxis and intermittent treatment consistently reduced clinical malaria and admission to hospital. The effect of intermittent treatment on the incidence of severe anaemia appeared to be modest compared with the marked reduction observed in clinical malaria episodes and hospital admissions. Intermittent treatment did not appear to be effective in reducing the incidence of anaemia in the three trials enrolling already moderately anaemic children (secondary prevention), although it clearly was effective in preventing severe anaemia in the primary prevention trials. The children in the primary prevention trials were mainly non-anaemic and younger than those in the secondary prevention trials.

This review did not provide convincing evidence that either prophylaxis or intermittent treatment reduced the risk of death in preschool children, although the point estimate and confidence intervals are compatible with a potentially important effect.

It has been widely speculated that giving prophylaxis to infants and preschool children resident in malaria-endemic areas would pre-

vent natural immunity and result in (rebound) increase in morbidity and mortality after stopping prophylaxis. Data on possible rebound effect of prophylaxis in this review were scanty and showed inconsistent results. One prophylaxis trial detected a statistically significant increase in the incidence of clinical malaria and anaemia among children who had previously received pyrimethamine-dapsone prophylaxis compared to the control group (Menendez 1997). The other two trials did not demonstrate any significant deleterious effects of taking the intervention (Otoo 1988a; Greenwood 1995), but sample sizes were small. The results of four trials of adequate methodological quality included in the meta-analysis demonstrated that intermittent treatment given over a short period during early childhood is unlikely to result in rebound effect malaria morbidity and mortality. While these trials are few with short follow-up periods, these results appear to support the hypothesis that intermittent treatment allows longer periods in between treatments for children to acquire protective malarial immunity and is therefore less likely to cause rebound morbidity and mortality than continuous prophylaxis.

Adverse events were reported in only a few trials. The commonest adverse events were minor skin rash, pruritis, and vomiting, and they tended to occur more in the intervention than control groups. One trial reported three cases of Stevens-Johnson syndrome (a severe life-threatening skin reaction) – two in the intermittent treatment group and one in the placebo group (Kobbe 2007). Only five of the 11 prophylaxis trials reported on adverse events. Reporting of adverse events is important when antimalarial drugs are given on a long-term basis, so future trials need to adopt more robust approaches to measure adverse events.

Giving intermittent treatment to infants attending routine immunization clinics would help to ensure that drugs are used appropriately, but there is a concern that concurrent administration of routine childhood vaccine and intermittent treatment could impact negatively on the development of vaccine-induced protective immunity (Rosen 2004). The findings of two trials that provided adequate data for meta-analysis in this review (Schellenberg 2001; Macete 2006) showed that intermittent treatment did not reduce the potency of four routine childhood vaccines, namely measles, diphtheria, tetanus, and hepatitis B vaccines. Few data were available for this review and more trials will be required to adequately test the hypothesis that co-administration of childhood vaccines and antimalarial drugs could reduce the protective immunity of these vaccines.

While available evidence from randomized controlled trials examined in this systematic review has demonstrated that continuous prophylaxis and intermittent treatment with antimalarial drugs reduce the incidence of malaria and severe anaemia, it has not demonstrated effect on death and has not resolved pertinent questions about long-term safety. There are ongoing trials of intermittent treatment regimens involving a large consortium of researchers (see 'Characteristics of ongoing studies'). It is hoped that

in the near future these trials would contribute data to confirm or disprove some of the inconclusive observations made in this review. In addition to providing more information on the effectiveness of these regimens, we expect that these trials will conduct long-term, follow-up studies to explore this and other research questions related to cost effectiveness, relative safety, and emergence of parasite resistance.

AUTHORS' CONCLUSIONS

Implications for practice

Giving antimalarial drugs at regular intervals (prophylaxis or intermittent treatment) reduces clinical malaria, severe anaemia, and hospital admissions. There are insufficient data to know whether such preventive interventions impact on mortality or if there are any detrimental impacts on health when the prophylaxis or intermittent treatment is stopped. Intermittent preventive treatment of infants (IPTi) along with routine childhood immunization is a potentially beneficial public health intervention, but decisions to promote its use on a wide scale should await the result of long-term follow-up studies to resolve uncertainties about long-term safety. There are some large trials in progress evaluating intermittent treatment that will help inform policy.

Implications for research

There is a need to further evaluate the benefits of intermittent treatment in areas of perennial and seasonal malaria transmission. These trials should measure mortality and have long-term follow up to examine potential impact on the person's natural immunity. These studies could also assess the possible effects on parasite susceptibility. Also, the hypothesis that co-administration of antimalarial drugs and childhood vaccines could make the vaccines less effective needs clarifying. Trials should also aim to ensure that reliable surveillance strategies are used to detect and appropriately report adverse events. Ongoing trials should provide some of the answers to these research questions in the near future.

There is need to evaluate the benefits of intermittent treatment with sulfadoxine-pyrimethamine in areas with high levels of *P. falciparum* resistance to sulfadoxine-pyrimethamine. Research to explore alternative antimalarial drugs for intermittent treatment is a priority given that increasing resistance to sulfadoxine-pyrimethamine may compromise benefits.

POTENTIAL CONFLICT OF INTEREST

None known.

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* Indicates the major publication for the study

T A B L E S**Characteristics of included studies**

Study	Alonso 1993
Methods	Randomized controlled trial* Length of follow up: 1 year
Participants	Number enrolled: 1898 children Inclusion criteria: children aged 6 months to 5 years
Interventions	Prophylaxis: weekly dose for 5 months (during rainy season) (1) Pyrimethamine-dapsone (Maloprim): 12.5 mg pyrimethamine and 50 mg dapsone; 952 children (2) Placebo; 946 children All used insecticide-treated nets
Outcomes	(1) Clinical malaria episodes (2) Death (3) Parasitaemia (4) Enlarged spleen

Characteristics of included studies (Continued)

Notes	Location: The Gambia (17 rural villages) Malaria transmission: seasonal/holoendemic
Allocation concealment	B – Unclear
Study	Chandramohan 2005
Methods	Cluster-randomized controlled trial* Average cluster size = 26; ICCs and additional data provided by trial author Length of follow up: 24 months
Participants	Number enrolled: 96 clusters (unit of randomization = households) comprising a total of 2485 infants attending routine immunization clinics for second (DPT-2) and third doses of DPT vaccine (DPT-3), measles vaccine (usually at age 9 months) and at age 12 months (2386 actually received treatment or placebo) Inclusion criteria: infants living in selected clusters attending routine immunization clinics Exclusion criteria: allergy to sulfadoxine-pyrimethamine
Interventions	Intermittent treatment: sulfadoxine-pyrimethamine first dose given at 2 months, second dose at 3 months, third at 9 months, and fourth dose at 12 months (1) Sulfadoxine-pyrimethamine (500 mg sulfadoxine and 25 mg pyrimethamine): 1/2 tablet at time of DPT-2 and DPT3 vaccines; 1 tablet at time of measles vaccine and at 12 months; 1183 children (2) Placebo; 1203 children All participants concurrently received routine immunization with DPT and measles vaccines
Outcomes	(1) Clinical malaria episodes (2) Anaemia (3) Hospital admissions (4) Death (5) Adverse events
Notes	Location: Kassena-Nankana District, Upper East Region, Ghana (96 out of 244 clusters) Malaria transmission: high/seasonal; entomological inoculation rate = 418 infective bites per person per year (almost all between June and November)
Allocation concealment	A – Adequate
Study	Cissé 2006
Methods	Randomized controlled trial* Length of follow up: 12 months
Participants	Number enrolled: 1088 children aged 2 to 59 months Inclusion criteria: age 2 to 59 months; residence in study area Exclusion criteria: severe illness including severe anaemia
Interventions	Intermittent treatment: sulfadoxine-pyrimethamine plus artesunate given once monthly (1) Sulfadoxine-pyrimethamine (25 mg/kg sulfadoxine and 1.25 mg/kg pyrimethamine) plus artesunate (4 mg/kg give once monthly for 3 consecutive months); 542 children (2) Placebo; 546 children All participants concurrently received routine immunization with DPT and measles vaccines
Outcomes	(1) Clinical malaria episodes (2) Anaemia (3) Hospital admissions (4) Death (5) Adverse events (6) Sulfadoxine- pyrimethamine resistance markers
Notes	Location: Niakkhar, Senegal Malaria transmission: high/seasonal

Characteristics of included studies (Continued)

Registration number: NCT00132561

Allocation concealment A – Adequate

Study David 1997

Methods Randomized controlled trial*
Length of follow up: 1 year

Participants Number enrolled: 2000 children
Inclusion criteria: children living in the area aged 3 months to 6 years

Interventions Prophylaxis: twice weekly for 1 year
(1) Pyrimethamine-dapsone (Maloprim): 1.6 mg pyrimethamine for age 3 to 11 months, 3.1 mg for 1 to 4 years, and 9.4 mg for > 5 years; 12.5 mg dapsone for age 3 to 11 months, 50 mg for 1 to 4 years, and 75 mg for > 5 years old; 436 children
(2) Placebo; 450 children

Following 2 arms not included in review:
(3) Pyrimethamine-dapsone (Maloprim) and insecticide-treated nets; 467 children
(4) Insecticide-treated nets; 470 children

Outcomes (1) Adverse events

Notes Location: Bo, Sierra Leone
Malaria transmission: perennial

Allocation concealment B – Unclear

Study Desai 2003

Methods Randomized controlled trial*
Length of follow up: 1 to 2 years

Participants Number enrolled: 546 children
Inclusion criteria: children aged 2 to 36 months; consent; mild anaemia (haemoglobin concentration 7.0 to 10.9 g/dL); aparasitaemia or parasite count < 20,000/cubic mm
Exclusion criteria: intake of iron supplement; sulfadoxine-pyrimethamine treatment or blood transfusion within the last 2 weeks

Interventions Intermittent treatment: sulfadoxine-pyrimethamine given every 4 weeks for 3 doses; iron given daily for 12 weeks
(1) Sulfadoxine-pyrimethamine: 25 mg/kg sulfadoxine and 1.25 mg/kg pyrimethamine per tablet with 1/2 tablet for children < 10 kg or 1 tablet for children \geq 10 kg; 271 children
(2) Iron (ferrous sulphate): 3 to 6 mg/kg/day; 139 children
(3) Iron and sulfadoxine-pyrimethamine; 135 children
(4) Placebo; 275 children

Outcomes (1) Clinical episodes of malaria
(2) Severe anaemia
(3) Death
(4) Parasitaemia
(5) Adverse events

Notes Location: Asemo, Bondo district, Western Kenya
Malaria transmission: perennial/holoendemic

Allocation concealment A – Adequate

Study Greenwood 1988

Methods Cluster-randomized controlled trial (households)*; no estimates of average cluster size or ICC given

Characteristics of included studies (Continued)

	Length of follow up: 1 year
Participants	Number enrolled: 1488 children Inclusion criteria: age 3 to 59 months; resident in the area
Interventions	Prophylaxis: every 2 weeks for 1 year (1) Pyrimethamine-dapsone (Maloprim): 6.25 mg pyrimethamine and 25 mg dapsone with 1 tablet for 3 to 11 months old or 2 tablets for 1 to 4 years old; 783 children (2) Placebo; 705 children
Outcomes	(1) Clinical malaria episodes (2) Severe anaemia (3) Death (4) Parasitaemia (5) Enlarged spleen (6) Mean packed-cell volume (haematocrit) Outcomes assessed after stopping intervention: clinical episodes of malaria and death
Notes	Location: Farafeni, The Gambia Malaria transmission: seasonal Completion rates: 96% (1982) and 94% (1984) The Gambian trials were conducted in the same population at different time points: this is the main study and provided results from children in 38 villages (13 intervention and 25 placebo) between 9 and 21 months of the trial
Allocation concealment	B – Unclear

Study	Greenwood 1989
Methods	Cluster-randomized controlled trial (households)*; no estimates of average cluster size or ICC given Length of follow up: 3 years
Participants	Number analysed: 560 children Inclusion criteria: age 3 to 59 months; resident in the area
Interventions	Prophylaxis: every 2 weeks for 3 years (1) Pyrimethamine-dapsone (Maloprim) and folic acid: 6.25 mg pyrimethamine and 25 mg dapsone per tablet with 1 tablet for 3 to 11 months old or 2 tablets for 1 to 4 years old (2) Pyrimethamine-dapsone (Maloprim) and placebo: 76 children (all Maloprim) (3) Chlorproguanil and folic acid: 20 mg (4) Chlorproguanil and placebo; 192 children (all chlorproguanil) (5) Placebo and folic acid (6) Placebo and placebo; 192 children (all placebo)
Outcomes	(1) Clinical malaria episodes (2) Death Same outcomes assessed after stopping intervention
Notes	Location: Sarakund, The Gambia Malaria transmission: seasonal The Gambian trials were conducted in the same population at different time points: this is a subsidiary investigation to Greenwood 1988 (main study) comparing an additional antimalarial
Allocation concealment	B – Unclear

Study	Greenwood 1995
Methods	Cluster-randomized controlled trial (households)*; average cluster size and ICC not given Length of follow up: 1 year

Characteristics of included studies (Continued)

Participants	Number analysed: 408 children Inclusion criteria: age 3 to 59 months; resident in the area
Interventions	Prophylaxis: every 2 weeks for 1 year (1) Pyrimethamine-dapsone (Maloprim): 6.25 mg pyrimethamine and 25 mg dapsone per tablet with 1 tablet for 3 to 11 months old or 2 tablets for 1 to 4 years old; 208 children (2) Placebo; 200 children
Outcomes	(1) Clinical malaria episodes (2) Death (3) Parasitaemia (4) Enlarged spleen (5) Mean packed-cell volume (haematocrit)
Notes	Location: Farafeni, The Gambia Malaria transmission: seasonal Completion rates 96% (1982) and 94% (1984) The Gambian trials were conducted in the same population at different time points: this trial was conducted one year after the end of prophylaxis described in Greenwood 1988 (main study)
Allocation concealment	B – Unclear

Study **Hogh 1993**

Methods	Randomized controlled trial* Length of follow up: 1 year
Participants	Number enrolled: 262 children Inclusion criteria: children aged 6 months to 6 years; resident in the area; consent
Interventions	Prophylaxis: every 3 weeks for 1 year (1) Chloroquine: 5 mg/kg; 158 children (2) Placebo; 104 children
Outcomes	(1) Clinical malaria episodes (2) Parasitaemia (3) Splenomegaly (enlarged spleen) (4) Packed-cell volume (haematocrit) Not included in review: (5) Inoculation rate (6) Haemoglobinopathies
Notes	Location: Mount Nimba region, north-western Liberia Malaria transmission: perennial
Allocation concealment	B – Unclear

Study **Kobbe 2007**

Methods	Randomized controlled trial* Length of follow up: 21 months
Participants	Number enrolled: 1070 children Inclusion criteria: age 3 months (4-weeks tolerance accepted); permanent residence in study area Exclusion criteria: severe illness
Interventions	Intermittent treatment: sulfadoxine-pyrimethamine given at age 3 months, 9 months, and 15 months (1) Sulfadoxine-pyrimethamine: 1 tablet (250 mg sulfadoxine and 12.5 mg pyrimethamine) per dose; 1 dose given at age 3 months, 9 months, and 15 months; 535 children (2) Placebo; 535 children

Characteristics of included studies (Continued)

	All participants concurrently received routine immunization with DPT and measles vaccines
Outcomes	(1) Clinical malaria episodes (2) Anaemia/severe anaemia (3) Hospital admissions (4) Death (5) Adverse events (6) Sulfadoxine- pyrimethamine resistance markers
Notes	Location: Afigya Sekyere district, Ghana Malaria transmission: holoendemic, intense perennial (with seasonal peaks)
Allocation concealment	A – Adequate

Study Lemnge 1997

Methods	Randomized controlled trial* Length of follow up: 1 year
Participants	Number enrolled: 249 children; we included only the 117 children in the subgroup of those aged 1 to 4 years Inclusion criteria: age 1 to 9 years at admission and permanent residence in village Exclusion criteria: gross malnutrition; severe illness; severe anaemia (packed-cell volume < 20%); severe glucose-6-phosphate dehydrogenase deficiency
Interventions	Prophylaxis: once weekly for 1 year (1) Pyrimethamine-dapsone (Maloprim): 3.125 mg pyrimethamine and 25 mg dapsone with 1 tablet for age 1 to 4 years or 2 tablets for age 5 to 9 years; 58 children (2) Placebo; 59 children
Outcomes	(1) Clinical malaria episodes (2) Death (3) Parasitaemia (4) Splenomegaly (enlarged spleen) (5) Packed-cell volume (haematocrit) (6) Adverse effects Not included in review: (7) Compliance
Notes	Location: Magoda village, north-eastern Tanzania Malaria endemicity: holoendemic
Allocation concealment	A – Adequate

Study Macete 2006

Methods	Randomized controlled trial* Length of follow up: 9 months
Participants	Number enrolled: 1503 children Inclusion criteria: infants (age 3 at first dose); permanent residence in study area Exclusion criteria: allergy to sulfa drugs; illness that required admission to hospital
Interventions	Intermittent treatment: sulfadoxine-pyrimethamine given at age 3 months, 9 months, and 15 months (1) Sulfadoxine-pyrimethamine (administered according to weight): < 5 kg, 1/4 tablet; 5 to 10 kg, 1/2 tablet; > 10 kg, 1 tablet; 748 children (2) Placebo; 755 children All participants received routine immunization with DPT and measles vaccines
Outcomes	(1) Clinical malaria episodes (2) Severe anaemia

Characteristics of included studies (Continued)

	(3) Hospital admissions (4) Death (5) Parasitaemia (6) Adverse events
Notes	Location: Manhica District (Maputo Province) Mozambique Malaria endemicity: perennial
Allocation concealment	A – Adequate
Study	Massaga 2003
Methods	Randomized controlled trial* Length of follow up: 10 months Intention-to-treat analysis
Participants	Number enrolled: 291 infants Inclusion criteria: infants aged 12 to 16 weeks attending Maternal and Child Health (MCH) clinics for growth monitoring or to receive their third DPT and oral poliovirus vaccine Exclusion criteria: congenital malformation; severe conditions that needed treatment in hospital; fever within past 2 days; packed-cell volume < 24; taking chemoprophylaxis
Interventions	Intermittent treatment: amodiaquine every 2 months and daily iron for 6 months (1) Amodiaquine and iron: 25 mg/kg over 3 days, with 10 mg/kg on first 2 days and 5 mg/kg on third day; 72 children (2) Amodiaquine and placebo; 74 children (3) Iron and placebo: 7.5 mg elemental iron; 73 children (4) Placebo and placebo; 72 children
Outcomes	(1) Clinical malaria episodes (2) Hospital admissions (3) Death (4) Adverse events Not included in review: (5) Anaemia
Notes	Location: Muheza district, north-eastern Tanzania Malaria transmission/endemicity: perennial/holoendemic
Allocation concealment	A – Adequate
Study	Menendez 1997
Methods	Randomized controlled trial* Length of follow up: 1 year
Participants	Number enrolled: 832 infants Inclusion criteria: infant aged 8 to 52 weeks; born at district hospital; permanent resident in Ifakara Exclusion criteria: birth weight > 1.5 kg; congenital malformation; cerebral asphyxia; congenital/neonatal infection; packed-cell volume < 25
Interventions	Prophylaxis: weekly pyrimethamine-dapsone (Deltaprim) and daily iron for 40 weeks (1) Pyrimethamine-dapsone (Deltaprim) and placebo: 2.5 mL of syrup containing 3.125 mg pyrimethamine and 25 mg dapsone/5 mL syrup; 208 children (2) Pyrimethamine-dapsone (Deltaprim) and iron; 213 children (3) Iron and placebo: 2 mg/kg iron syrup; 204 children (4) Placebo and placebo; 207 children
Outcomes	(1) Hospital admissions (2) Death

Characteristics of included studies (Continued)

	(3) Severe anaemia (4) Adverse events
Notes	Location: Ifakara, south-eastern Tanzania. Malaria transmission: perennial/holoendemic
Allocation concealment	A – Adequate
Study	Menon 1990
Methods	Cluster-randomized controlled trial (households)*; no estimate of the average cluster size or ICCs Length of follow up: 1 year
Participants	Number enrolled: 1792 children Inclusion criteria: age 3 to 59 months; resident in study area
Interventions	Prophylaxis: every 2 weeks for up to 1 year (1) Pyrimethamine-dapsone (Maloprim): 6.25 mg pyrimethamine and 25 mg dapsone per tablet with 1 tablet for 3 to 11 months old or 2 tablets for 1 to 4 years old; 888 children (2) Placebo; 904 children
Outcomes	(1) Clinical episodes of malaria (2) Death (3) Parasitaemia (4) Enlarged spleen (5) Mean packed-cell volume (haematocrit)
Notes	Location: Farafeni, The Gambia Malaria transmission: seasonal The Gambian trials were conducted in the same population at different time points: this trial was conducted 3 to 4 years after the start of the prophylaxis in the main study (Greenwood 1988) and reported on 41 villages (15 intervention and 26 placebo; 3 villages that initially declined to participate later joined the trial)
Allocation concealment	B – Unclear
Study	Otoo 1988a
Methods	Cluster-randomized controlled trial (households)*; average cluster size and ICC not given Length of follow up: 1 year
Participants	Number analysed: 95 children Inclusion criteria: aged 5 years; stopped chemoprophylaxis with Maloprim during the preceding 6 months and had achieved at least 50% compliance during the preceding 2 years Exclusion criteria: none stated
Interventions	Prophylaxis: every 2 weeks for 2 years (1) Pyrimethamine-dapsone (Maloprim): 6.25 mg pyrimethamine and 25 mg dapsone per tablet with 1 tablet for 3 to 11 months old or 2 tablets for 1 to 4 years old; 48 children (2) Placebo; 47 children
Outcomes	(1) Clinical episodes of malaria (2) Death (3) Parasitaemia (4) Enlarged spleen Not included in review: (5) Malaria antibody levels Also assessed 6 months after stopping intervention
Notes	Location: Farafenni, The Gambia Malaria transmission: seasonal

Characteristics of included studies (Continued)

Same population as Greenwood 1988 and Otoo 1989 but 2.5 years after stopping chemoprophylaxis

Allocation concealment B – Unclear

Study	Schellenberg 2001
Methods	Randomized controlled trial* Length of follow up: 18 months
Participants	Number enrolled: 701 children aged 2, 3, and 9 months attending routine immunization clinics for second dose of DPT vaccine Inclusion criteria: children have just received second dose of DPT and oral poliovirus vaccine Exclusion criteria: illness requiring hospital admission
Interventions	Intermittent treatment: first dose at 2 months, second dose at 3 months, and third at 9 months (1) Sulfadoxine-pyrimethamine: 25 mg/kg sulfadoxine and 1.25 mg/kg pyrimethamine, with 1/4 tablet for children < 5 kg, 1/2 tablet for children 5 to 10 kg, or 1 tablet for children > 10 kg; 350 children (2) Placebo; 351 children
Outcomes	(1) Clinical episodes of malaria (2) Severe anaemia (3) Hospital admissions (4) Death (5) Adverse events
Notes	Location: Ifakara, Tanzania Malaria transmission: perennial/holoendemic
Allocation concealment	A – Adequate

Study	Schellenberg 2005
Methods	Randomized controlled trial* Length of follow up: 18 months
Participants	Number analysed: 555 children aged up to 2 years at time of assessment; and 2, 3, and 9 months at time of treatment during routine immunization for DPT and measles Inclusion and exclusion criteria: as applied to the initial enrolment (Schellenberg 2001)
Interventions	Intermittent treatment with full dose of sulfadoxine-pyrimethamine: first dose at 2 months, second dose at 3 months, and third at 9 months (1) Sulfadoxine-pyrimethamine: 1/4 tablet (< 5 kg); 1/2 tablet (5 to 10 kg); 1 tablet (> 10 kg); 277 children (2) Placebo; 278 children
Outcomes	(1) Clinical episodes of malaria (2) Severe anaemia Assessed 18 months following treatment
Notes	Location: Ifakara, Tanzania Malaria transmission: perennial/ holoendemic This trial used the same population as Schellenberg 2001
Allocation concealment	A – Adequate

Study	Tomashak 2001
Methods	Randomized controlled trial* Length of follow up: 12 weeks
Participants	Number enrolled: 238 children Inclusion criteria: age 6 to 59 months; haemoglobin 5.0 to 8.0 g/dL; parental consent

Characteristics of included studies (Continued)

	Exclusion criteria: signs or symptoms of heart failure; severe malaria infection; splenomegaly; or sickle cell disease or trait
Interventions	Intermittent treatment: iron and folic acid given 3 times weekly for 12 weeks; sulfadoxine-pyrimethamine given at weeks 4, 8, and 12 follow-up visits; vitamins A and C both given 3 times weekly (1) Sulfadoxine-pyrimethamine, iron, folic acid, and vitamins A and C; 75 children (2) Sulfadoxine-pyrimethamine, iron, and folic acid; 81 children (3) Placebo, iron, and folic acid; 82 children Iron: ferrous sulphate (60 mg elemental iron for children 18 months or 30 mg for children < 18 months) and folic acid (250 g for children 18 months or 125 g for children < 18 months) Sulfadoxine-pyrimethamine: 500 mg sulfadoxine and 25 mg pyrimethamine per tablet with 1 tablet for children > 48 months, 1/2 tablet for children 12 to 47 months, or 1/4 tablet for children 6 to 12 months Vitamin A: 400 g all age groups Vitamin C: 75 mg for children 18 months, 30 mg for children < 18 months
Outcomes	(1) Malaria blood smear (parasitaemia) (2) Mean haemoglobin (haematocrit) (3) Death Not included in review: (3) Anaemia prevalence (4) Iron-deficiency anaemia
Notes	Location: Nduta refugee camp, Kigoma Region, western Tanzania Malaria transmission: intense (perennial)
Allocation concealment	B – Unclear

Study	Verhoef 2002
Methods	Randomized controlled trial* Length of follow up: 12 weeks
Participants	Number enrolled: 328 children Inclusion criteria: age 2 to 36 months; haemoglobin 60 to 110 g/L; axillary temperature < 37.5 °C; resident in area; parental consent Exclusion criteria: symptom suggestive of malaria or anaemia; systemic illness occurring in combination with a blood dipstick test result indicating current or recent malarial infection
Interventions	Intermittent treatment: sulfadoxine-pyrimethamine given every 4 weeks for 3 doses; iron given twice weekly for 12 weeks; supervised by clinical officer (1) Sulfadoxine-pyrimethamine: 25 mg/kg sulfadoxine and 1.25 mg/kg pyrimethamine; 82 children (2) Iron (ferrous fumarate 6.25 g/L): 6 mg elemental iron/kg; 82 children (3) Sulfadoxine-pyrimethamine and iron; 82 children (4) Placebo; 82 children
Outcomes	(1) Clinical episodes of malaria Not included in review: (2) Haemoglobin (3) Iron-deficiency anaemia
Notes	Location: Mtito Andei, eastern Kenya Malaria transmission: seasonal
Allocation concealment	A – Adequate

Study	Wolde 1994
Methods	Randomized controlled trial* Length of follow up: 10 weeks

Participants	Number enrolled: 1005 children (age group 1 to 5 years only) Inclusion criteria: aged 1 to 14 years, stratified as 1 to 5 and 6 to 14 years
Interventions	Prophylaxis: weekly for 10 weeks (1) Chloroquine: 5 mg/kg base; 504 children (2) Placebo (multivitamin tablets); 501 children
Outcomes	(1) Clinical episodes of malaria
Notes	Location: Awash Rift Valley, Ethiopia Malaria transmission: seasonal
Allocation concealment	B – Unclear

Allocation concealment: A = adequate, B = unclear, *see 'Methods of the review' for details and a summary of the methodological quality assessment in Table 03; DPT: diphtheria-pertussis-tetanus; ICC: intra-cluster correlation coefficient

Characteristics of excluded studies

Study	Reason for exclusion
Akenzua 1985	Includes participants aged more than 6 years
Allen 1990	Cross-sectional survey to determine sensitivity of Plasmodium falciparum after chemoprophylaxis
Archibald 1956	Non-randomized intervention trial
Bjorkman 1985a	Non-randomized prospective study to investigate susceptibility of Plasmodium falciparum following a period of chemosuppression
Bjorkman 1985b	Surveys
Bjorkman 1986	Non-randomized study
Bradley-Moore 1985	Quasi-randomized controlled trial
Charles 1961	Randomized controlled trial with participants aged 5 to 14 years
Colbourne 1955	Non-randomized intervention study
Coosemans 1987	Randomized controlled trial with participants aged 6 to 14 years and no group given placebo only
Coulibaly 2002	Randomized controlled trial; adults and older children included as participants
Delmont 1981	Mass drug administration with participants > 5 years
Escudie 1961	Not a randomized controlled trial
Fasan 1970	Randomized controlled trial with participants aged 6 to 12 years
Fasan 1971	Randomized controlled trial with participants aged 5 to 12 years
Fernando 2006	Randomized controlled trial of school children aged 6 to 12 years
Harland 1975	Longitudinal observational study
Hogh 1994	Randomized controlled trial with participants aged 7 to 12 years
Karunakaran 1980	Small sample size: randomized controlled trial, but only 8 out of 230 participants were below 5 years old
Karwacki 1990	Two randomized controlled trials with participants aged 6 to 15 years
Kollaritsch 1988	Randomized controlled trial with participants > 5 years
Laing ABG 1970	Non-randomized controlled trial
Lell 1998	Randomized controlled trial with participants aged 4 to 16 years
Lell 2000	Randomized controlled trial with participants aged 12 to 20 years
Lewis 1975	Not randomized controlled trial
Limsomwong 1988	Randomized controlled trial with participants aged 5 to 16 years

Characteristics of excluded studies (Continued)

Lucas 1969	Randomized controlled trial with participants aged 8 to 17 years
Lwin 1997	Possible randomized controlled trial with participants of all ages
MacCormack 1983	Malaria suppression project with chloroquine (not a randomized controlled trial)
McGregor 1966	Randomized controlled trial with both children and adult participants
Miller 1954	Not randomized controlled trial
Murphy 1993	Chemoprophylaxis for Plasmodium vivax malaria (not a randomized controlled trial)
Nevill 1988	Randomized controlled trial with participants aged 6 to 18 years
Nevill 1994	Randomized controlled trial with participants aged 8 to 9 years
Nwokolo 2001	Randomized controlled trial with both children and adult participants
Onori 1982	Seroepidemiological survey to determine whether chloroquinized salt affected immunity to malaria.
Oyediran 1993	Quasi-randomized (alternate allocation) of preschool children
Pang 1989	Randomized controlled trial with participants aged 6 to 15 years
Panton 1985	Drug sensitivity survey
Pividal 1992	Randomized controlled trial with participants aged 7 to 12 years
Pribadi 1986	Chemoprophylaxis given to all villagers (including adults)
Pringle 1966	Observational study following chemoprophylaxis to document early course of untreated falciparum malaria in semi-immune children
Ringwald 1989	Randomized controlled trial with adult participants
Robert 1989	Prospective non-randomized study
Rooth 1991	Randomized controlled trial with participants aged 6 to 14 years
Rosen 2005	Not randomized controlled trial
Saarinen 1988	Not randomized controlled trial
Schapira 1988	Randomized controlled trial with participants aged 7 to 14 years
Schellenberg 2004	Open-label randomized controlled trial of participants aged 2 months to 4 years in which sulfadoxine-pyrimethamine was given to both the control group (1 dose) and intervention group (3 doses at monthly intervals)
Schneider 1962	Randomized trial in which the control group received a different antimalarial and not placebo
Stace 1981	Not randomized controlled trial
Sukwa 1999	Randomized controlled trial with adult participants
Thera 2005	Randomized controlled trial with participants aged 5 to 15 years
Vrbova 1992	Randomized controlled trial with participants aged 7 to 14 years
Watkins 1987	Randomized controlled trial with participants aged 6 to 10 years
Weiss 1995	Randomized controlled trial with participants aged 9 to 14 years
Win 1985	Randomized controlled trial with adult participants aged 18 to 40 years
von Seidlein 2003	Adults and children > 6 years included as participants

Characteristics of ongoing studies

Study	Kremsner ongoing
Trial name or title	“Intermittent sulfadoxine/pyrimethamine administration to infants to reduce malaria morbidity in Gabon: assessment of efficacy, safety, and potential for malaria rebound”
Participants	531 children in each group

Characteristics of ongoing studies (Continued)

Interventions	Sulfadoxine-pyrimethamine or placebo given during EPI at 3, 9, and 15 months of age
Outcomes	(1) Episodes of anaemia (2) Efficacy (3) Safety (4) Rebound effects
Starting date	December 2002
Contact information	Prof Peter Kremsner (peter.kremsner@uni-tuebingen.de), Institute of Tropical Medicine, Eberhard Karls University, Tuebingen, Germany Prof Martin Grobusch (grobuschmp@pathology.wits.ac.za), Infectious Diseases Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
Notes	Location: Gabon Source of funding: Intermittent Preventive Treatment in Infants Consortium; Project 1 Randomized, double blind, placebo-controlled trial

Study **Lemnge ongoing**

Trial name or title	“Drug options for intermittent presumptive treatment for malaria in infants in an area with high resistance to sulfadoxine/pyrimethamine: an evaluation of short and long-acting antimalarial drugs”
Participants	1280 infants in western Usambara and 2440 infants in south Pare
Interventions	Following drugs, or placebo, given during EPI at 2, 3, and 9 months of age: (1) Mefloquine for 1 day (2) LapDap (chlorproguanil-dapsone) for 3 days (3) Sulfadoxine-pyrimethamine for 1 day
Outcomes	Primary outcome measure: incidence of malaria in infancy Secondary outcome measures include: (1) Mean haemoglobin level at 10 to 12 months of age (2) Incidence of severe anaemia during infancy (3) Prevalence of malaria parasitaemia at 10 to 12 months of age (4) Incidence of malaria in the second year of life
Starting date	September 2004
Contact information	Dr Martha Lemnge (mlemnge@amani.mimcom.net), National Institute for Medical Research (NIMR), Amani Medical Research Centre, Tanzania Prof Brian Greenwood (Brian.Greenwood@lshtm.ac.uk), London School of Hygiene and Tropical Medicine, London, UK Prof Thor G Theander (theander@cmp.dk), Centre for Medical Parasitology, Institute for Medical Microbiology and Immunology, University of Copenhagen Panum Institute, Denmark
Notes	Location: Tanzania Source of funding: Intermittent Preventive Treatment in Infants Consortium; Project 4 Randomized, double-blind, placebo-controlled trial

Study **Menendez ongoing**

Trial name or title	“Intermittent preventive treatment in infants delivered through the EPI scheme in Mozambique: community response and cost effectiveness, and impact on morbidity and development of malaria immunity”
Participants	750 children in each group

Characteristics of ongoing studies (Continued)

Interventions	Sulfadoxine-pyrimethamine or placebo is given during EPI at 3, 4, and 9 months of age
Outcomes	(1) Clinical malaria (2) Anaemia (3) Frequency and type of potential side effects (4) Development of resistance and the spread of molecular markers associated with SP resistance (5) Immune response to routine EPI immunizations (6) Development of specific and non-specific immune responses to <i>P. falciparum</i> infection (7) Cost effectiveness of intervention under close to programme conditions (8) Community perception and response to the introduction of intervention within the EPI scheme
Starting date	September 2002
Contact information	Dr Clara Menendez (cmendez@clinic.ub.es), Centre de Salut, Internacional Hospital Clínic, Universitat de Barcelona, Barcelona, Spain
Notes	Location: Mozambique Source of funding: Intermittent Preventive Treatment in Infants Consortium; Project 2 Randomized, double blind, placebo-controlled trial

Study NCT00111163

Trial name or title	“Efficacy and safety of pediatric immunization-linked preventive intermittent treatment with antimalarials in decreasing anemia and malaria morbidity in rural western Kenya”
Participants	Age 5 to 16 weeks Expected total enrolment: 1516 Inclusion criteria: presenting for Pentavalent 1 immunization; age 5 weeks to 16 weeks; parent or guardian currently resident in study catchment area; parent or guardian has given permission for their child to participate Exclusion criteria: known allergy to any of the study drugs; current cotrimoxazole prophylaxis; concomitant disease requiring hospitalization or transfusion; plans to be away from the study area for > 6 months during the next year
Interventions	Given at routine EPI visits: 1. Iron supplementation and intermittent preventive treatment with sulfadoxine-pyrimethamine plus 3 doses of artesunate 2. Iron supplementation and intermittent preventive treatment with chlorproguanil-dapsone (Lapdap) 3. Iron supplementation and intermittent preventive treatment with amodiaquine plus 3 doses of artesunate 4. Iron supplementation alone plus placebo
Outcomes	Primary outcome: clinical malaria in the first year of life Secondary outcomes: (1) Moderate and severe anaemia in the first year of life (2) Serologic responses to EPI vaccines (polio, diphtheria, tetanus, pertussis, hepatitis B, Haemophilus Influenzae type B, and measles) (3) Nasal carriage rates of Haemophilus influenzae type b (4) All-cause hospitalization in the first year of life
Starting date	March 2004
Contact information	Robert D Newman MD, MPH (ren5@cdc.gov), Principal Investigator, U.S. Centers for Disease Control and Prevention, USA Laurence Slutsker MD, MPH, Principal Investigator, U.S. Centers for Disease Control and Prevention, USA
Notes	Location: Kenya Registration number: NCT00111163 Source of funding: Centers for Disease Control and Prevention; Kenya Medical Research Institute; Bill and Melinda Gates Foundation

Characteristics of ongoing studies (Continued)

Prevention, randomized, double blind, placebo control, single group assignment, safety/efficacy study

Study	NCT00119132
Trial name or title	“A study of impact of intermittent preventive treatment In children with amodiaquine plus artesunate versus sulphadoxine-pyrimethamine on hemoglobin levels and malaria morbidity in Hohoe District of Ghana”
Participants	2240 children aged 3 to 59 months will be randomly allocated to 4 groups (560 per arm) Inclusion criteria: children between the ages of 3 and 59 months resident in the selected communities; children likely to be available for follow up for 18 months; consent by parent/guardian of child Exclusion criteria: chronic illness; history of hypersensitivity to any of the study drugs
Interventions	(1) Artesunate-amodiaquine given at 2 different intervals (monthly or bimonthly) (2) Sulfadoxine-pyrimethamine (3) Placebo
Outcomes	Primary outcome: Mean haemoglobin at end of high transmission season Secondary outcomes: (1) Incidence of moderate (haemoglobin < 8.0 g/dL > 5.0 g/dL) and severe anaemia (haemoglobin < 5.0 g/dL) during the period of the intervention (2) Incidence of severe and clinical malaria during the period of the intervention (3) Prevalence of anaemia at the post intervention survey (4) Prevalence of parasitaemia and gametocytemia at the post intervention survey (5) Prevalence of molecular markers of resistance to sulfadoxine-pyrimethamine among children who have malaria at the post-intervention survey
Starting date	Study start: June 2005 Expected completion: June 2007
Contact information	Margaret Kweku MBChB, MPH (margaret.kweku@lshtm.ac.uk), Principal Investigator, London School of Hygiene and Tropical Medicine, London, UK Daniel Chandramohan MBBS, PhD Principal Investigator London School of Hygiene and Tropical Medicine Brian Greenwood FRCP, FRS Principal Investigator London School of Hygiene and Tropical Medicine
Notes	Location: Ghana Registration number: NCT00119132 Source of funding: Gates Malaria Partnership; Ghana:INDEPTH Network Randomized, double blind, placebo control, parallel assignment, safety/efficacy study

Study	Schellenberg ongoing
Trial name or title	“Community effectiveness of intermittent preventive treatment delivered through the Expanded Programme of Immunisation for malaria and anaemia control in Tanzanian infants”
Participants	12,000 infants per year
Interventions	Sulfadoxine-pyrimethamine will be given during EPI at 2, 3, and 9 months of age Evaluation will be based on comparisons between areas with and without intervention
Outcomes	(1) All-cause mortality (2) Anaemia (3) Parasitaemia

Characteristics of ongoing studies (Continued)

- (4) Probable malaria episodes
- (5) Cost effectiveness
- (6) Effect of the intervention on community perceptions of, and compliance with, the EPI programme
- (7) Impact of intervention on rate of development of drug resistance
- (8) Consolidate the safety profile of sulfadoxine-pyrimethamine in infants

Starting date	January 2005
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Contact information	Dr David Schellenberg (DMSchellenberg@aol.com), Ifakara Health Research & Development Centre, Dar es Salaam, Tanzania
	Prof Marcel Tanner (marcel.tanner@unibas.ch), Swiss Tropical Institute, Basel, Switzerland

Notes	Location: Tanzania
	Source of funding: Intermittent Preventive Treatment in Infants Consortium; Project 5
	Implementation study

Study **Slutsker ongoing**

Trial name or title	“Efficacy and safety of paediatric, immunization-linked, intermittent preventive treatment with antimalarials in decreasing anaemia and malaria morbidity in rural western Kenya”
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Participants	379 children recruited in each group
	Enrolled children followed through active and passive surveillance until 18 months of age

Interventions	Following drugs, or placebo, given during EPI at 2, 3, and 9 months of age: (1) Sulfadoxine-pyrimethamine for 1 day and artesunate for 3 days (2) LapDap (chlorproguanil/dapsone) for 3 day (3) Amodiaquine for 3 days and artesunate for 3 days (4) Iron supplementation alone
	Infants will receive iron supplementation from 2 to 6 months of age and 1 of 4 treatments at EPI visits

Outcomes	(1) Clinical malaria (2) Moderate and severe anaemia (3) Serological responses to EPI vaccines
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Starting date	March 2004
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Contact information	Dr Larry Slutsker (LSlutsker@kisian.mimcom.net), CDC/KEMRI Research Station, Kisumu, Kenya
	Dr Robert Newman (rnewman@cdc.gov), Malaria Branch, Division of Parasitic Diseases, Centers for Disease Control and Prevention, Atlanta, USA

Notes	Location: Kenya
	Source of funding: Intermittent Preventive Treatment in Infants Consortium; Project 3
	Randomized, double-blind, placebo-controlled trial

EPI: Expanded Programme of Immunization

ADDITIONAL TABLES

Table 01. Detailed search strategies

Search set	CIDG SR*	CENTRAL	MEDLINE**	EMBASE**	LILACS**
1	malaria	malaria	MALARIA	MALARIA	malaria
2	prophylaxis	prophylaxis	malaria	malaria	prophylaxis
3	intermittent treatment	intermittent treatment	1 or 2	1 or 2	prevention
4	--	presumptive treatment	prophylaxis	prophylaxis	2 or 3
5	--	2 or 3 or 4	chemoprophylaxis	chemoprophylaxis	1 and 4
6	--	1 and 5	prevention	prevention	--
7	--	--	intermittent treatment	intermittent treatment	--
8	--	--	presumptive treatment	presumptive treatment	--
9	--	--	4 or 5 or 6 or 7 or 8	4 or 5 or 6 or 7 or 8	--
10	--	--	3 and 9	3 and 9	--

*Cochrane Infectious Diseases Group Specialized Register

**Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Higgins 2006); upper case: MeSH or Emtree heading; lower case: free text term

Table 02. Types of intervention

Trial	No. arms	Intervention	IT or prophylaxis	Iron or folic acid	ITN
Alonso 1993	1	Pyrimethamine-dapsone	Prophylaxis	No	Yes
	2	Placebo		No	Yes
Chandramohan 2005	1	Sulfadoxine-pyrimethamine	IT	Yes	Unclear
	2	Placebo		Yes	Unclear
Cissé 2006	1	Sulfadoxine-pyrimethamine plus artesunate	IT	No	Unclear
	2	Placebo			Unclear
David 1997	1	Pyrimethamine-dapsone	Prophylaxis	No	No
	2	Placebo		No	No
Desai 2003	1	Sulfadoxine-pyrimethamine	IT	No	Yes*
	2	--		Iron	Yes*

Table 02. Types of intervention (Continued)

Trial	No. arms	Intervention	IT or prophylaxis	Iron or folic acid	ITN
	3	Sulfadoxine-pyrimethamine		Iron	Yes*
	4	Placebo		No	Yes*
Greenwood 1988	1	Pyrimethamine-dapsone	Prophylaxis	No	No
	2	Placebo		No	No
Greenwood 1989	1	Pyrimethamine-dapsone	Prophylaxis	Folic acid	No
	2	Pyrimethamine-dapsone		No	No
	3	Chlorproguanil		Folic acid	No
	4	Chlorproguanil		No	No
	5	Placebo		Folic acid	No
	6	Placebo		No	No
Greenwood 1995	1	Pyrimethamine-dapsone	Prophylaxis	No	No
	2	Placebo		No	No
Hogh 1993	1	Chloroquine	Prophylaxis	No	No
	2	Placebo		No	No
Kobbe 2007	1	Sulfadoxine-pyrimethamine	IT	No	Unclear
	2	Placebo		No	Unclear
Lemnge 1997	1	Pyrimethamine-dapsone	Prophylaxis	No	No
	2	Placebo		No	No
Macete 2006	1	Sulfadoxine-pyrimethamine	IT	No	Unclear
	2	Placebo		No	Unclear
Massaga 2003	1	Amodiaquine	IT	Iron	No
	2	Amodiaquine		No	No
	3	Placebo		Iron	No
	4	Placebo		No	No
Menendez 1997	1	Pyrimethamine-dapsone	Prophylaxis	No	No
	2	Pyrimethamine-dapsone		Iron	No
	3	Placebo		Iron	No
	4	Placebo		No	No
Menon 1990	1	Pyrimethamine-dapsone	Prophylaxis	No	No
	2	Placebo		No	No
Otoo 1988	1	Pyrimethamine-dapsone	Prophylaxis	No	No

Table 02. Types of intervention (Continued)

Trial	No. arms	Intervention	IT or prophylaxis	Iron or folic acid	ITN
	2	Placebo		No	No
Schellenberg 2001	1	Sulfadoxine-pyrimethamine	IT	No	No
	2	Placebo		No	No
Schellenberg 2005	1	Sulfadoxine-pyrimethamine	IT	No	No
	2	Placebo		No	No
Tomashek 2001	1	Sulfadoxine-pyrimethamine plus vitamins A and C	IT	Iron, folic acid	No
	2	Sulfadoxine-pyrimethamine		Iron, folic acid	No
	3	Placebo		Iron, folic acid	No
Verhoef 2002	1	Sulfadoxine-pyrimethamine	IT	No	No
	2	--		Iron	No
	3	Sulfadoxine-pyrimethamine		Iron	No
	4	Placebo		No	No
Wolde 1994	1	Chloroquine	Prophylaxis	No	No
	2	Placebo		No	No

Footnotes

IT: intermittent treatment

ITN: insecticide-treated nets

*ITN not given to participants

but reported that they

benefited from their "area-wide

deployment"

Table 03. Methodological quality of included trials

Trial	Sequence*	Concealment*	Blinding	Primary outcome (n)	Number at follow up	Percentage loss
Alonso 1993	Unclear	Unclear	Participants and care providers were blinded	Clinical malaria (1898 participants)	Unclear	Unclear
Chandramohan 2005	Adequate (computer-generated random numbers)	Adequate (identical and centrally coded drugs and placebo)	Participants, care providers, and assessor were blinded	Incidence of anaemia (2191 participants)	2191	11.8% (per protocol - inadequate)
Cissé 2006	Adequate (computer-generated random)	Adequate (identical and centrally coded drugs and	Participants, care providers, and assessor were blinded	Clinical malaria (985 participants)	985	9.5% (adequate)

Table 03. Methodological quality of included trials (Continued)

Trial	Sequence* numbers)	Concealment* placebo)	Blinding	Primary outcome (n)	Number at follow up	Percentage loss
David 1997	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Desai 2003	Adequate (block randomization)	Adequate (identical and centrally coded drugs and placebo)	Participants, care providers, and assessor were blinded	Clinical malaria (428 participants)	468	14% (inadequate)
Greenwood 1988	Unclear	Unclear	Participants and care providers were blinded	Clinical malaria, severe anaemia (2718 participants)	Unclear	Unclear
Greenwood 1989	Unclear	Unclear	Participants and care providers were blinded	Clinical malaria (560 participants)	Unclear	Unclear
Greenwood 1995**	Unclear	Unclear	Participants and care providers were blinded	Unclear	Unclear	19% to 22% (inadequate)
Hogh 1993	Unclear	Unclear	Participants and care providers were blinded	Unclear	Unclear	Unclear
Kobbe 2007	Adequate (computer-generated random numbers)	Adequate (identical and centrally coded drugs and placebo)	Participants, care providers, and assessor were blinded	Clinical malaria (1080 participants; intention to treat)	827	18.5% (per protocol)
Lemnge 1997	Unclear	Adequate (identical and centrally coded drugs and placebo)	Participants, care providers, and assessor were blinded	Unclear	234	6% (adequate)
Macete 2006	Adequate (computer-generated random numbers)	Adequate (identical and centrally coded drugs and placebo)	Participants, care providers, and assessor were blinded	Clinical malaria (1375 participants)	1375	8.5% (adequate)
Massaga 2003	Adequate (computer-generated random numbers)	Adequate (identical and centrally coded drugs and placebo)	Participants, care providers, and assessor were blinded	Clinical malaria (291 participants)	231	21% (inadequate)
Menendez 1997	Adequate (block randomization)	Adequate (identical and centrally coded	Participants, care providers, and assessor	Severe anaemia (832 participants)	NA	7% (adequate)

Table 03. Methodological quality of included trials (Continued)

Trial	Sequence*	Concealment*	Blinding	Primary outcome (n)	Number at follow up	Percentage loss
		drugs and placebo)	were blinded			
Menon 1990	Unclear	Unclear	Participants and care providers were blinded	Unclear	Unclear	Unclear
Otoo 1988a**	Unclear	Unclear	Participants and care providers were blinded	Clinical malaria (95 participants)	Unclear	16% (inadequate)
Schellenberg 2001	Adequate (computer-generated)	Adequate (sealed, opaque envelopes and identical, centrally coded drugs and placebo)	Participants, care providers, and assessor were blinded	Clinical malaria, severe anaemia (701 participants)	677	3% (adequate)
Schellenberg 2005	Adequate (computer-generated)	Adequate (sealed, opaque envelopes and identical, centrally coded drugs and placebo)	Participants, care providers, and assessor were blinded	Clinical malaria, severe anaemia, protective antibody titres against measles (555 participants)	555	Unclear
Tomashek 2001	Adequate (computer-generated)	Unclear	Only participants and assessor were blinded; care provider was not	Anaemia prevalence (238 participants)	215	9.7% (adequate)
Verhoef 2002	Adequate (block randomization)	Adequate (identical and centrally coded drugs and placebo)	Participants, care providers, and assessor were blinded	Clinical malaria (328 participants)	309	6% (adequate)
Wolde 1994	Unclear	Unclear	Unclear	Clinical malaria (1005 participants)	997	9% (adequate)

Footnotes

*Generation of allocation sequence; concealment of allocation

**Late impact trials

NA: not

Table 03. Methodological quality of included trials (Continued)

Trial	Sequence*	Concealment*	Blinding	Primary outcome (n)	Number at follow up	Percentage loss
available						

Table 04. Adverse event information not appropriate for meta-analysis

Trial	Method to detect AE*	Results
Chandramohan 2005	Vomiting Skin rashes	“The proportions of children who vomited after administration of drugs was similar between the two groups (0.4% in the placebo group versus 0.3% in the sulfadoxine-pyrimethamine group).” “Among children who were visited at home within four weeks after administration of IPTi dose 1 (n = 1765, 74%) or dose 2 (n = 214, 9%), 32 (3.3%) children in the placebo group and 27 (2.7%) in the sulfadoxine-pyrimethamine group had skin rashes. None of the skin rashes was severe or suggestive of a drug sensitivity reaction.”
Cisse 2006	Severe skin reaction Convulsions	“No severe skin or neurological reactions were reported” One participant among 455 participants assessed in control group had convulsion, while none among 486 in the treatment group had this adverse event
Greenwood 1988	White cell count in randomly selected subset of 68 participants on Maloprim (pyrimethamine-dapsone) and 78 on placebo	Almost identical mean white cell count for the Maloprim group ($9.3 \times 10^6/L$) and placebo group ($9.6 \times 10^6/L$) Lowest white cell count recorded was $2.8 \times 10^6/L$ (study group not indicated) No severe adverse event reported Almost identical mean white cell count for the Maloprim group ($9.3 \times 10^6/L$) and placebo group ($9.6 \times 10^6/L$) Lowest white cell count recorded was $2.8 \times 10^6/L$ (study group not indicated) No severe adverse event reported
Greenwood 1989	Clinical assessment and white cell count White cell counts on alternate participants in 1983 and attempted on all participants in 1984	White cell count and clinical assessment showed no features suggestive of agranulocytosis in treatment (Maloprim) and placebo groups Results from Fuller 1988 (reporting on the Greenwood 1989 trial): “Mean WBC [white blood cell] count of children and the distribution of WBC counts were very similar in children who received

Table 04. Adverse event information not appropriate for meta-analysis (Continued)

Trial	Method to detect AE*	Results
Kobbe 2007	Vomiting	Maloprim, chlorproguanil and placebo during each survey." "Vomiting was more frequent in the SP group (72 events among 1516 applications) than in the placebo group (32 events among 1525 applications; 4.7% vs 2.1%; risk ratio, 2.26; p < .001). Other adverse events occurred at similar frequencies in both groups."
Lemnge 1997	White cell count; weight and height	Results available for 242 participants: 65 placebo, 58 iron, 60 amodiaquine, and 59 amodiaquine and iron "No serious side effect was observed." "Reduction in ... neutrophil counts, in children with normal baseline values, were sometimes seen but these were temporary." "No pronounced weight loss was observed in any child."
Macete 2006	Severe skin reactions Haematological and biochemical parameters	"No severe skin reactions were reported for any child at any time of the follow-up" ".... there were no statistically significant differences in mean values or in the percentage of abnormal values of any of the hematological and biochemical parameters analyzed 1 month after the second dose of SP or placebo"
Massaga 2003	Total and differential white cell counts	"No clinical adverse effects such as sore throat or agranulocytosis were reported or observed during the study." "No significant difference in mean leucocyte counts between the groups."

Footnotes

AE: adverse event; IPTi: intermittent preventive treatment of infants; SP: sulfadoxine-pyrimethamine

Table 05. Prophylaxis vs control: outcomes not included in meta-analysis

Outcome	Trial	Antimalarial: n/N	Control: n/N	RR or WMD	95% CI	Remarks
DURING INTERVENTION						
Severe anaemia	Greenwood 1988	0/110	4/131	0.13	0.01 to 2.43	RR
Death from any	Greenwood 1988	26/688	39/671	0.65	0.40 to 1.06	RR

Table 05. Prophylaxis vs control: outcomes not included in meta-analysis (Continued)

Outcome	Trial	Antimalarial: n/N	Control: n/N	RR or WMD	95% CI	Remarks
cause						
	Greenwood 1989	6/176	9/192	0.73	0.26 to 2.00	RR
	Menon 1990	13/888	26/904	0.51	0.26 to 0.98	RR (favours intervention)
Parasitaemia	Greenwood 1988	13/116	49/137	0.31	0.18 to 0.55	RR (favours intervention)
	Menon 1990	11/158	76/180	0.16	0.04 to 0.30	RR (favours intervention)
Enlarged spleen	Greenwood 1988	8/117	36/135	0.26	0.12 to 0.53	RR (favours intervention)
	Menon 1990	4/159	44/183	0.10	0.04 to 0.88	RR (favours intervention)
Mean haematocrit (SD)	Greenwood 1988	33.90 (4.7); N = 110	31.20 (5.7); N = 131	2.70	1.39 to 4.01	WMD (favour intervention)
	Menon 1990	33.50 (3.7); N = 154	31.90 (4.7); N = 181	1.60	0.70 to 2.50	WMD (favours intervention)
AFTER INTERVENTION						
Clinical malaria	Otoo 1988a	4/48	5/57	0.78	0.22 to 2.74	RR
	Menendez 1997	NA	NA	1.8	1.3 to 2.6	RR; trial authors' calculation (favours control)
Severe anaemia	Menendez 1997	NA	NA	2.2	1.3 to 2.7	RR; trial authors' calculation (favours control)
Death from any cause	Greenwood 1995	4/203	5/200	0.79	0.21 to 2.89	RR
Parasitaemia	Otoo 1988a	24/39	32/38	0.73	0.55 to 0.97	RR (favours intervention)
	Greenwood 1995	47/107	44/114	1.14	0.83 to 1.56	RR
Enlarged spleen	Otoo 1988a	5/37	5/37	1.0	0.32 to 3.17	RR
	Greenwood 1995	22/109	26/122	0.95	0.57 to 1.57	RR
Mean haematocrit	Greenwood 1995	3.42 (4.5); N = 207	3.39 (4.7); N = 200	0.30	-0.59 to 1.19	WMD

Footnotes

CI: confidence interval; n: number affected; N: total assessed;

Table 05. Prophylaxis vs control: outcomes not included in meta-analysis (Continued)

Outcome	Trial	Antimalarial: n/N	Control: n/N	RR or WMD	95% CI	Remarks
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NA: not available;
RR: relative risk;
SD: standard deviation; WMD: weighted mean difference

ANALYSES

Comparison 01. Antimalarial vs placebo: individually randomized trials [main analysis]

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Clinical malaria	10	7037	Relative Risk (Random) 95% CI	0.53 [0.38, 0.74]
02 Severe anaemia	9	5445	Relative Risk (Random) 95% CI	0.70 [0.52, 0.94]
03 Death from any cause	10	7369	Relative Risk (Fixed) 95% CI	0.90 [0.65, 1.23]
04 Hospital admission for any cause	5	3722	Relative Risk (Random) 95% CI	0.64 [0.49, 0.82]
05 Parasitaemia	5	2080	Relative Risk (Random) 95% CI	0.44 [0.23, 0.86]
06 Enlarged spleen			Relative Risk (Random) 95% CI	Subtotals only
07 Impact on routine immunization: adequate protective antibodies			Relative Risk (Fixed) 95% CI	Subtotals only

Comparison 02. Antimalarial vs placebo: cluster-randomized trials

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Clinical malaria			Incidence rate ratio (Fixed) 95% CI	Totals not selected
02 Severe anaemia			Incidence rate ratio (Fixed) 95% CI	Totals not selected
03 Death from any cause			Incidence rate ratio (Fixed) 95% CI	Subtotals only
04 Hospital admission for any cause			Incidence rate ratio (Fixed) 95% CI	Subtotals only

Comparison 03. Antimalarial vs placebo: by drug group

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Clinical malaria			Relative Risk (Random) 95% CI	Subtotals only
02 Severe anaemia			Relative Risk (Random) 95% CI	Subtotals only

Comparison 04. Antimalarial vs placebo: by seasonality

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Clinical malaria			Relative Risk (Random) 95% CI	Subtotals only
02 Severe anaemia			Relative Risk (Random) 95% CI	Subtotals only

Comparison 05. Intermittent treatment vs placebo: by presence of anaemia

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Severe anaemia			Relative Risk (Random) 95% CI	Subtotals only

Comparison 06. Antimalarial vs placebo: adverse events

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Prophylaxis			Relative Risk (Fixed) 95% CI	Totals not selected
02 Intermittent treatment			Relative Risk (Fixed) 95% CI	Totals not selected

Comparison 07. Antimalarial vs placebo: adequately concealed trials

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Clinical malaria	8	5308	Relative Risk (Random) 95% CI	0.50 [0.33, 0.76]
02 Severe anaemia	8	5282	Relative Risk (Random) 95% CI	0.67 [0.50, 0.91]
03 Death from any cause	8	5308	Relative Risk (Random) 95% CI	0.87 [0.62, 1.24]

Comparison 08. Antimalarial vs placebo: impact after stopping intervention

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Clinical malaria (relative risk)	2	1625	Relative Risk (Random) 95% CI	0.87 [0.59, 1.26]
02 Clinical malaria (incidence rate ratio)			Incidence rate ratio (Random) 95% CI	Totals not selected
03 Severe anaemia (relative risk)	2	1625	Relative Risk (Random) 95% CI	1.13 [0.71, 1.79]
04 Severe anaemia (incidence rate ratio)			Incidence rate ratio (Fixed) 95% CI	Totals not selected
05 Death from any cause (relative risk)	2	1482	Relative Risk (Random) 95% CI	0.80 [0.32, 2.03]
06 Death from any cause (incidence rate ratio)			Incidence rate ratio (Random) 95% CI	Totals not selected
07 Impact on routine immunization: adequate protective antibody			Relative Risk (Fixed) 95% CI	Totals not selected

INDEX TERMS

Medical Subject Headings (MeSH)

Antimalarials [*administration & dosage]; Chloroquine [administration & dosage]; Dapsone [administration & dosage]; Malaria [mortality; *prevention & control]; Pyrimethamine [administration & dosage]; Randomized Controlled Trials as Topic

MeSH check words

Child, Preschool; Humans; Infant

COVER SHEET

Title	Chemoprophylaxis and intermittent treatment for preventing malaria in children
Authors	Meremikwu MM, Donegan S, Esu E
Contribution of author(s)	Martin Meremikwu and Sarah Donegan identified and extracted data from eligible trials for this update. Both authors analysed data with Sarah Donegan playing the key role in handling the cluster-randomized trials. Martin Meremikwu prepared the first draft, and Sarah Donegan read through and made input to all sections of the review.
Issue protocol first published	2002/3
Review first published	2005/4
Date of most recent amendment	20 February 2008
Date of most recent SUBSTANTIVE amendment	20 February 2008
What's New	<p>2008, Issue 2: We included four new trials of intermittent treatment (Chandramohan 2005; Cissé 2006; Macete 2006; Kobbe 2007). We removed quasi-randomized controlled trials from the inclusion criteria and excluded two such trials (Bradley-Moore 1985; Oyediran 1993) that were included in the Meremikwu 2005 version of this review. The evidence on benefits regarding reduction of malaria episodes, severe anaemia, and admissions remains strong and consistent with these changes. We also updated the analysis methods to stratify the individual and cluster-randomized trials. S Donegan and E Esu joined the author team, while P Garner and A Omari stepped down.</p> <p>2005, Issue 4: First version of review (Meremikwu 2005). We deviated from the protocol as follows: revised the title; slightly modified the participant age to include "children aged one month to six years or less" instead "children aged five and under" since the definition of pre-school age includes age up to 72 months; simplified the wording of the outcome measures; modified the data analysis methods to include sensitivity analyses using only adequately controlled trials for the clinical malaria, severe anaemia, and death outcomes; stratified the trials for the severe anaemia outcome by whether the children enrolled were from the general population or were selected because they were anaemic; simplified the wording of the subgroup analyses for exploring heterogeneity; decided not to include the "levels of adherence to the antimalarial drug" subgroup in the review; and summarized available data on "protective measles antibody" for the trials that administered preventive treatment concurrently with childhood immunization.</p> <p>2002, Issue 3: Protocol published (Meremikwu 2002).</p>
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
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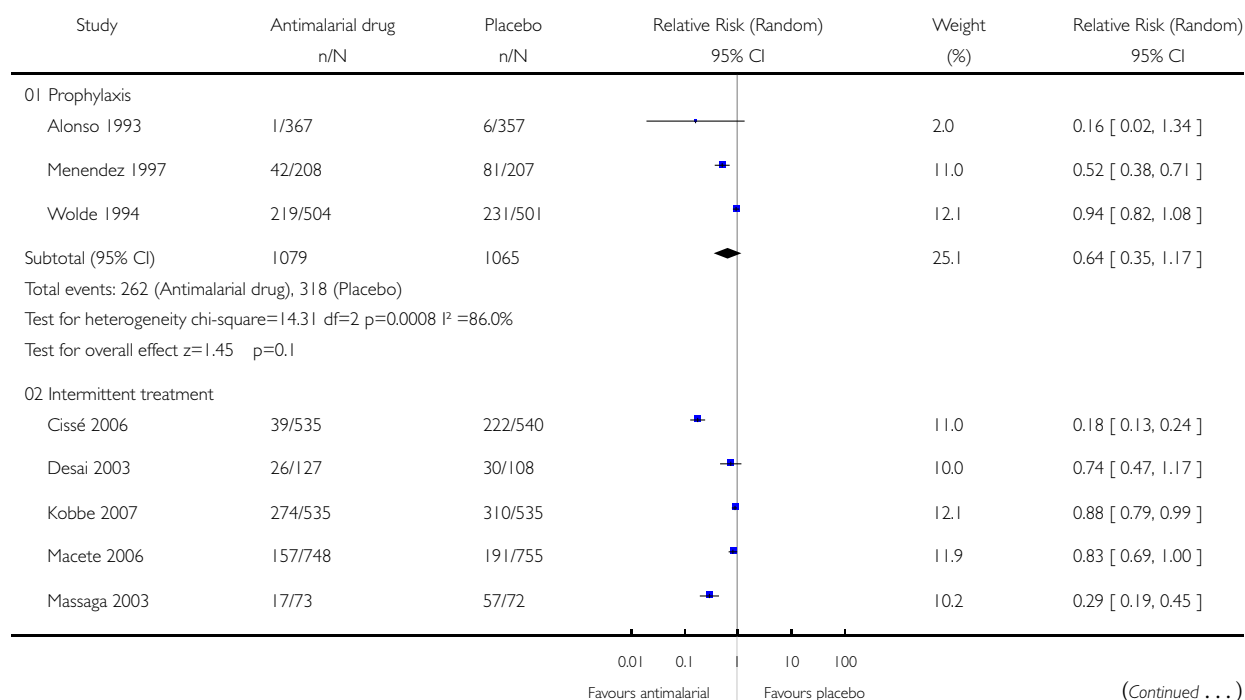
GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Antimalarial vs placebo: individually randomized trials [main analysis], Outcome 01 Clinical malaria

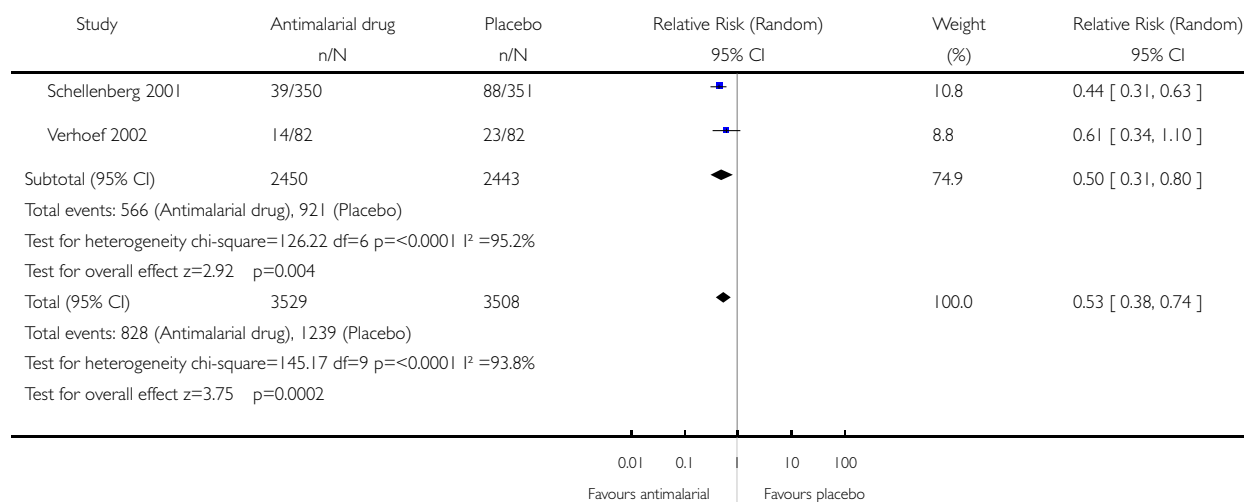
Review: Chemoprophylaxis and intermittent treatment for preventing malaria in children

Comparison: 01 Antimalarial vs placebo: individually randomized trials [main analysis]

Outcome: 01 Clinical malaria



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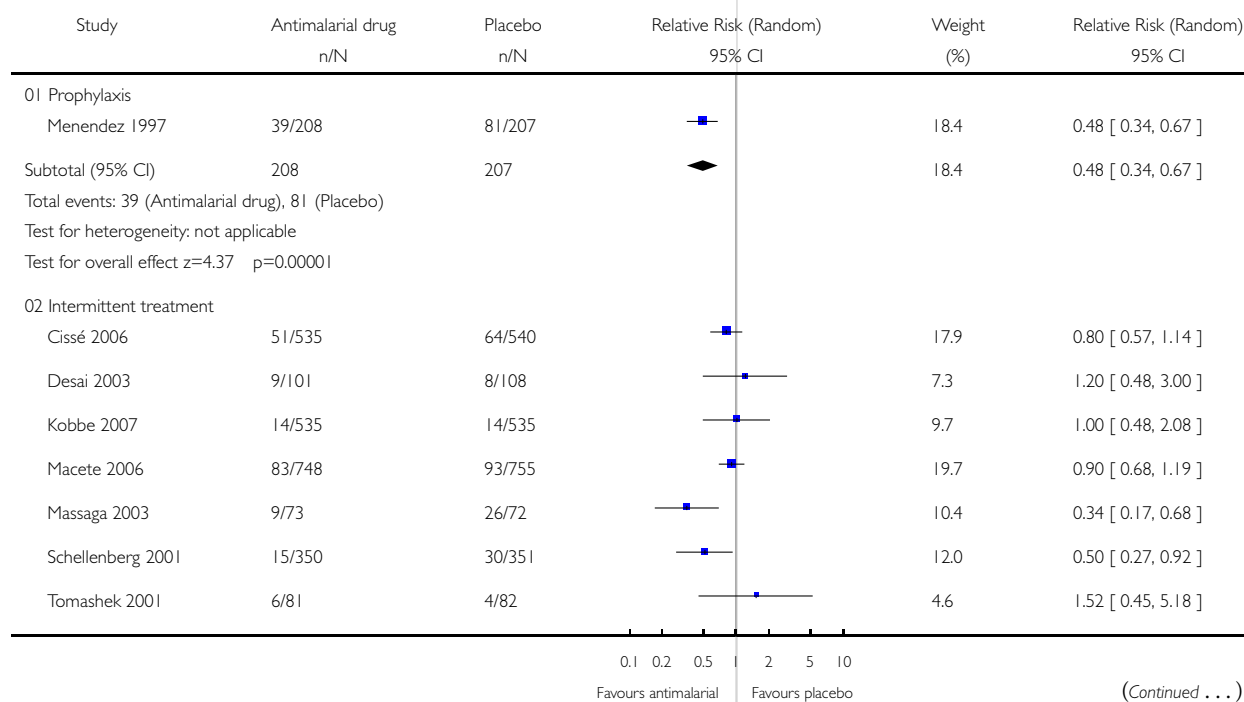


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Review: Chemoprophylaxis and intermittent treatment for preventing malaria in children

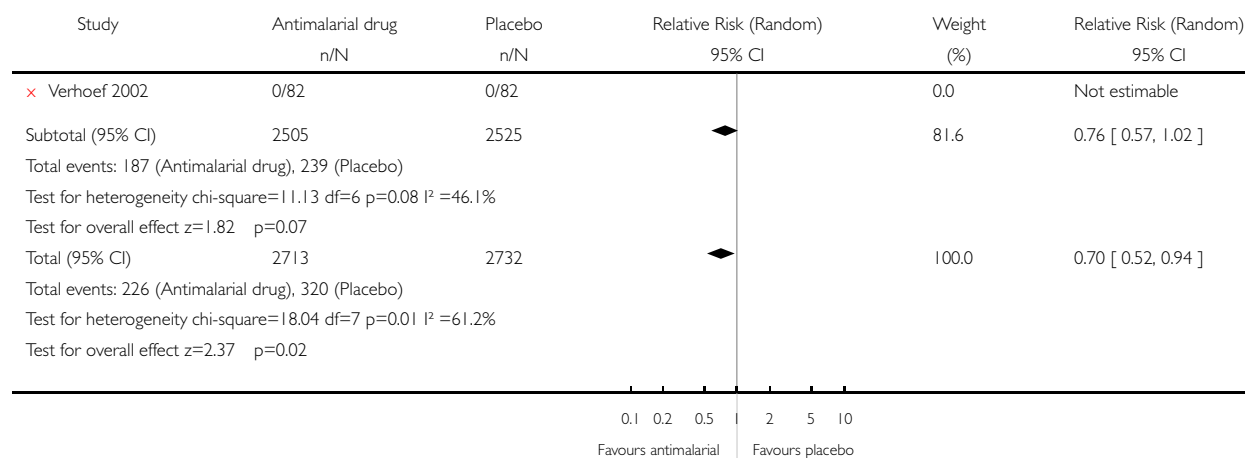
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Outcome: 02 Severe anaemia



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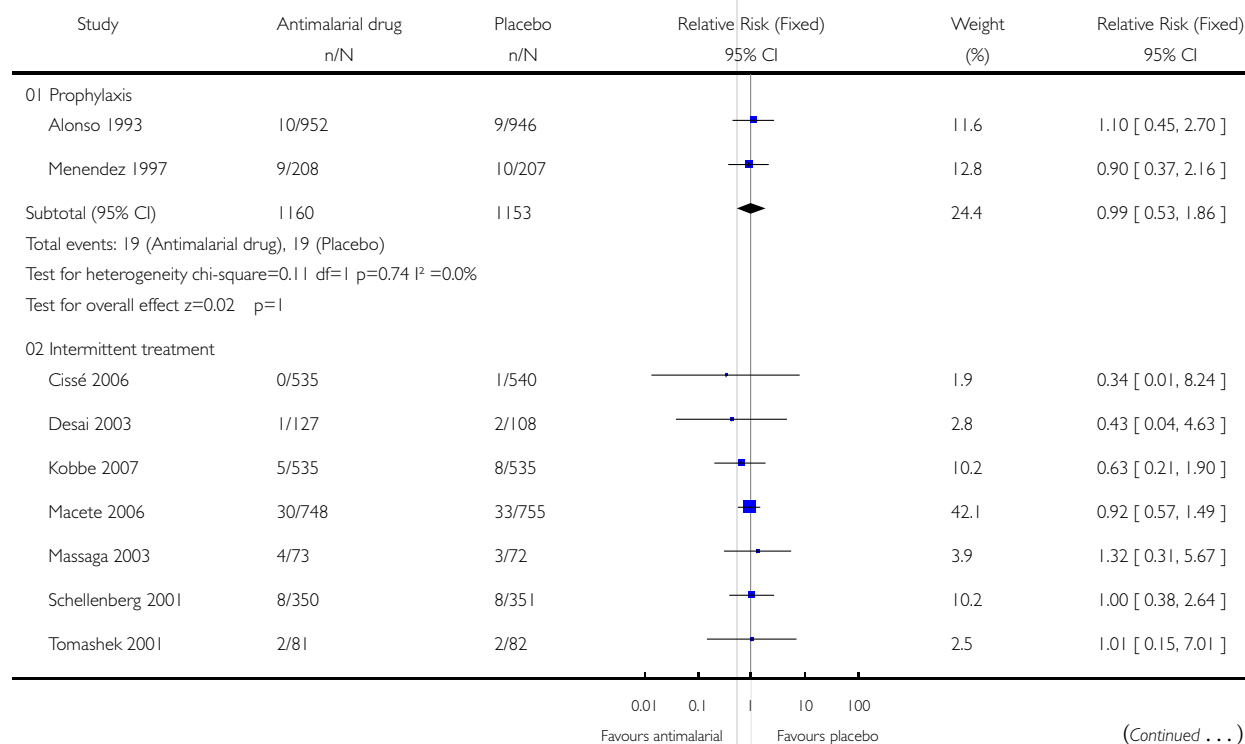


Analysis 01.03. Comparison 01 Antimalarial vs placebo: individually randomized trials [main analysis], Outcome 03 Death from any cause

Review: Chemoprophylaxis and intermittent treatment for preventing malaria in children

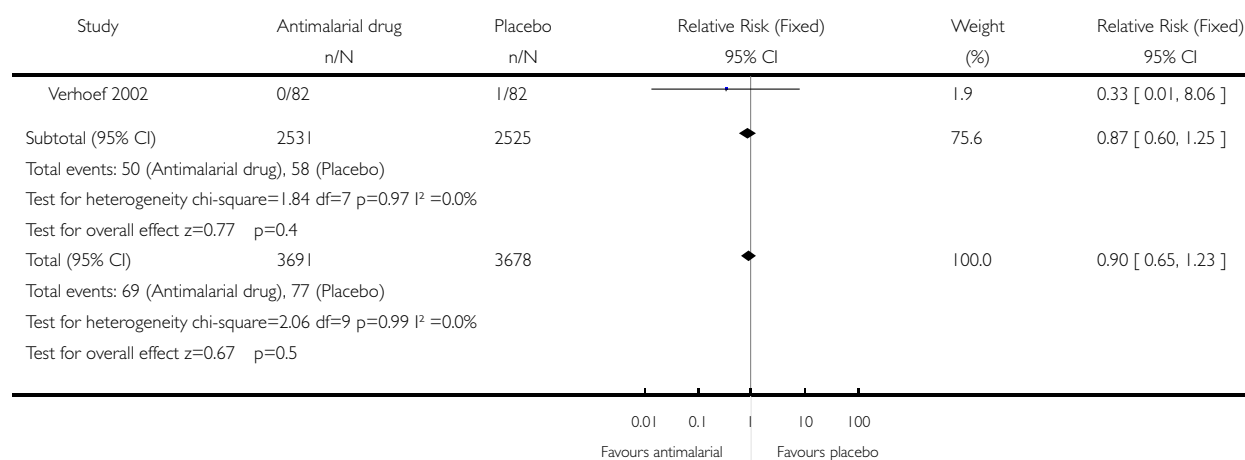
Comparison: 01 Antimalarial vs placebo: individually randomized trials [main analysis]

Outcome: 03 Death from any cause



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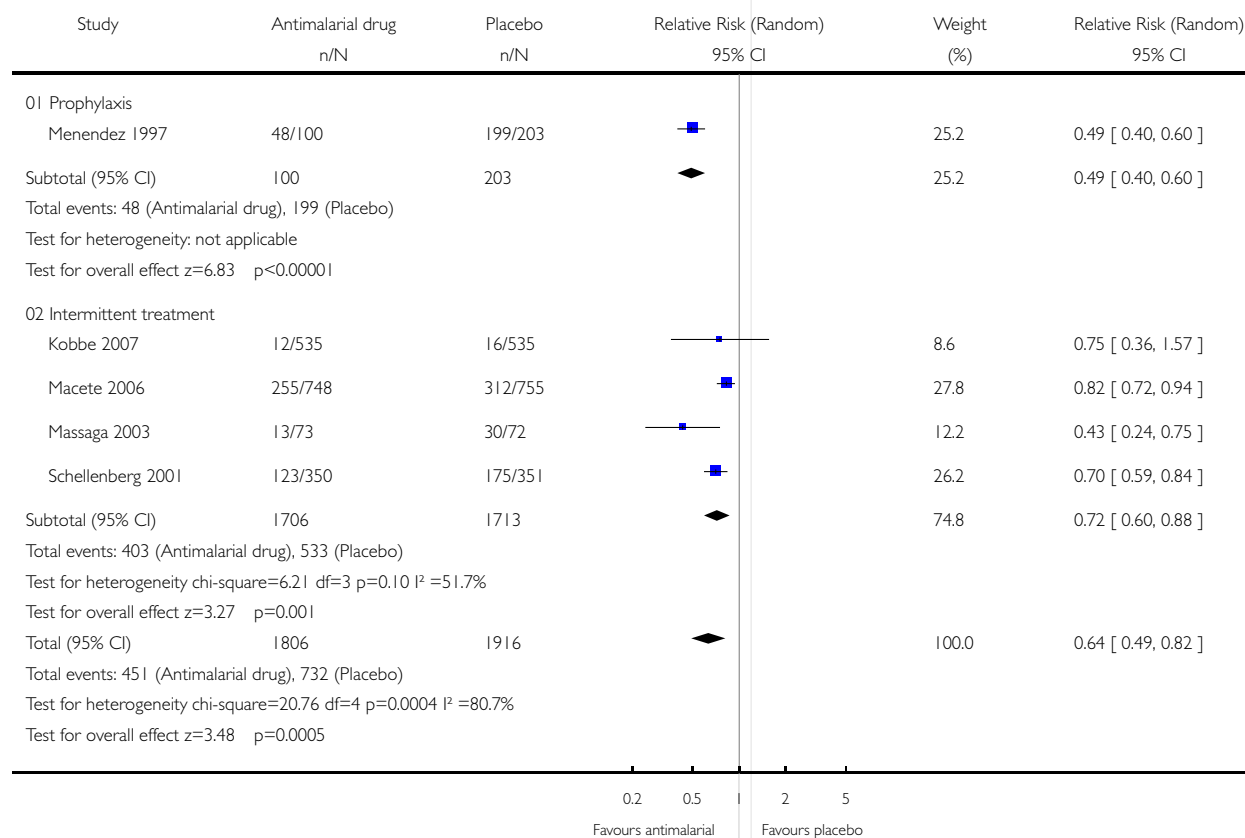


Analysis 01.04. Comparison 01 Antimalarial vs placebo: individually randomized trials [main analysis], Outcome 04 Hospital admission for any cause

Review: Chemoprophylaxis and intermittent treatment for preventing malaria in children

Comparison: 01 Antimalarial vs placebo: individually randomized trials [main analysis]

Outcome: 04 Hospital admission for any cause

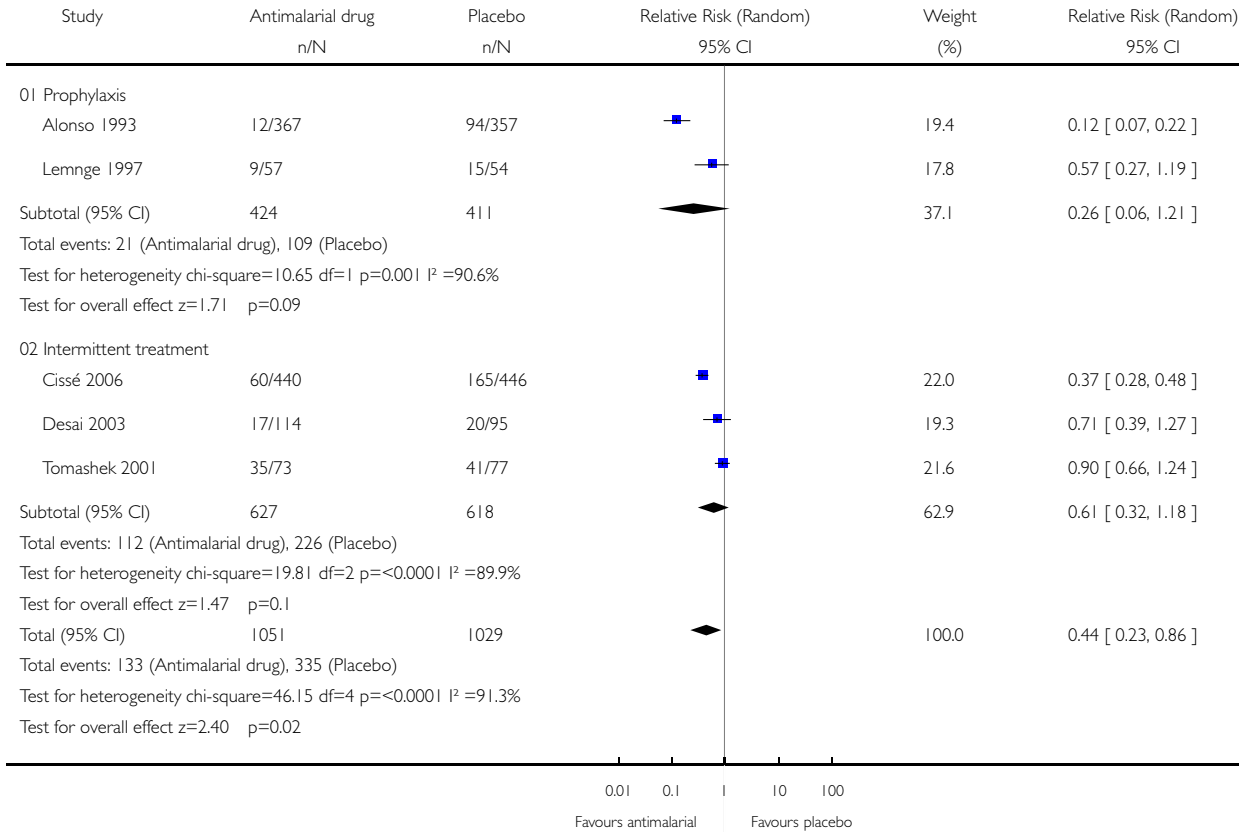


Analysis 01.05. Comparison 01 Antimalarial vs placebo: individually randomized trials [main analysis], Outcome 05 Parasitaemia

Review: Chemoprophylaxis and intermittent treatment for preventing malaria in children

Comparison: 01 Antimalarial vs placebo: individually randomized trials [main analysis]

Outcome: 05 Parasitaemia

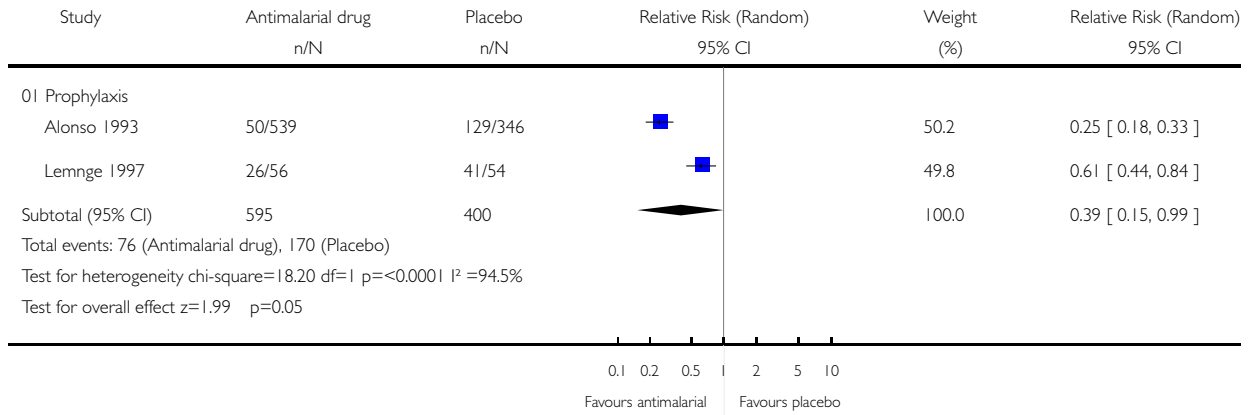


Analysis 01.06. Comparison 01 Antimalarial vs placebo: individually randomized trials [main analysis], Outcome 06 Enlarged spleen

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Comparison: 01 Antimalarial vs placebo: individually randomized trials [main analysis]

Outcome: 06 Enlarged spleen

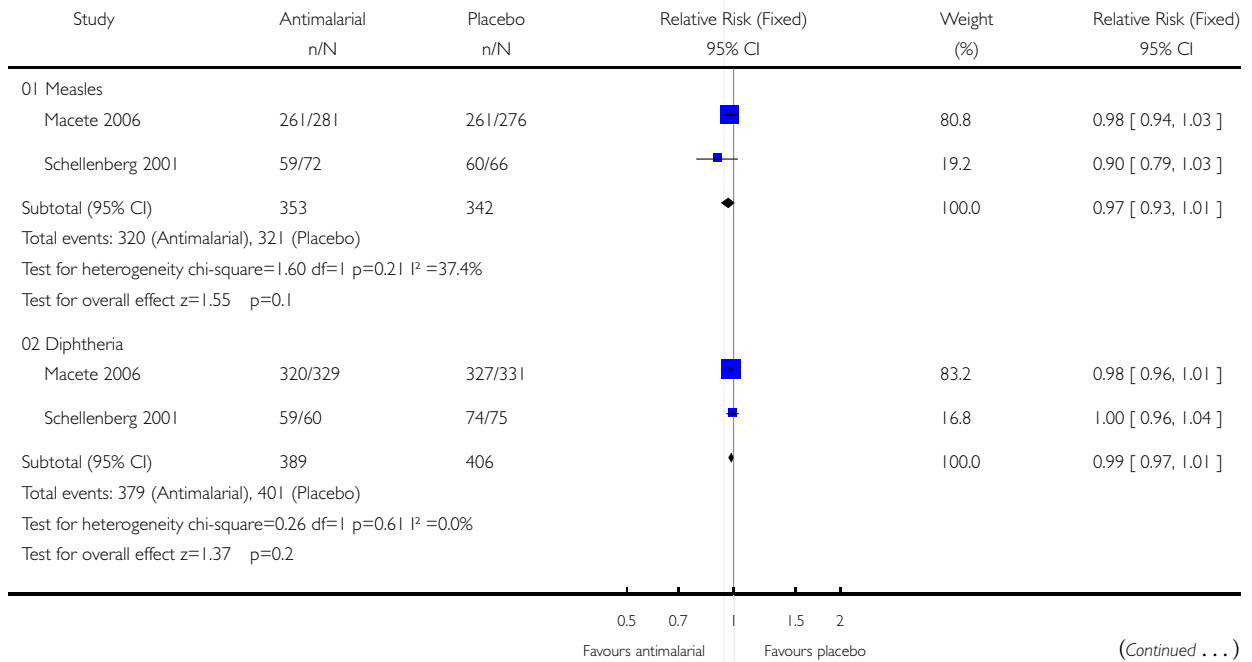


Analysis 01.07. Comparison 01 Antimalarial vs placebo: individually randomized trials [main analysis], Outcome 07 Impact on routine immunization: adequate protective antibodies

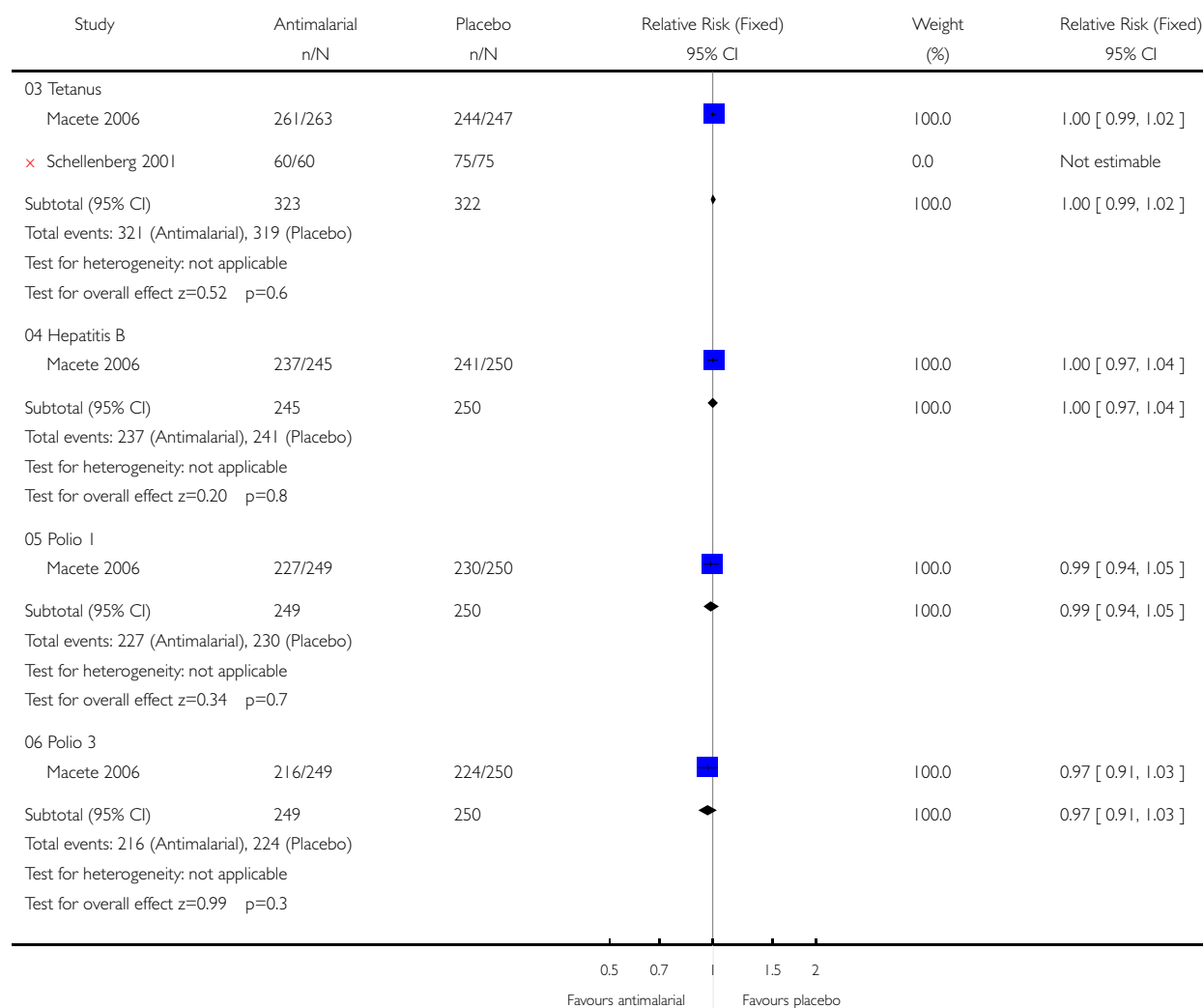
Review: Chemoprophylaxis and intermittent treatment for preventing malaria in children

Comparison: 01 Antimalarial vs placebo: individually randomized trials [main analysis]

Outcome: 07 Impact on routine immunization: adequate protective antibodies



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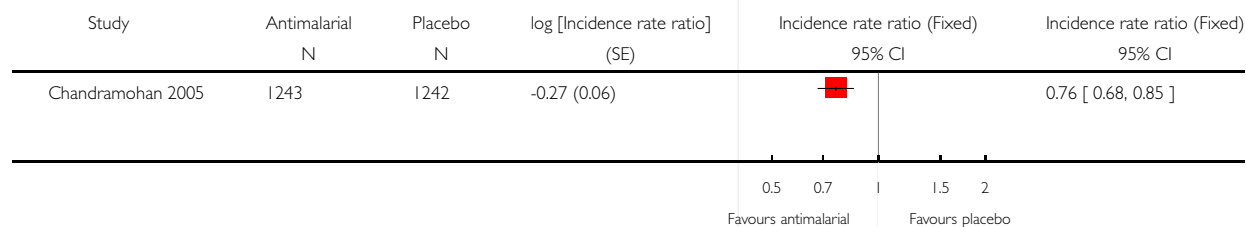


Analysis 02.01. Comparison 02 Antimalarial vs placebo: cluster-randomized trials, Outcome 01 Clinical malaria

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Comparison: 02 Antimalarial vs placebo: cluster-randomized trials

Outcome: 01 Clinical malaria

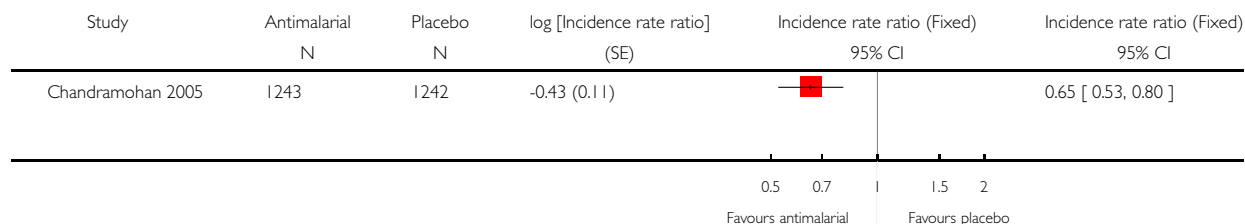


Analysis 02.02. Comparison 02 Antimalarial vs placebo: cluster-randomized trials, Outcome 02 Severe anaemia

Review: Chemoprophylaxis and intermittent treatment for preventing malaria in children

Comparison: 02 Antimalarial vs placebo: cluster-randomized trials

Outcome: 02 Severe anaemia

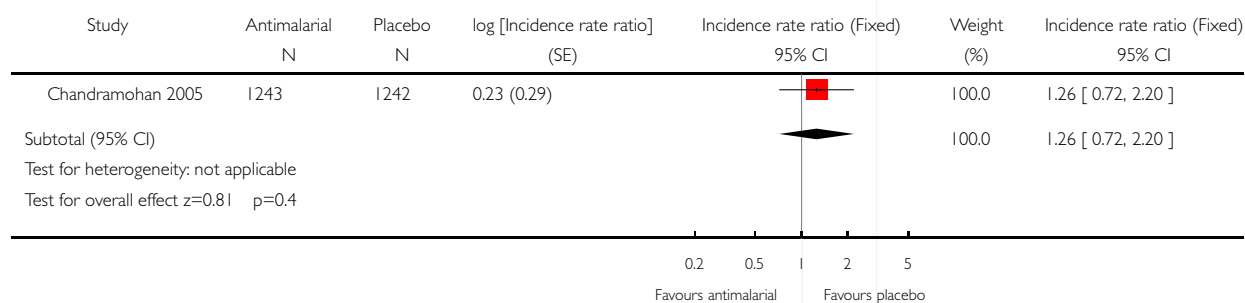


Analysis 02.03. Comparison 02 Antimalarial vs placebo: cluster-randomized trials, Outcome 03 Death from any cause

Review: Chemoprophylaxis and intermittent treatment for preventing malaria in children

Comparison: 02 Antimalarial vs placebo: cluster-randomized trials

Outcome: 03 Death from any cause

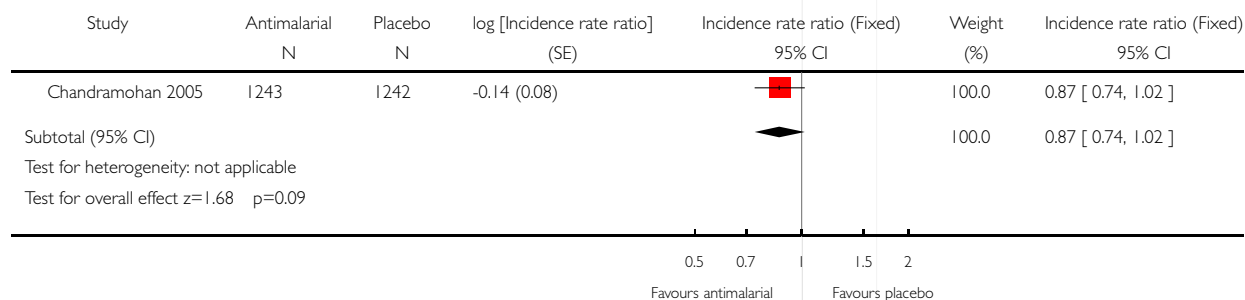


Analysis 02.04. Comparison 02 Antimalarial vs placebo: cluster-randomized trials, Outcome 04 Hospital admission for any cause

Review: Chemoprophylaxis and intermittent treatment for preventing malaria in children

Comparison: 02 Antimalarial vs placebo: cluster-randomized trials

Outcome: 04 Hospital admission for any cause

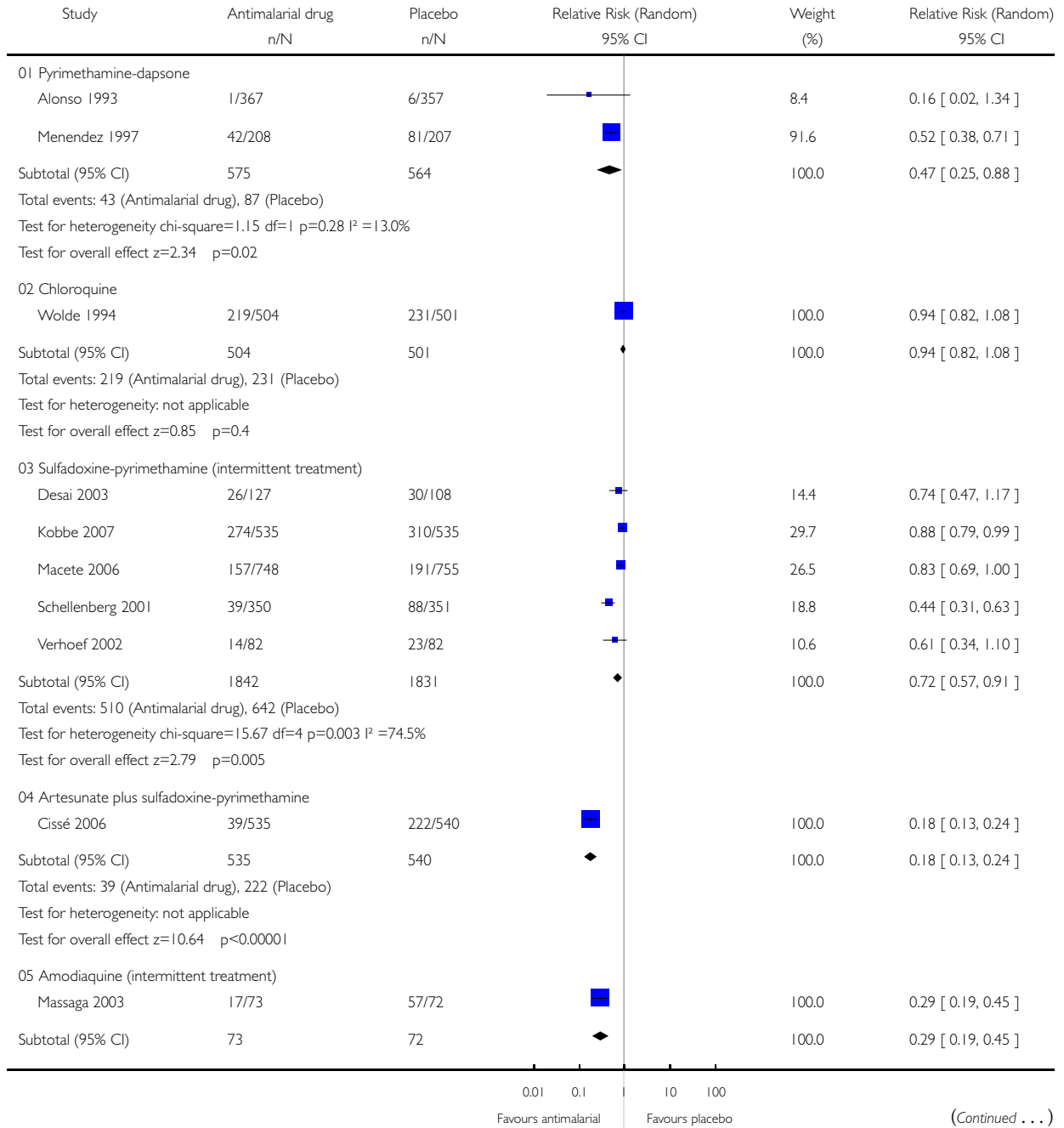


Analysis 03.01. Comparison 03 Antimalarial vs placebo: by drug group, Outcome 01 Clinical malaria

Review: Chemoprophylaxis and intermittent treatment for preventing malaria in children

Comparison: 03 Antimalarial vs placebo: by drug group

Outcome: 01 Clinical malaria



(... Continued)

Study	Antimalarial drug n/N	Placebo n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
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Total events: 17 (Antimalarial drug), 57 (Placebo)

Test for heterogeneity: not applicable

Test for overall effect $z=5.54$ $p<0.00001$

0.01 0.1 10 100
Favours antimalarial Favours placebo

Analysis 03.02. Comparison 03 Antimalarial vs placebo: by drug group, Outcome 02 Severe anaemia

Review: Chemoprophylaxis and intermittent treatment for preventing malaria in children

Comparison: 03 Antimalarial vs placebo: by drug group

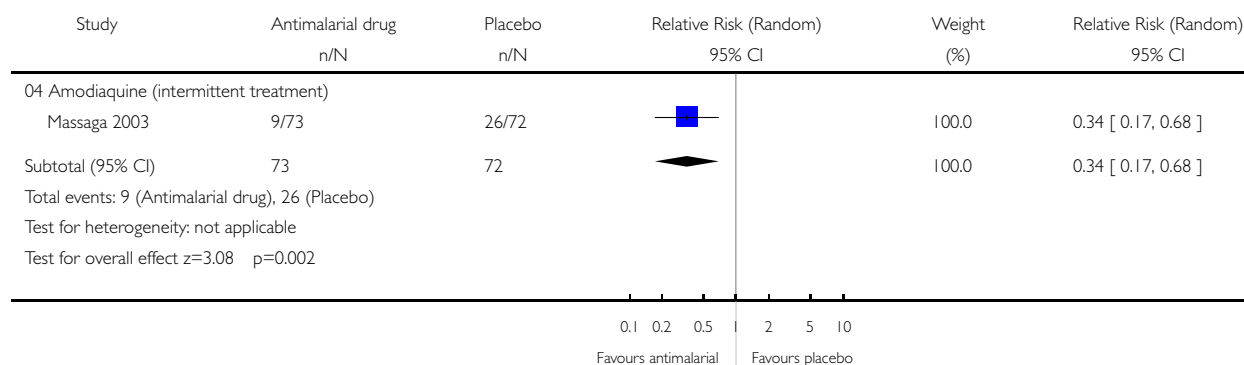
Outcome: 02 Severe anaemia

Study	Antimalarial drug n/N	Placebo n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 Pyrimethamine-dapsone					
Menendez 1997	39/208	81/207		100.0	0.48 [0.34, 0.67]
Subtotal (95% CI)	208	207		100.0	0.48 [0.34, 0.67]
Total events: 39 (Antimalarial drug), 81 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect $z=4.37$ $p=0.00001$					
02 Sulfadoxine-pyrimethamine (intermittent treatment)					
Desai 2003	9/101	8/108		8.8	1.20 [0.48, 3.00]
Kobbe 2007	14/535	14/535		13.2	1.00 [0.48, 2.08]
Macete 2006	83/748	93/755		54.5	0.90 [0.68, 1.19]
Schellenberg 2001	15/350	30/351		18.5	0.50 [0.27, 0.92]
Tomashek 2001	6/81	4/82		5.1	1.52 [0.45, 5.18]
Subtotal (95% CI)	1815	1831		100.0	0.86 [0.65, 1.14]
Total events: 127 (Antimalarial drug), 149 (Placebo)					
Test for heterogeneity $\chi^2=4.70$ $df=4$ $p=0.32$ $I^2=14.9\%$					
Test for overall effect $z=1.02$ $p=0.3$					
03 Artesunate plus sulfadoxine-pyrimethamine					
Cissé 2006	51/535	64/540		100.0	0.80 [0.57, 1.14]
Subtotal (95% CI)	535	540		100.0	0.80 [0.57, 1.14]
Total events: 51 (Antimalarial drug), 64 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect $z=1.23$ $p=0.2$					

0.1 0.2 0.5 2 5 10
Favours antimalarial Favours placebo

(Continued ...)

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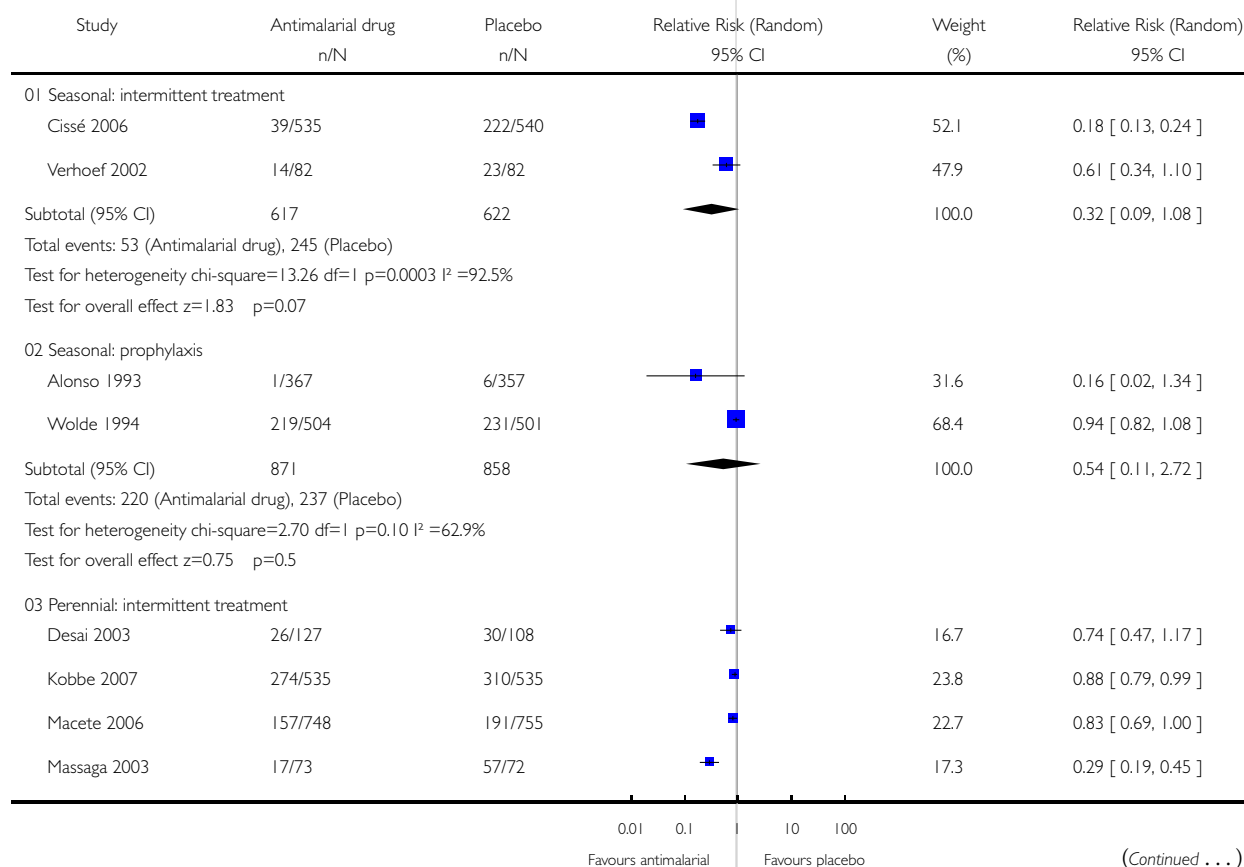


Analysis 04.01. Comparison 04 Antimalarial vs placebo: by seasonality, Outcome 01 Clinical malaria

Review: Chemoprophylaxis and intermittent treatment for preventing malaria in children

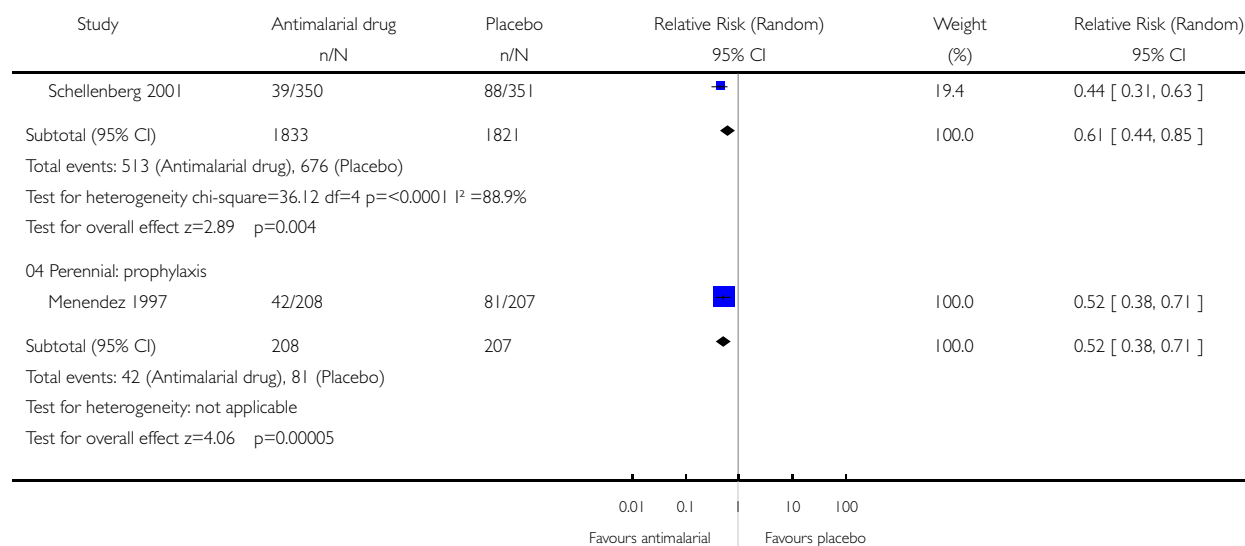
Comparison: 04 Antimalarial vs placebo: by seasonality

Outcome: 01 Clinical malaria



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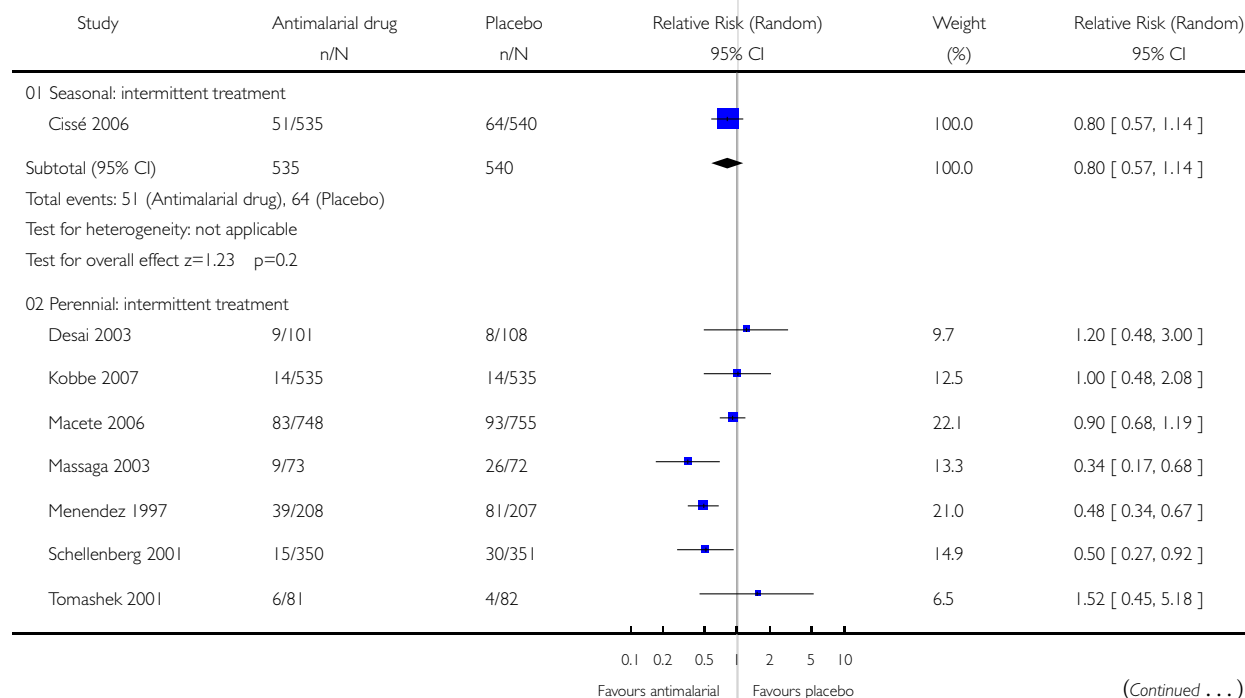


Analysis 04.02. Comparison 04 Antimalarial vs placebo: by seasonality, Outcome 02 Severe anaemia

Review: Chemoprophylaxis and intermittent treatment for preventing malaria in children

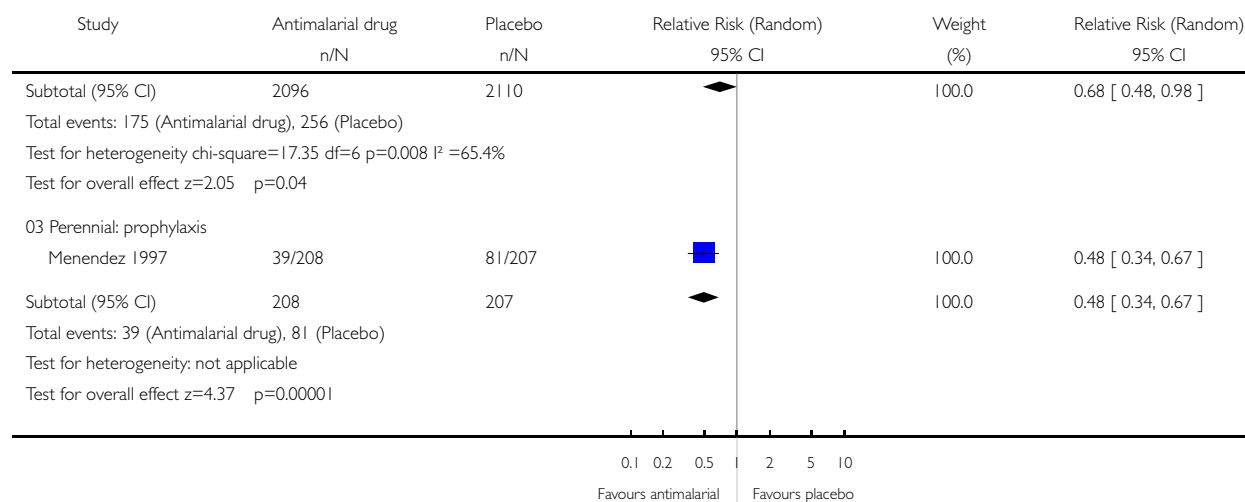
Comparison: 04 Antimalarial vs placebo: by seasonality

Outcome: 02 Severe anaemia



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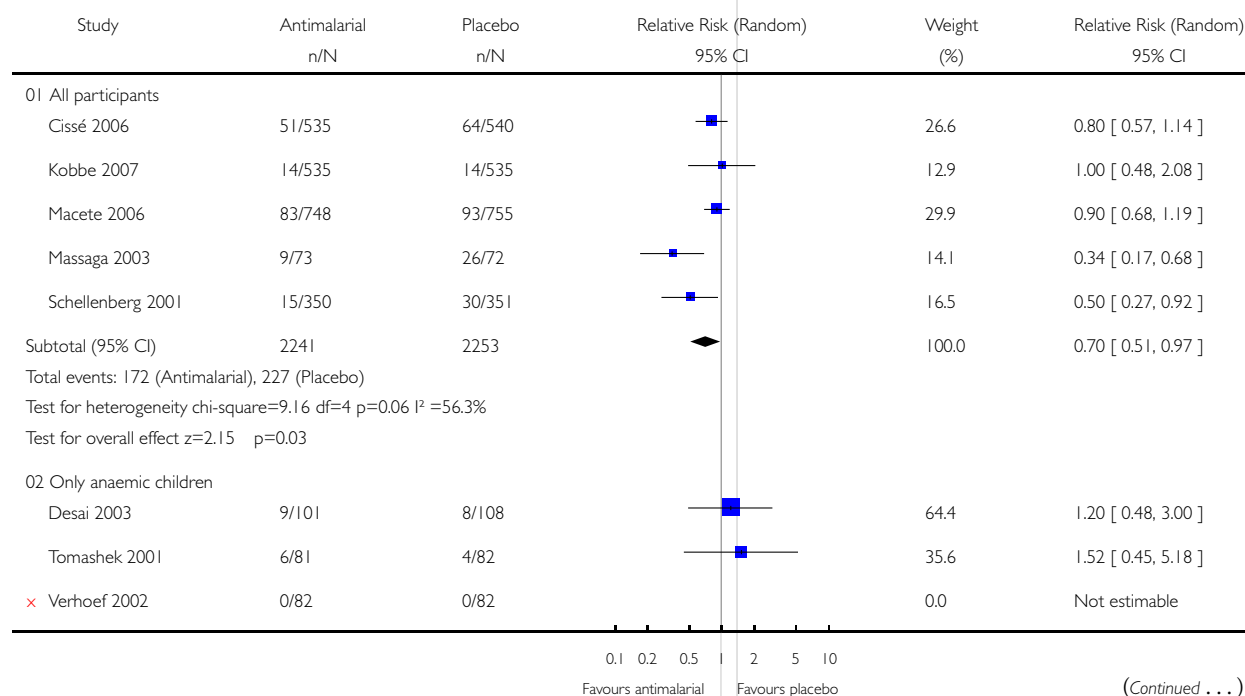


Analysis 05.01. Comparison 05 Intermittent treatment vs placebo: by presence of anaemia, Outcome 01 Severe anaemia

Review: Chemoprophylaxis and intermittent treatment for preventing malaria in children

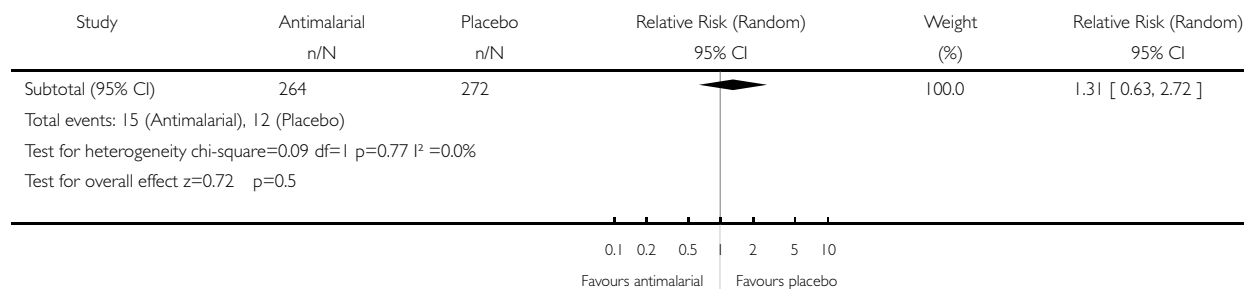
Comparison: 05 Intermittent treatment vs placebo: by presence of anaemia

Outcome: 01 Severe anaemia



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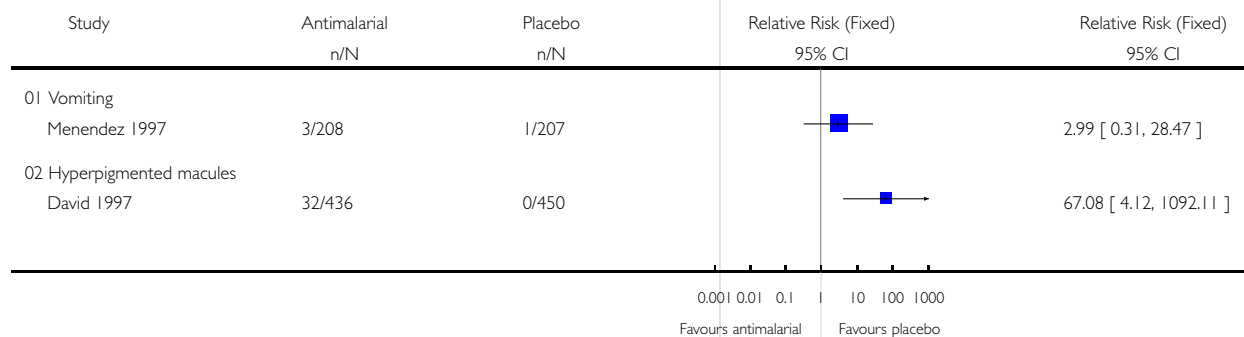


Analysis 06.01. Comparison 06 Antimalarial vs placebo: adverse events, Outcome 01 Prophylaxis

Review: Chemoprophylaxis and intermittent treatment for preventing malaria in children

Comparison: 06 Antimalarial vs placebo: adverse events

Outcome: 01 Prophylaxis

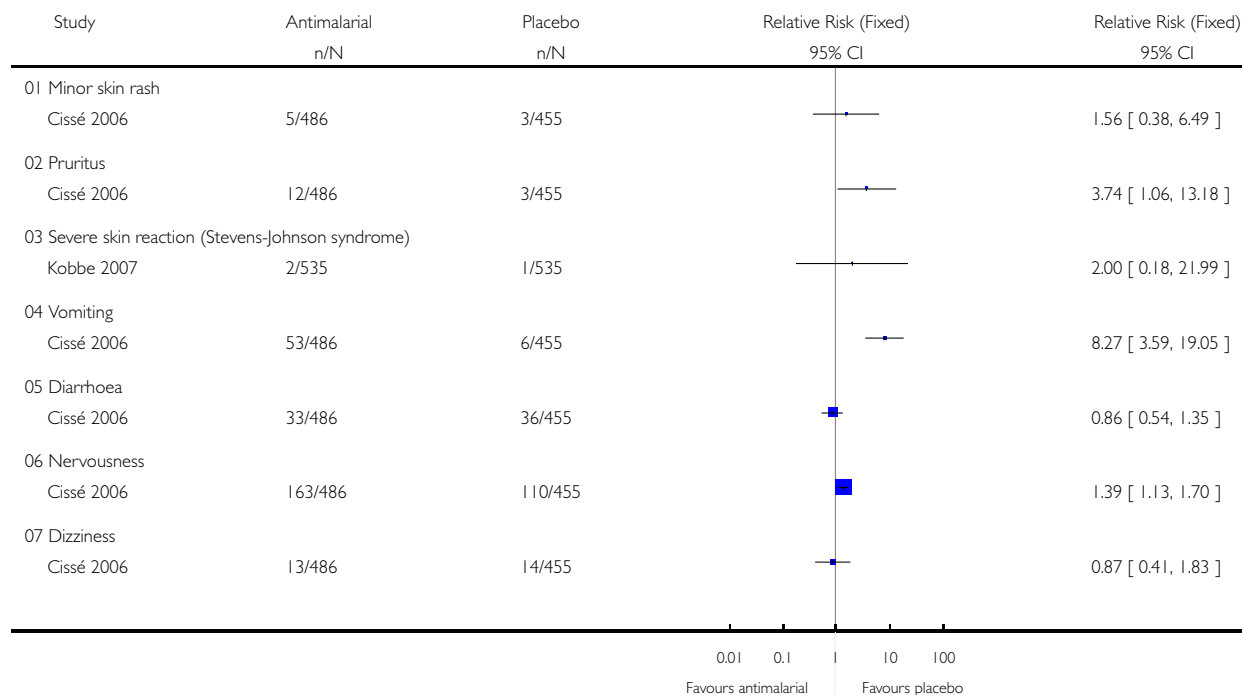


Analysis 06.02. Comparison 06 Antimalarial vs placebo: adverse events, Outcome 02 Intermittent treatment

Review: Chemoprophylaxis and intermittent treatment for preventing malaria in children

Comparison: 06 Antimalarial vs placebo: adverse events

Outcome: 02 Intermittent treatment

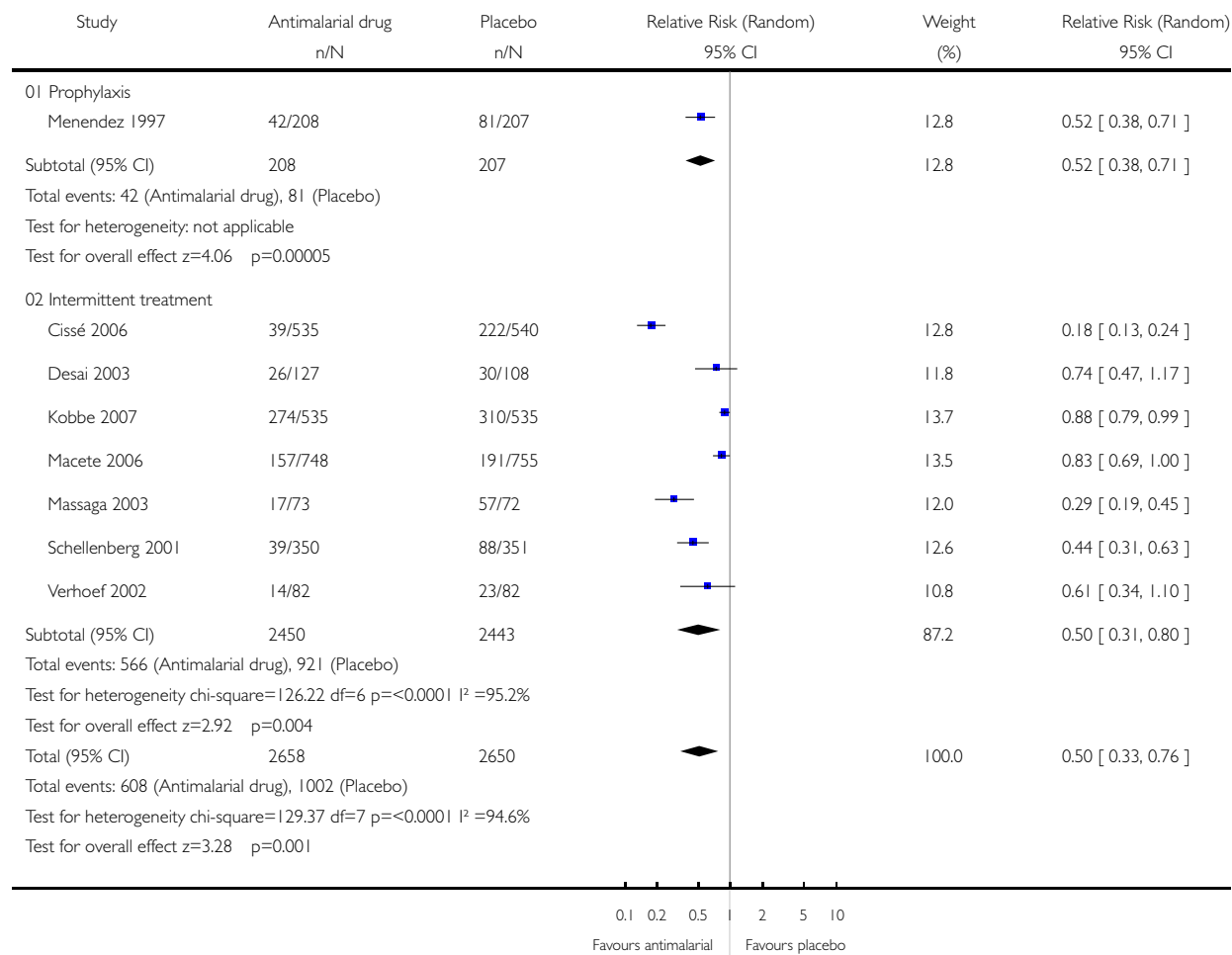


Analysis 07.01. Comparison 07 Antimalarial vs placebo: adequately concealed trials, Outcome 01 Clinical malaria

Review: Chemoprophylaxis and intermittent treatment for preventing malaria in children

Comparison: 07 Antimalarial vs placebo: adequately concealed trials

Outcome: 01 Clinical malaria

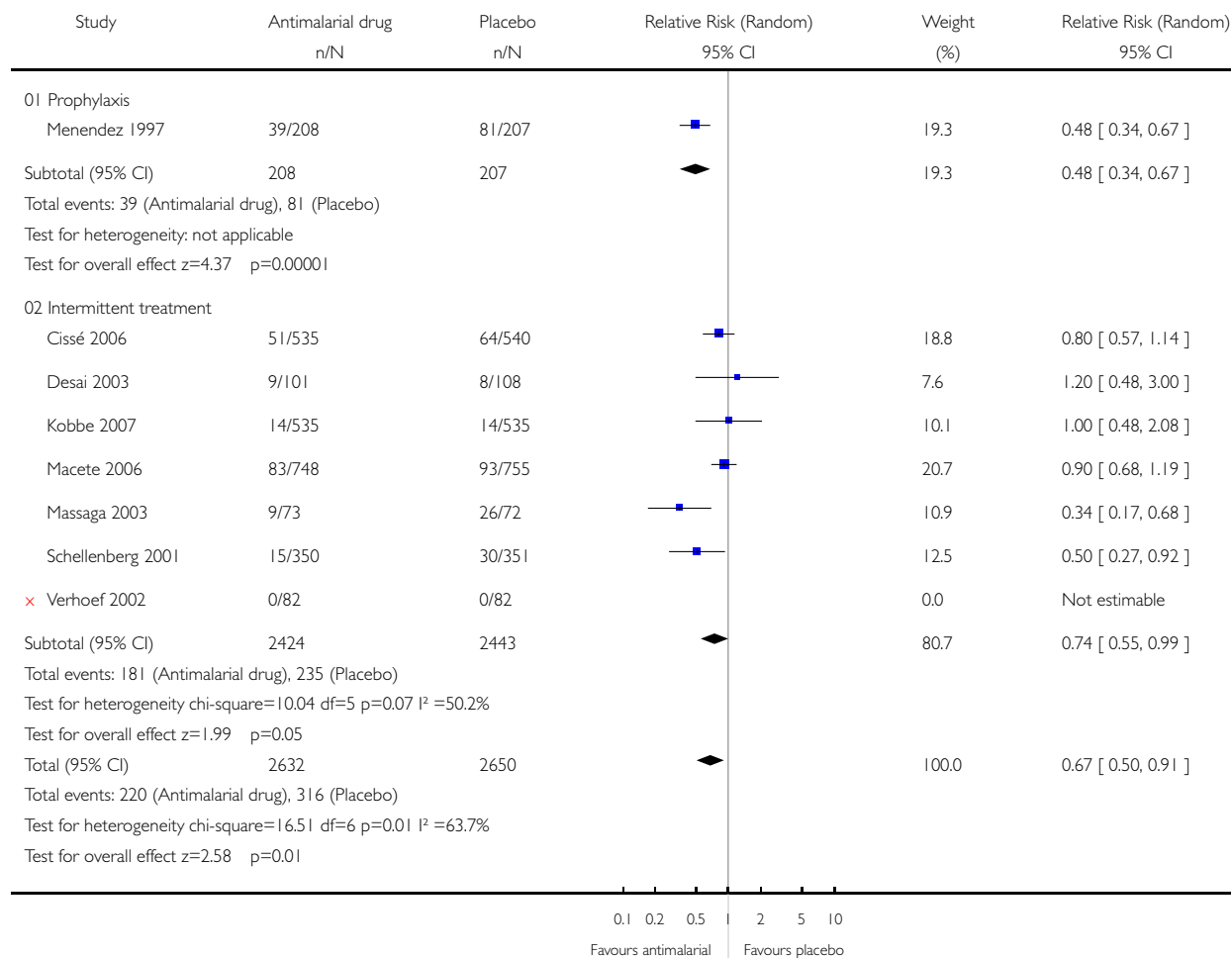


Analysis 07.02. Comparison 07 Antimalarial vs placebo: adequately concealed trials, Outcome 02 Severe anaemia

Review: Chemoprophylaxis and intermittent treatment for preventing malaria in children

Comparison: 07 Antimalarial vs placebo: adequately concealed trials

Outcome: 02 Severe anaemia

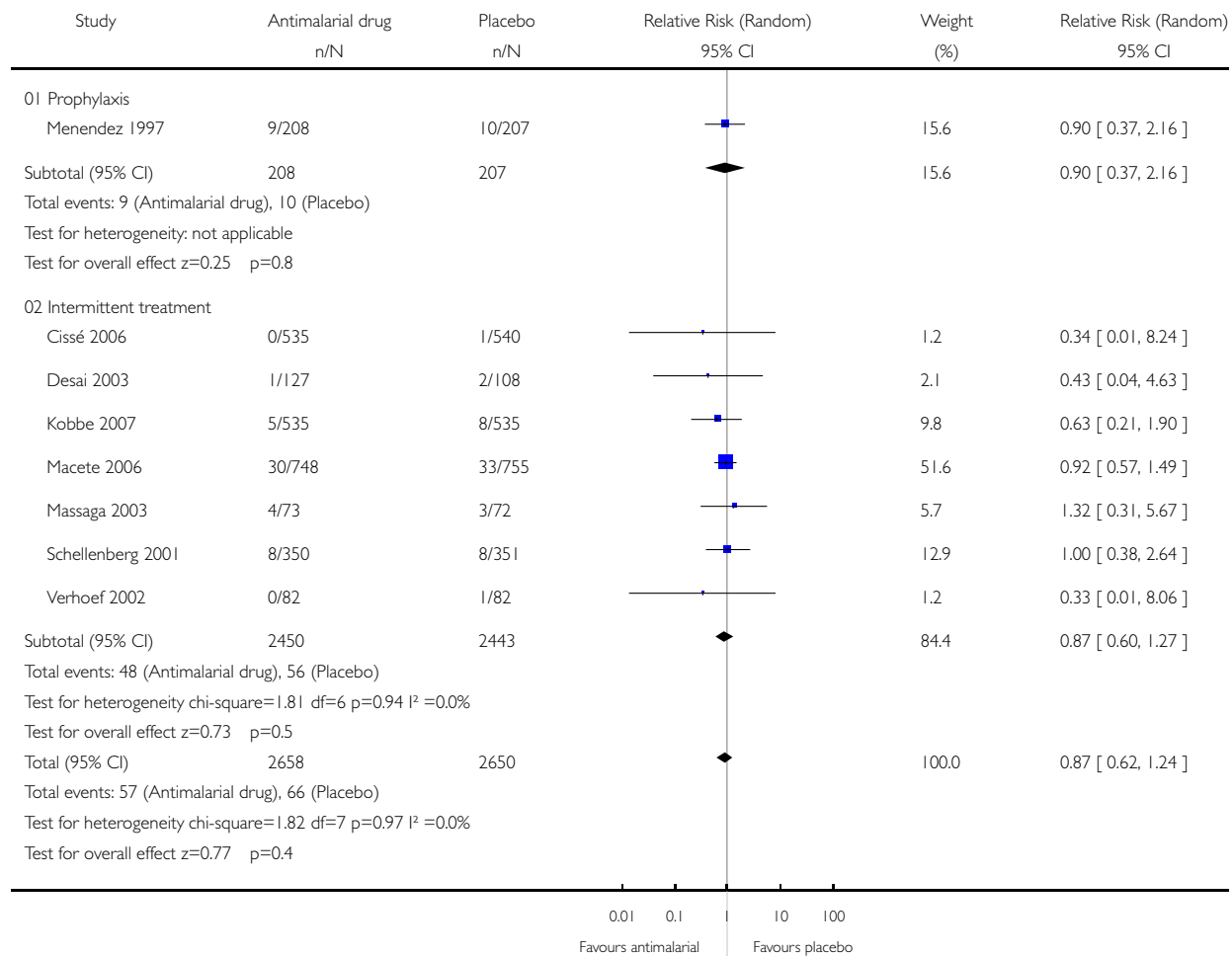


Analysis 07.03. Comparison 07 Antimalarial vs placebo: adequately concealed trials, Outcome 03 Death from any cause

Review: Chemoprophylaxis and intermittent treatment for preventing malaria in children

Comparison: 07 Antimalarial vs placebo: adequately concealed trials

Outcome: 03 Death from any cause

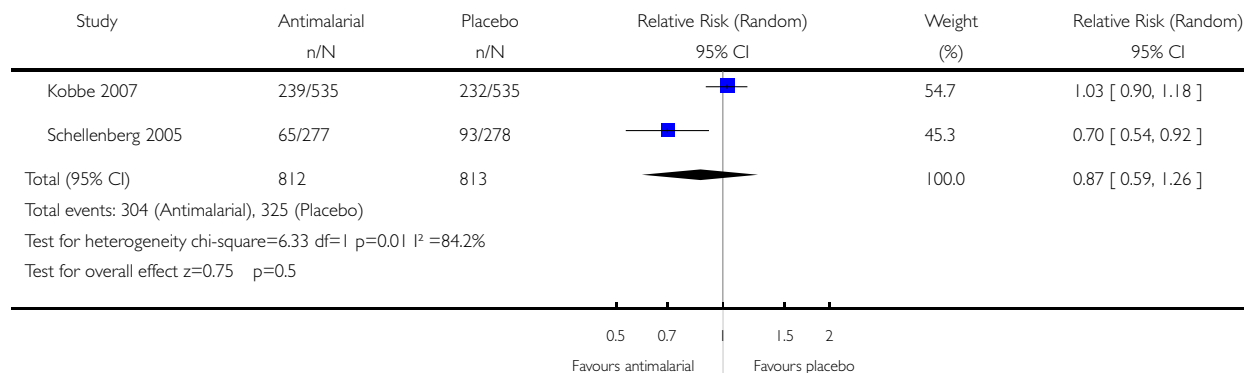


**Analysis 08.01. Comparison 08 Antimalarial vs placebo: impact after stopping intervention, Outcome 01
Clinical malaria (relative risk)**

Review: Chemoprophylaxis and intermittent treatment for preventing malaria in children

Comparison: 08 Antimalarial vs placebo: impact after stopping intervention

Outcome: 01 Clinical malaria (relative risk)

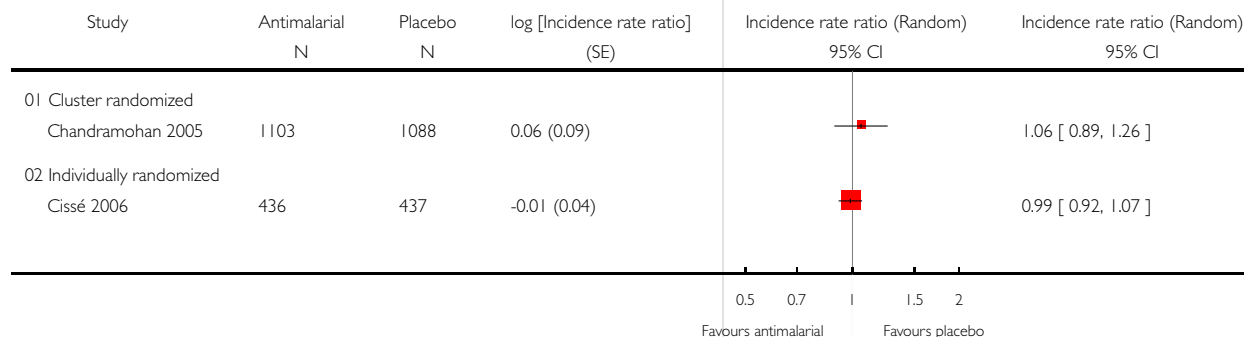


**Analysis 08.02. Comparison 08 Antimalarial vs placebo: impact after stopping intervention, Outcome 02
Clinical malaria (incidence rate ratio)**

Review: Chemoprophylaxis and intermittent treatment for preventing malaria in children

Comparison: 08 Antimalarial vs placebo: impact after stopping intervention

Outcome: 02 Clinical malaria (incidence rate ratio)

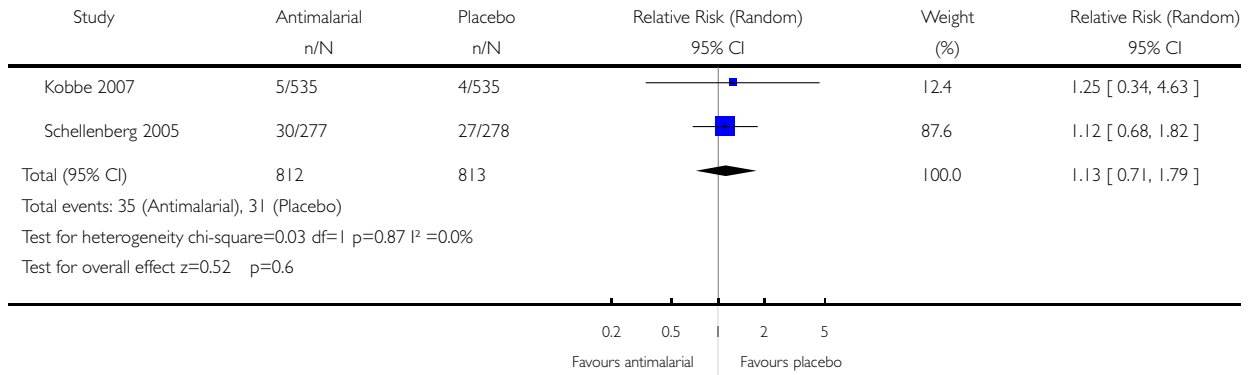


Analysis 08.03. Comparison 08 Antimalarial vs placebo: impact after stopping intervention, Outcome 03 Severe anaemia (relative risk)

Review: Chemoprophylaxis and intermittent treatment for preventing malaria in children

Comparison: 08 Antimalarial vs placebo: impact after stopping intervention

Outcome: 03 Severe anaemia (relative risk)

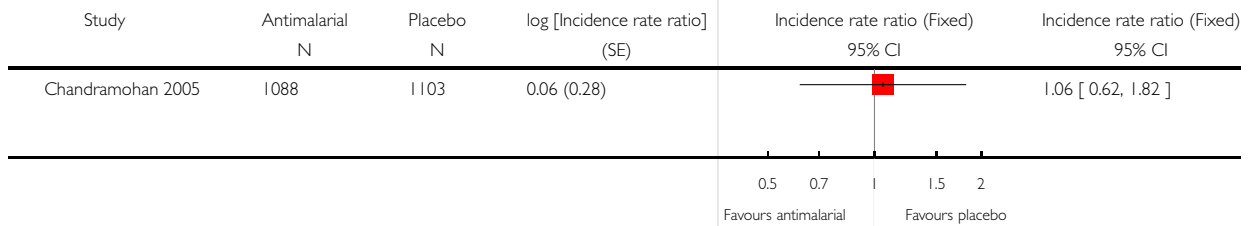


Analysis 08.04. Comparison 08 Antimalarial vs placebo: impact after stopping intervention, Outcome 04 Severe anaemia (incidence rate ratio)

Review: Chemoprophylaxis and intermittent treatment for preventing malaria in children

Comparison: 08 Antimalarial vs placebo: impact after stopping intervention

Outcome: 04 Severe anaemia (incidence rate ratio)

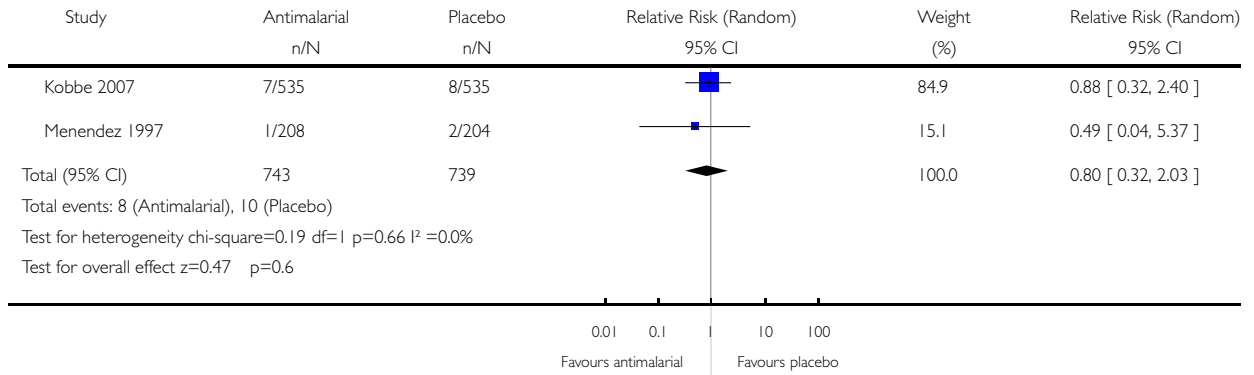


**Analysis 08.05. Comparison 08 Antimalarial vs placebo: impact after stopping intervention, Outcome 05
Death from any cause (relative risk)**

Review: Chemoprophylaxis and intermittent treatment for preventing malaria in children

Comparison: 08 Antimalarial vs placebo: impact after stopping intervention

Outcome: 05 Death from any cause (relative risk)



**Analysis 08.06. Comparison 08 Antimalarial vs placebo: impact after stopping intervention, Outcome 06
Death from any cause (incidence rate ratio)**

Review: Chemoprophylaxis and intermittent treatment for preventing malaria in children

Comparison: 08 Antimalarial vs placebo: impact after stopping intervention

Outcome: 06 Death from any cause (incidence rate ratio)



**Analysis 08.07. Comparison 08 Antimalarial vs placebo: impact after stopping intervention, Outcome 07
Impact on routine immunization: adequate protective antibody**

Review: Chemoprophylaxis and intermittent treatment for preventing malaria in children

Comparison: 08 Antimalarial vs placebo: impact after stopping intervention

Outcome: 07 Impact on routine immunization: adequate protective antibody

